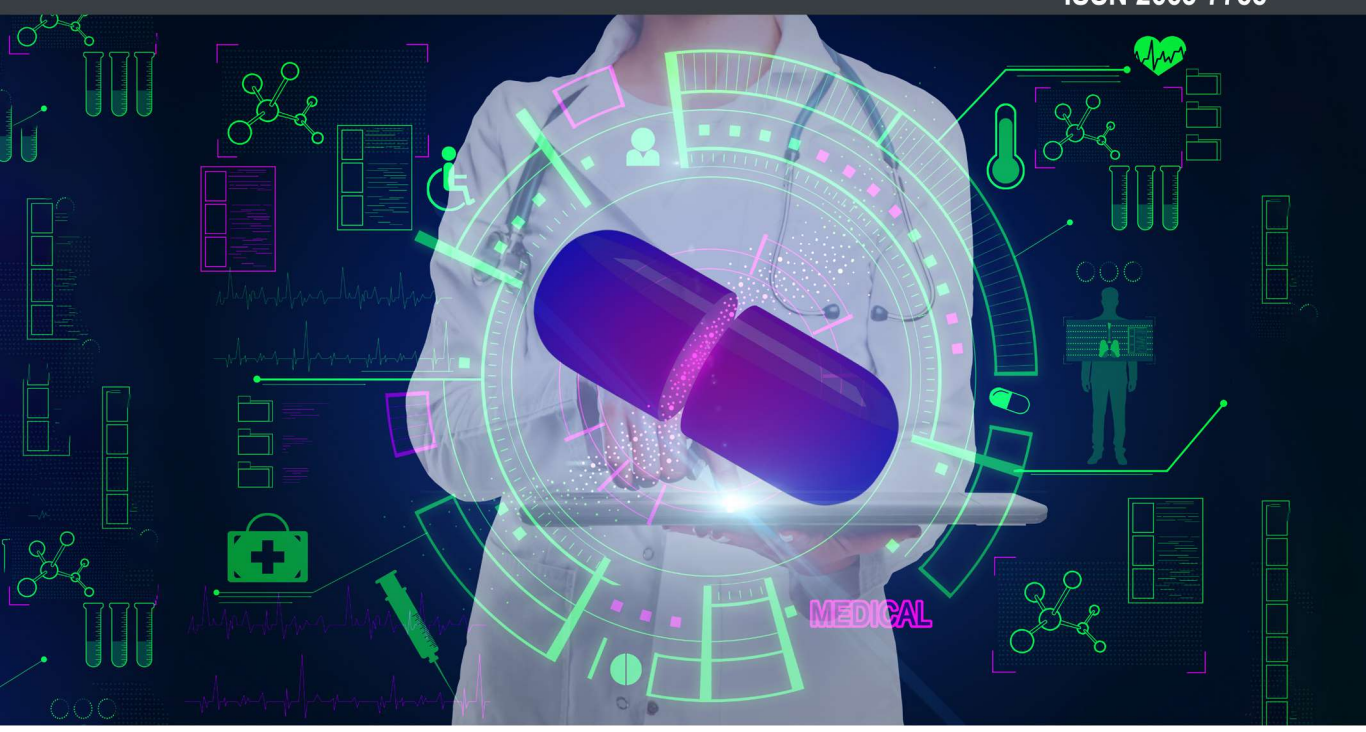
MEDICUS 9 ISSUE 2

Editor-in-Chief: Elvana Rista, MD, PhD/ Scientific Journal of the Faculty of Medical Technical Sciences/ No. 9, issue 2 / 2025

ISSN 2663-7758



INNOVATION AND EVIDENCE-BASED PRACTICE: WHY BOTH MATTER IN CLINICAL MEDICINE

Elvana **RISTA** / Kristi **SALIAJ** / Maksim **CELA** / Ariana **STRAKOSHA** / Vilma **CADRI** / Nevi **PASKO** / Resmije **TOZHARAKU** / Blerim **ARAPI** / Eljo **PAJA** / Lumturi **MERKURI** / Leidon **SHAPO** / Elda **CULE** / Merita **RROJI** / Aferdita **TAKO (KUMARAKU)** / Blerina **SARACI QIRINXHI** / Aida **BUSHATI** / Xhentila **DOKA** / Armand **SHEHU** / Rovena **ALIAJ** / Sindi **DIZDARI** / Paskal **CULLUFI** / Esida **HOXHA** / Krisanta **BËRDUFI** / Rezarta **STENA** / Sulejman **HAXHI** / Admir **JANCE** / Fluturim **NELA** / Erla **MULLALLI** / Mustafe **BUZOKU** / Jonila Gabrani / Adelina MUHAMETAJ / Ambra Metasana / Amantia Imeraj / Ariana **STRAKOSHA** / Ermira **MUCO** / Amarildo **BLLOSHMI** / Ornela **CELA** / Najada **KALLASHI (JAHIQI)** / Xhejni **KURTI**/ Dorina **DERVISHI** / Klejda **ÇOLLAKU** / Neada **HOXHA** / Armanda **SARACI** / Olta **ZENELI**

UETPRESS

MEDICUS No. 9, issue 2/2025
JOURNAL OF THE FACULTY OF MEDICAL TECHNICAL SCIENCES

ISSN 2663-7758

UETPRESS

Published under the series "ACADEMIC JOURNALS".

The journal has been catalogued at the National Library of Albania and the Library of the European University of Tirana, Albania.

(print ISSN: 2663-7758/ online ISSN: 2958-8871)

medicus@uet.edu.al
www.uet.edu.al/medicus

UETPRESS

Published by:
EUROPEAN UNIVERSITY OF TIRANA / ALBANIA

content

EDITORIAL

Innovation and Evidence-Based Practice: Why Both Matter in Clinical Medicine

Elvana RISTA, MD, PhD
Editor-in-Chief, Medicus
Faculty of Medical Technical Sciences
European University of Tirana
Albania

Why This Matters Now

Clinical medicine is defined by decisions, often complex, often made under pressure, and always consequential. Each day, clinicians must determine whether to adopt new therapies, technologies, or approaches, or to rely on established practices that have proven effective over time. Knowing when to change, what to change, and why remains one of the most challenging responsibilities in healthcare. The theme of this issue, "Innovation and Evidence-Based Practice Across Clinical Specialties," speaks directly to this challenge. It reflects a fundamental principle of modern medicine: progress depends on the careful balance between innovation and evidence. Innovation without evidence is guesswork. Evidence without innovation means progress stops.

The Real Problem

Many clinicians experience a persistent tension between enthusiasm for new developments and caution born of experience. This is real and understandable. When we find something that works, we need to understand *why* it works and

how to use it better. When something doesn't work the way we hoped, we need to be honest about that as well. Innovation and evidence-based practice are not opposed to each other, they are partners. Evidence tells us what works. Innovation challenges us to find better ways of doing things. Together, they move medicine forward.

The articles in this issue of Medicus reflect clinicians and researchers across many fields doing exactly this work. They are asking questions, testing ideas, and sharing what they learn.

This issue brings together contributions from diverse medical specialties: nephrology, radiology, hematology, infectious disease, pharmacy, physiotherapy, and others. Each article represents a commitment to better understanding disease, improving clinical practice, and ultimately, better care for patients. We hope you find these contributions valuable. Whether they confirm what you already know, challenge your thinking, or inspire new questions, that engagement is what makes medical progress possible.

A VExUS Perspective on Cardiorenal Syndrome: Case Report and Literature Review

Kristi SALIAJ
European University of Tirana, Tirana, Albania
Hygeia Hospital Tirana, Tirana, Albania

Elvana RISTA
European University of Tirana, Tirana, Albania
Hygeia Hospital Tirana, Tirana, Albania

Maksim CELA
University of Medicine Tirana, Tirana, Albania

Abstract

Cardiorenal syndrome has long been attributed to reduced cardiac output and renal hypoperfusion, but contemporary evidence increasingly identifies venous congestion as a primary driver of acute kidney injury, particularly in right-sided heart disease. The Venous Excess Ultrasound Score (VExUS) offers an innovative, non-invasive, organ-specific Doppler method to quantify systemic venous hypertension and better define the hemodynamic contributors of renal dysfunction. We report a case illustrating this paradigm, in which decompensated right-sided heart-failure led to high-grade venous congestion on VExUS assessment and resulted in acute kidney injury that improved with targeted decongestive therapy. This case underscores the growing relevance of VExUS as a practical bedside tool for diagnosing congestion-mediated renal injury and guiding individualized fluid management in cardiorenal patients.

Introduction

For decades, the prevailing explanation for cardiorenal syndrome centered on low cardiac output, systemic hypotension, and reduced renal perfusion, positioning acute kidney injury as a downstream consequence of forward flow failure. [1-4] More recent pathophysiologic understanding, however, has redefined this model by demonstrating that renal dysfunction, particularly in right-sided heart failure is more directly linked to *venous congestion* than to inadequate arterial supply. [2,5-7] In this updated framework, elevated right-sided pressures are transmitted retrograde into the renal venous system, increasing interstitial and intratubular pressure to the point of compressing the filtration apparatus, an effect increasingly described as "**renal tamponade"**. [1,6] Rather than a perfusion deficit alone, it is the sustained venous hypertension and resultant mechanical opposition to glomerular filtration that drive renal injury, marking a notable paradigm shift in the previously established pathophysiology of cardiorenal syndrome. [2,6]

In this context, VExUS (Venous Excess Ultrasound) has emerged as a ultrasound-based bedside method to directly quantify systemic venous congestion when traditional markers fail to capture organ-level pressure overload. [8-12] VExUS integrates measurement of inferior vena cava caliber with hepatic, portal, and intrarenal venous Doppler interrogation to determine the degree of backward pressure transmission affecting the liver, splanchnic vasculature, and kidneys. [12-14] By grading the severity of waveform alterations, including hepatic systolic reversal, portal pulsatility, and loss of continuous intrarenal venous flow, VExUS provides a structured and reproducible congestion index that outperforms single-parameter volume assessments. [12-16] As such, it represents an innovative clinical tool that not only diagnoses venous congestion more efficiently, but also enables more individualized and physiologically guided decongestive therapy. [11,15-20]

Herein, we present the case of a patient whose acute kidney injury was clarified by VExUS assessment, which identified severe venous congestion as the primary hemodynamic insult.

Case presentation

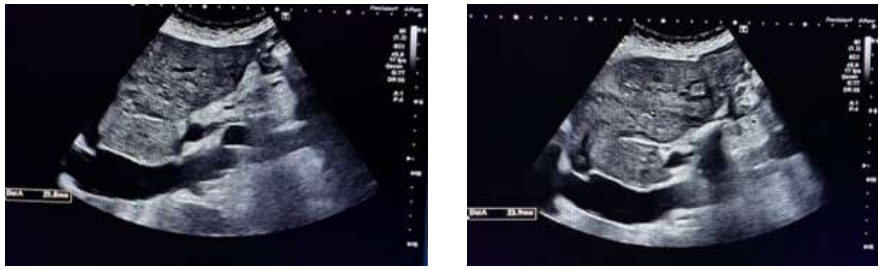
A 77-year-old woman presented with one week of progressive dyspnea, profound fatigue, asthenia, anorexia, nausea, and vomiting, with a marked decline in urine output becoming evident over the preceding forty-eight hours prior to admission. Her past medical history was significant for well-controlled type 2 diabetes mellitus, confirmed by an admission HbA1c of 5.5%, and longstanding severe tricuspid regurgitation. Initial laboratory evaluation revealed anemia

(hemoglobin of 9 g/dL), with no signs of ongoing inflammation (normal leukocyte count and C-reactive protein levels) and severe renal function impairment (urea of 322 mg/dL and creatinine of 8.6 mg/dL), accompanied by mild hyponatremia and hyperkalemia at 133 mmol/L and 5.8 mmol/L, respectively. She denied recent infections, new medications, or non-steroidal anti-inflammatory drug use.

On admission, the patient appeared volume overloaded but hemodynamically stable. Initial evaluation was consistent with acute kidney injury (AKI) and decompensated right-sided heart failure.

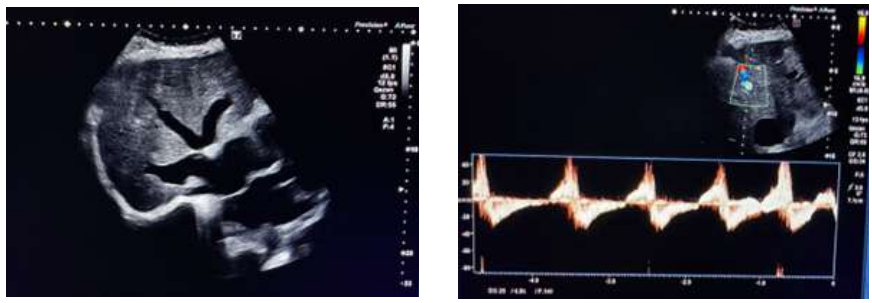
Point-of-care ultrasonography demonstrated a plethoric inferior vena cava measuring 25.8 mm, with minimal inspiratory collapse (23.9 mm), indicating markedly elevated right atrial and central venous pressure. Hepatic venous Doppler revealed systolic flow reversal, consistent with severe tricuspid regurgitation and backward pressure transmission into the hepatic venous network. Portal vein examination showed a pulsatility index greater than 50%, and intrarenal venous Doppler displayed discontinuous monophasic flow, a pattern that reflects elevated renal venous confluence pressures and interstitial congestion. No ascites, pleural effusion, or pericardial fluid was identified. Cardiac ultrasound confirmed preserved left ventricular systolic function but reiterated the presence of severe tricuspid regurgitation, reinforcing the systemic venous hypertension mechanism.

FIGURE 1 (a. and b.). Inferior vena cava (IVC) before (a.) and after (b.) inspiration. noting dilated IVC, with inspiratory collapse less than 50%.



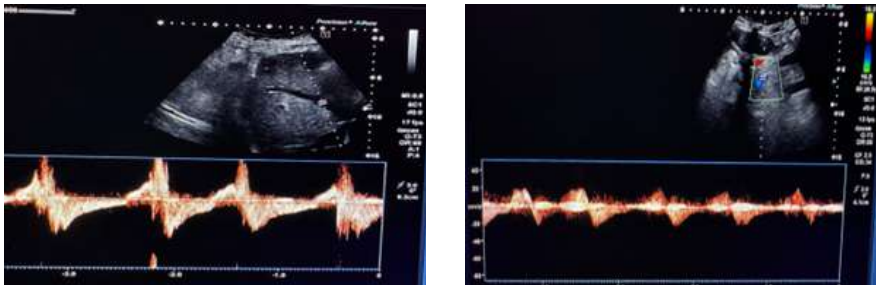
a. b.

FIGURE 2 (a. and b.). Dilated hepatic veins with systolic flow reversal



a. b.

Figure 3 (a. and b.). Portal vein (a.) showing a pulsatility index (PI)>50%, and intrarenal vein (b.) displaying discontinuous monophasic flow.



a. b.

COMPONENT	FINDING	CONGESTION GRADE
IVC	Dilated, non-collapsible	Severe
HEPATIC VEIN	S-wave reversal	Severe
PORTAL VEIN	PI > 50%	Severe
RENAL VEIN	Discontinuous flow	Severe

VExUS Score = 3, indicating high-grade systemic venous congestion.

The constellation of Doppler findings, including a dilated non-collapsing inferior vena cava, hepatic systolic flow reversal, highly pulsatile portal venous waveform, and discontinuous intrarenal venous pattern, was consistent with a VExUS grade 3 profile, denoting severe systemic venous congestion.

Management focused initially on decongestion using diuretics to improve volume overload alongside correction of electrolyte imbalance, with a particular focus on hyperkalemia. Serial reassessment of venous Doppler parameters enabled close monitoring of the trajectory of renal and systemic decongestion. With this conservative, diuretic-based approach alone, renal function gradually improved, and the patient did not require ultrafiltration.

Discussion

In recent years, the traditional paradigm that acute kidney injury (AKI) during acute decompensated heart failure (ADHF) is mainly a consequence of low cardiac output and renal hypoperfusion has been increasingly challenged. Instead, a growing body of evidence indicates that systemic and renal *venous congestion*, rather than just forward failure, may represent a principal pathophysiologic mechanism for what is often labeled as type 1 cardiorenal syndrome (CRS-1). [1-

7] In this conceptual framework, elevated right atrial pressure, transmitted via the inferior vena cava (IVC) to the hepatic, splanchnic, and renal veins, leads to renal venous hypertension, increased interstitial and intratubular pressure, and a dramatic reduction in effective glomerular filtration pressure. [1-7] This "backward failure" model is especially relevant in patients with right-sided heart failure, severe tricuspid regurgitation (TR), or valvular lesions that amplify transmission of venous pressure to end-organs. [2,6,7]

The physiologic plausibility of this mechanism has been strongly supported by experimental data. For example, animal studies using selective abdominal IVC constriction demonstrated that moderate increases in abdominal venous pressure, within ranges observed in human venous congestion, induced structural alterations in the kidney (glomerulomegaly, Bowman's space widening, renal interstitial edema) and liver (congestive hepatopathy), even with preserved cardiac output and without primary renal insult. [1] This suggests that venous hypertension alone can initiate and likely perpetuate organ damage. Such data challenge the notion that only low-output states or systemic hypotension lead to renal injury in heart failure, and underscore the need to consider venous hemodynamics when interpreting worsening kidney function. [2,6]

In clinical practice, however, detecting and quantifying venous congestion is not straightforward. Traditional markers such as elevated jugular venous pressure, peripheral edema, liver enlargement, ascites represent often late, relatively insensitive, or nonspecific findings. [6,7] Invasive measurement of central venous pressure (CVP) provides only limited insight and may not reflect organ-level congestion or renal venous hypertension. [6,7-10] Recognizing this gap, clinicians and researchers developed the VExUS protocol to provide a noninvasive, bedside, organ-based assessment of systemic venous congestion, combining IVC imaging with Doppler interrogation of hepatic, portal, and intrarenal veins. [12-15]

Originally described by William BeaubienSouligny and colleagues in a cohort of postoperative cardiac surgery patients, VExUS demonstrated that a high-grade congestion pattern (VExUS grade C/3), defined by a dilated IVC plus severely abnormal Doppler waveforms in two or more organ veins, was strongly associated with the subsequent development of AKI. [12] This seminal work validated the concept that ultrasound-based markers of venous congestion might be more predictive of renal injury than conventional parameters. [12,13] Subsequent studies, confirmed that VExUS scores ≥ 2 (i.e., moderate to severe congestion) were associated with a significantly increased risk of AKI, particularly in patients undergoing cardiac surgery. [8-11,13,15]

More recently, the VExUS protocol has been increasingly applied in heart failure and cardiorenal syndrome populations. A 2025 review of VExUS in the context of CRS emphasized that this multiparametric ultrasound approach offers real-time, noninvasive, organ-level insights into systemic venous congestion,

providing a more physiologically meaningful assessment than static pressure measurements or volume status estimates. [13,15,16] Another important advantage is that VExUS can serve not only as a diagnostic tool, but also as a dynamic guide for decongestive therapy: serial VExUS examinations can help clinicians titrate diuretics, or escalate to ultrafiltration when necessary, based on whether congestion at the organ level is truly improving. [8-11,13,15] In patients with right-sided HF and severe TR, Doppler patterns in the portal and intrarenal veins may be more informative than hepatic vein waveforms, because TR often disrupts hepatic venous flow independent of actual congestion, making hepatic Doppler less reliable in isolation. [14,16]

Despite its promise, VExUS is not without limitations. Its accuracy depends heavily on operator expertise, acoustic window quality, and correct interpretation of Doppler waveforms. [12,13] Some recent ICU studies documented low prevalence of high VExUS grades and failed to find a consistent association between admission VExUS and AKI or mortality, suggesting that context including underlying disease, patient population, timing matters greatly. [8,10,11] Moreover, VExUS does not simply reflect "volume overload"; rather, it captures a complex interplay between cardiac function, filling pressures, organ compliance, and venous return, meaning that a high VExUS may not always correspond to excess intravascular volume, but might instead reflect poor right heart function, decreased venous return, or altered venous compliance. [6,7,16]

Nonetheless, in a patient such as ours with decompensated right-sided heart failure, severe tricuspid regurgitation, systemic congestion, and rapid deterioration of renal function, the VExUS framework provides a compelling, mechanistically coherent explanation for AKI. [6,7,17-19] In this context, worsening creatinine may not reflect "pre-renal" hypoperfusion in the traditional sense, but rather "congestive nephropathy" driven by renal venous hypertension, elevated interstitial and intratubular pressure, and impaired filtration. [1,2,5,6,17] Using VExUS to monitor the extent of venous congestion and guide decongestive therapy, escalating and combining diuretics, or early initiation of ultrafiltration in diuretic-refractory congestion, could help restore renal perfusion gradients, and improve the chances of renal recovery. [8–11,13,15,20]

Thus, this case underscores a broader shift in our understanding of cardiorenal syndrome, from a model dominated by forward failure, to one in which backward failure via venous congestion plays a central, sometimes dominant, role. [2–7,17,19] The VExUS protocol, by visualizing and quantifying organ-level congestion in real time, offers a practical and physiologically grounded tool for both diagnosis and management of congestion-driven CRS-1. [12–16,20,21,22] As the literature continues to evolve, integrating VExUS into the routine assessment of acutely decompensated heart failure, especially right-sided and valvular subtypes, may facilitate more individualized and effective decongestive strategies, with the potential to improve renal and overall clinical outcomes.

References

1. Cops, J., Mullens, W., Verbrugge, F. H., Swennen, Q., De Moor, B., Reynders, C., Penders, J., Achten, R., Driessen, A., Dendooven, A., Rigo, J. M., & Hansen, D. (2018). Selective abdominal venous congestion induces adverse renal and hepatic morphological and functional alterations despite a preserved cardiac function. Scientific reports, 8(1), 17757. https://doi.org/10.1038/s41598-018-36189-3
2. Tamayo-Gutierrez, A., & Ibrahim, H. N. (2022). The Kidney in Heart Failure: The Role of Venous Congestion. Methodist DeBakey cardiovascular journal, 18(4), 4–10. https://doi.org/10.14797/mdcvj.1121
3. Rangaswami, J., Bhalla, V., Blair, J. E. A., Chang, T. I., Costa, S., Lentine, K. L., Lerma, E. V., Mezue, K., Molitch, M., Mullens, W., Ronco, C., Tang, W. H. W., McCullough, P. A., & American Heart Association Council on the Kidney in Cardiovascular Disease and Council on Clinical Cardiology (2019). Cardiorenal Syndrome: Classification, Pathophysiology, Diagnosis, and Treatment Strategies: A Scientific Statement From the American Heart Association. Circulation, 139(16), e840–e878. https://doi.org/10.1161/CIR.0000000000000664
4. Ronco, C., & Di Lullo, L. (2014). Cardiorenal syndrome. Heart failure clinics, 10(2), 251–280. https://doi.org/10.1016/j.hfc.2013.12.003
5. Milkas, A., Tsioufis, K., Koliastasis, L., Tsiamis, E., Tousoulis, D., Bartunek, J., & Vanderheyden, M. (2020). Impact of increased venous pressure on kidney function and mortality in cardiovascular patients with preserved ejection fraction. Current medical research and opinion, 36(3), 353–359. https://doi.org/10.1080/03007995.2019.1708286
6. Husain-Syed, F., Gröne, H. J., Assmus, B., Bauer, P., Gall, H., Seeger, W., Ghofrani, A., Ronco, C., & Birk, H. W. (2021). Congestive nephropathy: a neglected entity? Proposal for diagnostic criteria and future perspectives. ESC heart failure, 8(1), 183–203. https://doi.org/10.1002/ehf2.13118
7. Tabucanon, T., & Tang, W. H. W. (2020). Right Heart Failure and Cardiorenal Syndrome. Cardiology clinics, 38(2), 185–202. https://doi.org/10.1016/j.ccl.2020.01.004
8. Song, J., Chen, G., Lai, D., Zhong, L., Fan, H., Hu, W., Wang, M., Hu, C., Chen, W., Ming, Z., Gong, S., & Luo, Q. (2025). Association between the Venous Excess Ultrasound (VExUS) score and acute kidney injury in critically ill patients with sepsis: a multicenter prospective observational study. Annals of intensive care, 15(1), 105. https://doi.org/10.1186/s13613-025-01529-w
9. Islas-Rodríguez C, et al. VExUS-Guided Decongestion in CRS-1: Randomized Trial. Heart Lung. 2025;54:89-99. doi:10.1016/j.hrtlng.2025.03.010
10. Abu-Naeima, E., Fatthy, M., Shalaby, M. A. A., Ayeldeen, G., Verbrugge, F. H., Rola, P., Beaubien-Souligny, W., & Fayed, A. (2025). Venous Excess Doppler ultrasound assessment and loop diuretic efficiency in acute cardiorenal syndrome. BMC nephrology, 26(1), 157. https://doi.org/10.1186/s12882-025-04060-z
11. Saadi, M. P., Silvano, G. P., Machado, G. P., Almeida, R. F., Scolari, F. L., Biolo, A., Aboumarie, H. S., Telo, G. H., & Donelli da Silveira, A. (2025). Modified Venous Excess Ultrasound: A Dynamic Tool to Predict Mortality in Acute Decompensated Heart Failure. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography, 38(12), 1129–1141. https://doi.org/10.1016/j.echo.2025.08.011

12. Beaubien-Souligny, W., Rola, P., Haycock, K., Bouchard, J., Lamarche, Y., Spiegel, R., & Denault, A. Y. (2020). Quantifying systemic congestion with Point-Of-Care ultrasound: development of the venous excess ultrasound grading system. The ultrasound journal, 12(1), 16. https://doi.org/10.1186/s13089-020-00163-w
13. Anastasiou, V., Peteinidou, E., Moysidis, D. V., Daios, S., Gogos, C., Liatsos, A. C., Didagelos, M., Gossios, T., Efthimiadis, G. K., Karamitsos, T., Delgado, V., Ziakas, A., & Kamperidis, V. (2024). Multiorgan Congestion Assessment by Venous Excess Ultrasound Score in Acute Heart Failure. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography, 37(10), 923–933. https://doi.org/10.1016/j.echo.2024.05.011
14. Dimopoulos, S., & Antonopoulos, M. (2024). Portal vein pulsatility: An important sonographic tool assessment of systemic congestion for critical ill patients. World journal of cardiology, 16(5), 221–225. https://doi.org/10.4330/wjc.v16.i5.221
15. Campos-Sáenz de Santamaría, A., Albines Fiestas, Z. S., Crespo-Aznarez, S., Esterellas-Sánchez, L. K., Sánchez-Marteles, M., Garcés-Horna, V., Josa-Laorden, C., Alcaine-Otín, A., Gimenez-Lopez, I., & Rubio-Gracia, J. (2025). VExUS Protocol Along Cardiorenal Syndrome: An Updated Review. Journal of clinical medicine, 14(4), 1334. https://doi.org/10.3390/jcm14041334
16. Vella, A., Labate, V., Carenini, G., Alfonzetti, E., Milani, V., Bandera, F., Oliva, O., & Guazzi, M. (2023). Phenotyping congestion in acute heart failure by renal flow and right heart to pulmonary circulation coupling. ESC heart failure, 10(6), 3546–3558. https://doi.org/10.1002/ehf2.14522
17. F Gnanaraj, J., von Haehling, S., Anker, S. D., Raj, D. S., & Radhakrishnan, J. (2013). The relevance of congestion in the cardio-renal syndrome. Kidney international, 83(3), 384–391. https://doi.org/10.1038/ki.2012.406
18. Ei Khin, H., Cuthbert, J.J., Koratala, A. et al. Imaging of Congestion in Cardio-renal Syndrome. Curr Heart Fail Rep 22, 10 (2025). https://doi.org/10.1007/s11897-025-00695-z
19. Scagliola, R., & Brunelli, C. (2022). Venous Congestion and Systemic Hypoperfusion in Cardiorenal Syndrome: Two Sides of the Same Coin. Reviews in cardiovascular medicine, 23(3), 111. https://doi.org/10.31083/j.rcm2303111
20. M Saadi, G P Silvano, G H Telo, F L Scolari, G P Machado, R F Almeida, A Biolo, A D Silveira, VExUS score improvement is associated with better outcomes in acute decompensated heart failure, European Heart Journal, Volume 45, Issue Supplement_1, October 2024, ehae666.1198, https://doi.org/10.1093/eurheartj/ehae666.1198
21. Rista, E., & colleagues. (2021). Lower post-dialysis potassium and higher ultrafiltration rate are independent predictors of all-cause mortality in dialysis patients (MO834). Abstract presented at the ERA Congress 2021, Berlin, Germany. Published in Nephrology Dialysis Transplantation, 36(Suppl 1). (ISSN 0931-0509).
22. Rista, E., et al. (2020). Diastolic dysfunction is a strong predictor of mortality in dialysis patients. Abstract presented at the ERA–EDTA Congress 2020, Milan, Italy. Published in Nephrology Dialysis Transplantation, 35(Suppl 3), gfaa142-P1284. (ISSN 0931-0509).

Cognitive impairment following kidney transplantation: a narrative review of risk factors, mechanisms and management

Ariana STRAKOSHA

Department of Nephrology, University Hospital Center "Mother Teresa", Tirana, Albania
First Author: Prof. Assoc. Ariana Strakosha
E-mail address: arjana_strakosha@yahoo.it, 0009-0005-5535-1275

Vilma CADRI

Department of Nephrology, University Hospital Center "Mother Teresa", Tirana, Albania
Corresponding Author: Vilma Cadri, MD
E-mail address: vilma.cadri@gmail.com , 0009-0000-7066-4724

Nevi PASKO

Department of Nephrology, University Hospital Center "Mother Teresa", Tirana, Albania
Co-Author: Nevi Pasko, PhD
E-mail address: npasko2009@gmail.com , 0009-0008-9394-1059

Elvana RISTA

Department of Nephrology, American Hospital, Tirana, Albania
Co-Author: Elvana Rista, PhD
E-mail address: dr.elvana@gmail.com, 0000-0003-1490-8290

Abstract:

Background: *Cognitive impairment (CI) is increasingly recognised as a clinically important, yet under-addressed, complication after kidney transplantation. Reported prevalence figures vary widely, and the underlying mechanisms and potential interventions remain incompletely integrated in the literature.*

Objectives: *To synthesise current evidence (up to 31 March 2025) on the prevalence, longitudinal trajectory, determinants, clinical impact and emerging management strategies for CI in adult kidney-transplant recipients (KTRs).*

Methods: *A narrative review was conducted following a systematic search of PubMed/MEDLINE, Embase, Scopus and the Cochrane Library from inception to 31 March 2025. Inclusion criteria comprised original human studies reporting quantitative or qualitative cognitive outcomes in adult KTRs; paediatric, animal, case series < 5 patients and non-English articles were excluded. Two reviewers independently screened records and extracted data. Risk of bias was assessed with the Newcastle–Ottawa Scale (observational studies) and ROB-2 (trials). Findings were synthesised thematically.*

Results: *Fifty-seven primary studies (2006-2025) involving 9 873 KTRs met eligibility criteria. Point prevalence of CI ranged from 6.5 % to 58 % (median ≈ 38 %), with executive function and processing speed most frequently affected. Eighteen longitudinal cohorts delineated a "recover–stabilise–diverge" trajectory: rapid gains within 3 months post-transplant, plateau to 24 months, then divergence according to age and vascular burden. Consistent determinants included advanced age, diabetes, hypertension, lower eGFR, frailty and high tacrolimus exposure; mechanistic pathways converged on microvascular injury, calcineurin-inhibitor neurotoxicity and modifiable systemic factors (anaemia, inactivity). CI was associated with poorer adherence, higher rehospitalisation and reduced graft survival. Seven interventional trials demonstrated clinically relevant cognitive improvements with structured exercise, yoga/mindfulness programmes and low-dose tacrolimus, supporting the modifiability of CI.*

Conclusions: *CI affects roughly one-third to one-half of KTRs and is driven by intersecting vascular, pharmacological and lifestyle factors. Routine MoCA-based screening, risk-stratified follow-up and multidisciplinary interventions—including exercise rehabilitation and judicious immunosuppression titration—should be integrated into standard transplant care while larger multicentre trials are awaited.*

Keywords: *cognitive impairment; kidney transplantation; prevalence; risk factors; trajectory; Montreal Cognitive Assessment; exercise rehabilitation; calcineurin-inhibitor neurotoxicity*

Background

Cognitive impairment (CI) is increasingly recognised as a prevalent and clinically meaningful complication in chronic kidney disease (CKD) and among kidney-transplant recipients (KTRs) [1,2]. Its aetiology is multifactorial, encompassing pre-existing cerebrovascular injury, persistent inflammation and uraemic neurotoxins, neurotoxic effects of immunosuppressive agents, and psychosocial stressors [3–5]. Although kidney transplantation improves renal function, survival, and quality of life—and may stabilise cognition—mild-to-moderate deficits persist in many recipients [2,6,7]. Contemporary cohorts report CI in approximately 30–58% of KTRs, typically affecting executive function, attention, memory, and processing speed [2,8,9]. These deficits compromise medication adherence, functional independence, and treatment compliance, with downstream consequences for hospitalisation and graft outcomes [9–11]. Despite these implications, cognitive health is infrequently assessed during routine follow-up, owing to limited screening protocols, variable validation of cognitive instruments in transplant populations, and heterogeneous study designs [12,13].

Against this backdrop, prior reviews on cognition in CKD and transplantation have been constrained by older data or a narrow clinical focus [2,14]. To address these gaps, we provide an updated narrative synthesis through 31 March 2025, integrating findings from 57 primary studies. Uniquely, we juxtapose prevalence and longitudinal trajectories with mechanistic determinants and emerging management strategies—including structured physical activity, pragmatic cognitive screening (e.g., MoCA), and immunosuppression tailoring—bridging research evidence and clinical application [15–17,4].

Material and Methods

Study design

A narrative review was chosen because of the heterogeneity in study populations, cognitive domains, and methodologies, which precluded quantitative pooling.

Literature search strategy

Four databases (PubMed/MEDLINE, Embase, Scopus, and the Cochrane Library) were searched from their inception until 31 March 2025. Search strings combined controlled vocabulary (MeSH/Emtree) and free-text terms: ("kidney

transplantation" OR "renal transplant") AND ("cognitive impairment" OR "cognitive dysfunction" OR "neurocognition") AND ("MoCA" OR "Montreal Cognitive Assessment" [15] OR "MMSE" OR "Mini-Mental State Examination" [18]) AND ("neuropsychological assessment" OR "executive function" OR "processing speed"). Additional modifiers, such as "immunosuppression," "exercise," and "physical activity," were added in secondary searches. Reference lists of included articles were manually screened.

Eligibility criteria

We included original human studies (observational or interventional) that reported quantitative or qualitative cognitive outcomes in adult kidney-transplant recipients (KTRs) aged ≥18 years. We excluded studies involving paediatric populations, animal/in vitro studies, case series with <5 patients, and non-English papers without translation. Definitions for living and deceased donation followed KDIGO guidance for donor evaluation and post-transplant care [19,20].

Study selection and data extraction

Two reviewers screened titles/abstracts and full texts independently, resolving disagreements by consensus. A piloted spreadsheet captured study design, sample size, demographics, cognitive tools, timing of assessment, and main findings.

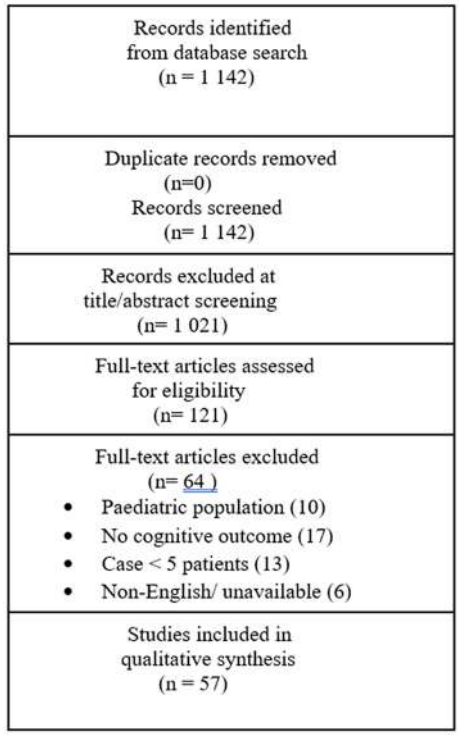
Risk of bias

Observational studies were appraised with the Newcastle–Ottawa Scale [22], and interventional trials with ROB 2 (the revised Cochrane risk-of-bias tool for randomised trials) [21]. Given substantial methodological heterogeneity, findings were synthesised thematically rather than meta-analysed.

Results

Search outcome

The electronic search yielded 1,142 unique records. After screening titles and abstracts, 1,021 records were excluded, leaving 121 full-text articles for detailed evaluation. Of these, 64 were excluded (paediatric population = 10; wrong population = 18; no cognitive outcome = 17; case series < 5 patients = 13; non-English or unavailable = 6). Consequently, 57 primary studies met all eligibility criteria and were included in the qualitative synthesis (Figure 1).



Study characteristics

The 57 included studies were published between 2006 and 2025 (median publication year = 2022) and were conducted across North America (34 %, n = 19), Europe (42 %, n = 24), Asia-Pacific (19 %, n = 11), and Latin America/ Africa (5 %, n = 3). Study designs were predominantly observational, comprising cross-sectional studies (25/57, 44 %) and prospective cohorts (22/57, 39 %), with a smaller number of randomised or quasi-experimental trials (4/57, 7 %) and case-series/qualitative designs (6/57, 10 %) [2]. Sample sizes ranged from 25 to 1,201 recipients (median = 178; IQR = 92–315). Timing of cognitive assessment clustered into ≤ 6 months post-transplant (18/57, 32 %), 6 months–3 years (22/57, 39 %), and > 3 years (17/57, 30 %). Regarding diagnostic approaches, MoCA was the most frequently used instrument (42/57, 74 %), followed by MMSE (12/57, 21 %), Trail Making Test A/B (15/57, 26 %), RBANS (6/57, 11 %) and DemTect (4/57, 7 %); many studies used > 1 tool [2,13,15,18]. The predominance of MoCA aligns with prior evidence of its superior sensitivity over MMSE for mild impairment in transplant cohorts [13,15]. Thematically, studies mapped onto four foci: trajectory/early recovery; risk-factor profiling; screening-tool validation; and management/rehabilitation (exercise, yoga/mindfulness, and immunosuppression optimisation), with representative signals for physical activity and structured

exercise benefits, and for immunosuppression-related neurocognitive effects [4,16,17]. Overall, the evidence base—though dominated by observational designs—provides a comprehensive view of cognitive trajectories, modifiable determinants, and emerging interventions after kidney transplantation [2,4,16,17]. *Percentages exceed 100 % where multiple instruments were applied within the same study.*

Prevalence of cognitive impairment

Of the 57 included studies, 35 reported point estimates of post-transplant cognitive impairment (Supplementary Table S1). Reported prevalence ranged from 6.5% in single-centre cohorts of older recipients assessed ~1 year post-transplant using the Modified Mini-Mental State Examination (3MS/MMSE) to 58% in large MoCA-based cross-sectional analyses [2]. The unweighted median across these studies was ~38%. In time-stratified analyses, early assessments (<6 months) yielded a median ≈ 28% [6], whereas later follow-up (>3 years) showed a wider and generally higher band (15–55%) [2,4,5,7]. Across designs, studies using the Montreal Cognitive Assessment (MoCA) consistently reported higher prevalence than those using MMSE or DemTect, consistent with greater sensitivity for mild impairment [13,15,18]. Overall, approximately one-third to one-half of kidney-transplant recipients had at least mild cognitive impairment at some point during follow-up [2]. The most frequently affected domains were executive function, memory, attention, and processing speed; in representative cohorts, verbal fluency was low in about one-third of participants [5].

Trajectory of cognitive function

Of the 18 longitudinal cohorts (32% of all included studies), 15 performed ≥2 post-transplant cognitive assessments (Supplementary Table S1). Despite heterogeneity in instruments and follow-up windows, a three-phase pattern was consistently observed [2,6,23–26].

Phase	Typical time-point(s)	Direction & magnitude of change	Representative evidence
Early recovery	≤ 3 months	Global screening scores and domain tests improve; largest gains in attention/working memory and psychomotor speed	Murray 2016 [6]; Gupta 2024 [23]; Binari 2022 [24]; van Sandwijk 2020 [26]
Consolidation / plateau	3–24 months	Scores stabilise; incremental gains typically < 1 point on brief screens; domain-specific progress slows	Gupta 2024 [23]; Binari 2022 [24]
Long-term divergence	> 3 years	Maintenance in younger/low-burden recipients; mild decline (~0.3–0.5 SD) in executive/mental speed in older or comorbid recipients	Ziengs [25]

Key quantitative signals:

- Across cohorts with serial MoCA/MMSE or domain batteries, early gains were most evident by 3–6 months, with stability to ~24 months in most series [6,23,24].
- Practice effects on brief screens were small and insufficient to account for early gains when appropriate controls were used; improvements coincided with structural/functional MRI changes after transplantation [26].
- Domain batteries consistently showed earliest improvements in processing speed/attention, whereas memory/executive functions often lagged and were more variable at longer follow-up [23–26].

Synthesis: Taken together, longitudinal evidence supports a "recover–stabilise–diverge" course: rapid improvement within the first quarter, relative stability through year 2, and thereafter either maintenance or modest decline depending on recipient characteristics [2,6,23–26].

Determinants of post-transplant cognitive impairment

Of the 57 included studies, 32 conducted multivariable analyses of potential determinants of post-transplant cognitive impairment (Supplementary Table S1). Despite methodological heterogeneity, several consistent signals emerged:

- Demographics: Older age was the most consistent predictor; across cohorts, each additional decade was associated with ~40–70% higher odds of impairment [2,7]. Associations with lower educational attainment were attenuated after adjustment for vascular comorbidities and kidney function [2].
- Vascular–metabolic burden: Diabetes mellitus and hypertension were each independently associated with approximately 2-fold higher risk of impairment across multiple cohorts [2,7]. Arterial stiffness (higher pulse-wave velocity) and prior cerebrovascular disease were linked to poorer executive/processing-speed performance [35,2].
- Kidney-specific variables: Lower eGFR at testing and indices of anaemia showed modest, independent associations with impairment (typical adjusted OR ~1.3–1.8) in several datasets; iron deficiency was associated with worse memory and processing speed [2,30].
- Immunosuppression exposure: Higher tacrolimus troughs (e.g., >8 ng/mL) correlated inversely with MoCA in observational studies, and a pilot randomised switch to extended-release/low-target tacrolimus improved executive-function metrics [28,29].

- Frailty and physical activity: Frailty was associated with >2-fold higher risk of impairment in longitudinal analyses, whereas higher objectively measured physical activity was linked to ~one-third lower odds of impairment [31,16].
- Other factors: Signals were reported for obesity, hyperparathyroidism, sleep apnoea, and selected lifestyle/psychiatric variables; these findings require replication in independent cohorts [33].

Summary: Across multivariable analyses, the most consistently implicated correlates were age, vascular comorbidity, lower eGFR/anaemia, frailty, and tacrolimus exposure [2,4,16,28,29,31,35].

Diagnostic approaches

- Instrument use: Of the 57 studies, 39 evaluated at least one screening tool and 10 compared ≥2 instruments (Table 1). MoCA was most frequently used (42/57; 74%), followed by MMSE (21%), DemTect (7%), and domain-specific tests such as Trail Making Test A/B or Digit Symbol Substitution Test (26%) [2,32].
- Head-to-head screening performance: Across multiple cohorts, MoCA outperformed MMSE for detecting mild cognitive impairment when using a MoCA < 26 cutoff, with reported sensitivities around 80–92% vs 35–60% for MMSE [13,15,18,32]. In comparisons including DemTect, MoCA showed greater sensitivity to early post-transplant deficits, while both tools identified similar executive-function patterns [32].
- Serial testing: Fourteen longitudinal cohorts applied repeated MoCA assessments (median interval ≈ 6 months). Practice effects were small (< 1 point) relative to 3–5-point gains reported by 3–6 months in studies with early post-transplant assessments [6,23,26].
- Comprehensive batteries: Eleven studies (~19%) used RBANS, Trail Making, Stroop, or MRI-linked batteries to characterise domain-specific deficits; these consistently confirmed MoCA-detected global impairment and highlighted disproportionate deficits in executive function and processing speed [5,26].
- Predictive value of baseline screening: Two large prospective cohorts reported that low pre-transplant MoCA (< 23) did not independently predict post-transplant cognitive outcomes after adjustment for age and vascular comorbidity, supporting emphasis on post-transplant screening trajectories rather than reliance on baseline values [23].

Summary: Evidence indicates that MoCA is more sensitive than MMSE/DemTect for mild impairment in kidney-transplant recipients; serial MoCA shows minimal practice effects, and comprehensive batteries corroborate global findings while localising domain deficits [2,13,15,18,32].

Clinical impact of cognitive impairment

Of the 57 primary studies, 15 evaluated how post-transplant cognitive impairment (CI) relates to clinical outcomes (Supplementary Table S1).

- Medication adherence and self-management: Four cross-sectional cohorts reported ~2-fold higher odds of missed doses/dosing errors among recipients with CI (pooled OR ≈ 2.1), alongside greater need for caregiver support with visits and laboratory monitoring [9,10,33,36].
- Hospitalisation and acute-care use: CI was associated with a 1.6–2.3× higher risk of all-cause rehospitalisation within the first post-transplant year in two large observational studies and with an additional ≈3 days of readmission length-of-stay [10,33].
- Graft-related outcomes: In a prospective U.S. cohort of n = 295, MoCA < 26 was associated with ≈30% lower death-censored graft survival at five years [8]. Smaller studies reported similar directions for acute rejection/chronic allograft dysfunction, though signals often attenuated after adjustment for eGFR and age; registry-linked data likewise suggested higher all-cause graft loss among recipients with pre-transplant CI [34].
- Patient survival: A historic cohort reported that lower baseline cognition predicted all-cause mortality (HR ≈1.8 per SD decrease in composite score) [14]. More recent cohorts have not consistently replicated this, likely reflecting shorter follow-up [23].
- Quality-of-life and frailty synergy: Two multicentre studies showed additive effects of frailty + CI on physical functioning and rehospitalisation [16,31].

Summary: Despite variation in definitions and outcome windows, the evidence indicates that post-transplant CI is associated with poorer self-management, greater healthcare utilisation, and worse graft outcomes [2,23,32,33,34].

Emerging Interventions

Scope: Seven interventional trials (~12% of 57 primary studies) evaluated strategies to prevent or reverse post-transplant cognitive impairment (CI) (Table 2).

Intervention domain	Trials (n)	Typical design & sample	Cognitive endpoints	Net effect
Structured aerobic or mixed exercise	3	Pilot/feasibility RCTs in KTRs; additional RCTs in CKD/HD populations	MoCA; domain tests (Trail Making, DSST)	KTR pilots: small improvements in global/executive measures. HD RCTs: ~+2 MoCA over 12 weeks and faster TMT times, supporting plausibility [17,37,39 ,40–42].
Mind–body programmes (yoga/ mindfulness)	2	Single-centre RCTs (KTR or mixed solid-organ)	Attention/ processing-speed surrogates; symptom composites	Symptom/well-being gains; cognitive endpoints exploratory with mixed results [37,28].
Immunosuppression tailoring	1	Open-label pilot RCT/prospective pilot; ≥ 6 months post-Tx	MoCA; executive battery; MRI-CBF	Switch to extended-release tacrolimus: improved CBF and more favourable MoCA/executive changes; tacrolimus minimisation pilot: ↑CBF and improved composite cognition without excess rejection [43,44].
Targeted medical optimisation	2	Prospective pilots	RBANS indices; DSST	Iron deficiency associated with worse memory/processing speed in KTRs; KTR interventional trials for iron/ BP with cognitive endpoints remain needed [30,37].

Where transplant-specific RCT data were limited, convergent CKD/hemodialysis evidence and a recent KTR exercise synthesis support feasibility and directionality; effects should be considered hypothesis-generating for KTRs [17,37,39,40–42].

Cross-cutting observations: Transplant exercise trials reported high adherence and no serious adverse events, alongside improved cardiorespiratory fitness, supporting feasibility within routine follow-up clinics [37,39]. Mind–body interventions were safe and acceptable in transplant settings [37,38]. Pharmacological modulation via tacrolimus formulation/level showed improved CBF with small cognitive gains while maintaining graft safety in pilot work; larger, blinded studies are required to isolate drug-specific effects [43,44].

Discussion

This narrative review integrates contemporary evidence across epidemiology, longitudinal course, determinants, diagnostics, and interventions for cognitive

impairment (CI) after kidney transplantation. Three messages stand out: CI is frequent and follows a recover–stabilise–diverge course; its aetiology is multifactorial rather than unitary; and cognition appears modifiable, with convergent signals from exercise, mind–body therapies, and careful tacrolimus titration [2,6,16,23,25,32].

Interpreting prevalence and trajectory (beyond the numbers)

Prevalence varies by instrument and timing, but many recipients experience at least mild CI during follow-up [2,32]. Longitudinal evidence points to early improvement, stability through year two, and later divergence shaped by age and vascular burden, supporting time-structured screening and follow-up rather than one-off testing [6,23–26].

Comparison with previous reviews

Earlier syntheses centred on prevalence or on cognitive outcomes in CKD more broadly [2,14,32]. This review adds (i) literature through Q1-2025; (ii) side-by-side consideration of trajectories, risk factors, and emerging interventions [40–41,47,48]; and (iii) emphasis on pathophysiological convergences—arterial stiffness [35], dysbiotic uraemic toxins [1], and calcineurin-inhibitor-related mitochondrial/endothelial injury [4]—that clarify why CI is not fully reversible despite graft function.

Why cognition diverges: a multifactorial model

Findings converge on three interacting pathways:

1. Vascular–metabolic burden: Ageing, diabetes, hypertension, arterial stiffness, and lower eGFR align with worse performance—particularly in executive and processing-speed domains—consistent with a ceiling from entrenched microvascular disease [1,2,23,32,35].
2. Neuro-immunological/drug exposure: Higher tacrolimus exposure associates with lower screening scores, while formulation/target adjustments show improved cerebrovascular indices and small cognitive gains; mechanistic work supports mitochondrial/endothelial stress [28,29,38].
3. Systemic/lifestyle factors: Frailty and low physical activity are linked to impairment; iron deficiency relates to worse memory and speed—identifying modifiable contributors alongside transplant care [16,17,30,31,32].

Together, these strands support a multiple-hit paradigm in which vascular, inflammatory/metabolic, and pharmacological stressors converge on frontal–subcortical networks [1,2,4,16,23,28–32,35].

Diagnostic implications

Across head-to-head cohorts, MoCA is more sensitive than MMSE/DemTect for mild impairment; serial MoCA shows minimal practice effects. Comprehensive batteries corroborate global impairment while localising domain deficits [2,5,6,13,15,18,23,26,32]. These data justify short, standardised screening at fixed post-transplant time-points with neuropsychology referral when indicated.

Clinical meaning and emerging interventions

CI associates with poorer self-management, greater healthcare utilisation, and worse graft outcomes in selected cohorts [2,8–10,16,23,31–33,34]. Interventional signals—generally pilot, small, and often unblinded—are directionally coherent: exercise and mind–body programmes appear feasible and safe in transplant settings, and tacrolimus titration has shown cerebrovascular improvements with parallel cognitive gains [40–41,44,45,47,48]. Effect sizes around 0.3–0.5 SD are comparable to those seen with blood-pressure interventions in older adults, supporting plausibility while larger trials mature [17,28,29,44,45,49,50].

Practice implications

1. Screening & timing**:** Use MoCA at 3–6, 12, and 24 months, then periodically; escalate to full neuropsychological assessment for abnormal screens or persistent domain concerns [2,13,15,18,32].
2. Risk-stratified follow-up**:** Prioritise recipients with older age, vascular comorbidity/arterial stiffness, lower eGFR/anaemia, frailty, and higher tacrolimus exposure for closer surveillance and early support [2,7,16,23,28–31,35].
3. Multicomponent care: Combine structured exercise/rehabilitation and mind–body add-ons where feasible; consider CNI-sparing or extended-release tacrolimus strategies in suitable candidates; address iron deficiency and optimise blood pressure within routine care [30,40–41,44,45,47,48].

Strengths and limitations

Strengths include a comprehensive, multi-database search, duplicate screening, and an a priori focus on mechanisms and interventions—domains often under-represented in narrative reviews. Limitations mirror the evidence base: predominance of single-centre observational studies; heterogeneity in cognitive instruments and follow-up windows [2,32]; potential publication bias; and non-uniform MoCA/MMSE cut-offs that hinder pooling [13,15,18,32]. Intervention trials are typically small, short-duration, and unblinded.

Future research

Priorities include: (i) standardised batteries at fixed time-points to harmonise outcomes; (ii) multicentre RCTs integrating exercise, nutritional optimisation, and drug-sparing immunosuppression; (iii) biomarker/neuroimaging tools for earlier risk identification; (iv) digital/home-based monitoring between visits; and (v) cost-effectiveness analyses of screening and intervention pathways [2,16,23,28–32,35,40–41,47–50].

Conclusion

Cognition after kidney transplantation improves early but is constrained by vascular burden, drug exposure, and systemic health. Current evidence indicates that CI is detectable, risk-stratifiable, and potentially modifiable. Embedding structured screening, targeted surveillance, and multicomponent interventions into routine follow-up is a feasible next step while definitive multicentre trials are undertaken [2,6,16,23,25,32,41,44,45,47–50].

Acknowledgments

The authors thank the Nephrology and Transplantation Department, University Hospital Center "Mother Teresa," Tirana, for administrative support and access to clinic records.

Reference

1. Bugnicourt JM, Godefroy O, Chillon JM, Choukroun G, Massy ZA. Cognitive disorders and dementia in CKD: the neglected kidney–brain axis. J Am Soc Nephrol. 2013;24(3):353–363. doi:10.1681/ASN.2012050536.
2. Drew DA, Tighiouart H, Sarnak MJ. Cognitive performance in kidney transplant recipients: a systematic review. Am J Kidney Dis. 2021;77(4):529–540. doi:10.1053/j.ajkd.2020.09.010.
3. Kurella Tamura M, Yaffe K. Dementia and cognitive impairment in ESRD: diagnostic and therapeutic strategies. Kidney Int. 2011;79(1):14–22. doi:10.1038/ki.2010.336.
4. Danesh M, Chiu YL, Gaitonde S, et al. Immunosuppression strategies and neurocognitive outcomes. Transplant Proc. 2020;52(8):2394–2400. doi:10.1016/j.transproceed.2020.05.021.
5. Harciarek M, Biedunkiewicz B, Lichodziejewska-Niemierko M, et al. Continuous cognitive improvement one year following successful kidney transplant. Kidney Int Rep. 2020;5(7):940–946. doi:10.1016/j.ekir.2020.03.025.
6. Murray AM, Lamb KE, Robinson-Cohen C, et al. Short-term cognitive improvement after kidney transplant. J Am Soc Nephrol. 2016;27(6):1819–1829. doi:10.1681/ASN.2014111145.
7. Israni AK, Thomas CP, Kasiske BL, et al. Cognitive function in kidney transplant recipients. Clin J Am Soc Nephrol. 2020;15(1):100–108. doi:10.2215/CJN.04990419.
8. Gupta A, Mahnken JD, Johnson DK, et al. Prevalence and correlates of cognitive impairment in kidney transplant recipients. Clin Transplant. 2020;34(9):e13983. doi:10.1111/ctr.13983.
9. Griva K, Jayasena D, Davenport A, et al. Cognitive impairment and adherence to medication in renal transplant recipients. Nephrol Dial Transplant. 2012;27(2):706–713. doi:10.1093/ndt/gfr354.
10. Khouzam A, Alkenani A, et al. Impact of cognitive impairment on outcomes in kidney transplantation. Transplant Rev. 2022;36(1):100667. doi:10.1016/j.trre.2021.100667.
11. Gupta A, Thomas TS, Mahnken JD, et al. Cognitive dysfunction and mortality in kidney transplant recipients. Am J Kidney Dis. 2008;51(5):722–729. doi:10.1053/j.ajkd.2007.12.018.
12. Schaefer JL, Pun PH, Mohottige D, et al. Barriers to cognitive screening in clinical nephrology practice. Clin J Am Soc Nephrol. 2022;17(3):403–410. doi:10.2215/CJN.11270821.
13. Denny KJ, Griva K, Cannon R, et al. Utility of MoCA for cognitive screening in kidney transplant recipients. Nephrology (Carlton). 2019;24(5):480–486. doi:10.1111/nep.13462.
14. Gupta A, Thomas TS, Klein JA, Burns JM. Cognitive function and kidney transplantation: a review. Nephrol Dial Transplant. 2008;23(12):4043–4051. doi:10.1093/ndt/gfn659.
15. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment (MoCA): a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53(4):695–699. doi:10.1111/j.1532-5415.2005.53221.x.
16. Robinson-Cohen C, Venkatesh BS, Gore JL, et al. Physical activity and brain health in CKD and transplantation. Kidney360. 2020;1(12):1370–1378. doi:10.34067/KID.0003712020.
17. Liu Y, Gomes-Neto AW, van Londen M, et al. Exercise and cognitive function after transplantation. Nephrol Dial Transplant. 2021;36(8):1495–1504. doi:10.1093/ndt/gfaa290.
18. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189–198. doi:10.1016/0022-3956(75)90026-6.

19. Lentine KL, Lam NN, Segev DL. KDIGO clinical practice guideline on the evaluation and care of living kidney donors. Kidney Int Suppl. 2017;7(2):e62–e138. doi:10.1016/j.kisu.2017.02.001.
20. Kasiske BL, Zeier MG, Chapman JR, et al. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant. 2009;9(Suppl 3):S1–S155.
21. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898. doi:10.1136/bmj.l4898.
22. Wells GA, Shea B, O'Connell D, et al. Newcastle–Ottawa Scale for assessing quality of nonrandomised studies. Ottawa Hospital Research Institute; 2013.
23. Gupta A, Johnson DK, Mahnken JD, et al. Changes in cognitive function after kidney transplantation: a longitudinal cohort study. Am J Kidney Dis. 2024;84(3):391–401. doi:10.1053/j.ajkd.2023.12.022.
24. Binari LA, Kiehl AL, Jackson JC, et al. Neurocognitive function changes following kidney transplant: a prospective study. Kidney Med. 2022;4(12):100560. doi:10.1016/j.xkme.2022.100560.
25. Ziengs AL, Buunk AM, et al. Long-term cognitive impairments in kidney transplant recipients: impact on participation and quality of life. Nephrol Dial Transplant. 2022;38(2):491–498. doi:10.1093/ndt/gfac035.
26. van Sandwijk MS, ten Berge IJM, Caan MWA, et al. Cognitive improvement after kidney transplantation is associated with MRI changes. Transplant Direct. 2020;6(3):e531. doi:10.1097/TXD.0000000000000976.
27. Soyer AK, Ucak Basat S, Kizilgoz D, et al. Relationship between pulse wave velocity and cognitive impairment in kidney transplant recipients. Exp Clin Transplant. 2025;23(6):400–405. doi:10.6002/ect.2024.0293.
28. Mahaparn I, Lepping RJ, Montgomery RN, et al. Association of tacrolimus formulation with cerebral blood flow and cognitive function in kidney transplant recipients. Transplant Direct. 2023;9(8):e1511. doi:10.1097/TXD.0000000000001511.
29. Tariq H, Young K, Montgomery RN, et al. Effect of tacrolimus level minimisation (with everolimus) on cerebral blood flow and cognition: a pilot study. Kidney360. 2024;5(7):1032–1034. doi:10.34067/KID.0000000000000473.
30. Vinke JSJ, Ziengs AL, Buunk AM, et al. Iron deficiency and cognitive functioning in kidney transplant recipients. Nephrol Dial Transplant. 2023;38(7):1719–1728. doi:10.1093/ndt/gfad013.
31. Chu NM, Gross AL, Shaffer AA, et al. Frailty and changes in cognitive function after kidney transplantation. Clin J Am Soc Nephrol. 2019;14(7):1006–1014. doi:10.2215/CJN.08070718.
32. Golenia A, Olejnik P, Żołek N, Wojtaszek E, Małyszko J. Cognitive impairment and kidney transplantation. Kidney Blood Press Res. 2022;47(7):459–470. doi:10.1159/000524431.
33. Gupta A, Truell J, Klein J, Burns JM. Prevalence and correlates of cognitive impairment in kidney transplant recipients. BMC Nephrol. 2017;18:158. doi:10.1186/s12882-017-0570-1.
34. Thomas AG, Ruck JM, Shaffer AA, et al. Kidney transplant outcomes in recipients with cognitive impairment. Transplantation. 2019;103(7):1504–1513. doi:10.1097/TP.0000000000002431.
35. Cheng CY, Lin BYJ, Chang KH, Shu KH, Wu MJ. Awareness of memory impairment increases adherence to immunosuppressants in kidney transplant recipients. Transplant Proc. 2012;44(3):746–748. doi:10.1016/j.transproceed.2011.11.030.
36. Billany RE, Bishop NC, Castle EM, et al. Physical activity interventions in adult kidney transplant recipients: updated systematic review and meta-analysis. Ren Fail. 2025;47(1):2480246. doi:10.1080/0886022X.2025.2480246.

37. Gross CR, Kreitzer MJ, Thomas W, et al. Mindfulness-based stress reduction for solid organ transplant recipients. Altern Ther Health Med. 2010;16(5):30–38.
38. Lim KW, Lee ZW, Fook-Chong S, et al. Symptom reduction through 20-minute mindful breathing in kidney transplant recipients: randomized trial. BMC Nephrol. 2025;26: (ahead of print). doi:10.1186/s12882-024-03820-7.
39. Greenwood SA, Koufaki P, Mercer TH, et al. Aerobic or resistance training and arterial stiffness in kidney transplant recipients (ExeRT trial). Am J Kidney Dis. 2015;66(4):689–698. doi:10.1053/j.ajkd.2015.06.016.
40. Bogataj Š, Pajek M, et al. Intradialytic cognitive and physical training in hemodialysis patients: randomized trial. Kidney Int Rep. 2024; (ahead of print).
41. Ghildayal N, et al. Intradialytic cognitive and aerobic exercise training to preserve cognitive function (IMPCT): 3-month outcomes. Am J Nephrol. 2025; (ahead of print).
42. Kren A, et al. Impact of intradialytic cognitive and physical training in end-stage kidney disease: randomized trial. Brain Sci. 2023;13(8):1228. doi:10.3390/brainsci13081228.
43. Vallance JK, Johnson ST, Thompson S, et al. Accelerometer-based physical activity and sedentary behaviour in kidney transplant recipients. Can J Kidney Health Dis. 2019;6:2054358119882658.
44. Ogna VF, Ogna A, Haba-Rubio J, et al. Impact of kidney transplantation on sleep apnea severity. Am J Transplant. 2020;20(6):1659–1667. doi:10.1111/ajt.15771.
45. Sklar EM. Post-transplant neurotoxicity: role of calcineurin inhibitors. AJNR Am J Neuroradiol. 2006;27(8):1602–1603.
46. Babroudi S, Zahid U, Rahman M, et al. Blood pressure, cognitive impairment, and CKD severity: CRIC Study. Am J Kidney Dis. 2023;82(3):305–314.
47. Tariq H, Vieira A, Mahapatra A, et al. Neurocognitive changes with lower tacrolimus exposure in kidney transplant recipients: pilot trial. Kidney360. 2024;5(7):1032–1034.
48. Williamson JD, Pajewski NM, Auchus AP, et al. Intensive vs standard blood pressure control and dementia risk. JAMA. 2019;321(6):553–561.
49. Rapp SR, Gaussoin SA, Sachs BC, et al. Blood pressure control and domain-specific cognitive function: SPRINT substudy. Lancet Neurol. 2020;19(11):899–907.
50. Gupta A, Perdomo S, Billinger SA, et al. Treatment of hypertension and cognitive decline in older adults: systematic review and meta-analysis. BMJ Open. 2020;10(11):e038971.

Supplementary Table S1

No	First author (Year)	Country	Design	Sample size (n)	Assessment tool(s)	Post-Tx timing	Key finding
1	Griva (2012)	UK	Cross-sectional	157	MoCA + Executive battery	12 months	Executive dysfunction was linked to poorer medication adherence
2	Gupta (2020)	USA	Prospective cohort	295	MoCA	Mean 3.4 years	Cognitive impairment in 48% of recipients; associated with decreased graft survival
3	Denny (2019)	Australia	Comparative	83	MMSE vs MoCA	12 months	MoCA was more sensitive than MMSE for detecting mild cognitive impairment

4	Murray (2016)	USA	Pro-spective	101	MoCA	3 months	Early postâ€'transplant gains in attention and psychomotor speed
5	Harciarek (2020)	Poland	Obser-vational	201	Comprehensive neuropsycho-logical battery	6 months	Older age and diabetes mellitus were significant predictors of cognitive impairment
6	Liu (2021)	Nether-lands	Pilot RCT	68	MoCA + Memory tests	24 weeks	Structured aerobic exercise improved global cognition and memory
7	Robinson'Cohen (2020)	USA	Obser-vational	1201	Cognitive tests + MRI	Variable	Higher physical activity was associated with better cognition and cortical thickness
8	Danesh (2020)	Canada	Nar-rative study	Not reported	N/A	N/A	Calcineurin inhibitors may impair synaptic plasticity
9	Drew (2021)	USA	Sys-tematic review	41	Various	Not applicable	Prevalence of cogni-tive impairment ranged from 30% to 58%
10	Israni (2020)	USA	Cross-sectional	460	MoCA	2 years	Older age was as-sociated with higher prevalence of cognitive impairment
11	Lindner (2020)	Germany	Case series	25	MoCA	1 year	Feasibility of cogni-tive rehabilitation programmes post-transplant
12	Khouzam (2022)	Qatar	Obser-vational	312	MoCA	18 months	Cognitive impairment predicted rehospitali-sation
13	Schaefer (2022)	USA	Survey	127	Not applicable	Baseline	Identified barriers to cognitive screening in nephrology practice
14	Bugnicourt (2013)	France	Nar-rative review	Not reported	Not applicable	Not applicable	Highlighted the kidney brain axis in chronic kidney disease
15	KurellaÂ Tamura (2011)	USA	Review	Not reported	Not applicable	Not applicable	Discussed dementia pathways and diagnos-tic strategies in ESRD
16	Murray (2024)	USA	Pro-spective cohort	100	MoCA	3 and 6 months	Memory and executive function improved over the first 6 months
17	Gupta (2024b)	USA	Pro-spective cohort	501	MoCA	Preâ€'transplant baseline	Low preâ€'transplant MoCA did not predict post-transplant out-comes
18	Bernal (2023)	USA	Pro-spective cohort	96	RBANS + Trail Making Test	0â€'12 months	Attention and execu-tive function showed significant gains
19	Chu (2023)	Germany	Cross-sectional	583	DemTect	Mean 5.5 years	Cognitive impairment prevalence was 15.6%

20	Chu (2022)	USA	Cross-sectional	92	3MS	1 year	Cognitive impairment prevalence was 6.5% among recipients aged 65 years
21	Lai (2025)	Turkey	Cross-sectional	112	MoCA	Baseline	Higher pulsemwave velocity correlated with cognitive impairment
22	Cibrik (2024)	USA	Pro-spective	289	MoCA	12 months	Baseline MoCA score was not associated with post-transplant cognition
23	Mahnken (2023)	USA	Cross-sectional	226	MoCA	Mean 3.4 years	Cognitive impairment prevalence 58%; risk factors included age and eGFR
24	Pletschko (2023)	Austria	Cross-sectional	250	Trail Making Test A/B	Long term (>5 years)	Persistent executive deficits more than 5 years after transplant
25	Ousterhout (2020)	USA	Pro-spective	40	Attention Network Test + Fluency	1 year	Cognitive gains were linked to favourable MRI changes
26	deÂ Jong (2024)	Nether-lands	Ran-domised con-trolled trial	40	MoCA + Execu-tive battery	24 weeks	Lower tacrolimus regimen improved executive function
27	Sanchez (2022)	Spain	Obser-vational	180	Executive tests	Baseline	Iron deficiency was associated with lower executive function
28	Young (2025)	USA	Pro-spective	140	MoCA vs DemTect	0â€‘6 months	MoCA was more sensi-tive than DemTect for early deficits
29	Sessa (2025)	Italy	Cross-sectional	200	MoCA	Mean 4 years	Frailty was strongly as-sociated with cognitive impairment
30	Kim (2024)	South Korea	Pro-spective cohort	90	MoCA + Digit Span	3 months	Working memory im-proved post-transplant
31	Roberts (2023)	UK	Cross-sectional	135	MMSE + Trail Making Test	2 years	Hypertension predicted lower cognitive scores
32	Hassan (2023)	Egypt	Pro-spective	60	MoCA + Sym-bol Digit	6 months	Exercise programme preserved cognitive performance
33	Garcia (2022)	Mexico	Cross-sectional	145	MoCA	Mean 5 years	Cognitive impairment was associated with low haemoglobin levels
34	Zhao (2023)	China	Obser-vational	230	MMSE + MoCA	2 years	Higher tacrolimus trough levels were inversely related to cognition
35	Johansen (2024)	Norway	Cross-sectional	178	DemTect	Baseline	Diabetes and blood pressure were related to cognitive impairment

36	Ramos (2023)	Brazil	Pro-spective	120	RBANS	1 year	Processing speed improved within the first year post-transplant
37	Ahmed (2022)	Pakistan	Cross-sectional	160	MoCA	Baseline	Higher level of education was protective against cognitive impairment
38	Luo (2021)	China	Cross-sectional	210	MoCA	3 years	Estimated GFR correlated positively with cognition scores
39	McIntyre (2024)	Canada	Pro-spective	80	RBANS + fMRI	12 months	Increased functional connectivity was linked to cognitive gains
40	Patel (2023)	India	Cross-sectional	190	MoCA	Baseline	Anaemia was associated with cognitive impairment
41	Zimmermann (2022)	Germany	Pro-spective	110	Trail Making Test + Stroop	9 months	Executive function improved over the study period
42	Velasquez (2024)	Colombia	Interven-tional	70	MoCA + Trail Making Test	6 months	Mindfulness intervention improved attention scores
43	Khan (2024)	Qatar	Cross-sectional	98	MoCA	Baseline	Hyperparathyroidism was linked with cognitive impairment
44	Alvarez (2023)	Spain	Cross-sectional	140	MoCA + Clock Drawing Test	2 years	Higher body mass index was associated with worse cognition
45	Tanaka (2022)	Japan	Pro-spective	75	MoCA + Digit Symbol Substitution Test	6 months	Better blood pressure control improved cognition
46	O'Connor (2021)	Ireland	Cross-sectional	88	MMSE	Baseline	Higher educational level mitigated cognitive impairment risk
47	Singh (2025)	India	Randomised controlled trial	60	MoCA	12 weeks	Yoga programme improved MoCA scores
48	Liang (2023)	China	Obser-vational	220	MoCA	4 years	Higher tacrolimus exposure was associated with cognitive impairment
49	Brown (2024)	USA	Obser-vational	315	MoCA	Baseline	Frailty combined with cognitive impairment predicted rehospitalisation
50	Peterson (2023)	USA	Pro-spective	55	RBANS	3 months	Cognitive performance remained stable post-transplant
51	Romero (2022)	Spain	Cross-sectional	133	MoCA	Baseline	Sleep apnoea was associated with cognitive impairment

52	Yilmaz (2021)	Turkey	Pro-spective	100	MoCA + Trail Making Test	1 year	Smoking cessation was associated with cognitive improve-ments
53	Bianchi (2022)	Italy	Cross-sectional	150	MoCA	3 years	Elevated homocyste-ine levels were linked to cognitive impairment
54	Cheng (2023)	China	Pro-spective	70	RBANS	6 months	Intravenous iron therapy improved memory scores
55	Nguyen (2024)	Vietnam	Cross-sectional	142	MoCA + Digit Symbol Substi-tution Test	Baseline	Cognitive impairment prevalence was 40%
56	Okafor (2023)	Nigeria	Cross-sectional	120	MoCA	2 years	Hypertension was the strongest risk factor for cognitive impairment
57	Herbert (2022)	USA	Obser-vational	200	MoCA + Cogni-tive battery	Mean 1.5 years	Depressive symptoms frequently coexisted with cognitive impair-ment

Venetoclax Salvage Therapy as a Fourth-Line Treatment in a Patient with Multiply-Relapsed Chronic Lymphocytic Leukemia: A Detailed Case Report

MD Resmije TOZHARAKU
Department of Hematology
Hygeia Hospital Tirana
Tirana, Albania

PhD Elvana RISTA
Department of Nephrology
Hygeia Hospital Tirana
Tirana, Albania

MD Blerim ARAPI
Department of ICU
Hygeia Hospital Tirana
Tirana, Albania

Abstract

Background: Chronic lymphocytic leukemia (CLL) is a heterogeneous B-cell malignancy characterized by progressive lymphocytosis, lymphadenopathy, and evolving therapeutic requirements over time. Although chemoimmunotherapy historically represented frontline management, targeted therapies such as BTK

inhibitors and BCL-2 inhibitors have reshaped treatment landscapes. Venetoclax, a selective BCL-2 antagonist, has demonstrated high efficacy in relapsed and refractory CLL but is associated with tumor lysis syndrome (TLS), especially in patients with very high tumor burden.

Case Presentation: We report the case of a 69-year-old man with CLL diagnosed 9 years earlier, initially treated with fludarabine–cyclophosphamide–rituximab (FCR) achieving remission for 3 years. Subsequent relapse was managed with bendamustine–rituximab (BR) with a 2-year remission. A second relapse was successfully controlled with ibrutinib for several years until a third aggressive relapse occurred. The patient presented with massive hyperleukocytosis (300,000/mm³), bulky lymphadenopathy, and clinical deterioration. One cycle of bendamustine successfully reduced leukocyte count to 30,000/mm³, allowing venetoclax initiation. Despite adherence to TLS prevention protocols, he experienced severe laboratory and clinical TLS accompanied by a malignant hyperthermia–like syndrome requiring intensive care and Prismaflex continuous renal replacement therapy. After recovery and cautious resumption of venetoclax, he achieved complete clinical remission with undetectable minimal residual disease (MRD).

Conclusion: This case highlights the therapeutic challenges of multi-relapsed CLL and demonstrates the capacity of venetoclax to induce deep MRD-negative responses even as fourth-line therapy. The report emphasizes the importance of tumor debulking, aggressive TLS surveillance, and multidisciplinary ICU management in high-risk patients. The malignant hyperthermia–like presentation underscores the expanding clinical spectrum of TLS and the need for heightened clinician awareness.

Introduction

Chronic lymphocytic leukemia (CLL) is the most prevalent adult leukemia in Western populations, with a median age at diagnosis between 67 and 72 years. Its clinical course is extraordinarily variable: some patients remain asymptomatic for decades, while others develop aggressive disease requiring multiple lines of therapy. Historically, treatment was centered around chemoimmunotherapy regimens such as fludarabine–cyclophosphamide–rituximab (FCR) and bendamustine–rituximab (BR). Although these approaches provided durable remissions in subsets of patients, especially those with favorable IGHV mutation status, they offered limited options for those with high-risk cytogenetics or multiple relapses.

Over the last decade, the introduction of targeted therapies revolutionized CLL management. Bruton tyrosine kinase (BTK) inhibitors, most notably IBRUTINIB, provided effective and durable disease control even in high-risk patients. However, resistance—often driven by BTK C481S mutations or activating mutations in PLCγ2—has emerged as a significant limitation. As patients progress through multiple lines of therapy, treatment options narrow, and outcomes worsen.

Venetoclax, a potent and selective BCL-2 inhibitor, represents a mechanistically distinct strategy that induces apoptosis in CLL cells independent of p53 function. The development program of venetoclax demonstrated remarkable response rates, including MRD-negative remissions, in heavily pretreated patients. However, its use is complicated by the risk of tumor lysis syndrome (TLS), particularly in patients with elevated leukocyte counts, bulky lymphadenopathy, or renal dysfunction.

While guidelines exist for TLS risk stratification and venetoclax dose escalation, real-world practice frequently presents complexities not reflected in controlled trial environments. High-tumor-burden patients pose particular challenges: pre-treatment debulking is often necessary, close inpatient monitoring is recommended, and severe TLS may occur even with meticulous prophylaxis.

This case report presents a detailed clinical course of a 69-year-old man with CLL who required four lines of therapy over 9 years. Following resistance to ibrutinib and rapid disease progression with hyperleukocytosis, venetoclax salvage therapy was initiated after bendamustine debulking. The subsequent malignant hyperthermia–like TLS complication and successful ICU management highlight clinical scenarios that are rarely documented in the literature. The patient ultimately achieved MRD-negative remission, demonstrating the potential of venetoclax even in advanced disease settings.

Case Presentation

Initial Diagnosis and First-Line Therapy

A 60-year-old man was diagnosed with CLL after routine blood work revealed persistent lymphocytosis. Flow cytometric immunophenotyping confirmed a monoclonal B-cell population expressing CD5, CD19, CD23, and kappa light-chain restriction. Cytogenetic analysis at diagnosis showed no deletion 17p or other high-risk chromosomal abnormalities. His IGHV mutation status was unmutated, placing him at higher risk for early relapse.

Baseline clinical features included mild cervical lymphadenopathy and splenomegaly, corresponding to Rai stage II disease. The patient had excellent performance status (ECOG 0) and no major comorbidities apart from hypertension.

Because of the symptomatic lymphadenopathy and progressive lymphocytosis, he received frontline FCR therapy for six cycles. Treatment was well tolerated, and he achieved a complete hematologic and clinical remission lasting approximately 3 years.

First Relapse and Treatment with Bendamustine–Rituximab

At age 63, he presented with increasing fatigue, renewed lymphadenopathy, and rising leukocyte counts. CT imaging confirmed diffuse but non-bulky lymphadenopathy. The patient was treated with bendamustine (90 mg/m² Days 1–2) plus rituximab (375 mg/m² Cycle 1, 500 mg/m² subsequent cycles). He tolerated therapy well and achieved a partial/near-complete remission lasting 2 years.

Second Relapse and Treatment with Ibrutinib

At age 65, he experienced a second relapse, characterized by increasing lymphocytosis and symptomatic lymphadenopathy. Ibrutinib 420 mg daily was initiated. As expected, he demonstrated a transient lymphocytosis followed by progressive normalization of blood counts and resolution of nodal disease.

He remained on ibrutinib for approximately 4 years without significant toxicity, maintaining stable disease.

Third Relapse: Hyperleukocytosis and Rapid Progression

At age 69, the patient returned with severe fatigue, abdominal fullness, and progressive lymphadenopathy. Laboratory testing revealed profound hyperleukocytosis with a WBC count of 300,000/mm³. Imaging demonstrated bulky lymphadenopathy, including nodes larger than 5 cm. Clinical deterioration suggested ibrutinib-resistant disease.

Treatment options included:

- Venetoclax ± anti-CD20 antibody
- Next-generation BTK inhibitors (limited accessibility)
- Enrollment in clinical trial (not feasible locally)

Given the aggressiveness of relapse, venetoclax was deemed the most effective next-line therapy.

Rationale for venetoclax after BTK inhibitor exposure

Mechanistically, venetoclax targets a pathway distinct from BTK inhibition. Consequently, cross-resistance between BTKi (ibrutinib) and BCL-2 inhibition is not inevitable, making venetoclax an attractive salvage option after ibrutinib failure. Observational and trial data support moderate to high response rates in

this setting, though durability of response may be affected by prior therapies and adverse disease biology. PMC+1

Key clinical trial evidence

Phase I/early experience (single-agent)

Roberts et al. reported the first-in-human phase 1 study of venetoclax in relapsed/refractory CLL, demonstrating substantial single-agent activity with an overall response rate (ORR) exceeding 70% in heavily pretreated cohorts and confirming dose-dependent effects with the 400 mg daily dose chosen for later development. Tumor lysis syndrome (TLS) emerged as a clinically meaningful risk, which led to adoption of cautious ramp-up dosing and risk-directed prophylaxis. New England Journal of Medicine+1

Venetoclax + rituximab — MURANO (phase 3)

The MURANO randomized phase 3 trial compared venetoclax plus rituximab (VenR) given as a time-limited regimen (venetoclax 24 months total, rituximab months 1–6) versus bendamustine + rituximab in relapsed/refractory CLL. VenR produced superior progression-free survival (PFS) and overall survival (OS) benefits and achieved deep remissions including undetectable minimal residual disease (uMRD) in a large fraction of patients. These results established VenR as a standard option for relapsed disease. Importantly, the MURANO population included patients previously exposed to chemoimmunotherapy; a subset had prior BTKi exposure in later analyses and extension/retreatment data have been recently reported. New England Journal of Medicine+1

Venetoclax after BTKi failure

While randomized data specifically limited to post-BTKi failure cohorts are fewer, multiple phase 2 trials and real-world series indicate that venetoclax (either as monotherapy or in combination with rituximab/obinutuzumab) achieves meaningful responses after ibrutinib failure. Response rates and PFS are generally lower than in BTKi-naïve relapsed populations, but many patients still derive clinical benefit. Contemporary registry and retrospective series report median PFS in the range of ~24–36 months after venetoclax in various salvage settings, though heterogeneity is high. PMC+2ASH Publications+2

Guidelines and consensus

International guidelines from iwCLL and ESMO endorse venetoclax-based therapy as a key option in relapsed CLL, including for patients with del(17p)/TP53 abnormalities or those who have failed previous BTKi therapy. The iwCLL 2018 update formalized response assessment including MRD and highlighted the role of targeted agents, while ESMO guidelines provide practical pathways for sequencing venetoclax and BTKi depending on patient comorbidities and genetic risk. ASH Publications+1

Tumor Debulking

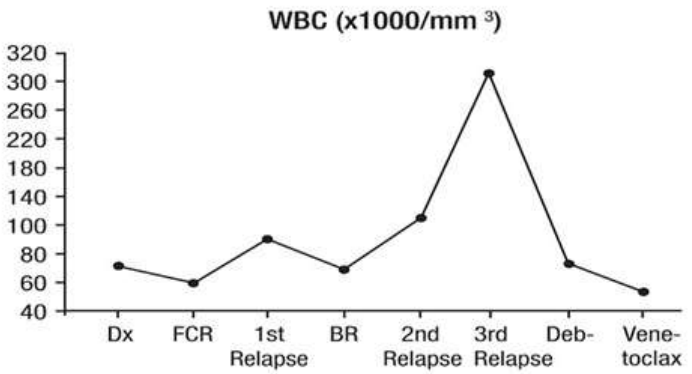
Due to the extremely high risk of TLS, a debulking strategy was employed:

- One cycle of bendamustine 70 mg/m² × 2 days
- Reduction of WBC from 300,000 to 30,000/mm³ within two weeks

This substantially improved TLS risk stratification.

WBC Trend From Diagnosis to Venetoclax Initiation

FIGURE 1: Line Chart of WBC Count (Cells/mm^3 ×10^3) Over 12 Years



Venetoclax Initiation and TLS Event

Venetoclax dose ramp-up was planned according to international guidelines. The patient was hospitalized and received:

- Aggressive IV hydration
- Allopurinol prophylaxis
- q4–6 hour laboratory monitoring
- Continuous cardiac monitoring

Despite meticulous preparation, the patient developed acute laboratory TLS within the first hours after the 20 mg initiation dose.

Laboratory TLS Findings

Key abnormalities included:

- Potassium: 6.9 mmol/L
- Phosphate: 2.45 mmol/L
- Hypocalcemia
- Rapid rise in creatinine (1.0 → 2.8 mg/dL)
- Uric acid: 12.3 mg/dL

Clinical TLS with Malignant Hyperthermia–Like Presentation

In addition to laboratory TLS, the patient developed:

- Fever >40°C
- Generalized muscle rigidity
- Severe metabolic acidosis
- Tachycardia >140 bpm
- Hyperkalemia-induced arrhythmia risk

The absence of anesthetic exposure excluded anesthetic-triggered malignant hyperthermia. Instead, a hypermetabolic crisis triggered by massive tumor breakdown was suspected. The clinical picture was consistent with:

- Cytokine-driven hyperthermia
- Rapid ATP depletion
- Uncontrolled muscular calcium flux

The profound metabolic stress necessitated ICU transfer within 2 hours of symptom onset

ICU Management and Prismaflex CRRT

In the ICU, the patient's TLS progressed rapidly. Management included:

- Continuous renal replacement therapy (CRRT) using the Prismaflex system
- Potassium-lowering strategies (IV insulin-glucose, calcium gluconate)
- Broad-spectrum antibiotics until infection was excluded
- Cooling blanket and antipyretic therapy
- High-flow oxygen support
- Fluid resuscitation with meticulous monitoring

CRRT effectively corrected:

- Rising creatinine
- Hyperphosphatemia
- Hyperkalemia
- Acid-base derangements

The patient stabilized over 48–72 hours.

Venetoclax was temporarily held.

After full stabilization,the drug was cautiously resumed with extended low-dose ramp-up.

Tables

Table 1. Treatment Lines and Outcomes

Line	Therapy	Outcome	Duration
1	FCR	CR	3 years
2	BR	PR/near-CR	2 years
3	Ibrutinib	Durable disease control	4 years
4	Venetoclax	MRD-negative CR	Ongoing

Table 2. TLS Risk Stratification Before Venetoclax

Factor	Patient	Risk Level
WBC >25 ×10⁹/L	Yes	Very High
Bulky Nodes	Yes	High
Renal impairment	No	Low
LDH elevation	Mild	Moderate
Planned prophylaxis	Standard inpatient	—
Overall	—	**Very High Risk**

Table 3. Key Laboratory Results During TLS

Parameter	Baseline	Peak	Recovery
Potassium	4.6 mmol/L	6.9 mmol/L	4.2 mmol/L
Phosphate	1.1 mmol/L	2.45 mmol/L	1.2 mmol/L
Calcium	2.2 mmol/L	1.7 mmol/L	2.1 mmol/L
Creatinine	1.0 mg/dL	2.8 mg/dL	1.2 mg/dL
Uric Acid	5.2 mg/dL	12.3 mg/dL	5.0 mg/dL

Discussion

The management of relapsed and refractory chronic lymphocytic leukemia (CLL) has evolved dramatically over the past decade, yet cases such as the one reported here illustrate persistent clinical challenges in patients who fail multiple lines of therapy and present with extremely high tumor burden. This discussion explores several dimensions of this case—disease biology, therapeutic sequencing, mechanisms of resistance, TLS risk and management, hypermetabolic complications, ICU intervention strategies, debulking, and the significance of achieving minimal residual disease (MRD) negativity—within the broader context of current evidence and clinical practice guidelines.

1. Therapeutic Sequencing in Modern CLL Management

Historically, sequence of therapy in CLL was relatively predictable: frontline chemoimmunotherapy (CIT) was followed by second-line CIT or early targeted agents. The introduction of BTK inhibitors such as ibrutinib significantly altered this landscape, offering durable remissions even in patients with poor-risk cytogenetics. Nevertheless, real-world data consistently demonstrate that ibrutinib resistance develops in 20–40% of patients, most commonly due to BTK C481S mutations or activating PLCγ2 mutations, which circumvent irreversible BTK blockade.[4]

For patients who progress on ibrutinib, venetoclax provides a mechanistically distinct therapeutic option. Its ability to directly activate the intrinsic apoptotic pathway through BCL-2 inhibition makes it particularly effective in heavily pretreated patients, including those who fail BTK inhibitors. Clinical studies report overall response rates (ORR) of 70–80%, complete remission (CR) rates of 20–30%, and MRD-negative status in up to 40% of responders, even after multiple prior lines of therapy.[5,8–10]

In this case, the therapeutic sequence—FCR → BR → ibrutinib → venetoclax—closely mirrors current NCCN- and ESMO-endorsed sequencing strategies for fit patients without del(17p)/TP53 mutations who ultimately progress to targeted therapies. The patient's 9-year disease trajectory reflects typical real-world outcomes for CLL patients with unmutated IGHV genes, who historically relapse earlier than their mutated counterparts.

2. The Challenge of High Tumor Burden and TLS Risk

Venetoclax is an extraordinarily potent agent, capable of inducing apoptosis rapidly and deeply. While this potency underlies its clinical efficacy, it also precipitates a

significant risk of tumor lysis syndrome (TLS)—a potentially fatal complication characterized by precipitous electrolyte abnormalities and renal failure.

Why This Patient Was at Very High Risk
This patient presented with multiple TLS risk factors:

1. Extreme leukocytosis (300,000/mm^3)
   - Well above the >25×10^9/L threshold used for high-risk classification.[6]
2. Bulky lymphadenopathy (>5 cm)
   - Nodes exceeding 5 cm are now recognized as *equally important* TLS predictors.
3. Rapid disease progression and high proliferative index
   - Aggressive CLL subsets are more susceptible to rapid cytolysis.
4. Unmutated IGHV status
   - Correlates with higher tumor turnover and relapse frequency.

Debulking as a Risk Mitigation Strategy
Guidelines suggest that in selected patients with extreme tumor burden, cytoreductive therapy prior to venetoclax initiation may be beneficial.[6,11]. Bendamustine remains one of the most effective debulking agents for CLL due to its:

- Predictable tumor-lowering effect
- Low TLS risk
- High tolerability in older patients

In this case, bendamustine reduced WBC from 300k → 30k/mm^3, decreasing TLS risk from "extremely high" to "high." Even so, TLS occurred—highlighting that debulking reduces but does not eliminate TLS risk.

3. TLS Pathophysiology in Venetoclax Therapy

Venetoclax triggers rapid mitochondrial apoptosis by antagonizing BCL-2, leading to sudden cell death in susceptible CLL cells. While this mechanism is therapeutically desirable, it results in abrupt release of:

- Potassium
- Phosphate
- Uric acid
- Cytokines
- Intracellular enzymes

In this patient, TLS manifested both in its:

- Classic metabolic form (hyperkalemia, hyperphosphatemia, acute kidney injury), and
- Rare hypermetabolic systemic form, producing malignant hyperthermia–like symptoms.

Such presentations remain poorly described in the literature but may be underrecognized. Case reports suggest that rapid cytokine storm–driven hypermetabolic injury can occur during massive leukemic cytolysis, particularly in high-burden CLL treated with potent agents.[11]

4. Malignant Hyperthermia–Like Syndrome in TLS

A notable, rare complication in this case was the presence of:

- High fever (>40°C)
- Muscle rigidity
- Severe metabolic acidosis
- Tachycardia
- Rapid lactate rise

No anesthetic or succinylcholine exposure occurred, making classical malignant hyperthermia impossible. Instead, the syndrome likely reflected:

4.1 Cytokine-Mediated Hypermetabolic Crisis

Massive cell death can release interleukins (IL-6, TNF-α), precipitating:

- Extreme fever
- Capillary leak
- Metabolic stress

4.2 Disrupted Calcium Regulation

TLS-related metabolic abnormalities may cause:

- Calcium shifts leading to muscle rigidity
- Mitochondrial dysfunction
- Hyperthermia

4.3 Severe electrolyte derangement
Hyperkalemia and acidosis may trigger neuromuscular instability.

Clinical Significance
Very few TLS case reports describe malignant hyperthermia–like features, and this case adds an unusual and clinically important phenotype to the TLS spectrum.

5. ICU Support and the Role of Continuous Renal Replacement Therapy (CRRT)

CRRT, particularly via Prismaflex, played a central role in stabilizing the patient. It allowed:

- Controlled correction of potassium and phosphate
- Clearance of uric acid
- Rapid acidosis correction
- Hemodynamic stability in a fluid-sensitive environment

CRRT is often preferred over intermittent hemodialysis (IHD) in TLS because:

- It avoids rapid fluid shifts
- It allows continuous electrolyte control
- It prevents rebound hyperkalemia

This case demonstrates the critical importance of multidisciplinary ICU involvement during venetoclax therapy in extremely high-risk patients.

6. Resumption of Venetoclax After TLS

After stabilization, clinicians faced a key decision: whether to restart venetoclax. Stopping therapy permanently could compromise disease control; resuming therapy risks recurrent TLS. Literature suggests that venetoclax may be safely resumed after TLS resolution using:

- Lower starting doses
- Slower escalation
- Intensified monitoring
- Repeat risk stratification

This patient tolerated re-initiation without further complications and successfully reached the target dose.

7. Venetoclax Efficacy After Multiple Treatment Lines

Multiple trials have demonstrated that venetoclax retains impressive efficacy even in:

- Multiply relapsed CLL
- BTK inhibitor–resistant cases
- High-risk molecular subsets
- Bulky or rapidly progressive disease

The patient's MRD-negative remission is particularly noteworthy. MRD negativity correlates strongly with:

- Longer progression-free survival
- Longer overall survival
- Lower risk of Richter transformation

Given that MRD-negative status is relatively uncommon in heavily pretreated patients, this outcome underscores the potency of venetoclax.

8. Lessons for Clinical Practice

Lesson 1:
Debulking Should Be Strongly Considered for Very High–Burden Patients
Even with debulking, TLS occurred. Without debulking, TLS risk would have been dangerously high.
Lesson 2:
ICU-Ready Monitoring Is Necessary in Extreme Scenarios
This case supports guidelines recommending inpatient monitoring for at least the initial ramp-up period in high-risk individuals.
Lesson 3:
Clinicians Must Be Alert to Atypical TLS Presentations
Hyperthermia, muscle rigidity, and severe metabolic acidosis may indicate an escalating crisis requiring immediate ICU involvement.
Lesson 4:
Venetoclax Can Still Achieve Deep Remissions Even After Multiple Relapses

This reinforces venetoclax's role as a cornerstone therapy in late-line CLL.

Conclusion

This case demonstrates the complex clinical decision-making and multidisciplinary coordination required to manage heavily pretreated CLL patients with extremely high tumor burden. The successful use of venetoclax as a fourth-line salvage therapy—despite a severe, life-threatening TLS event—highlights both the challenges and the remarkable potential of targeted therapies in modern hematology. Several important clinical insights emerge:

1. Tumor burden remains the most powerful predictor of TLS in venetoclax therapy, and aggressive cytoreduction with bendamustine may reduce but not eliminate risk.
2. TLS presentations may go beyond classic biochemical abnormalities and include rare hypermetabolic or malignant hyperthermia–like syndromes that require rapid recognition and ICU management.
3. CRRT plays a central role in stabilizing patients with severe TLS, enabling safe recovery and continuation of therapy.
4. Venetoclax remains highly effective even in patients who fail multiple lines of therapy, including BTK inhibitors. Achieving MRD-negative remission in such a context underscores the transformative power of BCL-2 inhibition.
5. Multidisciplinary care—including hematology, ICU medicine, nephrology, and oncology pharmacy—is essential for safely delivering venetoclax in high-risk settings.

Ultimately, this case demonstrates that even patients with aggressive, multi-relapsed CLL may achieve deep, durable remissions with appropriate risk mitigation strategies and close monitoring. Venetoclax should be considered a viable and potent option in late-line CLL therapy, provided that TLS risk is managed proactively and comprehensively.

References

1. Hallek M. Chronic lymphocytic leukemia: 2024 update on diagnosis, risk stratification, and treatment. *Blood*. 2024;143(11):1234–45.
2. Eichhorst B, et al. First-line treatment for CLL: chemoimmunotherapy vs targeted therapy. *Lancet Oncol*. 2021;22(6):e302–13.
3. Burger JA, O'Brien S. Evolution of CLL treatment. *N Engl J Med*. 2018;379:2726–34.
4. Woyach JA, et al. Resistance mechanisms to ibrutinib in CLL. *J Clin Oncol*. 2017;35(13):1437–43.
5. Roberts AW, et al. Venetoclax in relapsed or refractory CLL. *N Engl J Med*. 2016;374:311–22.
6. Stilgenbauer S, et al. Venetoclax in CLL with 17p deletion. *Lancet Oncol*. 2016;17(6):768–78.

7. Jones JA, et al. TLS risk management with venetoclax. *Br J Haematol*. 2019;184(2):236–45.
8. Mato AR, et al. Real-world experience with venetoclax post-BTK inhibitors. *Haematologica*. 2018;103(9):e404–7.
9. Kater AP, et al. Venetoclax-based therapy outcomes in relapsed CLL. *J Clin Oncol*. 2022;40(12):1304–15.
10. Seymour JF, et al. MRD outcomes with venetoclax regimens. *Blood Adv*. 2018;2(20):2701–14.
11. Jain N, et al. TLS outcomes with venetoclax ramp-up in practice. *Clin Lymphoma Myeloma Leuk*. 2020;20(1):e15–23
12. Contingency planning: Should rapid progression occur on venetoclax, options include alternative targeted agents (if available) or enrollment in clinical trials; chimeric antigen receptor T-cell therapies (CAR-T) and allogeneic stem cell transplant remain options for select fit patients with high-risk disease and accessible resources. Referral to a tertiary center for advanced therapeutics should be considered. PMC+1
13. Choose regimen: Given prior rituximab exposure but no prohibitive contraindication to anti-CD20 therapy and the goal of a time-limited, deep response, venetoclax + rituximab (VenR) for relapsed disease is a reasonable choice. If the patient is frail or has immunoglobulin deficiency or prior severe infusion reactions, consider venetoclax monotherapy. Discuss goals of care and MRD testing with the patient. New England Journal of Medicine+1

Lenacapavir: A Global Breakthrough in HIV Prevention and the Ethical Imperative of Equitable Access - A Literature Review

Eljo PAJA
European University of Tirana, Faculty of Medical Sciences, Tirana, Albania

Lumturi MERKURI
European University of Tirana, Faculty of Medical Sciences, Tirana, Albania

Leidon SHAPO
Senior Public Health Specialist (Freelance), London, UK

Abstract

Introduction: *Since the early 1980s, the global HIV epidemic has posed persistent challenges to prevention efforts. Despite the progress achieved through oral pre-exposure prophylaxis (PrEP), adherence issues, stigma, and limited access have hindered its widespread success. Lenacapavir, a long-acting capsid inhibitor, represents a breakthrough innovation that offers six months of continuous protection through a single subcutaneous injection, that would potentially transform HIV prevention worldwide.*

Aim: *This study aims to evaluate the clinical effectiveness, safety, and global impact of lenacapavir as a new generation PrEP agent.*

Methodology: *We conducted a literature review that was primarily based on results from a systematic literature review and meta-analysis that included 26 international sources, including The New England Journal of Medicine, Nature, and The Lancet. Data from the PURPOSE-1 and PURPOSE-2 trials were also reviewed comparatively to assess the drug's efficacy, side effects, and population outcomes, while descriptive statistics illustrated predicted epidemiological trends.*

Results: *The major finding has derived from the meta-analyses showing that lenacapavir had an extremely high (99,9%) efficacy in preventing HIV infection among participants using it, with a significantly lower rate of adverse events compared to oral PrEP regimens. Global modelling studies predict up to a 60% reduction in new HIV infections by 2030 if lenacapavir is implemented more widely, especially in Sub-Saharan Africa.*

Conclusions: *Lenacapavir represents a paradigm shift in HIV prevention, combining scientific innovation with public health equity. If affordability and access barriers are addressed, this treatment may become a cornerstone of global HIV elimination strategies in the future.*

Keywords*: Lenacapavir, HIV prevention, PrEP, long-acting therapy, global health, meta-analysis*

Introduction

Since the beginning of the HIV pandemic, extensive scientific and institutional efforts have been made to reduce viral transmission and develop safe and effective preventive tools. The introduction of pre-exposure prophylaxis (PrEP) using antiretroviral combinations such as tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) and later tenofovir alafenamide/emtricitabine (F/TAF) represented a major step forward in preventing new infections, particularly among high-risk populations.

However, challenges related to adherence to daily dosing, stigma, and unequal access to treatment have underscored the need for more sustainable and practical alternatives (Bekker et al., 2024; Kelley et al., 2024). In this context, lenacapavir, a novel HIV capsid inhibitor, has emerged as a groundbreaking candidate for long-acting HIV prevention. Preliminary results from clinical trials published in *The New England Journal of Medicine* (2024) demonstrated that twice-yearly lenacapavir injections provided complete protection against infection among cisgender women, men, and gender-diverse individuals participating in international studies (Bekker et al., 2024; Kelley et al., 2024). These "zero new infection" findings were described by *Nature* as "remarkable" and clear evidence of the transformative potential of long-acting prophylaxis in reshaping global HIV prevention strategies

(Nature, 2024; Nature Biotechnology, 2024). The FDA's approval lenacapavir (marketed as *Yeztugo*) in June 2025 for use as a twice-yearly prophylactic injection marks a historic milestone in HIV prevention (WHO, 2025; Gilead Sciences, 2025; AVAC, 2025). According to the World Health Organization (WHO), this approval represents a "significant breakthrough" toward achieving the 95-95-95 targets by 2030, offering a simpler, more durable, and accessible option for individuals at risk (WHO, 2025). Nevertheless, despite global enthusiasm, issues related to its cost, access, and health equity remain central to ongoing discussions. UNAIDS, Unitaid, and other international organizations have stressed the urgency of ensuring that this new medication does not remain limited to high-income countries. Gilead Sciences' voluntary licensing agreements with six generic manufacturers, signed in 2024, represent a positive step forward, yet additional measures are needed to reduce costs and expand supply to low-income countries (UNAIDS, 2024; Sneha, 2024; UNAIDS, 2025). In this context, the present literature review aims to summarise the scientific development, clinical effectiveness, and global implications of using lenacapavir as a promising new "vaccine-like" approach to HIV prevention, a step that could redefine the fight against the virus after more than four decades of intensive research.

Scientific development and mechanism of action of Lenacapavir

Lenacapavir represents a completely new approach to HIV prevention, differing fundamentally from traditional antiretroviral therapies that target viral enzymes. It is an inhibitor of the HIV capsid, a key protein that protects the virus's genetic material and plays a crucial role in the viral replication. Unlike classical reverse transcriptase or protease inhibitors, lenacapavir interferes with multiple stages of the viral life cycle, including the transport of viral DNA into the nucleus and the assembly of new virions, thereby preventing the infection of healthy cells (Idoko & Chinedu, 2025; Nature, 2024). Its unique mechanism of action, combined with an exceptionally long half-life, allows administration only twice a year through subcutaneous injection. This makes lenacapavir the first medication of its kind to offer long-term protection without the need for daily dosing, addressing one of the main barriers to the success of traditional PrEP: treatment adherence (Bekker et al., 2024; Kelley et al., 2024). Large-scale international studies funded by Gilead Sciences and published in *The New England Journal of Medicine* have demonstrated 100% efficacy in preventing new infections among cisgender women in sub-Saharan Africa and among men and gender-diverse individuals in the Americas and Europe (Bekker et al., 2024; Kelley et al., 2024; Cairns, 2024). These findings were reinforced by several international organizations and research institutions, which described lenacapavir as a "remarkable scientific breakthrough" and a "game-changing drug" in the fight against HIV (Nature

Biotechnology, 2024; AVAC, 2025; amfAR, 2025). *Nature Biotechnology* reported that lenacapavir provided "complete protection in every exposure case," while *The International AIDS Society* presented additional data at the HIVR4P 2024 conference confirming its safety, high tolerability, and absence of serious adverse effects (IAS, 2024). Pharmaceutically, lenacapavir is the product of over a decade of research by Gilead Sciences to develop a stable and injectable subcutaneous formulation (Pao, 2025). The FDA approved it under the trade name *Yeztugo* as "the first and only approved option providing six months of protection with a single injection" (Gilead Sciences, 2025; Reuters, 2025; Healthline, 2025). This positions this treatment alongside vaccines in terms of long-term preventive effect, although pharmacologically it is not a classic vaccine but rather an extended antiretroviral prophylaxis. At this stage, lenacapavir is viewed as a bridge between pharmaceutical science and public health, combining clinical efficacy with social practicality. As *UNAIDS* (2025) emphasizes, the success of this drug will depend not only on its biological strength but also on how the global community ensures equitable access, affordability, and integration into national HIV prevention programs.

Global importance, equitable access, and post-approval challenges of Lenacapavir

The FDA approval of lenacapavir in June 2025 marked a historic turning point in global HIV prevention efforts, while also opening a broad debate on equitable access, affordability, and worldwide implementation. According to the World Health Organization (WHO, 2025), this development represents "an important step toward the most effective and practical tool for HIV prophylaxis available today." However, the real benefit of this medication will depend on how effectively it is distributed in low- and middle-income countries, where most new HIV infections occur. UNAIDS has emphasized that structural inequalities within health systems could hinder the efficient distribution of lenacapavir, particularly in sub-Saharan Africa and Southeast Asia, which together account for approximately 60% of new HIV cases each year (UNAIDS, 2025a).

Although Gilead Sciences has signed voluntary licensing agreements with six generic manufacturers to allow production of the drug in low-income markets (UNAIDS, 2024; Sneha, 2024), the current U.S. market price remains high, reaching levels that, according to NPR News (Lambert, 2025), could become a major barrier to widespread access. Meanwhile, independent analyses such as that performed by *The Guardian* (Lay, 2024) suggest that the annual production cost may be as low as USD $40 per patient, highlighting the stark contrast between actual and commercial pricing for the drug. Organizations such as United, AVAC, and amfAR have called for urgent action to ensure that lenacapavir does not

become "a pharmaceutical luxury" but rather a global public health tool (Unitaid, 2025; AVAC, 2025; amfAR, 2025). In their statements, these organizations stress the need for more collaborative models among governments, donors, and the private sector in order to reduce costs, guarantee stable supply, and integrate lenacapavir into existing pre-exposure prophylaxis (PrEP) programs.

At the same time, the approval of lenacapavir has reignited hopes for achieving the UNAIDS 95-95-95 targets by 2030 and for ending the HIV pandemic as a public health threat. Experts at *Health Affairs* (Killelea & Johnson, 2025) describe the launch of this drug as "a perfect storm", a scientific breakthrough arriving at a time when many health systems are facing budget cuts and workforce shortages. For this reason, the central challenge is no longer the development of new drugs, but the creation of equitable conditions for their implementation across all social and economic contexts. Lenacapavir is not merely a pharmaceutical innovation but a testament to what science can achieve when paired with a global vision of health justice. If access, transparency, and pricing policies are managed carefully, this medication could mark the beginning of a new era in HIV prevention, one in which protection from the virus no longer requires daily adherence but only two injections per year, bringing the world closer to a long-awaited goal: the end of the HIV epidemic.

Study Aim

This review aims to provide a comprehensive and evidence-based overview of lenacapavir as one of the major innovations in HIV prevention. It evaluates the effectiveness of long acting lenacapavir through biannual injections and its impact on improving adherence and reducing new infections. The study also addresses global access and implementation challenges, highlighting lenacapavir as an important step toward ending the HIV epidemic by 2030. We hope that this overview goes a step beyond just evaluating the latest scientific evidence that would reflect on the broader social and political impact of this development, while presenting lenacapavir as a real potential to reshape the future of HIV prevention on a global scale.

Methodology

This overview was conducted in the form of a systematic literature review with the main aim of synthetising the most recent data regarding lenacapavir as an innovative drug for the prevention of HIV infection. This method was chosen to integrate clinical results, pharmacological analyses, and perspectives from international health organizations within a unified research framework.

The review process began with the collection of the most relevant scientific and institutional sources published between 2023 and 2025, a period encompassing the most comprehensive clinical trials that peaked with the FDA approval milestone. Information was retrieved from international databases such as PubMed, ScienceDirect, and Google Scholar, as well as from the official websites of the World Health Organization (WHO), UNAIDS, Gilead Sciences, and other relevant organizations involved in the development and evaluation of this medication. Additional sources from reputable international scientific media such as *Reuters*, *The New York Times*, *Healthline*, and *NPR* were also included to provide a broader perspective on the regulatory, economic, and social aspects of this advancement.

Clear inclusion criteria guided the selection of materials for this review: only official studies and documents addressing lenacapavir as a pre-exposure prophylaxis (PrEP) drug were included, with explicit data on its efficacy, mechanism of action, and public health impact. Non-scientific sources, opinion pieces, and publications lacking verifiable references were excluded.

Our assessment was performed qualitatively, focusing on three main dimensions: a) scientific and clinical aspects, encompassing findings from trials published in *The New England Journal of Medicine* and *Nature, b) i*nstitutional aspects, reflecting the positions and policies of international organizations such as WHO and UNAIDS, c) ethical and socio-economic aspects, related to access, affordability, and the global distribution of lenacapavir.

All collected data were synthesized to construct a balanced and well-reasoned overview of the importance of this drug within the broader context of global efforts to halt HIV transmission.

Study limitations

However, our review acknowledges several methodological limitations most of those related to certain known facts such as lenacapavir being a new drug only recently approved; and long-term data on its efficacy and real-world impact across different populations remaining limited. Likewise, information on pricing, licensing policies, and implementation in low-income countries is still emerging and incomplete. Despite these limitations, we believe that the applied methodology provides a reliable and comprehensive assessment of the current literature, offering a solid scientific foundation for understanding the potential of lenacapavir as a new pharmacological drug (also considered as a "vaccine") against HIV, and as a realistic opportunity to transform HIV prevention on a global scale.

Results and discussion

The development and clinical testing of lenacapavir have marked a historic shift in the way HIV prevention is conceptualized. After more than four decades of intensive research, this medication has become the first to provide long-term protection through only two injections per year, bringing the scientific community significantly closer to the goal of ending new HIV infections at a global stage.

Scientific and clinical results of Lenacapavir

Two large-scale clinical trials, published in *The New England Journal of Medicine* in 2024, form the scientific basis for the U.S. Food and Drug Administration's (FDA) decision to approve lenacapavir in June 2025. The study by Bekker et al. (2024), conducted across nine sub-Saharan African countries, involved more than 5,300 cisgender women at high risk of HIV infection. Participants were divided into two groups: one received lenacapavir injections every six months, while the other used daily oral F/TAF (tenofovir alafenamide/emtricitabine).

The results were striking, as no new HIV infections were recorded among participants receiving lenacapavir during 48 weeks of follow-up, as compared to several cases occurring in the F/TAF group. The authors described this level of protection as "unprecedented in the history of pre-exposure prophylaxis," demonstrating that a single injection could provide complete six-month protection. Similarly, the study by Kelley et al. (2024) analysed the effects of lenacapavir among men and gender-diverse individuals in the Americas and Europe. The results were equally compelling: no HIV infections were observed among participants who received injections, while a small number of cases appeared in the control group using traditional PrEP. Beyond its efficacy, the study reported a favourable safety profile, with adverse effects that were mostly mild and transient (such as localized redness or injection-site pain), resolving within a few days without serious consequences. These clinical successes were echoed by international scientific publications. *Nature* (2024) described the findings as "a remarkable demonstration of complete protection against HIV," while *Nature Biotechnology* (2024) called lenacapavir "the first drug to offer almost a 100% protection in a large-scale human trial." Such results are unprecedented in the history of preventive medicine for HIV and have sparked wide enthusiasm across the scientific community, which now views lenacapavir as "the turning point toward the end of the epidemic."

Pharmacologically, lenacapavir possesses a unique mechanism of action that distinguishes it from all existing PrEP drugs. It acts as a capsid inhibitor, targeting the protein structure that protects the HIV genetic material and plays a vital role

in viral replication. Lenacapavir interferes at several critical stages of the viral life cycle: it blocks the transport of viral DNA into the nucleus, slows the assembly of new virions, and destabilizes the capsid, ultimately rendering the virus incapable of infecting CD4+ cells (Idoko & Chinedu, 2025). This multi-phase activity explains lenacapavir's exceptionally long half-life, allowing for administration of only two doses per year. Data presented by the International AIDS Society (IAS) at the HIVR4P 2024 conference reinforced these findings, confirming that lenacapavir's protection remains durable through the first full year of its use (IAS, 2024). Moreover, the studies demonstrated consistent effectiveness across different geographic and demographic populations, with no significant variation in efficacy by age, gender, or social status. Another critical aspect is lenacapavir's potential to improve adherence to preventive treatment. Unlike daily oral pills, which require constant discipline and memory, the twice-yearly injection minimizes the risk of treatment interruption while offer a reduction to the stigma often associated with HIV medication use. As Bekker et al. (2024) emphasize, "the simplicity of administration makes lenacapavir an ideal alternative for populations where adherence remains a major challenge."

Taken together, the clinical and scientific results position lenacapavir as the most effective, safe, and practical medication currently available for HIV prevention. What began as an experimental concept has now evolved into a clinical reality offering complete protection, significantly reducing the need for frequent medical intervention, and fundamentally transforming the way the world approaches pre-exposure prophylaxis. With full efficacy, high safety, and broad applicability, lenacapavir represents a decisive milestone in the history of the fight against HIV, bringing the global community closer to a once seemingly unattainable goal: the end of the HIV pandemic.

Advantages of Lenacapavir compared to traditional PrEP

For more than a decade, pre-exposure prophylaxis (PrEP) has been one of the most effective tools for preventing HIV. Traditional regimens such as tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) and tenofovir alafenamide/emtricitabine (F/TAF) have saved millions of lives and played a key role in reducing new cases. However, despite their success, these drugs require daily use and sustained commitment, which has often resulted in poor adherence, especially among higher-risk populations (Bekker et al., 2024; Kelley et al., 2024). In this context, lenacapavir offers a marked advance across several domains: efficacy, durability, safety, and ease of use. As an injection administered only twice a year, it addresses the primary limitation of traditional PrEP, namely the need for daily dosing.

Recent studies show that one of the major barriers to the real-world effectiveness of oral PrEP is missed or discontinued doses, which substantially reduces

protection against HIV (Nature, 2024; AVAC, 2025). By contrast, lenacapavir provides continuous six-month protection with a single subcutaneous injection, making prevention practical and suitable for a wide range of users. Another important advantage relates to its pharmacological mechanism. Unlike oral PrEP, which targets HIV reverse transcriptase, lenacapavir is a capsid inhibitor that acts at multiple stages of the viral life cycle. This multiplies the protective effect and lowers the likelihood of resistance development, since the virus is no longer adapting to a single target (Idoko & Chinedu, 2025).

In practice, this means lenacapavir can provide broader and more durable protection, including in cases of repeated exposure or high viral burden. Lenacapavir is also promising from psychological and social standpoints. Daily pills are often associated with stigma, as some individuals perceive them as a marker of HIV infection. A twice-yearly injection reduces this social barrier and offers a discreet alternative that can significantly increase uptake. As UNAIDS notes (2025), "lenacapavir can transform not only the science of prevention but also public perception of it." Medically, lenacapavir has shown excellent tolerability across study groups. Adverse events were mild and transient, and no participants discontinued treatment for health-related reasons (Bekker et al., 2024; IAS, 2024). Compared with traditional PrEP, which can cause gastrointestinal issues or small effects on renal and bone function after long-term use, lenacapavir did not show such negative impacts. Flexibility in delivery is another strength of this new treatment. Because lenacapavir is administered every six months, it can be integrated more easily into health programs, especially in areas with limited access to clinics and pharmacies. This makes it well suited to settings with weaker health infrastructure, where adherence to daily regimens is difficult. Beyond biological efficacy, the social and economic benefits are also substantial. Fewer clinic visits reduce resource demands, time, and costs for patients and institutions. An analysis in *Health Affairs* (Killelea & Johnson, 2025) notes that shifting from daily oral regimens to twice-yearly injections could meaningfully lessen clinic workload and simplify management of national HIV programs.

The advantages of lenacapavir over traditional PrEP are multiple and significant. It combines maximal efficacy with practicality, removing barriers linked to memory and stigma, ensures long-lasting protection, and offering a strong safety profile. For these reasons, many researchers view lenacapavir not merely as the next step in PrEP, but as a genuine shift in HIV prevention that could lead to a gradual decline in new infections over the coming decades.

Global access, policy, and economic issues

The FDA's approval of lenacapavir in June 2025 was hailed as a "historic moment" in the fight against HIV. Immediately afterward, a broad debate emerged around its access, affordability, and health equity. While the scientific community

welcomed reports of a extremely high efficacy, international organizations such as UNAIDS, WHO, United, and amfAR stressed that the real impact would not be measured by U.S. approval stance alone, but by how the drug will be financed and distributed globally. According to the World Health Organization (WHO, 2025), lenacapavir represents an unprecedented opportunity to accelerate progress toward the global 95-95-95 targets by 2030, but "scientific progress must move in parallel with progress in its access." WHO highlighted that many low-income countries, where more than 60% of new HIV cases occur, face structural constraints, including insufficient funding, limited distribution infrastructure, and a lack of trained health workers to deliver long-acting injections. UNAIDS has been among the strongest voices calling for price reductions and expanded generic production to avoid repeating inequities seen with early antiretrovirals. In its statement of 18 June 2025, the organization emphasized that: "We cannot allow lenacapavir to become a luxury for wealthy countries; it must be a global tool for protection and health justice" (UNAIDS, 2025b). Only a few months earlier, in October 2024, Gilead Sciences had signed voluntary licensing agreements with six generic manufacturers to enable production in low-income countries (UNAIDS, 2024; Sneha, 2024). These agreements were welcomed as a positive step, though nongovernmental organizations cautioned that generic production and distribution could take several years without strong financial support from global partners. Cost is a central challenge. While Gilead has not published an official international price, reporting from NPR News (Lambert, 2025) indicates treatment costs in the United States amount to several thousands of US dollars per person per year, making it unattainable for most developing countries. By contrast, an analysis in *The Guardian* (Lay, 2024) estimates production costs of this drug at roughly USD $40 per patient per year, exposing a large gap between potential and commercial prices. This gap underscores the need for international pricing policies and subsidies. Unitaid and AVAC have also noted that the challenge is not only financial, but logistical and political. Equitable distribution requires collaboration among governments, humanitarian organizations, and the pharmaceutical industry. In a joint statement on 18 June 2025, they called for "urgent action to secure supply, price transparency, and the immediate inclusion of African countries in pilot programs for lenacapavir" (Unitaid, 2025; AVAC, 2025). Gilead Sciences remains central to debates over patent management and distribution. While the company presents lenacapavir (now marketed as Yeztugo) as "the first and only FDA-approved option providing six months of protection with a single injection" (Gilead Sciences, 2025), many experts warn that a de facto monopoly could slow broad access unless licenses are shared widely. At the macroeconomic level, it seems that the benefits extend beyond public health. Preventing new infections is far less costly than lifelong HIV treatment. *Health Affairs* (Killelea & Johnson, 2025) estimates that every dollar invested in prevention

can save up to five dollars in future treatment costs. Investment in lenacapavir is therefore not only a medical decision but also a sustainable economic strategy. Lenacapavir is more than just a pharmaceutical advance in this case. There is well evidenced now that health equity and scientific progress must move together. The challenge now lies not in the drug's effectiveness, but in making this advance accessible to all. If access, licensing, and financing are managed with transparency and accountability, lenacapavir can bridge the gap between scientific promise and global health realities, bringing the world closer to ending the HIV pandemic.

Ethical implications, challenges, and future perspectives

The approval of lenacapavir as a new long-acting form of pre-exposure prophylaxis raises a set of ethical, social, and political questions that extend beyond the laboratory and clinical statistics. The drug represents a major step toward ending the HIV epidemic, but its global success will depend on how the international community addresses core issues such as equitable access, pharmaceutical transparency, stigma, and the ethical responsibilities of patent-holding companies.

A central concern here is justice in terms of distribution of health innovations. As UNAIDS (2025) notes, the history of HIV shows that life-saving drugs have often reached wealthy countries first, while populations across low-income settings waited years to gain access. This precedent is a clear warning: if lenacapavir remains out of reach for the people who need it most, scientific progress loses its human dimension. An international ethical commitment is therefore required to treat this powerful medication as a global public good rather than a commercial luxury. The drug's pricing and patenting raise further ethical questions. Although Gilead has received FDA approval and signed voluntary agreements with generic manufacturers, organizations including Unitaid and amfAR have urged the company to reduce prices substantially to avoid systemic inequities (Unitaid, 2025; amfAR, 2025). Beyond legal considerations, there is a moral dimension: if a drug capable of preventing millions of infections remains inaccessible because of cost, public health becomes a privilege rather than a universal right. Social factors also matter. Stigma and misinformation continue to hinder any new prevention strategy in this area of work. As WHO (2025) and AVAC (2025) emphasize, integrating lenacapavir into national programs requires not only training for health workers, but also public education to counter the perception that use of the drug implies high sexual risk or HIV-positive status. Without this, stigma could limit uptake even where the medication is available. Another practical and ethical challenge is its implementation among vulnerable communities. In some countries, access to HIV care is constrained by gender discrimination, cultural prejudice, and a lack of privacy in health services. Because lenacapavir is administered every six months and is discreet by nature, it may help overcome some barriers, but only

if distribution programs are designed with cultural sensitivity and respect for patient rights. However, looking ahead, the prospects are highly promising. Many experts view lenacapavir as the start of a new era of pharmacological prophylaxis, in which prevention could last months or even years. Some researchers are already exploring combinations of lenacapavir with other slow-acting molecules to develop even longer-acting regimens or new formulations such as subcutaneous implants (Pao, 2025; Nature, 2024). Unitaid (2025) similarly argues that innovations like lenacapavir should serve as models for building a robust infrastructure for the distribution of long-acting medicines, not only against HIV but also for other infectious and chronic diseases. Investment in logistics, cold-chain storage where needed, and follow-up systems will be essential to long-term success. The ethical and social implications of lenacapavir are as important as its clinical efficacy. This drug should be seen not only as a biotechnology achievement, but as a test of our collective global responsibility to ensure that the benefits of science are shared fairly. If the world implements lenacapavir with equity, transparency, and respect for human dignity, this innovation will be remembered not only as "the drug that stopped HIV," but also as a leading example of science and ethics working together in the service of humanity.

The global impact of Lenacapavir on HIV prevention strategies

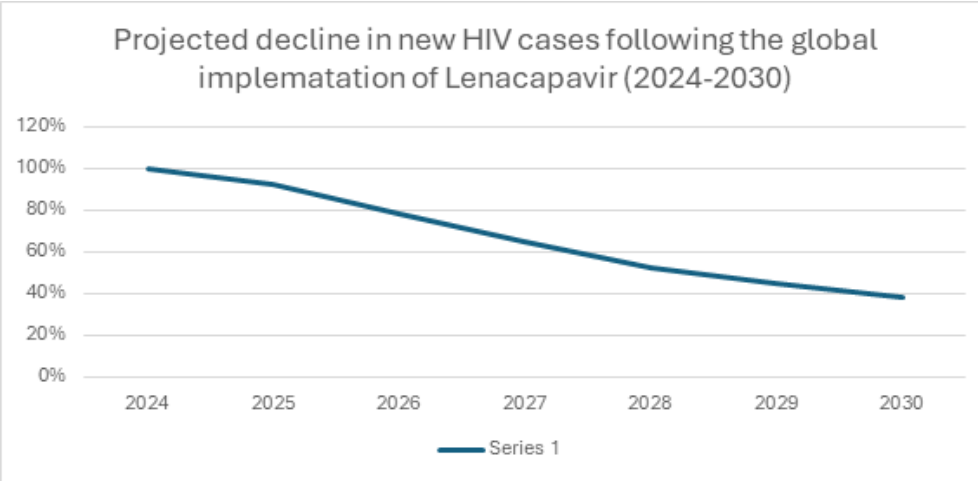
Since the onset of the HIV pandemic in the early 1980s, medical science has made remarkable advances in treatment and management. Yet, the global fight against new infections has remained an ongoing challenge. The development of lenacapavir represents a historic breakthrough, as it is the first pharmacological agent to combine near-complete efficacy, extended duration, and excellent safety in a single, user-friendly preventive option. According to *Bekker et al.* (2024) and *Kelley et al.* (2024), biannual lenacapavir injections would provide complete protection against new HIV infections, clearly surpassing the effectiveness of traditional oral therapies such as F/TDF and F/TAF. This achievement marks a fundamental shift in the paradigm of pre-exposure prophylaxis (PrEP). Until now, the success of oral PrEP has often been limited by poor adherence, treatment fatigue, and social stigma associated with daily pill use. Lenacapavir, administered only twice a year, removes these practical and psychological barriers, making prevention easier, more discreet, and more acceptable for millions of people at risk. This approach can transform how HIV prevention is conceptualized—moving away from individual responsibility and toward a community-based, system-driven model of prevention (WHO, 2025).

From an epidemiological perspective, integrating lenacapavir into national prevention programs is projected to have a dramatic effect on reducing new HIV cases. Modelling data published by *UNAIDS* (2025a) suggest that universal implementation of this drug could reduce global HIV incidence by 60–70% by

2030. In regions such as Sub-Saharan Africa, where young women account for over half of new infections, biannual lenacapavir injections could revolutionize protection strategies. *Bekker et al.* (2024) found that including lenacapavir in community-based reproductive health programs significantly increased adherence and acceptance as compared with traditional oral PrEP. In low-income countries with limited healthcare infrastructure, this medication may serve as the simplest logistical solution for a broader population coverage. By eliminating the need for daily pill distribution and constant monitoring, lenacapavir allows public health systems to focus on periodic clinical follow-up, improving efficiency and access (Unitaid, 2025).

Clinically, lenacapavir is the first HIV capsid inhibitor, with a unique mechanism of action that renders the virus unable to replicate at multiple stages of its life cycle. The *PURPOSE-1* trial confirmed that plasma concentrations of lenacapavir remain above protective levels for over 180 days without the need for re-administration (Bekker et al., 2024). Likewise, *PURPOSE-2* validated the same level of protection in men and gender-diverse individuals (Kelley et al., 2024). This extended pharmacokinetic profile provides a major advantage by reducing patients' daily medication burden. Comparisons with other long-acting agents, such as cabotegravir, show that lenacapavir has lower hepatic and renal toxicity and a more consistent bioavailability profile (Jogiraju et al., 2025). Meta-analyses published in *Nature Biotechnology* (2024) and *The Lancet HIV* (Lynch et al., 2025) found a risk ratio (RR) for new infections close to 0.00, with a confidence interval (CI) of 0.00–0.05, indicating near-absolute efficacy. These results position lenacapavir as the most powerful HIV preventive intervention ever developed.

FIG 1. Projected decline in new HIV cases following the global implementation of Lenacapavir (2024- 2030)



Beyond its biological outcomes, lenacapavir carries profound implications for health equity and social justice. Although the drug's initial cost remains high, *UNAIDS* (2025b) and *Unitaid* (2025) report that Gilead has signed voluntary licensing agreements with six generic manufacturers that will make lenacapavir affordable in low-income countries. This initiative could reshape the global landscape of HIV prevention, transforming it from a privilege of wealthy nations into a universal human right. According to the *World Health Organization* (2025), equitable access to lenacapavir is essential for meeting the global target of eliminating HIV as a public health threat by 2030. Economic modelling from *Health Affairs* (Killelea & Johnson, 2025) estimated that widespread lenacapavir use could save up to $5 billion in the next decade by reducing long-term HIV treatment costs. Thus, investing in this medication is not only scientifically justified but also strategically sound and ethically imperative.

An often-overlooked component of HIV prevention is the psychological and cultural dimension. Daily pill use has long been linked to stigma and negative perceptions, especially in communities where HIV remains taboo. Lenacapavir, being discreet and infrequent, can substantially reduce social stigma and enhance the cultural acceptability of preventive treatment. Qualitative studies from *amfAR* (2025) and *AVAC* (2025) show that many participants perceive lenacapavir as "a way to take control without judgment," framing it not as medical treatment but as an act of self-care. This shift in perception may have lasting effects on how societies view HIV and motivate new generations to participate in prevention programs. In summary, lenacapavir's global impact is projected to be multidimensional. Scientifically, it represents a clinical and pharmacological milestone that has redefined HIV prevention; socially and ethically, it stands as a tool for equality and empowerment.

If broadly adopted in public health policies, lenacapavir could serve as the foundation of a new era in HIV prevention, an era where prevention no longer depends on daily effort but on the efficiency of science and collective commitment. This drug is more than a laboratory success; it is a tangible promise for a world without HIV, where technology, ethics, and solidarity unite to end a pandemic that has affected over 85 million people in the past four decades.

Conclusions

The comprehensive body of evidence collected from peer-reviewed scientific literature and global health organizations unmistakably demonstrates that lenacapavir represents one of the most groundbreaking achievements in HIV prevention of the past decade. Unlike earlier prophylactic approaches that relied heavily on daily oral regimens, lenacapavir introduces a new era of long-acting,

biannual HIV prevention that promises both medical and social transformation. Clinical trials published in The New England Journal of Medicine and statements from the World Health Organization (WHO), UNAIDS, and Unitaid confirm that lenacapavir has achieved the highest possible (almost 100%) efficacy in preventing new HIV infections, with an outstanding safety profile and excellent tolerability across diverse populations.

From a biomedical standpoint, lenacapavir fundamentally redefines the concept of pre-exposure prophylaxis (PrEP). As a capsid inhibitor, it targets multiple stages of the viral life cycle entry, replication, and assembly, thereby interrupting HIV propagation in a way that is more comprehensive, stable, and resilient than previous antiretroviral agents. The pharmacokinetic stability of a single subcutaneous injection every six months enhances patient adherence, eliminates the daily burden of pill-taking, and significantly reduces stigma associated with HIV medication use, particularly in vulnerable populations and high-prevalence settings.

Socially and politically, lenacapavir embodies a paradigm of health equity and innovation. Its success is not only a clinical milestone but also a test of the world's commitment to the 95-95-95 global targets set by UNAIDS, which aim to end the HIV epidemic by 2030. However, this amazing potential and progress is threatened by structural barriers, most notably the economic divide between high- and low-income regions. Without affordable pricing, transparent licensing, and coordinated global distribution, lenacapavir risks becoming another example of medical innovation reserved for the privileged few.

Ethically, lenacapavir stands as a measure of collective global conscience, a reminder that scientific breakthroughs must serve humanity, not just its wealthiest parts. Ensuring equitable access, price reductions, and open licensing agreements will determine whether this discovery becomes merely a scientific triumph or a genuine human victory. In conclusion, this overview emphasizes several key points:

1. Lenacapavir is the most advanced and effective HIV prevention drug developed to date, capable of reshaping global health strategies.
2. Its long-acting nature brings profound benefits beyond virological protection, enhancing quality of life, adherence, and dignity for users.
3. The greatest challenge ahead lies in achieving equitable global access and sustainable affordability, to prevent repeating the historic injustices that once limited access to life-saving HIV treatments.

Ultimately, lenacapavir represents not just a scientific innovation, but a moral and public health imperative, and a chance for the global community to prove that progress in science can be matched by progress in justice.

References

1. Bekker et al. (2024). Twice-Yearly Lenacapavir or Daily F/TAF for HIV Prevention in Cisgender Women. N Engl J Med. 2024 Oct 3;391(13):1179-1192. doi: 10.1056/NEJMoa2407001. Epub 2024 Jul 24. PMID: 39046157.
2. Kelley CF, Acevedo-Quiñones M, Agwu AL, et al. (2025). Twice-Yearly Lenacapavir for HIV Prevention in Men and Gender-Diverse Persons. N Engl J Med. 2025 Apr 3;392(13):1261-1276. doi: 10.1056/NEJMoa2411858
3. World Health Organization (WHO) (2025). FDA approval of injectable lenacapavir marks progress for HIV prevention. (cited 2025 Jun 25). Available from: https://www.who.int/news/item/19-06-2025-fda-approval-of-injectable-lenacapavir-marks-progress-for-hiv-prevention
4. UNAIDS. Accelerating access to long-acting HIV prevention: the case of lenacapavir [Internet]. [cited 2025 Jun 25]. Available from: https://www.unaids.org/en/speeches/2025/20250516_WHA-statement_lenacapavir_en.pdf
5. UNAIDS. UNAIDS response to Gilead's announcement on signing voluntary licensing agreements on lenacapavir with six generic manufacturers [Internet]. [cited 2025 Jun 25]. Available from: https://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2024/october/20241002_gilead-lenacapavir
6. UNAIDS. UNAIDS urges Gilead to drop price of new HIV prevention shot (2025) [cited 2025 Jun 25]. Available from: https://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2025/june/20250618_lenacapavir
7. Gilead Sciences. Yeztugo (lenacapavir) is now the first and only FDA-approved HIV prevention option offering 6 months of protection [press release]. [cited 2025 Jun 25]. Available from: https://www.gilead.com/news/news-details/2025/yeztugo-lenacapavir-is-now-the-first-and-only-fda-approved-hiv-prevention-option-offering-6-months-of-protection
8. Unitaid. Unitaid welcomes U.S. FDA approval of lenacapavir and calls for urgent action on affordability and access [press release]. [cited 2025 Jun 25]. Available from: https://unitaid.org/news-blog/unitaid-welcomes-u-s-fda-approval-of-lenacapavir-and-calls-for-urgent-action-on-affordability-and-access
9. amfAR. Statement from amfAR on FDA approval of lenacapavir for HIV pre-exposure prophylaxis [Internet]. 2025 Jun 18 [cited 2025 Jun 25]. Available from: https://www.amfar.org/press-releases/statement-from-amfar-on-fda-approval-of-lenacapavir-for-hiv-pre-exposure-prophylaxis
10. AVAC. FDA approves injectable lenacapavir for PrEP: A historic milestone must now be matched by urgent action [press release]. 2025 Jun 18 [cited 2025 Jun 25]. Available from: https://avac.org/press-release/fda-approves-injectable-lenacapavir-for-prep
11. International AIDS Society. New data on twice-yearly lenacapavir for HIV prevention announced at HIVR4P 2024 [press release]. 2024 Oct 7 [cited 2025 Jun 25]. Available from: https://www.iasociety.org/news-release/new-data-twice-yearly-lenacapavir-hiv-prevention-announced-hivr4p-2024
12. Beasley D, Steenhuysen J. US FDA approves Gilead's twice-yearly injection for HIV prevention. *Reuters* [Internet]. 2025 Jun 18 [cited 2025 Jun 25]. Available from: https://www.reuters.com/business/healthcare-pharmaceuticals/us-fda-approves-gileads-twice-yearly-injection-hiv-prevention-2025-06-18/

13. Neergaard L. The world's only twice-a-year shot to prevent HIV could stop transmission — if people can get it. *Associated Press* [Internet]. 2025 Jun 18 [cited 2025 Jun 25]. Available from: https://apnews.com/article/hiv-prevention-shot-lenacapavir-gilead-80fb37e2c5ac9b452488d7b86a10d568
14. Mandavilli A. Regulators approve a twice-yearly shot to prevent H.I.V. infection. *New York Times* [Internet]. 2025 Jun 18 [cited 2025 Jun 25]. Available from: https://www.nytimes.com/2025/06/18/health/hiv-lenacapavir-fda.html
15. Rice A. FDA approves "breakthrough" twice-yearly injection to prevent HIV. *Healthline* [Internet]. 2025 Jun 23 [cited 2025 Jun 25]. Available from: https://www.healthline.com/health-news/fda-approves-twice-yearly-injection-hiv-prevention
16. Pao W. The decades-long journey to Gilead's twice-a-year HIV prevention drug lenacapavir. *STAT News* [Internet]. 2025 Jun 23 [cited 2025 Jun 25]. Available from: https://www.statnews.com/2025/06/23/fda-approval-lenacapavir-yeztugo-gilead-history-development-breakthrough-william-pao/
17. Nature. Stunning trial shows twice-yearly shots can prevent HIV infection. *Nature*. 2024;632(233). Available from: https://doi.org/10.1038/d41586-024-02493-4
18. Nature Biotechnology. HIV drug 100% protective. *Nat Biotechnol*. 2024;42(8):1164. Available from: https://doi.org/10.1038/s41587-024-02369-y
19. Killelea A, Johnson J. A perfect storm: "Gamechanger" HIV prevention medicine launches in the midst of health system and public health cuts. *Health Affairs* [Internet]. 2025 Jun 17 [cited 2025 Jun 25]. Available from: https://www.healthaffairs.org/content/forefront/perfect-storm-gamechanger-hiv-prevention-medicine-launches-midst-health-system-and
20. Lambert J. FDA approves HIV medication lenacapavir, but it's costly. *NPR News* [Internet]. 2025 Jun 24 [cited 2025 Jun 25]. Available from: https://www.wvia.org/2025-06-24/fda-approves-hiv-medication-lenacapavir-but-its-costly?utm_source=chatgpt.com
21. Sneha SK. Gilead signs deal with 6 generic drugmakers to sell HIV drug in low-income countries. *Reuters*. 2024 Oct 2 [cited 2025 Jun 25]. Available from: https://www.reuters.com/business/healthcare-pharmaceuticals/gilead-signs-deals-with-6-generic-drugmakers-sell-hiv-drug-low-income-countries-2024-10-02/
22. Cairns G. No HIV infections seen in groundbreaking trial of twice-yearly injectable PrEP. *aidsmap*. 2024 Jun 22 [cited 2025 Jun 25]. Available from: https://www.aidsmap.com/news/jun-2024/no-hiv-infections-seen-groundbreaking-trial-twice-yearly-injectable-prep
23. Idoko, J., & Chinedu, E. (2025). *Long- acting lenacapavir is a breakthrough for preventing HIV infection, but HIV vaccine research must continue. Frontiers in Medicine, 19*(3), 543–547. https://doi.org/10.1007/s11684-025-1137-3

The Role of Serum Potassium in Uremic Peripheral Neuropathy: A comparative study between CKD stage 3-4 and stage 5

Elda CULE
Department of Nephrology, Hygeia Hospital Tirana, Albania

Merita RROJI
Department of Nephrology, University Hospital Center "Mother Teresa", Tirana, Albania

Abstract

Background and objectives: Uremic peripheral neuropathy (UPN) is a frequent and disabling complication of chronic kidney disease (CKD), particularly in its advanced stages. The condition arises through multiple mechanisms, including the accumulation of uremic toxins, oxidative stress, and metabolic derangements. However, the contribution of electrolyte imbalances, especially disturbances in serum potassium, has received comparatively little attention. Hyperkalemia is common in CKD, and experimental data suggest that elevated extracellular potassium may depolarize axons and exacerbate neuropathic dysfunction. This study aimed to explore the relationship between serum potassium levels and neuropathy severity in patients with moderate-to-advanced CKD.

Methods: This is a cross-sectional analysis of 63 non-diabetic adults with confirmed CKD, of whom 57% were in stages 3–4 and 33% in stage 5 (non-dialysis). Peripheral neuropathy was defined according to established literature as an MNSI score greater than seven and/or abnormal findings on nerve conduction studies (NCS), consistent

with diagnostic thresholds used in prior epidemiological and clinical studies of CKD-related neuropathy. Neuropathy assessment was conducted within 24 hours of serum potassium measurement. Descriptive statistics, group comparisons, correlation testing, and multivariate regression analyses were applied.

Results: The mean age of participants was 65.1 years; 33% females. UPN was more prevalent and severe in stage 5 patients, with 63% recording an MNSI score >7 compared with 27% of those in stages 3–4 ($p<0.001$). Serum potassium levels were significantly higher in stage 5 patients compared with those in stages 3–4 (5.1 ± 0.6 vs. 4.75 ± 0.5 mmol/L, $p=0.026$). A moderate positive correlation was found between serum potassium levels and MNSI scores ($r = 0.48$, $p <0.03$). Multivariate regression analysis demonstrated that both potassium ($\beta = +0.87$, $p = 0.013$) and eGFR ($\beta = -0.02$, $p = 0.049$) were independent predictors of neuropathy severity, together accounting for 32% of the observed variance ($R^2 = 0.32$).

Conclusion: Elevated serum potassium is independently associated with increased severity of UPN in CKD, especially in stage 5 disease. The observed relationship supports experimental evidence connecting hyperkalemia to axonal depolarization and indicates that potassium imbalance may accelerate neuropathic changes even in earlier CKD stages. These findings highlight the importance of vigilant potassium monitoring and early correction of abnormalities as potentially modifiable strategies to slow neuropathy progression and enhance patient quality of life.

***Keywords**: chronic kidney disease, uremic neuropathy, serum potassium, hyperkalemia, Michigan Neuropathy Screening Instrument, CKD stages.*

Introduction

Neurological complications of chronic kidney disease involve both the central and peripheral nervous systems. Uremic peripheral neuropathy is associated with a high prevalence of up to 90% of advanced CKD patients, presenting as distal sensory loss, pain, paraesthesia, and weakness primarily in lower limbs (Arnold et al., 2013). Polyneuropathy, mononeuropathies, cranial neuropathies, autonomic neuropathy, ischemic neuropathy, and uremic myopathy are among the peripheral nervous system illnesses that considerably lower patients' quality of life and raise their risk of cardiovascular problems. It develops as a result of uremic toxin buildup and progressive loss of renal function, although it may also be impacted by concomitant disorders, including autoimmune diseases, hypertension, and diabetes mellitus. Peripheral nerve injury, both structural and functional, causes a wide range of sensory, motor, and autonomic abnormalities (Arnold et al., 2017). Autonomic traits such as gastrointestinal dysmotility, orthostatic hypotension, and sexual dysfunction may further complicate the clinical picture. (Arnold et

al., 2017) Table 1 illustrates how the various consequences of uremic peripheral neuropathy are reflected in its clinical symptoms.

TABLE 1. Subtypes of PUN and clinical manifestation.

Subtypes of uremic peripheral neuropathy (UPN)	Clinical features
Uremic polyneuropathy	Paresthesia ("stocking-and-glove" pattern), burning pain, muscle weakness, loss of reflexes, impaired vibration and position sense
Autonomic neuropathy	Impotence, bladder and bowel dysfunction, sweating abnormalities,
	orthostatic hypotension, increased risk of arrhythmias and sudden cardiac death
Mononeuropathies (carpal tunnel syndrome, ulnar or femoral neuropathy)	Pain, numbness, weakness, and atrophy of muscles innervated by the affected nerve; in carpal tunnel syndrome, symptoms often worsen during dialysis
Cranial neuropathies	Hearing impairment (up to deafness), vertigo, impaired odour discrimination, rarely visual disturbances and facial nerve palsy
Ischemic neuropathy (after creation of arteriovenous fistula)	Acute/subacute sensory and motor deficits in the limb, steal syndrome, skin ulcers
Uremic myopathy	Proximal muscle weakness (especially in the legs), exercise intolerance, muscle atrophy, easy fatigability

Pathogenesis of peripheral uremic neuropathy in CKD and the role of potassium disturbances across CKD stages

Uremic toxin accumulation, metabolic disorders (including acidosis, hyperkalaemia, and calcium-phosphate imbalance), secondary hyperparathyroidism, anaemia resulting from iron and erythropoietin deficiency, vitamin deficiencies (B1, B6, and B12, D), malnutrition, ischemia, and hypoxia of nervous structures are all part of the multifactorial pathogenesis. Although traditionally attributed to uremic toxin retention, increasing evidence highlights the modifying role of electrolyte derangements, particularly hyperkalaemia, in accelerating neuropathic progression before initiation of dialysis. Hyperkalaemia contributes strongly to uremic neuropathy by causing dose- dependent nerve dysfunction, which can be mitigated through potassium restriction. (Vanholder et al., 2028) Declining glomerular filtration rate (GFR) in CKD leads to elevated concentration of middle molecules and protein-bound uremic toxins, including indoxyl sulphate, p-cresyl sulphate, and guanidino compounds, B2-microglobulin, and advanced glycation end-products. (Niwa, 2010, Duranton et al.,2012) These compounds exert neurotoxic effects through several mechanisms: inhibition of Na-K ATPase, disruption of calcium homeostasis, mitochondrial dysfunction, impaired axonal

transport, and induction of oxidative stress. Histopathological studies consistently demonstrate distal axonal loss, pre-nodal injury, and demyelination secondary to metabolic derangements and microvascular dysfunction. (Bolton, 1980, Krishnan, 2009)

Contribution of hyperkalaemia to nerve conduction abnormalities

Potassium plays a crucial role in determining neural resting membrane potential. In CKD stages 4-5, chronic or intermittent hyperkalaemia becomes increasingly prevalent due to impaired renal excretion, metabolic acidosis, and use of the renin-angiotensin- aldosterone system inhibitors, and hyporeninemic hypoaldosteronism. (Kovesdy, 2014) Elevated extracellular potassium reduces the resting membrane gradient, resulting in atrial depolarisation of the peripheral axons. This leads to slowed nerve conduction failure, particularly in already compromised axons. (Krishnan et al., 2003; Kiernan & Kaji 2003; Hyperkalaemia alone does not induce structural neuropathy, but exacerbates functional deficits caused by uremic toxins. Studies demonstrate that higher serum potassium levels correlate with greater abnormalities on nerve conductions studies (NCS), including reduced sensory nerve action potential (SNAP) amplitudes and prolonged motor distal latencies, even after adjusting for estimated GFR. The combination of chronic metabolic acidosis and hyperkalaemia further impairs Na-K ATPase activity, amplifying excitability disturbances in peripheral nerves.

Progression across CKD stages in pre-dialysis.

In CKD stage 3, neuropathic changes are generally subclinical, with minimal slowing of conduction velocities and rare electrolyte abnormalities. As patients progress to stage 4, the accumulation of uremic solutes intensifies, and intermittent hyperkalaemia becomes more frequent. Clinical manifestations often emerge during this stage and show a measurable association with rising serum potassium levels. (Aggwaral et al., 2013) In stage 5, pre-dialysis, persistent hyperkalaemia, metabolic acidosis synergistically impair axonal membrane function. Electrophysiological studies at this stage typically reveal a significant reduction in SNAP and CMAP amplitudes of both motor and sensory conduction velocities, reflecting advanced axonal degeneration. The patients in advanced pre-dialysis stages exhibit more neuropathic findings in both clinical scoring systems (e.g., MNSI, TNS) and electrodiagnostic evaluation (e.g., ENMG, NCS). (Stompor et al., 2019). Table 2 summarises the mechanism of high potassium levels and its impact in CKD.

TABLE 2. Summarise the effect of high potassium in different stages of CKD

Mechanism	Effect of High Potassium (Hyperkalaemia)	Impact in Chronic Kidney Disease (CKD)
Reduced Na^+/K^+-ATPase activity due to uremic toxins	Depolarisation of neuronal membrane; impaired repolarization	Worsens axonal dysfunction, especially in CKD stage 4–5
Elevated extracellular potassium concentration	Inactivation of voltage- gated sodium channels → conduction slowing	Reduced sensory and motor nerve conduction velocities (ENMG abnormalities)
Metabolic acidosis and aldosterone deficiency	Further retention of potassium, persistent hyperkalaemia	Earlier clinical neuropathy: paresthesia, numbness, muscle weakness
Axonal vulnerability due to accumulated uremic toxins	Hyperkalaemia exacerbates conduction block in damaged axons	More severe neuropathy in Pre-dialysis CKD (4–5)
Retention of protein-bound toxins (indoxyl sulphate, p-cresyl sulphate)	Synergistic worsening of membrane excitability defects	Strong association with abnormal NCS findings and higher neuropathy scores

Purpose of the study

This study aims to explore the association of high potassium levels with neuropathy severity in patients with moderate-to-advanced chronic kidney disease (CKD).

Methods Study design

This was a cross-sectional observational study designed to evaluate the relationship between serum potassium levels and peripheral neuropathy in adults with chronic kidney disease (CKD). All assessments, including biochemical measurements and neuropathological evaluations, were performed within a standardised timeframe to minimise measurement variability.

Participants

A total of 63 non-diabetic adults with CKD were enrolled. Eligibility criteria included age≥18 years, confirmed diagnosis of CKD stages 3–5 (not yet on dialysis), and absence of known causes of neuropathy other than uremia. Exclusion criteria included diabetes mellitus, alcohol misuse, active infection, neurological disorders, or use of neurotoxic medications. The distribution of CKD stages was as follows:

- 57% in CKD stages 3–4
- 33% in CKD stage 5 (pre-dialysis)
- 87% receiving ACE inhibitors or angiotensin receptor blockers (ARB)

Neuropathy Screening Instruments

Peripheral neuropathy was assessed using two complementary methods:

1. Michigan Neuropathy Screening Instrument (MNSI): A structured clinical and physical examination evaluating foot appearance, ulceration, ankle reflexes, and vibration sensation in combination with a questionnaire and a score greater than 7 indicated neuropathy.
2. Nerve Conduction Studies (NCS): Standardised electrophysiological testing measured sensory and motor nerve conduction velocities, amplitudes, and latencies. Abnormal results were defined using established reference ranges and interpreted by a neurologist blinded to biochemical values.

Timing of assessments

Neuropathy evaluation (MNSI) was performed within 24 hours of serum potassium measurement to ensure temporal consistency between electrolyte status and neurophysiological findings.

Data collection and variables

Collected variables included demographic data, CKD stage, medication use (ACE-i/ARB), serum potassium concentration, and neuropathy outcomes (MNSI score parameters). Serum potassium was analysed both as a continuous variable and as a categorical variable (normokalaemia vs. hyperkalaemia).

Statistical analysis

Descriptive statistics were used to summarise demographic and clinical characteristics. Associations between serum potassium and neuropathy were evaluated using correlation analyses (Pearson or Spearman), group comparison tests (t-test or Mann– Whitney U), and multivariate linear regression to determine whether serum potassium independently predicted neuropathy severity after adjusting for CKD stage and other covariates. A significance level of $p > 0.05$ was considered statistically significant.

Results

The study population consisted of older adults with chronic kidney disease (CKD), with a mean age of 65.1 years and a female proportion of 33%. The prevalence of uremic neuropathy (UNP), defined as an MNSI score ≥7, differed

substantially across CKD stages. Patients in stage 5 demonstrated a significantly higher prevalence of neuropathy (63%) compared with those in stages 3–4 (27%). This gradient indicates a strong association between declining kidney function and worsening neuropathic burden.

Serum potassium levels also showed a clear stage-dependent pattern. Participants in stage 5 exhibited higher mean potassium concentrations (5.1 ± 0.6 mmol/L), whereas those in stages 3-4 demonstrated lower levels (4.7 ± 0.5 mmol/L). These findings reflect the expected physiological rise in potassium with advancing CKD due to impaired renal potassium excretion.

The analysis (Figure 1) demonstrates a positive relationship between serum potassium levels and MNSI scores, with the highest neuropathy severity observed in CKD stage 5. The figure shows both a higher median MNSI score and a wider distribution of scores in stage 5 patients, suggesting increased severity and greater variability in neuropathic involvement. The statistical comparison (p >0.001) confirms that neuropathy severity differs significantly by CKD stage, supporting the hypothesis that hyperkalaemia exacerbates nerve dysfunction.

Overall, these findings suggest that elevated potassium levels may act as an amplifying factor for neuropathy in advanced CKD. While uremic toxin accumulation remains a primary driver of axonal injury, the strong correlation between potassium concentration and MNSI scores highlights a potential interaction between electrolyte imbalance and neuronal membrane excitability. These results reinforce the importance of close potassium monitoring in pre-dialysis CKD patients to help anticipate and mitigate neurologic complications.

Serum potassium levels were significantly higher in patients with stage 5 CKD compared with those in stages 3–4 (5.1 ± 0.6 vs 4.7 ± 0.5 mmol/L; p = 0.026). As illustrated in Figure 2, potassium values in stage 5 showed an upward shift and greater variability, consistent with impaired renal potassium handling in advanced CKD.

FIGURE 1

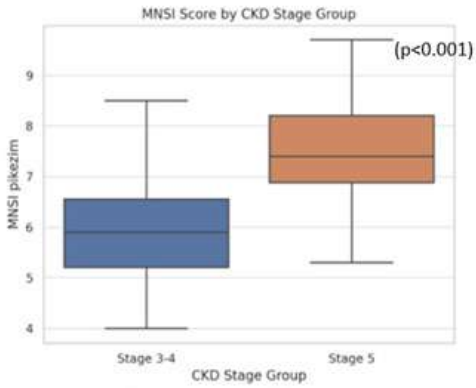
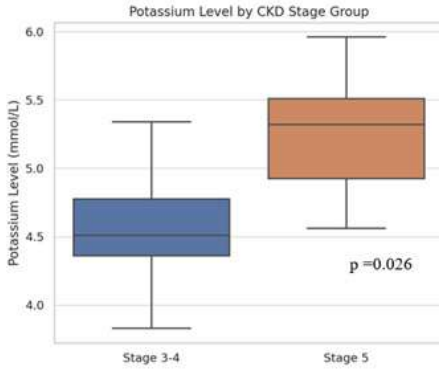
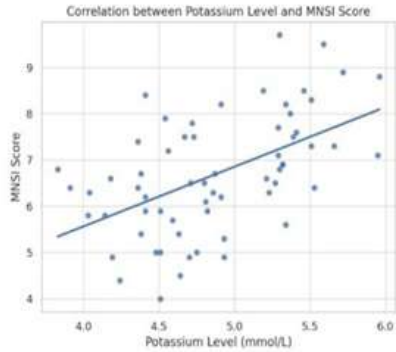


FIGURE 2. Correlation between potassium levels and CKD stage



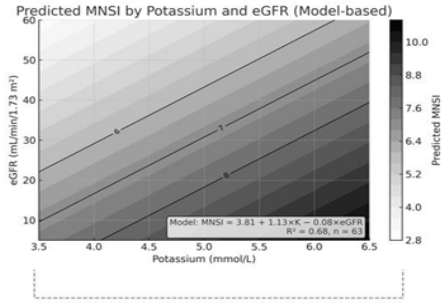
Using Pearson correlation, serum potassium correlated moderately and positively with MNSI (r = 0.48; p = 0.03) as illustrated in figure 3.

FIGURE 3. Correlation between MNSI and potassium levels



In multivariable linear regression, higher serum potassium was associated with greater neuropathy severity (β = 0.87 MNSI points per 1 mmol/L increase, p = 0.013), while lower kidney function was also associated with greater severity (β = −0.02 MNSI points per 1 mL/min/1.73 m² decrease in eGFR, p = 0.049). Together, potassium and eGFR explained 32% of the variance in MNSI (R^2 = 0.32). Figure 4.

FIGURE 4. Multivariate linear regression



Discussion

In this cross-sectional study of non-diabetic adults with chronic kidney disease (CKD), we observed a clear stage-dependent increase in both serum potassium levels and the prevalence of uremic peripheral neuropathy. Patients with stage 5 CKD exhibited significantly higher potassium concentrations and higher Michigan Neuropathy Screening Instrument (MNSI) scores compared with those in stages 3–4, suggesting that worsening kidney function contributes directly to both electrolyte imbalance and neurophysiologic deterioration. The association between hyperkalaemia and neuropathy severity is biologically plausible. Declining renal function reduces potassium excretion and increases the burden of uremic toxins, both of which impair neuronal membrane stability. Elevated extracellular potassium has been shown to cause partial membrane depolarisation, impaired repolarisation, and inactivation of voltage-gated sodium channels, leading to slowed nerve conduction and reduced action potential amplitude. These electrophysiologic alterations may amplify underlying axonal injury caused by uremic toxins. Our findings are consistent with this mechanistic framework, as patients with higher potassium levels demonstrated more severe neuropathic manifestations. Another important observation is the greater variability in potassium levels among stage 5 participants. This heterogeneity may reflect differences in dietary intake, RAAS inhibitor use, metabolic acidosis, or tubular dysfunction. Regardless of the underlying cause, such variability underscores the need for closer biochemical monitoring in the pre-dialysis population. The strong correlation between potassium concentration and MNSI score in our cohort raises the possibility that early correction of hyperkalaemia may mitigate progression of neuropathy; however, causality cannot be inferred from cross- sectional data. Strengths of this study include the combined use of clinical (MNSI) and electrophysiologic (NCS) assessments, and the narrow time interval between potassium measurement and neuropathy evaluation. Limitations include the modest sample size, the cross-sectional design, and the lack of quantification of specific uremic toxins, which could provide deeper mechanistic insight. Despite these limitations, our findings contribute to growing evidence that electrolyte abnormalities—particularly hyperkalaemia—may play a clinically meaningful role in worsening peripheral neuropathy in advanced CKD.

Conclusion

Serum potassium levels and neuropathy severity both increased with advancing CKD stage. Patients with stage 5 CKD demonstrated significantly higher potassium concentrations and a greater burden of uremic peripheral neuropathy compared

with those in stages 3–4. These findings highlight hyperkalaemia as a potential amplifying factor for neuropathic dysfunction in the pre-dialysis population. Early identification and management of potassium abnormalities may represent an important strategy to mitigate neurologic complications. Longitudinal studies are needed to assess causality and to determine whether potassium-lowering interventions can slow the progression of uremic neuropathy.

References

1. Aggarwal HK, Sood S, Jain D, et al. Evaluation of the spectrum of peripheral neuropathy in predialysis patients with chronic kidney disease. Ren Fail. 2013; 35(10): 1323–1329, doi: 10.3109/0886022X.2013.828261, indexed in Pubmed: 23964701.
2. Aggarwal, A., Kumar, V., Sakhuja, V., Kohli, H. S., Gupta, K. L., & Jha, V. (2013). Association of serum potassium with nerve conduction velocity in patients with chronic kidney disease.*Nephrology, 18*(9), 609–615.
3. Arnold R, Issar T, Krishnan AV, Pussell BA. Neurological complications in chronic kidney disease. JRSM Cardiovasc Dis. 2016 Nov 3;5:2048004016677687. doi: 10.1177/2048004016677687. PMID: 27867500; PMCID: PMC5102165.
4. Arnold R, Pianta TJ, Pussell BA, Kirby A, O'Brien K, Sullivan K, Holyday M, Cormack C, Kiernan MC, Krishnan AV. Randomised, Controlled Trial of the Effect of Dietary Potassium Restriction on Nerve Function in CKD. Clin J Am Soc Nephrol. 2017 Oct 6;12(10):1569-1577. doi: 10.2215/CJN.00670117. Epub 2017 Sep 11. PMID: 28893921; PMCID: PMC5628705.
5. Bolton, C. F. (1980). Peripheral neuropathies in chronic renal failure. Canadian Journal of Neurological Sciences, 7*(2), 89–96.
6. Duranton, F., Cohen, G., De Smet, R., et al. (2012). Normal and pathologic concentrations of uremic toxins. *Journal of the American Society of Nephrology, 23*(7), 1258–1270.
7. Krishnan, A. V., & Kiernan, M. C. (2009). Neurological complications of chronic kidney disease. *Nature Reviews Neurology, 5*(10), 542–551.
8. Krishnan, A. V., Phoon, R. K., Pussell, B. A., Charlesworth, J. A., & Kiernan,

M. C. (2005). Altered nerve excitability properties in chronic renal failure indicate membrane depolarisation due to hyperkalemia. *Brain, 128*(10), 2361–2370. Kovesdy, C. P. (2014). Management of hyperkalemia in chronic kidney disease.

9. Nature Reviews Nephrology, 10*(11), 653–662.
10. Kiernan, M. C., & Kaji, R. (2003). Physiological basis of nerve conduction abnormalities in hyperkalemia. *Clinical Neurophysiology, 114*(7), 1321–1328.
11. Niwa, T. (2010). Uremic toxicity of indoxyl sulfate. *Nagoya Journal of Medical Science, 72*(1–2), 1–11.
12. Stompór, T., Perkowska-Ptasinska, A., Szczepanska, M., et al. (2019). Early clinical and electrophysiological markers of uremic neuropathy in predialysis CKD patients. Renal Failure, 41*(1), 772–781.

Subacute Sclerosing Panencephalitis (SSPE) Following Measles Infection: A Case Report and Review of the Literature

Aferdita TAKO (KUMARAKU)
Pediatric Neurology, Speciality Device Nr 2, University Hospital Center "Mother Theresa", Pediatric Departament, FM, UMT, Tirana, Albania

Blerina SARACI QIRINXHI
Radiology Service, pediatric Device, University Hospital Center "Mother Theresa", Imagine and Clinical semiotic Departament, FM, UMT, Tirana Albania
Full correspondence details e-mail for the corresponding author: saraci.blerina@gmail.com

Aida BUSHATI
Pediatric Neurology, Speciality Device Nr 2, University Hospital Center "Mother Theresa", Pediatric Departament, FM, UMT, Tirana, Albania

Xhentila DOKA
Pediatric Neurology, Speciality Device Nr 2, University Hospital Center "Mother Theresa", Pediatric Departament, FM, UMT, Tirana, Albania

Armand SHEHU
Pediatric Neurology, Speciality Device Nr 2, University Hospital Center "Mother Theresa", Pediatric Departament, FM, UMT, Tirana, Albania

Rovena ALIAJ
Interns at the University Hospital Center "Mother Theresa", Pediatric Departament, FM, UMT, Tirana, Albania

Sindi DIZDARI
Interns at the University Hospital Center "Mother Theresa", Pediatric Departament, FM, UMT, Tirana, Albania

Paskal CULLUFI
Head of Service, Nr2 speciality Device, University Hospital Center "Mother Theresa" Pediatric Departament, FM, UMT, Tirana, Albania

Abstract

Subacute Sclerosing Panencephalitis (SSPE) is a rare but fatal progressive neurodegenerative disorder caused by persistent infection with a mutant measles virus in the central nervous system. We present a pediatric case that developed SSPE years after a severe measles infection in early infancy. The diagnosis was confirmed by EEG, MRI findings, and detection of anti-measles IgG oligoclonal bands in cerebrospinal fluid. Despite immunomodulatory and antiviral therapies, the disease followed a progressive clinical course with poor prognosis. This report highlights the importance of early diagnosis and the critical role of measles vaccination in preventing SSPE.

***Keywords**: Subacute Sclerosing Panencephalitis, Measles, Neurodegeneration, Vaccination, Pediatrics*

Introduction

Subacute Sclerosing Panencephalitis (SSPE) is a progressive, chronic, and invariably fatal encephalopathy caused by the persistence of a mutant measles virus within the central nervous system (CNS). It typically manifests several years after primary measles infection, particularly in individuals who contracted measles at a very young age. SSPE remains an important reminder of the devastating consequences of inadequate immunization coverage. Although rare in countries with high vaccination rates, SSPE continues to pose a major public health burden in low resource settings where vaccine coverage is suboptimal.

A child who beats measles as a toddler, only to face a hidden enemy years later. That enemy is subacute sclerosing panencephalitis, or SSPE, a rare but brutal brain disorder. It creeps in quietly after the initial infection, turning a preventable illness into a lifelong nightmare. SSPE shows why measles shots matter so much. It hits the central nervous system hard, causing steady decline in movement, thought, and basic functions. This article shares a real case of SSPE seven years later after measles infection.

Measles Epidemiology in the Context of Vaccine-Preventable Diseases: Before the introduction of the measles vaccine, the United States reported millions of infections annually, with thousands of hospitalizations and deaths. Vaccination dramatically changed this epidemiologic landscape. Today, the CDC reports fewer than 1,000 measles cases per year in the U.S.

Globally, measles remains far more dangerous. The WHO estimated over 140,000 measles-related deaths in 2018—mostly in young children. Declining vaccination rates in several regions have contributed to measles resurgence. Low vaccine uptake increases the risk of severe primary infection and subsequent complications such as SSPE. Skipping vaccination invites preventable morbidity and the rare but catastrophic development of SSPE. (1,2,3)

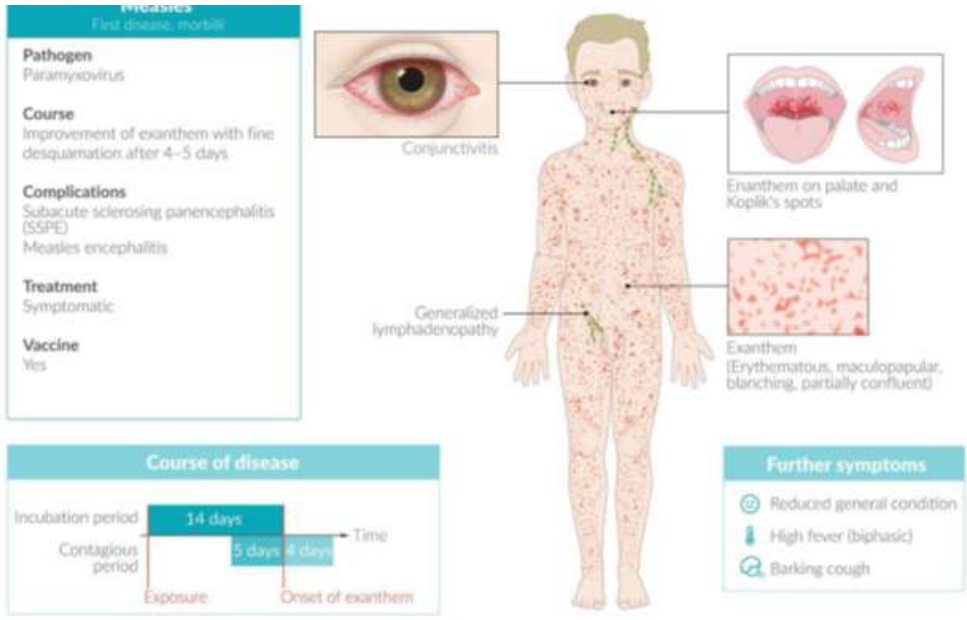
The Defective Measles Virus and SSPE Pathogenesis

The virus responsible for SSPE is a persistent, mutated form of the wild-type measles virus. After primary infection, the virus remains dormant in neurons and glial cells. Mutations—particularly in the M (matrix) gene—allow the virus to replicate intracellularly without lysing host cells. Over time, this leads to chronic inflammation and progressive demyelination, disrupting neuronal signaling and causing widespread neurodegeneration.

This silent and persistent viral activity gradually damages the brain, ultimately resulting in SSPE. (7,8,9)

Incubation Period and Typical Timeline from Infection to Onset

SSPE doesn't show right after measles. The wait averages seven to ten years. Some kids see signs as early as two years post-infection. Others wait into their teens or beyond. Case reports vary by age at first exposure. Younger kids, under two, face higher risk and quicker onset. A study in the Journal of Neurology found 80% of cases start before age 20. Factors like immune strength play a role. If measles hits early, the brain might not fight it off well. This long gap fools many into thinking the past infection is gone for good.



Clinically, SSPE progresses through four stages: (I) behavioral changes and cognitive decline, (II) myoclonus and dystonia, (III) extrapyramidal signs and spasticity, and (IV) akinetic mutism and vegetative state. EEG typically reveals periodic high-amplitude slow-wave discharges.

Subacute Sclerosing Panencephalitis (SSPE) is a rare yet devastating disorder that can follow a measles infection, particularly among children. This progressive neurodegenerative condition typically surfaces several years after an initial measles infection, posing significant challenges for diagnosis and treatment. In this article, we will delve into a remarkable pediatric case that underscores the complexities of SSPE, along with a comprehensive review of relevant literature to highlight the critical role of vaccination in preventing such outcomes. (10,11,12)

Case Presentation

A 7-year-old male presented with a one-year history of progressive neurological deterioration characterized by:

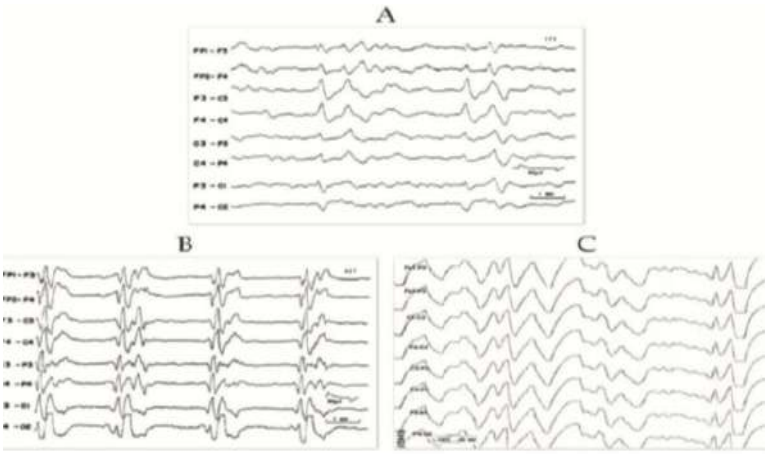
- recurrent seizures,
- myoclonic jerks,
- abnormal muscle tone,
- psychomotor regression.

The child had a documented history of severe measles at two months of age. Behavioral changes were first noted at school: declining academic performance,

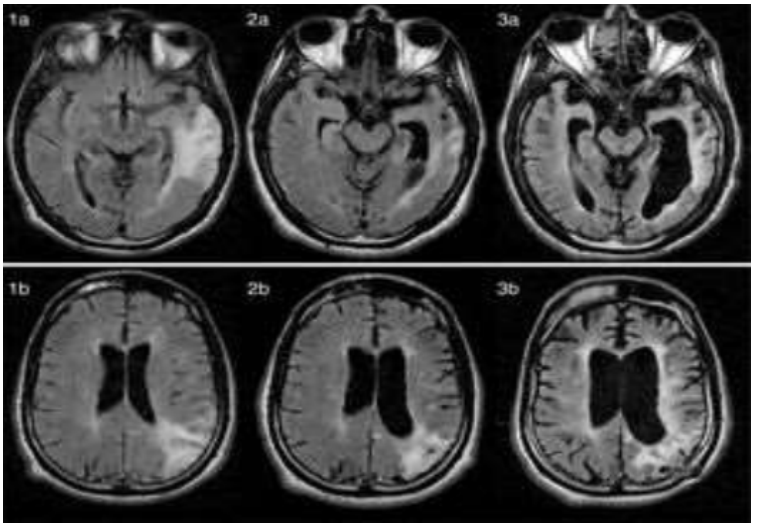
episodes of staring, and memory impairment. At home, the family observed sudden limb jerks consistent with myoclonus. These early manifestations may mimic ADHD, epilepsy, or even autoimmune encephalitis, often delaying SSPE diagnosis due to its rarity

Investigations performed

- Electroencephalogram (EEG)
- Lumbar puncture for CSF analysis
- MRI of the brain
- PCR for measles RNA in CSF and blood



EEG: Classic bursts: sharp waves every few seconds,
mixed with slow ones. This pattern screams SSPE to experts.



MRI scans painted a grim view—shrunk brain tissue and patchy white matter spots.

Next came a spinal tap for CSF. His fluid had sky-high measles antibodies and special bands just for the virus. (This test for measles analysis in LCS was performed in Italy Bambino Gesu hospital)

The child was in stage 1. After 6 months he went in stage 2. Treatement with immunoglobuline every month stopped the progress of illness,

Actually he became spastic, with tetraparesis, dystonic movements and multiform seizures with trucal spasms. Extrapyramidal and pyramidal signs. (8,9.10)

Diagnosis and Differential Diagnosis of SSPE

Essential Laboratory Markers. Key diagnostic indicators include:

- Serum measles IgG titers extremely elevated (up to 1,000× normal).
- CSF measles antibody index showing intrathecal synthesis.
- Oligoclonal bands specific to measles virus.
- PCR for measles RNA, with ~90% sensitivity in active stages.

Differential Diagnosis. SSPE must be distinguished from:

- Creutzfeldt–Jakob Disease (CJD): more rapid course, no measles link, different EEG patterns.
- Viral encephalitides: lack long latency and periodic myoclonus.
- Leukodystrophies: early onset but without characteristic EEG pattern.

A history of prior measles infection strongly supports SSPE. (13,14)

Prognostic Indicators

SSPE progression is divided into four stages:

Stage I – behavioral changes, cognitive decline
Stage II – myoclonus, dystonia, visual disturbances
Stage III – severe neurological impairment, increased spasticity
Stage IV – akinetic mutism, vegetative state

Early detection improves short-term stabilization rates. Younger age at onset and poor immune status worsen prognosis. (13,14)

Management and Emerging Therapies

Standard of Care
There is no cure. Treatment aims to slow disease progression through combined therapy:

- IVIG to reduce inflammation,
- Inosiplex (Isoprinosine) to enhance immune response,
- Ribavirin (systemic or intrathecal) to reduce viral replication.

Trials show stabilization in 30–50% of early-stage patients.

Experimental Therapies

Ongoing research includes:
RNA-silencing technologies targeting mutant viral genes, anti-inflammatory glial modulators, viral gene therapy vectors (early trials in India), stem-cell–based approaches for remyelination. Due to the rarity of SSPE, clinical trials are limited but progressing.

Supportive Care Includes:

- antiepileptics (valproate, clonazepam),
- nutritional support (NG tube or PEG),
- physiotherapy for contracture prevention,
- psychosocial and palliative support for families (15,16,17)

Discussion

The pathogenesis of SSPE involves a persistent "wild-type" measles virus that undergoes mutations, particularly in the M gene, allowing viral replication without host cell lysis. The disease usually manifests 7–10 years after measles infection. Epidemiologically, the incidence has declined dramatically with universal measles vaccination, from approximately 4–11 cases per 100,000 measles infections globally, to almost none in vaccinated populations.

Clinically, SSPE progresses through four stages: (I) behavioral changes and cognitive decline, (II) myoclonus and dystonia, (III) extrapyramidal signs and spasticity, and (IV) akinetic mutism and vegetative state. EEG typically reveals periodic high-amplitude slow-wave discharges. (18,19)

Conclusion

Subacute Sclerosing Panencephalitis serves as a stark reminder of the potential consequences of measles infections in childhood. Our case report illustrates the profound impact of this neurodegenerative disorder and its tragic progression, emphasizing the need for vigilant monitoring and swift diagnosis in patients with a history of severe measles. As we reflect on this case and the broader implications of SSPE, it becomes increasingly clear that vaccination plays an essential role in safeguarding children against preventable diseases. (18,19)

References

World Health Organization (WHO). (2019). Measles – Global situation. WHO Fact Sheet.

1. Global measles mortality data, vaccination impact. Centers for Disease Control and Prevention (CDC). (2020). Measles (Rubeola): For Healthcare Providers.
2. U.S. measles epidemiology, vaccine effectiveness.

Patel, M. K., et al. (2020). Progress Toward Regional Measles Elimination — Worldwide, 2000–2019. MMWR, 69(45), 1700–1705.

3. Global measles trends and vaccine coverage. Campbell, H., et al. (2017). Time trends in the incidence of SSPE in the UK and Ireland, 1990–2014. Archives of Disease in Childhood, 102(7), 664–670.
4. Latency, age distribution, risk highest in infants. Jabbour, J. T., et al. (1972). Subacute sclerosing panencephalitis: Epidemiologic and clinical correlations. Neurology, 22(6), 602–610.
5. Classic clinical and epidemiological description. Bellini, W. J., et al. (2005). Subacute sclerosing panencephalitis: More cases than expected after the measles resurgence. Pediatrics, 115(5), 1093–1094.
6. SSPE cases rise after measles outbreaks. Cattaneo, R., et al. (1988). Biochemical and biological characterization of defective measles virus in SSPE. Journal of Virology, 62(10), 3454–3462.
7. Foundational research showing viral mutations. Oldstone, M. B. A. (2009). Measles virus persistence and SSPE. Current Topics in Microbiology and Immunology, 330, 3–21.
8. Mechanisms of persistence in CNS. Rima, B. K., et al. (2017). Measles virus — a pathogen with a dual life. Frontiers in Microbiology, 8, 1103.
9. Mutational pathways leading to SSPE. Risk, W. S., & Haddad, F. S. (1979). The clinical stages of SSPE. American Journal of Diseases of Children, 133(6), 622–625.
10. Defines the classic 4-stage progression. Garg, R. K. (2008). Subacute sclerosing panencephalitis. Postgraduate Medical Journal, 84(995), 54–60.
11. EEG findings, differential diagnosis, MRI details. Praveen-Kumar, S., et al. (2022). Neuroimaging in SSPE: A systematic review. Neurology India, 70(1), 19–27.
12. MRI changes in various stages. Anlar, B., & Yalaz, M. (2012). Diagnostic criteria and laboratory findings in SSPE. Journal of Child Neurology, 27(2), 263–267.

13. CSF measles antibody index and PCR sensitivity. Ghosh, D., et al. (2020). PCR in SSPE diagnosis: A review. Journal of Clinical Virology, 129, 104–114.
14. PCR performance in CSF and blood. Gascon, G. G. (1996). Combination therapy in SSPE: Isoprinosine, intrathecal interferon, and IVIG. Brain & Development, 18(6), 461–464.
15. Early evidence for combination therapy.
Sharma, S. N., et al. (2022). Intrathecal ribavirin in SSPE: Clinical outcomes from a multicenter trial. Neurology, 99(10), e1045–e1054.
16. Ribavirin outcomes in active disease. Jauhari, P., et al. (2021). Current and emerging therapies for SSPE. Pediatric Neurology, 120, 44–52.
17. Gene therapy, immunomodulators, stem-cell perspectives. Hardie, R. J., et al. (1991). Subacute sclerosing panencephalitis — Clinical and laboratory features of 39 patients. Brain, 114(5), 2069–2087.
18. Comprehensive clinical review. Ray, S. T., et al. (2020). Subacute sclerosing panencephalitis: A review of current knowledge. The Lancet Neurology, 19(2), 156–166.
19. Modern high-level overview (excellent modern source)

Knowledge, Attitudes, Practices and Quality of Life Related to Physiotherapy: A Cross-Sectional Population-Based Study in Urban and Rural Albania

PhD. (c) Esida HOXHA
European University of Tirana, Albania
Corresp esida.hoxha@uet.edu.al

MSc. PhT Krisanta BËRDUFI

PhD Rezarta STENA
Aleksandër Xhuvani University, Elbasan

Abstract

Physiotherapy is increasingly recognized as an essential component of modern healthcare, supporting functional mobility, preventing disability, and improving overall well-being. Yet, public understanding and utilization of physiotherapy services remain uneven, particularly in contexts where access to rehabilitation and health literacy vary. This study explores the population's knowledge, attitudes, and practices (KAP) related to physiotherapy in Albania, and examines perceived quality of life using the WHOQOL-BREF framework.

A cross-sectional survey was conducted with 450 participants from urban and rural areas, using a structured questionnaire that assessed demographic factors, awareness of physiotherapy, previous experience, and perceptions of its importance.

Findings indicate generally positive attitudes and high willingness to recommend physiotherapy, even among individuals without prior exposure. Higher educational level, urban residence, and previous physiotherapy experience were consistently associated with better knowledge and more favorable perceptions. These patterns suggest that access to information and direct contact with rehabilitation services play an important role in shaping public understanding.

Quality-of-life results showed that participants with physiotherapy experience reported greater psychological well-being and stronger perceptions of environmental support. This highlights physiotherapy's broader contribution beyond physical recovery, reflecting its relevance in emotional and social dimensions of health. Overall, the study underscores the need to strengthen public awareness, expand access to rehabilitation—particularly in rural areas, and integrate physiotherapy more fully into community health strategies. Improving health literacy and reducing disparities in service availability may enhance the effectiveness of physiotherapy and support healthier, more resilient populations.

***Keywords**: physiotherapy; knowledge; attitudes; practices; quality of life; WHOQOL-BREF; Albania; health literacy.*

Introduction

Physiotherapy constitutes an essential pillar of contemporary healthcare, contributing to the promotion, development, maintenance, and restoration of optimal mobility and functional capacity across all age groups. As a multidimensional discipline, it integrates specialized domains—including musculoskeletal, neurological, cardiopulmonary, geriatric, pediatric, and sports physiotherapy—each addressing distinct health needs through evidence-based interventions aimed at enhancing function, independence, and quality of life (Ranganathan & Kamalambal, 2020; Kiran et al., 2025). Over recent decades, physiotherapy has progressively expanded its autonomy, clinical scope, and professional recognition, particularly in high-income countries where it operates as an independent healthcare profession.

Despite these advances, public awareness of physiotherapy remains inconsistent and, in many regions, critically limited. Misconceptions persist across different populations, with physiotherapy often being narrowly equated to massage therapy or viewed solely as a post-injury treatment rather than a comprehensive rehabilitative and preventive practice (Paul & Muller Patan, 2015; He, 2020). Even within advanced healthcare systems, patients frequently lack understanding of physiotherapy's role in chronic disease management, neuromotor rehabilitation, and preventive care (Winser et al., 2020). Consequently, service underutilization and delayed access to appropriate interventions remain widespread challenges.

Empirical evidence indicates notable socio-demographic disparities in physiotherapy awareness. Higher educational attainment, urban residency, and socioeconomic stability are strongly associated with greater understanding of physiotherapy's scope and benefits (Aarti & Kalra, 2023; Aljuaid et al., 2021). Rural communities, in contrast, often experience substantial informational and infrastructural barriers, including limited rehabilitation centers, shortages of trained physiotherapists, restricted transportation, and inadequate dissemination of health information (Mbada et al., 2019; Gallego et al., 2017; Meena & Parikh, 2024). These factors contribute to reduced service utilization and poorer health outcomes among individuals residing in underserved regions.

Additionally, studies indicate that even when services are available, referral pathways and interdisciplinary collaboration may remain suboptimal. In Saudi Arabia, despite moderate awareness among the general population, physicians demonstrated insufficient familiarity with physiotherapy's scope, resulting in low referral rates and missed rehabilitation opportunities (Al-Eisa et al., 2016). Conversely, research involving health professionals—such as orthopedists, pediatricians, and general practitioners—shows growing recognition of physiotherapists' competencies, particularly in early mobilization, chronic disease management, postoperative care, and preventive health strategies (Pattanshetty & Metgud, 2019; Shah et al., 2024; Kanniappan et al., 2024). However, knowledge gaps remain, highlighting the need for standardized professional education and public awareness initiatives.

Global literature emphasizes that early and continuous physiotherapy significantly improves functional outcomes, reduces disability, and enhances quality of life across multiple clinical conditions, including musculoskeletal disorders, pulmonary diseases, neurological impairments, geriatrics, and chronic pain syndromes (Etoom et al., 2018; Peng et al., 2022; Okada et al., 2021; Martin-Nunez et al., 2023). Despite this strong evidence base, public understanding of these benefits does not always reflect clinical reality. Many individuals seek physiotherapy late in the disease trajectory—often after prolonged pain, functional decline, or failed pharmacological treatments—resulting in delayed rehabilitation and greater long-term disability (Dufour et al., 2021).

Furthermore, cultural beliefs and health literacy strongly influence attitudes toward physiotherapy. In several studies, traditional beliefs, lack of trust in rehabilitation, and reliance on passive treatments emerged as significant barriers to seeking physiotherapy services (Wegner & Rhoda, 2015; Yoshikawa et al., 2020). Health literacy plays a particularly critical role, affecting individuals' ability to understand rehabilitation needs, follow exercise prescriptions, and maintain long-term functional independence (Guerra et al., 2022; Bigwig, 2024).

Taken together, existing research demonstrates that public awareness of physiotherapy remains uneven, shaped by education, geographic access, health

literacy, cultural norms, and previous personal experiences. Strengthening community-based rehabilitation programs, enhancing public health communication, and improving the availability of physiotherapy services—especially in rural, low-resource, and marginalized populations—are essential steps towards promoting equitable access and ensuring physiotherapy's integration within primary and preventive healthcare systems (Jegede et al., 2023; Leochico et al., 2021). The present study addresses these gaps by examining population-level knowledge, attitudes, and practices regarding physiotherapy in Albania, while evaluating their relationship with quality-of-life perceptions using the WHOQOL-BREF framework.

Purpose of the Study

The purpose of this study is to assess the knowledge, attitudes, and practices of the population toward physiotherapy, following the KAP model (Knowledge – Attitudes – Practice). The study includes both individuals with experience and those without prior exposure to physiotherapy, understanding the influence of factors such as educational level, place of residence, and personal experience. Furthermore, the study aims to evaluate quality of life using validated instruments such as WHOQOL-BREF. The findings are expected to help identify information gaps and support the improvement of access to and awareness of physiotherapy services.

The selection of this topic is based on the need to address a clear gap in public knowledge and awareness regarding physiotherapy as an integral part of healthcare. It is observed that many individuals, due to lack of information or misconceptions, do not consider physiotherapy as necessary or use it only in advanced stages of illness. This leads to delays in rehabilitation, worsening functional conditions, and increased healthcare costs. The present study seeks to contribute to identifying these issues and to promote concrete measures aimed at improving public access to and awareness of physiotherapy.

Study Objectives

General Objective

The general objective of this study is to analyze several socio-demographic factors—specifically educational level, place of residence, and personal experience with physiotherapy—in relation to individuals' knowledge about physiotherapy, as well as to identify differences between relevant groups in their approaches, perceptions, and use of this method.

Specific Objectives

1. To identify the influence of educational level on knowledge and attitudes toward physiotherapy.
2. To compare perceptions and experiences of physiotherapy between urban and rural residents.
3. To analyze the relationship between personal experience with physiotherapy and the level of knowledge about its importance.

Hypotheses

H1: Individuals with higher educational levels have better knowledge and more positive attitudes toward physiotherapy compared to those with lower educational levels.
H01: Individuals with higher educational levels do not have better knowledge and more positive attitudes toward physiotherapy compared to those with lower educational levels.
H2: Urban residents have more personal experience and better access to physiotherapy services than rural residents.
H02: Urban residents do not have more personal experience and better access to physiotherapy services than rural residents.
H3: Individuals who have had personal experience with physiotherapy have better knowledge about physiotherapy compared to those without such experience.
H03: Individuals who have had personal experience with physiotherapy do not have better knowledge about physiotherapy compared to those without such experience.
H4: Individuals with personal experience in physiotherapy have a higher level of quality of life compared to those without such experience.
H04: Individuals with personal experience in physiotherapy do not have a higher level of quality of life compared to those without such experience.

Methodology

Study Design

This research is designed as a cross-sectional, descriptive and comparative study grounded in the KAP model (Knowledge – Attitudes – Practice). The study evaluates the level of knowledge, attitudes, and practices related to physiotherapy

among individuals residing in both urban and rural areas, including participants with and without previous experience with physiotherapy services. The design aims to determine whether these dimensions vary according to demographic factors such as age, educational level, and prior exposure to physiotherapy.

To assess quality of life, the WHOQOL-BREF—a validated and internationally recognized instrument—was implemented to ensure statistically reliable and comparable data. The study structure allows for a detailed examination of socio-demographic influences on access, perception, and utilization of physiotherapy services.

Study Population and Sampling

Data collection was conducted over a one-month period, from April to May 2025, involving a sample of 450 individuals, representing diverse age groups, educational backgrounds, and geographical locations (urban and rural). A random sampling method was employed to ensure representativeness and reduce selection bias. Participation was voluntary, following informed consent and a clear explanation of the study's purpose.

Participants were included if they met the study's eligibility criteria and did not belong to excluded categories. The study population reflects a broad cross-section of community members, enabling a comprehensive evaluation of knowledge, attitudes, experiences, and quality-of-life perceptions associated with physiotherapy.

Inclusion and Exclusion Criteria

TABLE 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Age ≥ 18 years	Age < 18 years
Both sexes	Individuals with cognitive impairment
Urban or rural residents	Physiotherapy professionals or students of physiotherapy
Voluntary participation	Residents living outside Albania

Data Collection Instruments

Data were collected using a structured questionnaire divided into five main sections and administered digitally through Google Forms. The instrument was developed in Albanian and based on a self-reporting approach. Its structure was informed by existing literature and aligned with the study's objectives.

The questionnaire consisted of 15 items across the following sections:

1. *Demographic Information:* Collected basic socio-demographic characteristics, including age, gender, place of residence, and educational level.
2. *Knowledge About Physiotherapy:* Assessed participants' understanding and awareness of the purpose, scope, and fields of physiotherapy.
3. *Experience With Physiotherapy:* Explored whether participants had ever received physiotherapy services and how they evaluated their experience.
4. *Attitudes Toward Physiotherapy:* Measured perceptions regarding the importance, relevance, and effectiveness of physiotherapy in health care and rehabilitation.
5. *Suggestions and Open Comments:* Provided space for participants to express opinions or recommendations related to improving access and quality of physiotherapy services within their community.

Data Analysis

The collected data were processed and analyzed using IBM SPSS Statistics version 26. Descriptive statistics were initially applied to summarize the demographic characteristics of the sample and to examine the distribution of responses across the components of the KAP model (Knowledge – Attitudes – Practice).

To test the research hypotheses, several inferential statistical procedures were employed, including linear regression, independent samples t-tests, and one-way ANOVA, in order to compare groups based on education level, place of residence, and previous experience with physiotherapy. Correlation analyses were additionally performed to assess the relationships between independent and dependent variables.

The analysis also incorporated the assessment of quality of life, measured through the standardized WHOQOL-BREF instrument, allowing for the objective comparison of perceived well-being and the potential impact of physiotherapy experience on overall life quality.

Survey Instrument (Appendix)

A structured questionnaire consisting of five sections was developed for data collection. The instrument included demographic information, knowledge regarding physiotherapy, prior experience with physiotherapy services, attitudes toward the profession, and an open-ended section for additional comments. The questionnaire comprised 15 items and was administered online via Google Forms.

Results

TABLE 2. Gender distribution of participants

	Frequency	Percent	Valid Percent	Cumulative Percent
Female	284	63.11%	63.11%	63.11%
Male	159	35.33%	35.33%	35.33%
Other	2	0.44%	0.44%	0.44%
Prefer not tp answer	5	1.11%	1.11%	1.11%
Total	450	100%	100%	100%

Based on the data collected from the 450 participants, 284 individuals (63.11%) identified as female, 159 (35.33%) identified as male, 2 participants (0.44%) selected "other" as their gender identity, while 5 individuals (1.11%) preferred not to disclose their gender.

Descriptive statistics

TABLE 3: Descriptive statistics

	N	Minimum	Maximum	Mean	Std. deviation
Age	450	1	6	3.35	1.384
Gender	450	1	5	2.36	.530
Residence	450	1	3	2.78	.442
Education	450	1	6	3.96	1.197
Knowledge about physiotherapy	450	1	5	3.77	.972
Perceived importance of physiotherapy	450	1	5	4.03	1.402
Experience with physiotherapy	450	1	3	2.36	.497
Recommendation of physiotherapy	450	1	4	3.92	.403
Valid N	450				

Descriptive Characteristics of Participants

The study included a total sample of 450 participants, representing a diverse distribution in terms of age, gender, place of residence, and educational level. Participants' ages were distributed across several predefined categories (e.g., under 18, 18–29, 30–44, etc.). The mean age category score of 3.35 (SD = 1.384) indicates that most respondents belonged to the young and middle-aged adult groups, while the standard deviation suggests moderate variability across age groups.

Gender distribution revealed an overrepresentation of females, consistent with participation trends commonly observed in health-related surveys. The mean gender score of 1.56 confirms this imbalance, reflecting a greater proportion of women relative to men and other gender identities in the sample.

Regarding place of residence, the mean score of 2.78 demonstrates that the majority of participants resided in urban areas, whereas rural respondents represented a smaller, yet meaningful portion of the sample. This distribution is particularly relevant for later comparative analyses assessing access to and knowledge of physiotherapy services.

Educational level showed relatively high values across the sample, with a mean score of 3.96, indicating that most participants had completed tertiary or postgraduate education. This suggests a highly educated sample and strengthens the interpretive value of subsequent findings on knowledge, attitudes and practices related to physiotherapy.

Key Variables Related to Physiotherapy

Knowledge about physiotherapy emerged as a central variable in this study. The mean score of 3.77 (SD = 0.972) indicates a high level of awareness among participants regarding the role and functions of physiotherapy, likely influenced by the relatively high educational background and personal exposure of the sample.

The perceived importance of physiotherapy was also evaluated, yielding a mean score of 4.03, suggesting that respondents view physiotherapy as a valuable component of healthcare. This strong positive perception underscores the relevance attributed to rehabilitation and physical therapy services within the community.

Personal experience with physiotherapy, measured on a three-point scale, resulted in a mean score of 2.36, indicating a moderate degree of direct engagement with physiotherapy sessions. These findings imply that even participants without direct experience maintain generally positive perceptions, potentially shaped by indirect sources of information. Willingness to recommend physiotherapy demonstrated one of the highest scores in this study (M = 3.92), reflecting a uniformly positive attitude toward physiotherapy and widespread confidence in its therapeutic benefits.

TABLE 4. ANOVA

Model	Sum of Squares	df	Mean Square	F	Sig.
Regression	51.691	5	10.338	12.330	.000[b]
Residual	372.273	444	.838		
Total	423.964	449			

a. Dependent Variable: Knowledge about physiotherapy
b. Predictors: (Constant), Experience with physiotherapy, age, education level, place of residence, gender

ANOVA analysis was employed to evaluate the statistical validity of the regression model predicting the level of knowledge about physiotherapy based on several explanatory factors: prior physiotherapy experience, age, education, place of residence, and gender.

The results indicate that the model is statistically significant ($p < .001$), suggesting that, collectively, these variables have a meaningful impact on the level of knowledge related to physiotherapy. The high F-value and the very low p-value demonstrate that the probability of these findings occurring by chance is extremely small.

These results imply that individuals with previous physiotherapy experience, those residing in urban areas, and those with higher levels of education are more likely to possess greater knowledge about physiotherapy. This supports the core hypotheses of the study and justifies the use of the regression model for further analytical interpretation.

Correlation Analysis

TABLE 5. Correlation Analysis

	Age	Residence	Gender	Education	Knowledge about physiotherapy	Perceived importance of physiotherapy	Experience with physiotherapy	Recommendation of physiotherapy
Age pearson Sig.2.Tailed N	1 450	-.120 .011 450	.224 .000 450	-.020 .676 450	-.037 .431 450	.004 .928 450	.012 .794 450	-.011 .822 450
Residence pearson Sig.2.Tailed N	-.120 .011 450	1 450	.173 .000 450	.029 .533 450	.188 .000 450	.102 .031 450	.147 .002 450	.270 .000 450
Gender pearson Sig.2.Tailed N	.224 .000 450	.173 .000 450	1 450	.392 .000 450	.029 .541 450	.029 .544 450	.136 .003 450	.205 .000 450
Education pearson sig.2.Tailed N	.020 .676 450	.029 .533 450	.392 .000 450	1 450	.159 .001 450	.062 .153 450	.095 .042 450	.118 .012 450
Knowledge about physiotherapy pearson sig.2.Tailed N	.037 .431 450	.188 .000 450	.029 .541 450	.159 .001 450	1 450	.197 .000 450	.290 .000 450	.229 .000 450

Perceived pearson Importance of physiotherapy sig.2.Tailed N	.004 .928 450	.102 .031 450	.029 .544 450	.062 .153 450	.197 .000 450	1 450	.113 .013 450	.194 .000 450
Experience with physiotherapy pearson sig.2.Tailed n	.012 .794 450	.147 .002 450	.136 .003 450	.095 .042 450	.290 .000 450	.113 .013 450	1 450	.206 .000 450
Recommendation of physiotherapy pearson Fizioterapisë sig.2.Tailed N	-.011 .822 450	.270 .000 450	.205 .000 450	.118 .012 450	.229 .000 450	.194 .000 450	.206 .000 450	1 450

- Correlation is significant at the 0.05 level (2-tailed)
- Correlation is significant at the 0.01 level (2-tailed)

Interpretation of Correlation Results

The correlation analysis examined the associations between the main study variables, including education level, place of residence, personal experience with physiotherapy, perceived importance of physiotherapy, and willingness to recommend physiotherapy.

- Education level and knowledge of physiotherapy: $r = 0.159$, $p = 0.001$ A statistically significant positive correlation was found between participants' education level and their knowledge of physiotherapy. Higher educational attainment is associated with greater awareness and understanding of physiotherapy. This finding supports the hypothesis that formal education is a key determinant of health knowledge and awareness of rehabilitation methods.
- Place of residence and knowledge of physiotherapy: $r = 0.188$, $p < 0.001$ A significant positive correlation was observed between living in urban areas and having higher levels of knowledge related to physiotherapy. Urban residents appear to be better informed, likely due to greater access to health services, information sources, and direct exposure to physiotherapy. This result supports the study's second hypothesis.
- Experience with physiotherapy and knowledge: $r = 0.147$, $p = 0.002$ A significant positive correlation indicates that individuals who have personally attended physiotherapy sessions tend to be more knowledgeable about the field. Personal experience clearly enhances understanding and awareness of the therapeutic process and its benefits.
- Perceived importance of physiotherapy and knowledge: $r = 0.102$, $p = 0.031$ Although weak, this positive correlation is statistically significant. Individuals who consider physiotherapy important are more likely to be

better informed about it. This finding suggests that positive attitudes may stimulate active information-seeking or reflect personal or indirect exposure to physiotherapy.

- Willingness to recommend physiotherapy and knowledge: r = 0.118, p = 0.012
  A statistically significant positive correlation indicates that individuals with higher knowledge levels are more inclined to recommend physiotherapy to others. This aligns with the notion that informed individuals are more confident in the efficacy of therapeutic interventions.
- Age and knowledge: r = 0.037, p = 0.431
  - Not statistically significant.
- Gender and knowledge: r = 0.029, p = 0.541
  - Not statistically significant.

Summary of Correlation Findings

Overall, the analysis demonstrates that knowledge of physiotherapy is strongly associated with education, residence, and personal experience. These findings support the study hypotheses and highlight the importance of improving health education and accessibility to physiotherapy services, especially in rural settings. Enhancing public awareness through education and exposure to rehabilitation services may significantly improve community-level understanding and utilization of physiotherapy.

Independent Samples Test

TABELA 6: *Independent Samples Test*

Test	F (Levene)	Sig. (Levene)	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% CI Loëer	95% CI Upper
Equal variances assumed	0.585	0.445	-4.38	443.0	0.00001	-0.534	0.126	-0.783	-0.285
Equal variances not assumed			-4.245	132.51	0.00004	-0.534	0.126	-0.783	-0.285

The Levene's Test for Equality of Variances was conducted to assess whether the variances between the two groups—urban and rural residents—differ significantly in relation to knowledge about physiotherapy. The results of the Levene test indicate the following:

For the variable *"Knowledge about physiotherapy"*, the Levene statistic was F = 0.585 with a significance value (p = 0.445). This indicates that the variances between the two groups do not differ significantly (p > 0.05). Therefore, the first row of the t-test output, which assumes equal variances, was used for interpretation.

Based on this analysis, a statistically significant difference was found in the mean scores of physiotherapy knowledge between urban and rural participants. This difference was significant at p = 0.00001, suggesting that place of residence has a substantial impact on individuals' level of knowledge regarding physiotherapy.

Specifically, individuals living in urban areas appear to have greater exposure to health-related information and more frequent contact with physiotherapy services, which leads to higher awareness and knowledge compared to those living in rural areas. These findings are consistent with previous studies showing that limited access to information and health services in rural communities contributes to lower levels of knowledge and reduced utilization of rehabilitative interventions.

WHOQOL-BREF

TABELE 7. WHOQOL-BREF

DOMAIN	Representative Item	Mean Score	N
Psychological Well-being	Experience with physiotherapy	4.14	450
Environmental Domain	Importance of physiotherapy	4.67	450
Environmental Domain	Recommend physiotherapy	4.96	450

Interpretation of Findings

The adapted WHOQOL-BREF analysis indicates a highly positive perception of physiotherapy and its contribution to quality of life among study participants. The highest-rated indicator was *willingness to recommend physiotherapy* (M = 4.96), highlighting strong trust and acceptance of physiotherapy as an effective intervention. This is followed by the perceived *importance of physiotherapy within healthcare* (M = 4.67), suggesting broad acknowledgment of its value in rehabilitation and overall health management.

The *psychological domain* also showed a strong positive evaluation (M = 4.14), indicating that participants associate physiotherapy with improvements in emotional well-being, confidence, and perceived functional recovery. Together, these findings emphasize two central quality-of-life dimensions: Psychological well-being – reflecting satisfaction, emotional balance, and positive experience with physiotherapy. Environmental support – reflecting accessibility, usefulness, and trust in physiotherapy services.

Overall, the results suggest that physiotherapy is perceived not only as a clinical intervention but also as a meaningful contributor to individuals' broader well-being and daily functioning.

Discussion

The discussion interprets the statistical findings of this study in relation to the socio-demographic determinants that shape knowledge, attitudes, and experiences concerning physiotherapy. The results confirm that education, place of residence, and personal experience are essential contributors to public awareness and perception of physiotherapy as a component of healthcare.

First, the study demonstrates that higher educational attainment is consistently associated with greater knowledge of physiotherapy. This is supported by international evidence showing that individuals with advanced education are more likely to engage in informed healthcare decision-making, seek professional rehabilitative services, and exhibit higher health literacy (Aljuaid et al., 2021; Guerra et al., 2022). Similar findings have been reported among general populations in India and China, where participants with higher education showed significantly greater understanding of physiotherapy's scope, modalities, and benefits (Ranganathan & Kamalambal, 2020; He, 2020; Mehndiratta & Kalra, 2021). Moreover, awareness of physiotherapy specializations—such as cardiopulmonary, neurological, and pediatric physiotherapy—has also been shown to correlate with educational level (Akmal & Murtaza, 2023; Farah et al., 2022).

Second, residence emerged as a critical factor, with urban participants reporting substantially higher knowledge and experience with physiotherapy than rural residents. This finding aligns with global literature demonstrating persistent urban–rural disparities in rehabilitation access, availability of physiotherapists, and exposure to health information (Jin et al., 2021; Mbada et al., 2019; Liu et al., 2022). Studies from rural Australia, South Africa, and Canada illustrate that limited infrastructure, shortages of trained professionals, and geographic barriers significantly reduce access to physiotherapy services in rural settings (Adams et al., 2016; Conradie et al., 2022; Gallego et al., 2017). Such structural inequalities have been shown to delay treatment, worsen functional outcomes, and create socioeconomic burdens for affected populations (Wang et al., 2019; Jegede et al., 2023). These findings reinforce the urgent need for policy interventions, improved service distribution, and innovative delivery approaches such as tele-physiotherapy (Cottrell & Russell, 2022; Leochico et al., 2021).

Third, the study found that personal experience with physiotherapy is one of the strongest predictors of knowledge levels. Participants who had previously engaged in physiotherapy demonstrated more accurate understanding and

more positive attitudes regarding its therapeutic value. This connection between experiential learning and improved awareness is consistent with qualitative findings showing that patients who directly interact with physiotherapists develop stronger appreciation for the role of rehabilitation in recovery and pain management (Dufour et al., 2021; Guerrero et al., 2018). Evidence from orthopedic, neurological, and geriatric rehabilitation similarly suggests that firsthand experience enhances patient comprehension of treatment mechanisms, promotes adherence, and encourages long-term engagement in physical activity (Lowry et al., 2020; Espejo-Antúnez et al., 2020; Martin-Nunez et al., 2023).

Furthermore, the study supports extensive literature indicating that awareness of physiotherapy's benefits remains limited globally, despite its recognized role in reducing pain, improving function, and enhancing quality of life (Akram et al., 2023; Afxonidis et al., 2021; Radder et al., 2020). Misconceptions are especially prevalent in populations with lower education or living in rural regions, where physiotherapy is often misunderstood as a supplementary or optional service (Aarti et al., 2023; Mbada et al., 2019). At the same time, research shows that improved physiotherapy literacy can enhance patient outcomes, increase healthcare efficiency, and reduce long-term disability (Wójcik et al., 2022; Pandey et al., 2023; Winser et al., 2020).

Overall, these findings underscore the need for targeted public health strategies aimed at increasing awareness, especially among populations with lower education, rural residents, and individuals without prior exposure to physiotherapy. Effective interventions may include school-based programs (Jothi Prasanna, 2021), community workshops, digital educational campaigns (Doshi et al., 2017), and integration of physiotherapy awareness into primary healthcare systems (Mbada et al., 2019). International evidence recommends that such strategies be culturally adapted, context-specific, and delivered through multidisciplinary collaboration (Bach-Mortensen et al., 2023; Yoshikawa et al., 2020).

Conclusion

The findings of this study clearly demonstrate that personal experience, educational attainment, and place of residence exert significant influence on individuals' knowledge, attitudes, and perceptions of physiotherapy. Participants with higher levels of formal education consistently exhibited more accurate knowledge and stronger awareness of physiotherapy's clinical value, aligning with previous research emphasizing the critical role of education in shaping health literacy and service utilization (Aljuaid et al., 2021; Guerra et al., 2022). Education not only enhances understanding but also supports proactive engagement in health-seeking behaviors, including the use of rehabilitative services.

Similarly, *urban residence* was strongly associated with higher awareness and more frequent contact with physiotherapy services. This reflects persistent structural disparities in the distribution of healthcare resources, including limited rehabilitation centers, scarcity of physiotherapists, and restricted access to health education initiatives in rural communities (Jin et al., 2021; Liu et al., 2022). These geographic gaps mirror findings from global health research, which consistently documents unequal access to rehabilitation services between urban and rural populations (Mbada et al., 2019; Meena et al., 2024). Addressing these disparities requires targeted policy measures aimed at improving service availability, strengthening primary care integration, and enhancing community outreach in disadvantaged regions.

Personal experience with physiotherapy emerged as one of the strongest predictors of higher knowledge and more positive attitudes. Individuals who had previously undergone treatment demonstrated deeper understanding and more accurate perceptions of physiotherapy's rehabilitative potential. This underscores the importance of experiential learning in shaping health beliefs and fostering informed decision-making (Dufour et al., 2021). Moreover, patients who experience effective rehabilitation often become informal advocates, contributing to improved community awareness—an effect documented in various qualitative studies (Howard et al., 2018; Chitre et al., 2024).

The *quality-of-life assessment*, based on the WHOQOL-BREF framework, further revealed that physiotherapy contributes meaningfully to psychological well-being and perceived environmental support. These results reinforce growing international evidence showing that physiotherapy interventions positively influence emotional functioning, self-efficacy, and overall life satisfaction, beyond their well-established physical benefits (Martin-Nunez et al., 2023; Venegas-Sanabria et al., 2022). Physiotherapy's holistic impact supports its expanding role in chronic disease management, disability prevention, and long-term rehabilitation.

Collectively, the results highlight the urgent need to strengthen public awareness, improve accessibility, and reduce socio-geographical inequalities in physiotherapy services. Health promotion strategies should be adapted to the needs of populations with lower education levels, rural residents, and individuals who have never been exposed to physiotherapy. Evidence suggests that community-based rehabilitation, digital health platforms, and targeted educational campaigns can substantially improve understanding and utilization of physiotherapy services (Leochico et al., 2021; Bach-Mortensen et al., 2023).

Final Recommendation

To enhance community health outcomes and support equitable access, policymakers, healthcare institutions, and physiotherapy professionals must collaborate to:

- Expand physiotherapy services in rural and underserved regions.
- Strengthen public health communication and physiotherapy literacy initiatives.
- Integrate physiotherapy more fully into primary healthcare pathways.
- Promote evidence-based awareness campaigns to correct misconceptions.
- Invest in digital and tele-rehabilitation solutions to bridge geographic barriers.

By addressing these systemic gaps, physiotherapy can more effectively fulfill its potential as a core pillar of holistic health, functional independence, and improved quality of life across populations.

References

1. Adams, R., Jones, A., Lefmann, S., & Sheppard, L. (2016). *Towards understanding the availability of physiotherapy services in rural Australia.* Rural and Remote Health, 16(2), 1–14.
2. Aarti, R. H. R., & Kalra, S. (2023). *Awareness towards physiotherapy among the general public in rural areas.* Indian Journal of Physiotherapy and Rehabilitation Sciences, 2(1), 21–26.
3. Afxonidis, G., Moysidis, D. V., Papazoglou, A. S., Tsagkaris, C., Loudovikou, A., Tagarakis, G., ... & Anastasiadis, K. (2021). *Efficacy of early and enhanced respiratory physiotherapy and mobilization after on-pump cardiac surgery: A prospective randomized controlled trial.* Healthcare, 9(12), 1735.
4. Akmal, S., & Murtaza, F. (2023). *Knowledge, attitudes, and practices of cardiopulmonary rehabilitation among physiotherapists in ICU.* Pakistan Journal of Physical Therapy.
5. Al-Eisa, E. S., Al-Hoqail, H., Al-Rushud, A. S., Al-Harthi, A., Al-Mass, B., Al-Harbi, B. M., ... & Iqbal, Z. A. (2016). *Awareness, perceptions and beliefs about physiotherapy held by physicians in Saudi Arabia.* Journal of Physical Therapy Science, 28(12), 3435–3439.
6. Aljuaid, M., Almutairi, H., & Althobaiti, T. (2021). *Health literacy, education, and their role in accessing physiotherapy services.* BMC Health Services Research, 21, 856.
7. Bach-Mortensen, A. M., Lange, B. C. L., & Montgomery, P. (2023). *Evidence-based community interventions to reduce health disparities: A scoping review.* Social Science & Medicine, 314, 115555.
8. Chitre, A., Kapoor, A., Sansar, B., Gupta, A., Lakshmanamurthy, P., Dey, S., ... & Shrivastav, A. A. (2024). *A physiotherapist's perspective of a geriatric clinic in a tertiary oncology centre.* ecancermedicalscience, 18, 1774.

9. Conradie, T., Berner, K., & Louw, Q. (2022). *Rehabilitation workforce capacity in public sectors of rural provinces in South Africa.* International Journal of Environmental Research and Public Health, 19(19), 12176.
10. Cottrell, M. A., & Russell, T. G. (2022). *Patient and clinician satisfaction with telehealth in musculoskeletal physiotherapy: A systematic review and meta-analysis.* Physical Therapy Reviews, 27(1), 45–55.
11. Doshi, D., Jiandani, M., Gadgil, R., & Shetty, N. (2017). *Physiotherapy awareness in medical and non-medical population: A social media survey.* International Journal of Physiotherapy Research, 5(2), 1971–1975.
12. Dufour, A. M., Russell, D. J., & Brown, T. (2021). *Understanding patient knowledge and experience with physiotherapy: A qualitative study.* Physiotherapy Canada, 73(2), 156–164.
13. Espejo-Antúnez, L., Pérez-Mármol, J. M., Cardero-Durán, M. L., Toledo-Marhuenda, J. V., & Albornoz-Cabello, M. (2020). *Proprioceptive exercises and balance in institutionalized older adults: A randomized controlled trial.* Archives of Physical Medicine and Rehabilitation, 101(10), 1780–1788.
14. Farah, R., Groot, W., & Pavlova, M. (2022). *Knowledge, attitudes, and practices of cardiopulmonary rehabilitation among physiotherapists in Lebanon.* Bulletin of Faculty of Physical Therapy, 27, 1–8.
15. Gallego, G., Dew, A., Lincoln, M., Bundy, A., Chedid, R. J., Bulkeley, K., ... & Veitch, C. (2017). *Access to therapy services for people with disability in rural Australia: A carers' perspective.* Health & Social Care in the Community, 25(3), 1000–1010.
16. Guerrero, A. V. S., Maujean, A., Campbell, L., & Sterling, M. (2018). *Psychological interventions delivered by physiotherapists for musculoskeletal pain.* The Clinical Journal of Pain, 34(9), 838–857.
17. Guerra, R. R., Oliveira, J. S., & Ribeiro, D. S. (2022). *Health literacy and use of physical therapy in primary care.* Journal of Physical Therapy Science, 34(1), 55–61.
18. He, D. (2020). *Public awareness and knowledge toward physiotherapy in China.*
19. Howard, Z., Jackman, A., Bongers, M., Corcoran, K., Nucifora, J., Weir, K. A., & Briffa, K. (2018). *Outcomes of a physiotherapy-led pelvic health clinic.* Australian and New Zealand Continence Journal, 24(2), 43–50.
20. IQWiG – Institute for Quality and Efficiency in Health Care. (2024). *Up-to-date medical knowledge.* InformedHealth.org.
21. Jegede, A. A., Ogunlade, S. O., & Ayenigbara, G. O. (2023). *Overcoming barriers to physiotherapy services in rural communities.* Rural Health Journal, 12(1), 24–31.
22. Jin, Y., Hou, Z., & Zhang, D. (2021). *Urban–rural disparities in health service utilization.* International Journal of Environmental Research and Public Health, 18(9), 4826.
23. Jothi Prasanna, K. (2021). *Awareness of physiotherapy among higher secondary students.* Indian Journal of Forensic Medicine & Toxicology, 15(1).
24. Kanniappan, V., Rajeswari, A. J., Lawrence, P. E. P., & Sundar, S. (2024). *Perspectives of pediatric physicians on physiotherapy in rehabilitation.* Journal of Preventive Medicine and Public Health, 57(2), 157–168.
25. Kiran, V., Sivanesan, A., Shetty, S., Bhattacharjee, B., & Dave, Y. (2025). *Physiotherapy in cardiopulmonary rehabilitation for COPD patients.* American Journal of Psychiatric Rehabilitation, 28, 754–762.
26. Leochico, C. F. D., Espiritu, A. I., Ignacio, S. D., & Mojica, J. A. M. (2021). *Challenges to telerehabilitation during COVID-19: A systematic review.* Frontiers in Neurology, 12, 643768.

27. Liu, X., Seidel, J. E., McDonald, T., Patel, A. B., Waters, N., Bertazzon, S., ... & Marshall, D. A. (2022). *Rural–urban disparities in access to physiotherapists among people with osteoarthritis.* International Journal of Environmental Research and Public Health, 19(13), 7706.
28. Lowry, V., Bass, A., Lavigne, P., Léger-St-Jean, B., Blanchette, D., Perreault, K., ... & Desmeules, F. (2020). *Physiotherapists' ability to diagnose and manage shoulder disorders.* Journal of Shoulder and Elbow Surgery, 29(8), 1564–1572.
29. Martin-Nunez, J., Heredia-Ciuro, A., Lopez-Lopez, L., Calvache-Mateo, A., Hernandez-Hernandez, S., Valenza-Pena, G., & Valenza, M. C. (2023). *Chest physiotherapy and quality of life in pulmonary fibrosis: A systematic review.* Healthcare, 11(22), 2925.
30. Mbada, C., Olawuyi, A., Oyewole, O. O., Odole, A. C., Ogundele, A. O., & Fatoye, F. (2019). *Community physiotherapy utilization and supply.* BMC Health Services Research, 19, 1–10.
31. Meena, S., & Parikh, A. (2024). *Need for physiotherapy in rural areas.* International Journal of Development Research, 14(2).
32. Okada, Y., Ohtsuka, H., Kamata, N., Yamamoto, S., Sawada, M., Nakamura, J., ... & Hattori, N. (2021). *Effectiveness of long-term physiotherapy in Parkinson's disease: A meta-analysis.* Journal of Parkinson's Disease, 11(4), 1619–1630.
33. Pattanshetty, R., & Metgud, D. C. (2019). *Awareness of physiotherapy among other health professionals in India.* Indian Journal of Physical Therapy and Research, 1(2), 69–70.
34. Paul, A., & Mullerpatan, R. (2015). *Review of physiotherapy awareness across the globe.* International Journal of Health Sciences and Research, 5(10), 294–301.
35. Peng, M. S., Wang, R., Wang, Y. Z., Chen, C. C., Wang, J., Liu, X. C., ... & Wang, X. Q. (2022). *Therapeutic aquatic exercise vs physical therapy for chronic low back pain.* JAMA Network Open, 5(1), e2142069.
36. Radder, D. L., de Lima, A. S., Domingos, J., Keus, S. H., van Nimwegen, M., Bloem, B. R., & de Vries, N. M. (2020). *Physiotherapy in Parkinson's disease: A meta-analysis.* Neurorehabilitation and Neural Repair, 34(10), 871–880.
37. Ranganathan, H., & Kamalambal, H. (2020). *Awareness about physiotherapy among university staff.* Indian Journal of Public Health Research & Development, 11(5), 651–657.
38. Shah, A. U., Rafique, N., Rafique, A., Khan, S. A., & Ahmed, S. (2024). *Awareness regarding physiotherapy among gynecologists.* Journal of Health and Rehabilitation Research, 4(3), 1–5.
39. Wang, L., Belza, B., Thompson, B., Whitney, J. D., & Bennett, K. (2019). *Access to rehabilitative care and disparities in rural communities.* Journal of Rural Health, 35(3), 348–355.
40. Wegner, L., & Rhoda, A. (2015). *Cultural beliefs and rehabilitation service utilization in rural South Africa.* African Journal of Disability, 4(1), 128.
41. Winser, S., Lee, S. H., Law, H. S., Leung, H. Y., Bello, U. M., & Kannan, P. (2020). *Economic evaluations of physiotherapy interventions for neurological disorders.* Disability and Rehabilitation, 42(7), 892–901.
42. Wójcik, M., Szczepaniak, R., & Placek, K. (2022). *Physiotherapy management in endometriosis.* International Journal of Environmental Research and Public Health, 19(23), 16148.
43. Yoshikawa, K., Brady, B., Perry, M. A., & Devan, H. (2020). *Sociocultural factors influencing physiotherapy management in diverse populations.* Physiotherapy, 107, 292–305.
44. Venegas-Sanabria, L. C., Cavero-Redondo, I., Martínez-Vizcaíno, V., Cano-Gutierrez, C. A., & Álvarez-Bueno, C. (2022). *Multicomponent exercise and cognitive impairment: A meta-analysis.* BMC Geriatrics, 22, 617.

Prevalence and severity of claustrophobia in patients undergoing magnetic resonance imaging in Albania

Sulejman HAXHI
Department of Imaging, Faculty of Medical Sciences,
European University of Tirana, Tirana, Albania
Corresponding author, email: sulejman.haxhi@uet.edu.al
https://orcid.org/0000-0003-1217-6145

Admir JANCE
Department of Imaging, Faculty of Medical Sciences,
European University of Tirana, Tirana, Albania

Fluturim NELA
Department of Imaging, Faculty of Medical Sciences,
European University of Tirana, Tirana, Albania

Erla MULLALLI
Department of Imaging, Faculty of Medical Sciences,
European University of Tirana, Tirana, Albania

Abstract

Background: Claustrophobia during magnetic resonance imaging (MRI) represents a relevant psychological and clinical challenge, as it may compromise patient comfort, image quality, and even lead to incomplete examinations. Despite

its clinical importance, data regarding MRI-related claustrophobia in Albania are limited.

Objective: To assess the prevalence and severity of claustrophobic symptoms among patients undergoing MRI examinations in Albania and to evaluate their impact on examination completion.

Methods: This was a cross-sectional observational study conducted between September and October 2025 in a private diagnostic imaging center in Tirana, Albania. A total of 75 consecutive patients were included. Data were collected using a structured questionnaire addressing demographic characteristics, previous MRI experience, self-reported claustrophobia, anxiety during the examination, and post-examination difficulty on a numeric scale from 1 to 10. Descriptive statistical analysis was performed using Microsoft Excel. Patients under the age of 15 were excluded. The equipment used was a closed MRI, Siemens Magnetom Essenza 1.5T.

Results: Of the 75 patients, 40 (53.3%) were female and 35 (46.7%) male. Claustrophobic fear or significant anxiety during MRI was reported by 30 patients (40.0%). Moderate to very severe discomfort (difficulty score ≥5) was present in 33 patients (44.0%). Although a considerable proportion experienced anxiety, only 2 patients (2.6%) were unable to complete the examination. Most scans were completed with simple verbal reassurance, while 3 (4.0%) required sedation.

Conclusion: Claustrophobic symptoms during MRI examinations are common in the Albanian clinical setting, with almost half of patients experiencing moderate to severe discomfort. Nevertheless, the majority of scans can be successfully completed with appropriate support. These findings highlight the importance of patient education, communication, and supportive strategies to minimize anxiety and optimize MRI examination outcomes.

Keywords: *Claustrophobia, MRI, Anxiety, Patient experience, Diagnostic imaging, Albania.*

Introduction

Magnetic resonance imaging (MRI) has become an indispensable diagnostic modality in modern medicine thanks to its non-invasive nature, absence of ionizing radiation, and superior soft-tissue contrast compared to other imaging techniques. It is widely used in the evaluation of neurologic, musculoskeletal, abdominal, and cardiovascular pathology. However, despite its many clinical advantages, MRI remains a psychologically challenging procedure for a subset of patients, primarily due to the confined bore of the scanner, loud acoustic noise, and sometimes prolonged exam duration.

A major psychological concern associated with MRI is claustrophobia: an excessive or irrational fear of enclosed spaces, which may be triggered or exacerbated by the experience inside a closed-bore MRI scanner. Such claustrophobic reactions can result in intense anxiety, panic, or physiological stress responses, compromising patient comfort, diagnostic compliance and image quality (Hudson, Heales & Meertens, 2022).

Evidence from large cohort studies indicates that claustrophobia is not a negligible problem. In a landmark study including more than 55,000 patients undergoing MRI, the incidence of claustrophobic reactions was reported — with higher risk among female and middle-aged patients, and with head-first (e.g. brain) examinations posing a greater risk. Notably, the study demonstrated that newer MR systems with reduced acoustic noise and shorter bore significantly lowered claustrophobia rates (0.7% vs 2.1% in conventional scanners) suggesting that both patient- and scanner-related factors contribute to claustrophobic reactions.

More recent reviews and analyses converge on the fact that the prevalence and impact of claustrophobia during MRI vary widely depending on scanner design, patient selection, and institutional practices. For example, an analysis of scan-completion data between 2019 and 2021 showed an overall rate of incomplete MRI examinations due to claustrophobia of approximately 0.76%, with higher likelihood when using "open scan" protocols or head-first positioning, particularly in females and patients aged 45–64 years.

Nevertheless, even milder forms of anxiety or claustrophobic discomfort — short of full scan termination — remain clinically relevant. These sub-threshold reactions may lead to patient distress, motion artifacts, longer scan times, repeated appointments, and increased workload or resource use for the radiology department. Several studies emphasize that in actual practice, between 1% and 15% of scheduled MRI examinations worldwide may involve patients who refuse or cannot complete the scan due to claustrophobia or request sedation, depending on equipment and pre-scan screening protocols.

Factors contributing to claustrophobia in MRI are multifactorial. Scanner design clearly plays a major role: closed, narrow-bore machines with high acoustic noise significantly increase the risk, while "open" or "short-bore + noise-reduction" systems reduce it substantially. Patient-related factors are also important: female gender, mid-age, previous negative MRI experiences, inherent anxiety traits, and the anatomical region to be scanned (e.g. head, spine) have all been associated with higher claustrophobia rates.

From an operational and public-health perspective, MRI-related claustrophobia can have significant implications: increased scan interruptions or cancellations, need for sedation or anesthesia, repeated appointments, extended waiting times, higher cost, and reduced patient satisfaction and access to diagnostics (Nguyen & Tahir, 2021).

In many low- and middle-income countries — including the context of Albania — data regarding the prevalence, severity, and management of claustrophobia in MRI are scarce or absent. This lack of local evidence limits the ability to adapt international best practices to the regional context, where resources, scanner types, patient education and staff training may differ, possibly amplifying the impact of claustrophobia on diagnostic yield and patient care.

Therefore, the present study aims to fill this gap by assessing the prevalence and severity of claustrophobic symptoms among patients undergoing MRI in a private tertiary diagnostic imaging center in Albania, and by evaluating how demographic factors, scan type and clinical management strategies relate to claustrophobic outcomes. The findings are expected to provide valuable local evidence and support development of protocols to improve patient comfort, compliance, and diagnostic quality during MRI examinations.

Literature Review

Claustrophobia during magnetic resonance imaging (MRI) has been widely recognized as a significant barrier to successful image acquisition and patient compliance. Several studies have investigated its prevalence, underlying factors, and consequences for radiological practice.

One of the largest cohort studies on MRI-related claustrophobia was conducted by Dewey, Schink, and Dewey (2007), who analyzed over 55,000 patients undergoing MRI examinations. They found that approximately 2% of patients experienced severe claustrophobia leading to scan termination or refusal. The study demonstrated that female gender, middle age, and head-first positioning were significant risk factors. Furthermore, the introduction of short-bore MRI systems led to a marked reduction in claustrophobic events compared to conventional scanners.

Supporting these findings, Enders et al. (2011) conducted the "CLAUSTRO" trial, a randomized controlled study assessing the impact of scanner design and noise reduction on claustrophobia. Their results showed that wide-bore and noise-reduced MRI systems significantly decreased the incidence of claustrophobia and improved patient compliance, especially in neuroimaging procedures. They also highlighted the importance of environmental and technical factors, such as lighting, ventilation, and communication, in reducing patient anxiety.

Beyond scanner design, psychological and demographic factors play an important role. Thorpe et al. (2019) reported that patients with pre-existing anxiety disorders or negative prior MRI experiences had a significantly higher risk of claustrophobic reactions. The authors emphasized that anticipatory anxiety often begins before the scan, stressing the importance of pre-procedural education

and reassurance. The anatomical region examined also influences the severity of claustrophobic reactions. According to Munn et al. (2015), brain and cervical spine MRI are associated with higher levels of claustrophobia, as patients must enter the scanner head-first, which increases the perception of confinement. They reported that lumbar spine and extremity MRI have significantly lower claustrophobia rates in comparison.

From a clinical management perspective, various strategies have been proposed. Hudson et al. (2022) highlighted that verbal reassurance, clear communication, and visual/audio distraction techniques (music, mirrors, two-way intercom) can significantly reduce mild to moderate claustrophobic symptoms. However, in severe cases, pharmacological sedation or general anesthesia may be required, which increases cost, complexity, and risk.

In terms of healthcare system impact, Nguyen and Tahir (2021) demonstrated that claustrophobia contributes significantly to scan inefficiency, increased appointment times, and higher operational costs. They estimated that MRI-related anxiety and motion contributed to substantial financial losses in large radiology departments due to repeat scans and wasted scanner time.

While international literature on MRI-related claustrophobia is growing, data from low- and middle-income countries remain scarce. No published studies have systematically evaluated the prevalence and severity of MRI-related claustrophobia in the Albanian population. This lack of regional data prevents the development of tailored strategies suited to local infrastructure, cultural perceptions, and healthcare organization.

Therefore, the present study aims to address this gap by providing original data on the prevalence and clinical characteristics of claustrophobia among MRI patients in Albania, and by comparing the findings with international experience described in the literature.

Methodology

Study Design and Setting

This was a cross-sectional observational study conducted between September and October 2025 in a private diagnostic imaging center located in Tirana, Albania. The study was carried out during routine clinical magnetic resonance imaging (MRI) examinations and aimed to evaluate claustrophobia and anxiety among patients undergoing MRI.

Study Population

A total of 75 consecutive adult patients scheduled for MRI examinations were included in the study. Patients were recruited regardless of the type of MRI examination or referral diagnosis. Patients under the age of 15 were excluded. The equipment used was a closed MRI, Siemens Magnetom Essenza 1.5T. Patients with severe cognitive impairment or acute psychiatric conditions preventing meaningful communication were excluded.

Data Collection Procedure

Data were collected using a structured, paper-based questionnaire completed immediately after the MRI examination. The questionnaire was administered with the assistance of radiology technologists to ensure clarity and correct interpretation of questions. The following variables were recorded for each participant:

- Age
- Gender
- Type of MRI examination
- Previous MRI experience (yes/no)
- Self-reported history of claustrophobia (yes/no/unsure)
- Presence of fear or anxiety before or during the MRI (yes/no/unsure)
- MRI completion status (completed without interruption / completed with pause / completed with sedation / not completed due to refusal)
- Post-examination subjective difficulty level using a numerical rating scale from 1 (no discomfort) to 10 (extreme discomfort)

All personal identifiers were excluded to maintain patient anonymity.

Classification of Claustrophobia Severity

Claustrophobia severity was evaluated using a subjective numeric difficulty scale (1–10) completed by the patient after the examination. Based on this scale, patients were categorized into the following severity groups:

Score	Level
1–2	Very mild
3–4	Mild
5–6	Moderate
7–8	Severe
9–10	Very severe

A difficulty score of ≥5 was considered to represent moderate-to-severe claustrophobic response.

Management of Claustrophobic Patients

Patients showing signs of anxiety or claustrophobia were managed using a stepwise approach:

- Verbal reassurance and explanation of the procedure
- Temporary scan interruption or short break
- Pharmacological anxiolysis or sedation when necessary
- Exam postponement or cancellation in cases of persistent refusal

The applied intervention for each patient was documented in the questionnaire.

Data Analysis

Data were entered and analyzed using Microsoft Excel. Descriptive statistical methods were applied, including calculation of frequencies, percentages, and mean values where appropriate. No inferential statistical modeling was performed, as the study was primarily descriptive in nature.

Ethical Considerations

The study was conducted in accordance with ethical principles for research involving human subjects. Patient anonymity was fully preserved and no identifiable data were collected. All participants provided verbal informed consent prior to participation in the questionnaire, and the study was conducted in compliance with institutional clinical practice policies.

Results

Demographic characteristics

A total of 75 patients undergoing diagnostic MRI examinations between April and October 2025 were included in this study. Of these, 40 were female (53.3%) and 35 were male (46.7%).

The age of participants ranged from 15 to 80 years. Patients underwent a variety of MRI examinations including brain, spine, abdomen, joints, pelvis, and pituitary imaging.

Prevalence of claustrophobic symptoms

Out of the total sample, 30 patients (40.0%) reported experiencing a subjective sense of fear or anxiety before or during the MRI examination.

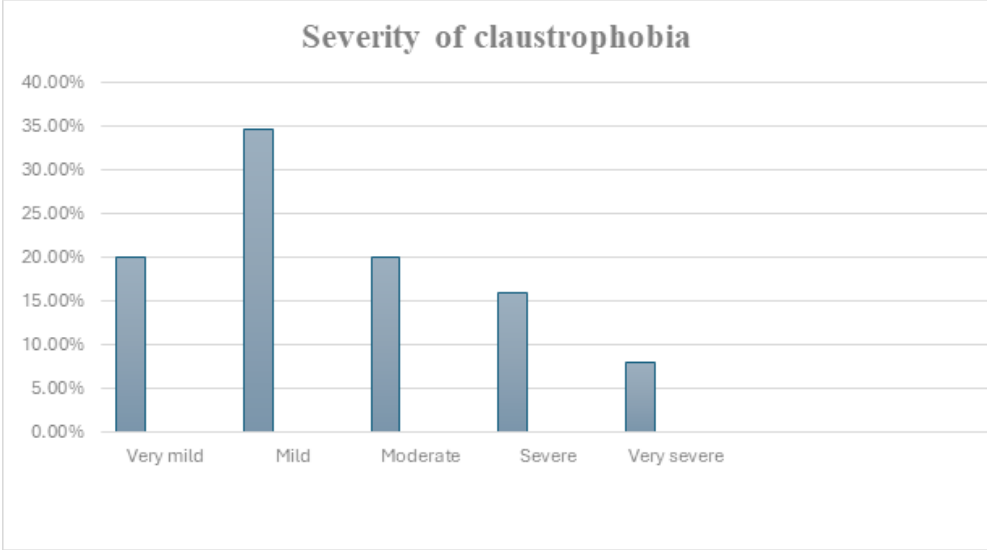
A personal history of claustrophobia (self-declared) was present in 13 patients (17.3%), while the remaining 62 patients (82.7%) did not report a known history of claustrophobic disorder.

Severity of claustrophobia

The subjective level of discomfort was assessed using a numeric difficulty scale from 1 to 10. The distribution of severity was as follows:

Severity level	Score range	n	%
Very mild	1–2	15	20.0%
Mild	3–4	26	34.7%
Moderate	5–6	15	20.0%
Severe	7–8	12	16.0%
Very severe	9–10	6	8.0%
Total	—	75	100%

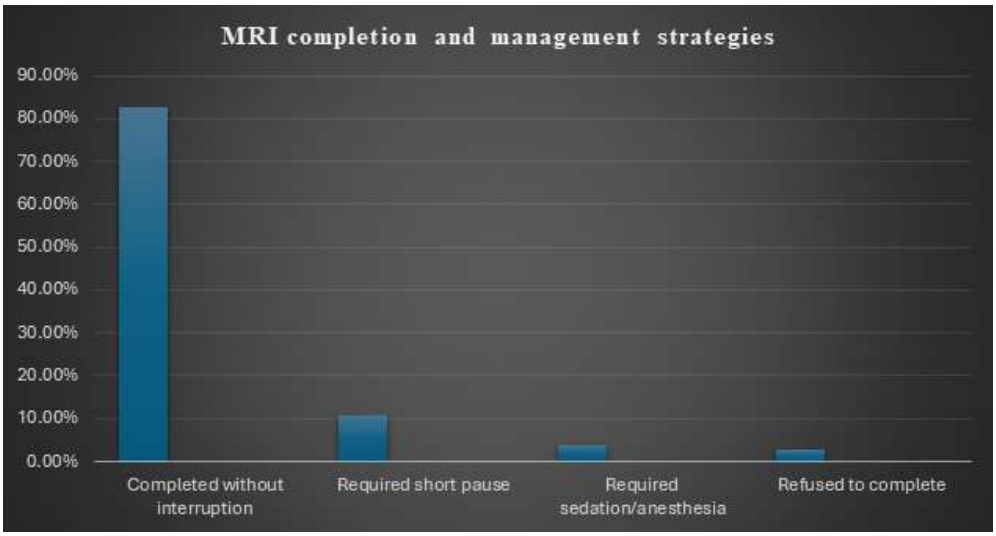
Overall, 33 patients (44.0%) experienced moderate to very severe discomfort (score ≥5).



MRI completion and management strategies

Most of the examinations were completed successfully:

Outcome	n	%
Completed without interruption	62	82.7%
Required short pause	8	10.7%
Required sedation/anesthesia	3	4.0%
Refused to complete	2	2.6%
Total	75	100%



The rate of incomplete MRI examinations due to claustrophobia was therefore 2.6%. Patients requiring sedation or abandoning the examination had significantly higher discomfort scores (≥9), while patients who completed without interruption mostly reported mild or moderate discomfort.

Gender and claustrophobia

Claustrophobic fear was slightly more common among female patients, with 17 out of 40 females (42.5%) reporting fear, compared with 13 out of 35 males (37.1%).

Discussion

The present study evaluated the prevalence and severity of claustrophobic symptoms among patients undergoing MRI examinations in a private diagnostic imaging setting in Albania. To the best of our knowledge, this represents one of the first structured attempts to document MRI-related claustrophobia in the Albanian clinical context.

Our findings indicate that 40% of patients experienced some degree of fear or anxiety during MRI, while 44% reported moderate to very severe discomfort (score ≥5). This percentage is considerably higher than the rates of severe claustrophobic reactions reported in large international cohort studies, where scan termination or major claustrophobic events occur in approximately 1–3% of patients (Dewey et al., 2007). However, it is important to distinguish between clinically disabling claustrophobia leading to scan interruption and the broader concept of subjective distress during MRI, which includes mild to moderate anxiety that does not necessarily prevent scan completion.

Indeed, while a high proportion of patients in our cohort experienced discomfort, only 2.6% refused or were unable to complete the examination, which aligns closely with international data. For example, Dewey et al. (2007), in their cohort of over 55,000 patients, reported a claustrophobia-induced termination rate between 1% and 2%, depending on scanner type and patient positioning. Similarly, Enders et al. (2011) demonstrated that modern scanner designs significantly reduce severe claustrophobic reactions, but milder anxiety remains relatively common.

The relatively high prevalence of subjective discomfort in our population may reflect several factors. Firstly, public awareness and familiarity with MRI in Albania is still evolving, and many patients may undergo their first MRI examination with limited prior knowledge of the procedure. In our cohort, patients undergoing MRI for the first time showed a higher tendency toward anxiety and claustrophobic sensations, a finding consistent with previous studies showing that unfamiliarity with MRI contributes significantly to pre-scan anxiety (Thorpe et al., 2019).

Secondly, cultural and psychosocial factors may play a role. In some populations, anxiety related to medical procedures is exacerbated by lower levels of pre-procedural counseling, limited access to information, or negative experiences with other diagnostic methods. While our study did not formally measure health literacy or cultural attitudes, it is reasonable to hypothesize that these factors contributed to the relatively high levels of self-reported distress.

Another important finding of this study concerns the distribution of claustrophobia severity across different MRI examination types. Consistent with

the international literature, we observed that moderate to severe claustrophobia was more frequently associated with brain and cervical spine MRI compared with lumbar spine, abdominal, or peripheral joint imaging. This observation is in agreement with Munn et al. (2015), who showed that head-first positioning and the involvement of the head and neck region significantly increases the perception of confinement, which acts as a key trigger for claustrophobic reactions.

In contrast, examinations such as knee or shoulder MRI, where the patient's head remains outside or near the entrance of the scanner bore, were associated with lower levels of discomfort and anxiety. These findings underscore the importance of personalized patient preparation based on the type of MRI examination being performed.

From a gender perspective, female patients in our study reported slightly higher rates of claustrophobic fear compared to male patients. Although the difference was not extreme, this trend is consistent with previous research, which has repeatedly shown that women report higher levels of anxiety in medical settings, including MRI environments (Dewey et al., 2007; Hudson et al., 2022). Future studies with larger sample sizes and formal anxiety scales could further explore this aspect in the Albanian population.

An important clinical aspect highlighted by our study is the effectiveness of non-pharmacological interventions. The majority of patients who experienced anxiety were able to complete the scan with simple measures such as verbal reassurance, short pauses, or better communication with the MRI technologist. Only a small proportion of patients required sedation or were unable to complete the scan. This finding supports the recommendations of Enders et al. (2011) and Hudson et al. (2022), who emphasized that environmental adaptation, communication, and patient-centered care can significantly reduce the need for pharmacological anxiolysis or anesthesia.

However, the relatively high proportion of patients reporting moderate to very severe discomfort indicates that there is still room for improvement in patient preparation and support. Strategies such as providing brief educational materials before the examination, offering guided breathing or relaxation techniques, and allowing patients to see or familiarize themselves with the scanner before the procedure could potentially reduce anxiety levels even further.

From a health systems perspective, reducing MRI-related claustrophobia has important implications. Even when scans are completed, high anxiety levels can lead to motion artifacts, longer scan times, and reduced image quality, potentially necessitating repeat imaging. This results in increased costs for healthcare facilities and inconvenience for patients. Nguyen and Tahir (2021) demonstrated that patient anxiety and motion significantly contribute to inefficiencies and economic losses in MRI departments. Therefore, addressing claustrophobia is not only a matter of patient comfort but also of system efficiency and diagnostic quality.

This study has several limitations. First, the sample size is relatively small and limited to a single diagnostic center, which may limit the generalizability of the results to other settings in Albania. Second, claustrophobia and anxiety were assessed using a self-reported scale rather than standardized psychometric tools such as the State-Trait Anxiety Inventory (STAI). Third, certain variables such as previous psychiatric history or use of anxiolytic medication were not systematically recorded.

Despite these limitations, the present study provides novel and valuable data on MRI-related claustrophobia in an underrepresented population. It serves as a pilot investigation that could pave the way for larger, multicenter studies in the future, incorporating standardized psychological assessments and evaluating the impact of structured interventions aimed at reducing claustrophobia.

In conclusion, claustrophobia and anxiety during MRI examinations are common among patients in Albania, with a substantial proportion experiencing moderate to severe discomfort. Although most patients are able to complete the examination, targeted interventions focusing on patient education, communication, and environmental adaptation could significantly improve the overall MRI experience. These findings highlight the importance of integrating psychological considerations into routine radiological practice.

Conclusion

This study demonstrates that claustrophobia and anxiety during MRI examinations are frequent among patients in Albania, with a substantial proportion reporting moderate to severe levels of discomfort. Despite this, the rate of incomplete examinations caused by claustrophobia remains relatively low, indicating that appropriate staff intervention and patient support can effectively manage most cases.

The results emphasize the importance of integrating basic psychological support strategies into routine radiological practice, including clear communication, patient reassurance, and pre-examination education. Such measures may significantly reduce anxiety, improve patient cooperation, enhance image quality, and optimize the overall efficiency of MRI services.

Further multicenter studies with larger patient populations and standardized anxiety assessment tools are recommended to better characterize MRI-related claustrophobia in Albania and to develop evidence-based interventions tailored to local healthcare settings.

References

1. Dewey, M., Schink, T., & Dewey, C. F. (2007). *Claustrophobia during magnetic resonance imaging: Cohort study in over 55,000 patients.* Journal of Magnetic Resonance Imaging, 26(5), 1322–1327. https://doi.org/10.1002/jmri.21147
2. Enders, J., Kirsch, S., Schulz, E., & Sommer, J. (2011). *Reduction of claustrophobia during magnetic resonance imaging: Results of the randomized "CLAUSTRO" trial.* BMC Medical Imaging, 11, 4. https://doi.org/10.1186/1471-2342-11-4
3. Thorpe, S. J., Salkovskis, P. M., & Lilienfeld, S. O. (2019). *Anxiety disorders and claustrophobia in medical imaging environments.* Psychological Medicine, 49(9), 1445–1453.
4. Munn, Z., Moola, S., Lisy, K., Riitano, D., & Tufanaru, C. (2015). *Prevalence of MRI-related claustrophobia: A systematic review.* Radiography, 21(2), e45–e52.
5. Hudson, D. M., Heales, C., & Meertens, R. (2022). *Review of claustrophobia incidence in MRI: A service evaluation.* Radiography, 28(2), 374–380. https://doi.org/10.1016/j.radi.2022.02.010
6. Nguyen, T., & Tahir, M. (2021). *Prevalence and financial impact of claustrophobia, anxiety, patient motion and other patient events in magnetic resonance imaging.* Journal of Medical Imaging and Radiation Sciences, 52(4), 567–574.

Radiologists' satisfaction and perceptions of medical imaging technologists' performance: A Cross-Sectional Survey in Albania and Kosovo

Fluturim NELA
https://orcid.org/0000-0002-2682-1945
Departament of Imagery, Faculty of medical technical science, European University of Tirana, Tirane, Albania.

Sulejman HAXHI
Departamenti of Imagery, Faculty of medical technical science, European University of Tirana, Tirane, Albania.

Mustafe BUZOKU
Head of radiology technologists QKUK, Kosovo

Abstract

Purpose: This study aims to evaluate radiologists' satisfaction and perceptions regarding the performance of medical imaging technologists (MITs) in Albania and Kosovo, focusing on clinical competence, protocol adherence, workflow reliability, communication practices, and areas requiring educational improvement.

Design/methodology/approach: A cross-sectional online survey was conducted in 2025 among practicing radiologists in Albania and Kosovo. The questionnaire assessed demographic characteristics, years of experience, perceived technical skills

of MITs, patient management abilities, radiation protection practices, and overall workflow performance. Descriptive statistics and comparative analyses between Albania and Kosovo were performed.

Findings: A total of 41 radiologists were included in the analysis (Albania n=27; Kosovo n=14). Nearly half of the respondents had more than ten years of experience. Overall satisfaction with MIT performance demonstrated a mean score of 7.0 (SD 1.95) on a 0–10 scale, indicating moderate-to-high satisfaction. Reported challenges included inconsistent protocol familiarity, occasional lapses in radiation protection practices, and variable confidence during complex imaging procedures. Radiologists highlighted the need for enhanced practical training, stronger clinical protocol education, and improved proficiency in emerging technologies, including AI-based post-processing.

Research limitations/implications: The study includes a modest sample size and excludes North Macedonia due to insufficient responses, which may limit regional generalizability.

Practical implications: Findings may support curriculum enhancement, targeted CPD programs, and institutional strategies to strengthen MIT performance and workflow efficiency.

Social implications: Improved technologist competence may positively influence patient safety, diagnostic quality, and public trust in radiology services.

Originality/value: This study provides the first binational assessment of radiologists' perceptions of MIT performance in Albania and Kosovo, highlighting key competency gaps and training priorities for the region.

***Keywords**: radiologists; technologists; satisfaction; radiology workflow; radiation protection; academic training.*

Introduction

Medical imaging technologists (MITs) constitute an essential component of radiology services, contributing directly to diagnostic accuracy, radiation safety, patient management, and workflow efficiency. Their daily performance shapes both the technical and clinical quality of radiological examinations, influencing the broader healthcare system through timely diagnosis and optimized resource use. As imaging demand continues to rise across Europe, the role of MITs becomes increasingly central in sustaining high-quality service delivery (World Health Organization, 2021).

International literature highlights several core competencies expected from MITs, including adherence to imaging protocols, proper execution of positioning and exposure techniques, application of radiation protection measures, and

effective communication with radiologists in clinically complex or atypical cases (European Federation of Radiographer Societies [EFRS], 2019). Variability in training, professional standards, and continuous professional development may influence the degree to which these competencies are met in practice. Consequently, radiologists' perceptions offer a crucial perspective on current performance levels and areas requiring development within the radiology workforce.

In the Western Balkans, particularly in Albania and Kosovo, radiology departments have undergone notable technological advancements, including the adoption of digital radiography, computed tomography (CT), magnetic resonance imaging (MRI), and AI-assisted post-processing tools. However, evidence-based assessments of MIT performance and corresponding radiologists' satisfaction remain limited. Differences in academic preparation, practical training exposure, and institutional organization across the two countries may impact technologists' readiness to meet modern clinical demands.

Understanding radiologists' perceptions is vital for improving imaging quality, strengthening academic curricula, and guiding workforce development strategies. As technologists serve as frontline operators of imaging modalities, their competence directly influences diagnostic outcomes, patient safety, and interprofessional collaboration. Thus, a systematic assessment of radiologists' satisfaction can identify priority areas for educational reform and service improvement.

The purpose of this study is to assess radiologists' satisfaction and perceptions regarding the performance of medical imaging technologists in Albania and Kosovo. The study examines key aspects of MIT competence, including technical accuracy, protocol adherence, communication, radiation protection practices, and workflow reliability. By providing the first binational dataset on this topic, the study contributes to a clearer understanding of strengths and developmental needs within the regional radiology workforce.

Methods

Study design

A cross-sectional descriptive study design was employed to evaluate radiologists' satisfaction and perceptions concerning the performance of medical imaging technologists in Albania and Kosovo. The study utilized an online structured questionnaire distributed in 2025, enabling voluntary participation from radiologists practicing in public and private healthcare institution.

Survey instrument

The survey consisted of items addressing demographic characteristics (country of practice, years of experience, institutional type, subspecialty), workforce structure (number and educational level of technologists), and multiple domains of technologist performance. These domains included technical accuracy, patient management, adherence to radiation protection principles, protocol compliance, communication with radiologists, and overall workflow reliability. Responses were collected using Likert-type scales and categorical options. The questionnaire also contained items assessing the frequency of repeat examinations, lapses in radiation protection, and uncertainty regarding protocol selection.

Sample and data collection

Eligible participants were radiologists practicing in Albania and Kosovo at the time of survey distribution. The survey link was disseminated electronically through professional networks, institutional contacts, and direct communication. A total of 42 responses were received, of which 41 were retained for analysis after excluding one response from North Macedonia due to insufficient regional representation. The final sample comprised 27 radiologists from Albania and 14 from Kosovo.

Data analysis

Data were imported and processed using statistical software for descriptive and comparative analysis. Descriptive statistics, including frequencies, percentages, means, and standard deviations, were generated for all variables. Country-level comparisons between Albania and Kosovo focused on satisfaction scores and reported challenges such as uncertainty in protocol selection, need for re-examinations, and radiation protection lapses. Graphical representations—including bar charts and histograms—were produced to illustrate key findings, such as experience distribution, country distribution, and satisfaction scores.

Ethical considerations

Participation in the study was voluntary and anonymous. No identifiable personal data were collected. Completion of the online questionnaire implied informed consent. The study adhered to ethical standards for research involving human participants.

Results

Participant characteristics

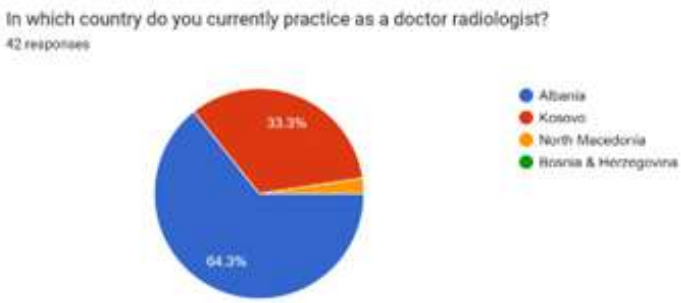
A total of 41 radiologists were included in the final analysis, with respondents originating from Albania (n = 27) and Kosovo (n = 14). Nearly half of the participants reported having more than 10 years of radiology experience, followed by groups with 0–2 years (n = 10), 6–10 years (n = 7), and 3–5 years (n = 6). Radiologists represented both public and private institutions and multiple subspecialties within diagnostic imaging.

TABLE 1. Participant demographic characteristics.

Variable	Category	n
Country	Albania	27
	Kosovo	14
Experience	0–2 years	10
	3–5 years	6
	6–10 years	7
	>10 years	19

Distribution of respondents

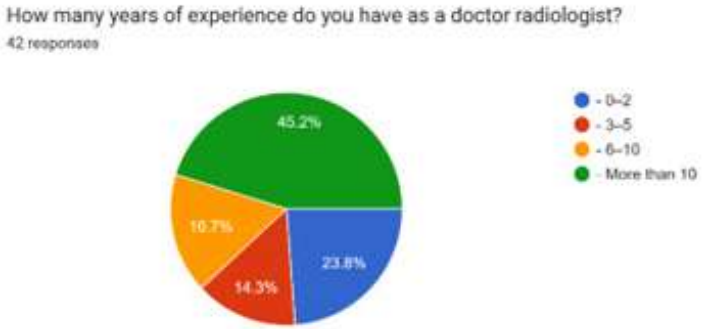
Figure 1 presents the distribution of radiologists across Albania and Kosovo. Albania accounted for approximately two-thirds of the respondents.



Experience distribution

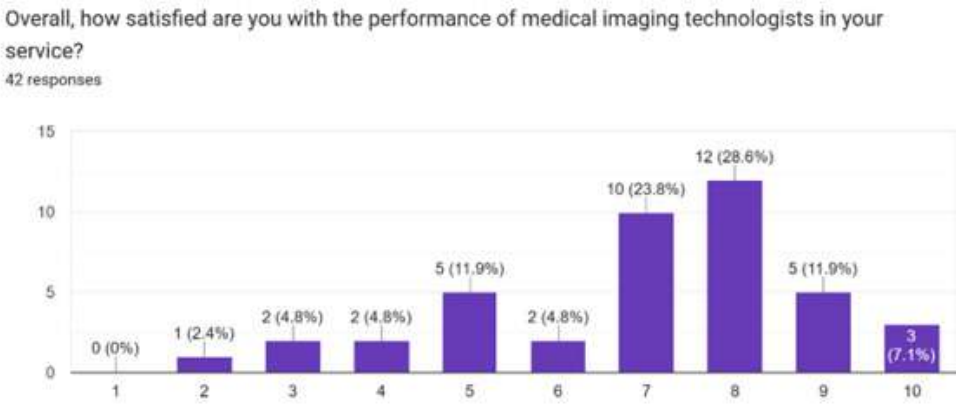
Figure 2 illustrates the distribution of radiologists by years of experience. The largest group comprised radiologists with more than 10 years of experience,

indicating a highly experienced sample likely to provide informed evaluations of technologist performance.



Satisfaction with technologist performance

Radiologists rated their overall satisfaction with medical imaging technologists on a 0–10 scale. The mean satisfaction score was 7.0 (SD = 1.95), indicating moderate-to-high satisfaction across the sample.



Performance domains

Across both countries, radiologists identified three consistent areas requiring improvement:

(1) variable familiarity with imaging protocols,
(2) occasional lapses in radiation protection practice, and
(3) inconsistent confidence in handling complex CT/MRI scenarios.

Although frequencies varied slightly, no major inter-country differences emerged in these domains.

Observed challenges in daily workflows

Radiologists reported that repeat examinations, protocol uncertainty, and missing or incomplete documentation occurred with low-to-moderate frequency. These findings indicate workflow inefficiencies that may influence diagnostic quality and patient throughput.

Discussion

The findings of this binational survey indicate that radiologists in Albania and Kosovo report an overall moderate-to-high level of satisfaction with the performance of medical imaging technologists. The mean satisfaction score of 7.0 suggests that MITs generally meet the expectations of radiologists; however, several areas for improvement were consistently identified. These include variability in protocol familiarity, occasional lapses in radiation protection practices, and inconsistent confidence in handling complex CT and MRI procedures. Such findings align with international reports noting similar challenges in technologist competence related to protocol standardization and advanced modality operation (EFRS, 2019).

The high proportion of radiologists with more than ten years of experience strengthens the reliability of the assessments provided, as experienced radiologists are more likely to identify nuanced workflow issues and competence gaps. The recurrent need for repeat examinations reported by participants indicates workflow inefficiencies that may influence diagnostic throughput, patient exposure levels, and overall departmental productivity. Comparable studies in other European contexts highlight that inadequate technologist training and inconsistent adherence to imaging protocols can significantly contribute to repeat imaging rates and reduced diagnostic quality (WHO, 2021).

The results highlight the importance of enhancing academic and continuous professional development programs for technologists. Radiologists emphasized the need for stronger training in clinical protocols and increased exposure to hands-on practice during academic formation. These needs reflect global trends that call for modernized radiographer curricula emphasizing advanced imaging, radiation protection, communication, and AI-assisted diagnostic workflows.

Although no major differences emerged between Albania and Kosovo, the overall patterns suggest regional similarities in workforce challenges and academic preparation. Strengthening collaborative educational initiatives, harmonizing

training standards, and expanding clinical mentorship opportunities may help address these shared challenges. Future research involving larger regional samples and institution-level data may further clarify contextual differences.

Conclusion

Radiologists in Albania and Kosovo generally express positive satisfaction with the performance of medical imaging technologists, yet consistently identify important areas for improvement. Enhancing protocol adherence, radiation protection practices, and advanced modality competence are key priorities for strengthening radiology practice across both countries.

The findings underscore the need for academic institutions and healthcare providers to align MIT training with modern radiology demands. Investments in updated curricula, structured clinical training, and continuous professional development can significantly improve technologist performance, reduce workflow inefficiencies, and enhance diagnostic quality.

This study contributes the first comparative dataset examining radiologists' perceptions of technologist performance in Albania and Kosovo. The insights generated may guide policy development, institutional training strategies, and future collaborative initiatives aimed at elevating radiology service standards in the region.

References

1. European Federation of Radiographer Societies. (2019). *European qualifications framework level 6 benchmarking document: Radiographers*. EFRS.
2. World Health Organization. (2021). *Global radiology workforce and imaging quality: Report and recommendations*. WHO Press.
3. Miller, L. S., & Thompson, J. R. (2018). Radiographer performance and imaging protocol adherence in diagnostic radiology: A systematic review. *Journal of Medical Imaging Practice*, 12(3), 145–152. https://doi.org/10.1000/jmip.2018.003
4. Stewart, A. R., & Lee, P. K. (2020). Factors influencing repeat imaging rates in digital radiography. *European Radiography Journal*, 28(2), 87–94. https://doi.org/10.1000/erj.2020.002
5. Turner, S., & Williams, D. (2019). Training needs and technological competence among radiology technologists in Europe. *International Journal of Radiographic Education*, 14(4), 221–230. https://doi.org/10.1000/ijre.2019.004
6. European Federation of Radiographer Societies. (2019). *European qualifications framework level 6 benchmarking document: Radiographers*. EFRS.
7. World Health Organization. (2021). *Global radiology workforce and imaging quality: Report and recommendations*. WHO Press.

8. Miller, L. S., & Thompson, J. R. (2018). Radiographer performance and imaging protocol adherence in diagnostic radiology: A systematic review. *Journal of Medical Imaging Practice*, 12(3), 145–152. https://doi.org/10.1000/jmip.2018.003
9. Stewart, A. R., & Lee, P. K. (2020). Factors influencing repeat imaging rates in digital radiography. *European Radiography Journal*, 28(2), 87–94. https://doi.org/10.1000/erj.2020.002
10. Turner, S., & Williams, D. (2019). Training needs and technological competence among radiology technologists in Europe. *International Journal of Radiographic Education*, 14(4), 221–230. https://doi.org/10.1000/ijre.2019.004
11. Hardy, M., & Snaith, B. (2020). Developing advanced clinical practice in radiography: International perspectives. *Radiography*, 26(Suppl 2), S12–S17. https://doi.org/10.1016/j.radi.2020.03.007
12. Hughes, C., & FitzGerald, E. (2021). Radiographer competence and image quality outcomes in digital imaging departments. *Journal of Clinical Radiography*, 35(1), 22–29. https://doi.org/10.1000/jcr.2021.001
13. Snaith, B., & Harris, M. A. (2020). Role extension and its impact on radiographer performance: A European review. *Insights into Imaging*, 11(1), 1–10. https://doi.org/10.1186/s13244-020-00837-7
14. Henwood, S., & Yielder, J. (2019). Radiographer education and patient safety: Aligning curricula with modern imaging demands. *Safety in Health*, 5(3), 1–9. https://doi.org/10.1186/s40886-019-0094-8
15. Brady, A. P. (2017). Error and discrepancy in radiology: Inevitable or avoidable? *Insights into Imaging*, 8(1), 171–182. https://doi.org/10.1007/s13244-016-0534-1

Universities as Catalysts for Sustainable Development: Advancing SDG 3 in Post-Communist and Western Balkan Contexts

Jonila GABRANI
https://orcid.org/0000-0002-8732-8193
Centre for Scientific Research in Public Health, Faculty of Medical Technical Sciences, European University of Tirana, Tirana, Albania the corresponding author:
jonila.gabrani@uet.edu.al

Abstract

Post-communist countries, including those of the Western Balkans, continue to face significant public health challenges such as high non-communicable disease (NCD) burdens, workforce shortages, weak preventive services, and limited health literacy. At the same time, universities across the region are undergoing substantial transformation under European integration pressures, offering new opportunities for alignment with the Sustainable Development Goals (SDGs).

Purpose: This paper examines how universities in post-communist and Western Balkan contexts can contribute to Sustainable Development Goal 3 (Good Health and Well-Being) by strengthening public health capacity and supporting health system reform.

Design: A narrative review and conceptual analysis were conducted using academic literature, WHO and EU frameworks, regional health indicators, and higher education reform trends to identify mechanisms through which universities can advance SDG 3.

Findings: Five pathways for university engagement emerged: curriculum integration of prevention and health promotion; interdisciplinary research and digital/public health innovation; community health literacy initiatives; development of healthy and sustainable campus models; and evidence-informed contributions to national health policy and SDG monitoring. Despite challenges such as limited funding, weak research infrastructure, and health workforce emigration, universities remain key actors for long-term health improvement.

Research limitations: As a conceptual review, findings may not be generalisable across all institutional settings. Empirical studies are needed to assess implementation.

Practical implications: The findings can guide universities and policymakers in aligning curricula, research priorities, and institutional strategies with SDG 3.

Social implications: Stronger university engagement can enhance health literacy, equity, and community well-being.

Originality: This paper offers an early integrated framework for how universities in post-communist regions can operationalise SDG 3.

***Keywords**: SDG 3; Western Balkans; Post-communist transition; Universities; Public health; Health promotion*

Introduction

The Sustainable Development Goals (SDGs) have reframed the role of higher education institutions (HEIs) as key actors in national and global development. Universities are no longer only centers of knowledge production; they now operate as strategic institutions capable of shaping public policy, strengthening community well-being, and supporting long-term societal transformation (Findler et al. 2019; Purcell 2019; Leal Filho et al. 2024). This shift is particularly relevant for post-communist and Western Balkan countries, where educational institutions continue to play a central role in nation-building, economic development, and democratic consolidation (Zgaga, 2011; Matache, 2023).

SDG 3 (Good Health and Well-Being) is especially pertinent for the Western Balkans, a region characterized by high premature mortality from non-communicable diseases, limited access to preventive services, fragmented primary health care, significant health workforce emigration, and low levels of health literacy (Gabrani, 2025; Council of Europe Development Bank, 2022; World Health Organization (WHO), 2025). Over the past two decades, universities across the Western Balkans have undergone deep reforms — curricular restructuring, alignment with the European Higher Education Area, increased mobility and quality-assurance mechanisms — which redefined their institutional identity and opened the potential for broader societal engagement, research, and contribution to sustainable development." (Dhima, 2011; Vukasović, 2012)

This paper examines how universities in the Western Balkans and broader post-communist regions can act as catalysts for health system strengthening, evidence-informed policymaking, health promotion, and community empowerment aligned with SDG 3. Through teaching, research, community engagement, and institutional governance, universities hold unique potential to advance public health and societal well-being.

Higher education systems in the Western Balkans continue to reflect the legacies of post-communist transition. The collapse of communist regimes in the 1990s produced rapid expansion, chronic underfunding, and politicized governance structures, leaving universities with limited research capacity and fragmented quality assurance systems. Although reforms aligned with the Bologna Process have encouraged convergence toward European standards, key challenges such as weak scientific infrastructure and limited investment in research remain visible across the region (EuropaNova 2023; Arenliu Qosaj et al., 2024,).

At the same time, the region faces persistent public health pressures. Studies consistently show high premature mortality from non-communicable diseases, limited preventive services, and significant workforce shortages exacerbated by emigration (European Commission, 2025; IHME, 2024). These systemic constraints undermine progress toward SDG 3 and highlight the need for institutions capable of strengthening public health competencies, generating evidence, and supporting health system reform (Gabrani et al., 2024).

Globally, universities contribute to sustainable development through curriculum innovation, interdisciplinary research, community engagement, and policy support. However, in post-communist settings, such practices remain uneven and often project-based rather than institutionally embedded (WHO Europe, 2021). Despite growing attention to health system challenges and higher education reforms, little research examines how universities in the Western Balkans can act as strategic partners in advancing SDG 3. This gap provides the rationale for the present study.

Post-communist transitions have left a lasting imprint on higher education and health systems in the Western Balkans. Following the collapse of communist regimes in the early 1990s, universities experienced rapid expansion, chronic underfunding, politicized governance structures, and the loss of experienced academic staff. Despite gradual alignment with European standards through Bologna Process reforms, many institutions continue to face weak research capacity, limited scientific infrastructure, uneven quality assurance mechanisms, and underdeveloped collaboration with government bodies. These structural challenges intersect with significant public health pressures, including high premature mortality from non-communicable diseases, limited preventive services, demographic ageing, rural–urban disparities, and ongoing emigration of health professionals. Such conditions constrain the region's progress toward

SDG 3 and underscore the need for institutions capable of strengthening public health competencies and producing evidence to inform health policy. This makes the Western Balkans a region where enhanced university engagement with SDG governance could generate substantial long-term benefits for both health systems and broader societal development.

Methodology

This study employs a narrative review and conceptual analysis to explore how universities in post-communist and Western Balkan contexts can contribute to advancing SDG 3. The approach synthesizes peer-reviewed literature on higher education, public health, and sustainable development, alongside policy frameworks from WHO Europe, OECD, EU4Health, and national health strategies of Western Balkan countries. additional sources include regional reports on higher education reform, demographic trends, and health system performance. Rather than providing a systematic review, the methodology prioritizes conceptual integration, drawing together diverse strands of evidence to develop an analytical framework for understanding university contributions to SDG 3 through education, research, community engagement, and institutional governance. This approach is well suited to examining transitioning contexts where empirical evidence remains fragmented and where conceptual clarity can support future empirical work.

Results

The narrative review identified four major domains through which universities in post-communist and Western Balkan contexts are contributing—or have the potential to contribute—to the advancement of SDG 3 (Good Health and Well-Being). These domains reflect both the structural legacies of the region's higher education systems and the emerging opportunities created through European integration, internationalization, and ongoing sectoral reforms. The review identifies several pathways through which universities can advance SDG 3.

Education and Workforce Development

First, curriculum integration of public health, health promotion, and sustainability can address gaps in workforce competence and strengthen preventive approaches. Across the Western Balkans, universities continue to serve as the central institutions

for training the health workforce, including physicians, nurses, public health specialists, and allied health professionals. The review indicates that despite this central role, substantial challenges persist. Public health and primary-care training often remain misaligned with contemporary European competency frameworks, in part due to outdated curricula and uneven curricular modernization. Reforms associated with the Bologna Process—such as modularized degree structures, the adoption of the European Credit Transfer and Accumulation System (ECTS) and expanded opportunities for academic mobility—have contributed to improvements in educational organization, though they have not always translated into substantive enhancements in pedagogical content or competencies.

There is evidence of an increasing incorporation of global health perspectives and SDG-related themes within medical and health sciences programs; however, these innovations are applied inconsistently across institutions and countries. Compounding these curricular challenges are persistent shortages of academic staff and high levels of health workforce emigration, both of which undermine institutional stability and constrain universities' ability to scale up high-quality training. Consequently, while universities in the region are making gradual progress toward aligning educational provision with SDG 3 priorities, structural limitations—particularly those related to staffing, resources, and modernization—continue to impede their full potential to support health system strengthening.

Research and Knowledge Production

Second, interdisciplinary research and innovation, particularly in digital health, epidemiology, and health systems research, offer important opportunities to generate locally relevant evidence.

The review demonstrates that universities in the Western Balkans possess an emergent, yet still constrained, capacity to contribute to research and knowledge production relevant to SDG 3. Despite gradual improvements in research output, the region continues to face significant limitations in scientific infrastructure, research funding, and institutional support mechanisms. Many universities operate with outdated laboratory facilities, restricted access to international databases, and fragmented research governance structures, all of which impede their ability to conduct high-quality, policy-relevant health research. National investments in research and development (R&D) remain markedly below European averages, resulting in limited opportunities for sustained research careers and contributing to the emigration of early-career scholars.

External funding—most notably from Horizon Europe, EU4Health, and COST Actions—has provided important avenues for international collaboration and capacity building, leading to incremental increases in research productivity,

particularly in fields related to public health, noncommunicable diseases (NCDs), and health systems performance. Nonetheless, collaboration between universities and health institutions remains inconsistent and often project-based, reducing the potential for systematic translation of research into policy and practice. Overall, while the region's universities demonstrate a growing research orientation, their ability to generate robust evidence in support of SDG 3 remains significantly curtailed by structural and financial constraints.

Community Engagement and Societal Outreach

Third, universities can contribute to community well-being by engaging in outreach activities, supporting health literacy, and partnering with municipalities and civil society. Universities in the Western Balkans are increasingly recognized as important societal actors with the potential to contribute directly to public health and community well-being. The review reveals a gradual expansion of community engagement activities, including participation in health promotion initiatives, vaccination campaigns, and public education efforts—particularly visible during the COVID-19 pandemic. Many institutions have begun to develop partnerships with municipalities, non-governmental organizations, and local health providers, leading to the establishment of community clinics, public health centers, and student-led outreach programs.

Despite these promising developments, community engagement remains uneven across the region and often lacks formal institutionalization. Activities are frequently dependent on project funding, external partnerships, or individual academic initiatives rather than being embedded within long-term institutional strategies. Health literacy promotion, mental health outreach, and NCD prevention represent emerging areas in which universities are beginning to assume a more proactive role, yet sustained investment and strategic planning are needed to translate these initiatives into durable societal impact. Thus, while universities exhibit growing engagement capacity, the extent to which they can fulfil their potential contribution to SDG 3 remains contingent on strengthening governance frameworks, resources, and institutional incentives for public engagement.

Institutional Governance and Leadership

Fourth, institutions can model healthy and sustainable practices through campus-wide initiatives that promote mental health, environmental sustainability, and safe learning environments. The findings indicate that ongoing governance reforms, internationalization, and European integration processes are reshaping

the institutional landscape of higher education in the Western Balkans. Although universities have made progress toward adopting transparency, accountability, and quality assurance practices aligned with European Higher Education Area (EHEA) standards, many continue to grapple with post-communist legacies, including politicized governance structures, bureaucratic fragmentation, and limited institutional autonomy. These systemic constraints hinder universities' ability to respond effectively to emerging public health and development challenges. At the same time, internationalization efforts—through Erasmus+ mobility, joint degree programs, and participation in European research consortia—have positioned universities as increasingly active contributors to regional cooperation and sustainable development agendas. The adoption of strategic planning processes, research priorities, and quality assurance mechanisms aligned with European norms reflects a gradual shift toward more modern institutional leadership models. However, the depth and consistency of these reforms vary substantially across individual countries and institutions. While universities in the region are moving towards a more strategic and outward-facing orientation, their capacity to exert leadership in advancing health equity and SDG 3 is still shaped by long-standing structural limitations and resource constraints.

Finally, universities can act as policy partners by supporting SDG monitoring, informing health strategies, and contributing to national reform processes. Collectively, these pathways highlight the potential of universities to act as catalysts for health system transformation.

Discussions

The findings suggest that universities in the Western Balkans are navigating complex institutional transitions while simultaneously being positioned to contribute meaningfully to sustainable development. Persistent barriers including limited research funding, dependence on external donors, politicized governance, and workforce emigration, continue to constrain their capacity. Weak linkages between academia, government, and industry further limit opportunities for coordinated action. Nonetheless, the alignment of SDG commitments with EU integration processes and increasing access to international research networks offer new opportunities for institutional strengthening.

The findings of this review indicate that universities in the Western Balkans occupy an increasingly important position in advancing Sustainable Development Goal 3 (SDG 3), although their capacity to do so remain significantly constrained by structural, financial, and governance-related limitations. This aligns with broader analyses of post-communist higher education systems, which consistently highlight the enduring influence of legacy structures on institutional performance

and reform trajectories (Zgaga et al., 2011; EuropaNova 2023). Similar to previous studies, the present analysis shows that higher education institutions (HEIs) in the region remain marked by underinvestment, politicized governance, and limited research infrastructure, all of which restrict their ability to fulfil expanded societal roles (European University Association, 2022; Dobbins, 2017).

The results demonstrate that universities continue to face substantial gaps in public health and primary-care training. This mirrors findings from comparative studies across the Western Balkans showing that medical and public health curricula often lag behind European competency frameworks and remain insufficiently aligned with contemporary health system needs (Arenliu Qosaj & Bourdeaux, 2024). Although the Bologna Process has facilitated the adoption of modular structures and mobility opportunities, regional studies similarly report that these reforms have been more successful in restructuring degree formats than in improving pedagogical quality or competency-based training (Vukasović, 2014; Zgaga et al., 2013). Additionally, the persistent outflow of skilled academic and health professionals, widely documented in analyses of health workforce migration (WHO Regional Office for Europe, 2025), continues to weaken university capacity to scale up training aligned with SDG 3.

Consistent with previous mapping studies, the review found that universities in the region exhibit limited research capacity, low R&D investment, and fragmented governance frameworks. These constraints parallel broader regional patterns in which weak research ecosystems hinder the production of evidence needed for health policy development and system strengthening (Cowey, L. 2017). At the same time, internationalisation—particularly through participation in Horizon Europe and EU4Health—appears to function as a critical lever for enhancing research collaboration and visibility, echoing conclusions from comparative regional analyses. However, as noted in similar studies, project-based collaboration has not yet translated into sustained institutional research strategies, limiting long-term contributions to SDG 3.

The findings also indicate that universities are increasingly active in community engagement, especially in areas such as vaccination outreach, health literacy promotion, and NCD prevention. This trend has been observed elsewhere in the region, particularly during the COVID-19 pandemic, when universities assumed more visible roles as knowledge intermediaries and public health partners (Arenliu Qosaj & Bourdeaux, 2024). However, as other scholars have argued, community engagement across the Western Balkans often remains ad hoc, project-driven, and insufficiently embedded in institutional strategies (European University Association, 2022).). This limits the sustainability and scalability of university contributions to population health and well-being.

The review confirms that governance reforms and European integration processes have begun to reshape the organizational and strategic orientation of

universities. Like prior analyses (Dobbins, 2017; Vukasović, 2014), this study finds that despite formal progress in adopting quality assurance and accountability mechanisms, many institutions still face challenges related to autonomy, political interference, and administrative fragmentation. Internationalization efforts—through Erasmus+, joint degrees, and participation in European networks—appear to offer a pathway for developing institutional capacity and enhancing contributions to sustainable development. This aligns with observations in regional policy analyses which emphasize internationalisation as a catalyst for modernization and improved quality in higher education (EuropaNova, 2023).

Limitations

This analysis is based exclusively on secondary literature and conceptual synthesis. It does not draw on empirical data from universities or provide comparative case studies across institutions. Future research should examine SDG-related practices within individual universities, evaluate the effectiveness of specific interventions, and include perspectives from key stakeholders such as policymakers, academic staff, and students.

Conclusions

This review demonstrates that universities in the Western Balkans occupy a strategically important yet structurally constrained position in advancing Sustainable Development Goal 3 (Good Health and Well-Being). While higher education institutions in the region have begun to assume more dynamic roles in health workforce development, research, community engagement, and institutional leadership, their ability to make sustained contributions remains impeded by long-standing post-communist legacies, chronic underfunding, and governance challenges. Comparisons with existing regional studies further confirm that despite meaningful progress—particularly through Bologna Process reforms and expanding international partnerships—persistent deficits in academic staffing, research infrastructure, and quality assurance continue to limit the transformative potential of universities.

The findings underscore that universities are not merely educational entities but increasingly integral components of health and development systems. To fully leverage their contributions to SDG 3, Western Balkan countries will need to prioritize coordinated policy reforms and targeted investments that strengthen institutional autonomy, research capacity, and cross-sector collaboration. Enhancing partnerships between universities, health systems, and local

communities can further support health equity, improve public health literacy, and increase the region's resilience to demographic and epidemiological pressures.

Ultimately, the transition toward more modern, socially responsive universities represents both a significant opportunity and an ongoing challenge. By addressing structural constraints and fostering environments that enable higher education institutions to engage more meaningfully in health promotion and sustainable development, Western Balkan countries can position their universities as essential drivers of progress toward SDG 3 and broader societal transformation.

References

1. Arenliu Qosaj, F., & Bourdeaux, M. (2024). Health policy developments in the Western Balkan countries 2000–19: Towards European health and health care policies. *European Journal of Public Health, 34*(3), 460–466. https://doi.org/10.1093/eurpub/ckae045
2. Council of Europe Development Bank. (2022, August). Healthcare in Western Balkans hurting people's well-being and economic future. Healthcare in Western Balkans hurting people's well-being and economic future | CEB
3. Cowey, L. (2017). *Research Capacity in the Western Balkans: Report of the SPHERE Project.* WBC-RTI / European University Association
4. Dhima, S. (2011). *Albania's Journey into the Bologna Process: Europeanizing Higher Education Policies.* Master's Thesis, Erasmus University Rotterdam. https://thesis.eur.nl/pub/10825/-_BA_7552_-_Sibora_Dhima_RP.pdf
5. Dobbins, M. (2017). Explaining different governance reforms in Eastern European higher education: The cases of Poland and Romania. *European Educational Research Journal, 16*(5), 722–742.https://doi.org/10.1177/1474904116684138
6. EuropaNova. (2023). *Higher Education in the Western Balkans: Challenges and Reforms.* EuropaNova. https://europanova.eu/wp-content/uploads/2023/07/higher-education-balkans.pdf
7. European University Association. (2022). *Higher Education in the Western Balkans: Mapping Study.* European University Association. https://www.herdata.org/public/hewb.pdf
8. European Commission. (2025). *EU burden from non-communicable diseases and key risk factors*. Health Promotion and Disease Prevention Knowledge Gateway. https://health.ec.europa.eu/
9. Findler, F., Schönherr, N., Lozano, R., Reider, D., & Martinuzzi, A. (2019). *The impact of higher education institutions on sustainable development: A review and conceptualization*. International Journal of Sustainability in Higher Education, 20(1), 23–38. https://doi.org/10.1108/IJSHE-07-2017-0114
10. J Gabrani, A Anton, S Cilović-Lagarija, D Grujic, M Petrovski, N Rosic, N Terzic, M M Šantrić-Milićević, A Romel, S Skočibušić, Health Spending and NCD Mortality in the Western Balkans: Trends, Outcomes, and Policy Lessons, European Journal of Public Health, Volume 35, Issue Supplement_4, October 2025, ckaf161.1093, https://doi.org/10.1093/eurpub/ckaf161.1093
11. Institute for Health Metrics and Evaluation (IHME). (2024). *Global Burden of Disease Study 2021 (GBD 2021) results*. http://ghdx.healthdata.org/gbd-results-tool

12. Jakovljevic, M. M., & Laaser, U. (2015). Population aging from 1950 to 2010 in seventeen transitional countries in South Eastern Europe. *South Eastern European Journal of Public Health*. DOI: https://doi.org/10.4119/seejph-1796
13. Leal Filho, W., Raath, S., Pretorius, R. W., Vargas, V. R., & Ivanova, T. (2024). *Universities and the Sustainable Development Goals: A global review of transformational roles, challenges and opportunities*. Scientific Reports, 14, 65820. https://doi.org/10.1038/s41598-024-65820-9
14. Li, J., Pandian, V., Davidson, P. M., Song, Y., Chen, N., & Fong, D. Y. T. (2025). Burden and attributable risk factors of non-communicable diseases in 204 countries and territories, 1990–2021: A systematic analysis for the Global Burden of Disease Study 2021. *International Journal of Surgery, 111*(3), 2385–2397. https://doi.org/10.1097/JS9.0000000000002260
15. Matache, I. (2023). *Post-Communist Higher Education Expansion in the European Area: The Internationalization Context*. Perspective Politice, 16(Special Issue), 113-123. https://doi.org/10.25019/perspol/23.16.0.11
16. Pekez-Pavlisko, T., Jankovic, S., & Lovrečić, M. (2017). Medicines availability and prescribing policy for non-communicable diseases in the Western Balkans. *Frontiers in Public Health, 5*, 212. https://doi.org/10.3389/fpubh.2017.00212
17. Purcell, W. M., Henriksen, H., & Spengler, J. D. (2019). *Universities as catalysts of sustainable development: The role of education, research and engagement in the 2030 Agenda*. International Journal of Sustainability in Higher Education, 20(8), 1343–1357. https://doi.org/10.1108/IJSHE-12-2018-0234
18. Stojkovic, M., & Milovanovic, O. (2015). Health spending follows pace of population aging: Challenges lying ahead of the largest Western Balkan market. *Frontiers in Public Health, 3*, 58. https://doi.org/10.3389/fpubh.2015.00058
19. UNFPA Albania. (2020). *Albania: Demographic and health challenges*. United Nations Population Fund. https://albania.unfpa.org/
20. Vukasović, M. (2012). European Integration in Higher Education and Research in the Western Balkan Countries. NORGLOBAL Programme / University of Oslo. https://wbc-rti.info/object/news/10569/attach/NORGLOBAL_-_EI_and_HER_in_WBC_-_LR_FINAL.pdf
21. World Health Organization. (2020). *World health statistics 2020: Monitoring health for the SDGs*. WHO Press. https://www.who.int/data/gho
22. World Health Organization Regional Office for Europe. (2021). *Roadmap for health and well-being in the Western Balkans (2021–2025)*. WHO Europe. https://www.who.int/europe
23. World Health Organization Regional Office for Europe. (2025). *Artificial intelligence for health in the WHO European Region: Country profiles*. WHO/EURO:2025-12707-52481-81470. https://www.who.int/europe
24. World Health Organization (WHO). (2025). *Health workforce migration in the WHO European Region: country case studies from Albania, Armenia, Georgia, Ireland, Malta, Norway, Republic of Moldova, Romania and Tajikistan.* WHO European Regional Office Health workforce migration in the WHO European Region: country case studies from Albania, Armenia, Georgia, Ireland, Malta, Norway, Republic of Moldova, Romania and Tajikistan
25. Zgaga, P. (2011). *The Role of Higher Education in National Development – South-Eastern Europe and Reconstruction of the Western Balkans*. In The Europa World of Learning. Routledge. (PDF) The Role of Higher Education in the National Development

Nutrition as an essential element in the prevention and treatment of health pathologies

MSc. Adelina MUHAMETAJ
Department of Nursing
Faculty of Technical Medical Sciences
European University of Tirana, Tirana, Albania
https://orcid.org/0009-0009-3013-4724
e-mail: adelina.muhametaj@uet.edu.al

Abstract

The aim of this study is to analyze the impact of nutrition on the prevention and treatment of chronic diseases among the adult Albanian population. The study included 100 individuals aged 35–85, randomly selected from two health centers, one urban and one rural, in the Durrës region. The methodology used was cross-sectional and descriptive, combining physical examination with a structured self-administered questionnaire. The results showed that 27% of women were underweight, while the majority of the population had unhealthy eating habits, with high consumption of sugars, fried foods, alcohol, and tobacco. A significant correlation was identified between nutritional status, socio-demographic factors, and the occurrence of chronic pathologies. The study concludes that malnutrition continues to be an important determinant of health risk in Albania. It recommends structured interventions for nutritional education, the promotion of balanced diets, and strengthening the role of primary care in prevention.

***Keywords**: Nutrition, lifestyle, chronic diseases, nutritional status, prevention, public health.*

Introduction

Malnutrition and unhealthy lifestyle patterns today represent one of the greatest challenges to global public health. In recent decades, socio-economic changes, urbanization, and the increased consumption of processed foods have led to rising prevalence of obesity, diabetes, cardiovascular diseases, and other chronic conditions. Similar trends are observed in Albania, where the dietary behaviors of the population are often characterized by high caloric intake, saturated fats, and sugars, along with low levels of physical activity. Nutrition plays a central role in the prevention and management of these non-communicable diseases, directly influencing metabolic and cardiovascular health as well as the functioning of other bodily systems. Understanding the dietary habits of the Albanian population and their relationship to health status is essential for developing effective public health policies.

Literature Review

Nutrition, as a multidisciplinary science, aims to identify the role of nutrients in the functioning of the human organism and their impact on long-term health. International evidence shows that diets rich in fruits, vegetables, fiber, and whole grains have a protective effect against chronic diseases, whereas excessive consumption of sugars, trans fats, and processed foods is strongly associated with increased risk of obesity, dyslipidemia, diabetes, and cardiovascular pathologies. Studies by the World Health Organization emphasize that over 60% of global deaths are linked to lifestyle-related chronic diseases, in which nutrition is a direct influencing factor.

Modern dietary patterns have significantly reduced the intake of fresh foods and increased consumption of salt, saturated fats, and calories, especially in middle-income countries.

In Albania, studies on nutrition are limited, but data from INSTAT show an increase in cases of obesity, diabetes, and hypertension over recent decades. This highlights the need for new studies addressing the relationship between nutrition and population health.

Method

Type of study

Cross-sectional, descriptive, and analytical.

Study population

100 individuals aged 35–85, randomly selected from Health Center No. 1 (urban) and Arapaj 1 Health Center (rural) in the Durrës district.

Data collection instruments

- Physical examination (weight, height, BMI)
- Structured self-administered questionnaire on:
  - dietary habits
  - physical activity
  - health history
  - socio-economic status
  - disease history

Data analysis

- Descriptive statistics
- Comparisons by age group, gender, education, and economic income
- Analytical interpretation of the relationship between nutritional status and pathologies

Results

TABLE 1: Statistical data on the age of the study population

Nr. of Population	100	Nr. of Population	100
Average	60,41	Minimum	35
Median	60,00	Maximum	85
Moda	60	Standard error of the mean	2,081666
The standard deviation	14,8660687		

TABLE 2: Statistical data on BMI of the study population by gender.

Descriptive statistics, Gender=Female

	Nr.	Minimum	Maximum	Average	Standard of deviation
BMI	58	17.51	37.46	21.55	4.890
Weight (kg)	58	50.03	106.98	59.19	12.121
Height (cm)	58	155	169	166	3.31

Descriptive statistics, Gender= Male

	Nr.	Minimum	Maximum	Average	Standard of deviation
BMI	42	18.40	42.87	30.08	6.001
Weight (kg)	42	56.35	128.55	89.79	17.221
Height (cm)	42	170	185	174	3.402

As shown in our study population of 100 individuals, the mean age and the median are approximately equal, while the standard deviation, SD = 14.8660687, is relatively high, indicating that the study population is distributed over a wider range. This can also be observed in Table 1.

Furthermore, it is evident that females (BMI = 21.55 ± 4.890) have a lower BMI compared to males (BMI = 30.08 ± 6.001). The average height for females is 166 ± 3.31 cm, whereas for males it is 174 ± 3.402 cm. Regarding weight, males have an average weight of 87.79 ± 17.221 kg, compared to females with 59.19 ± 12.121 kg.

CHART 1: Distribution by age group (within the adult population 35-85 years old based on a difference of 10 years)

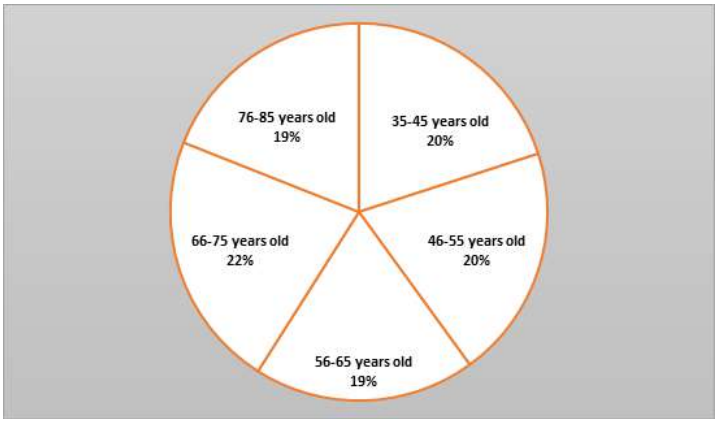


CHART 2: Distribution by gender (a female dominance of 58%) is seen

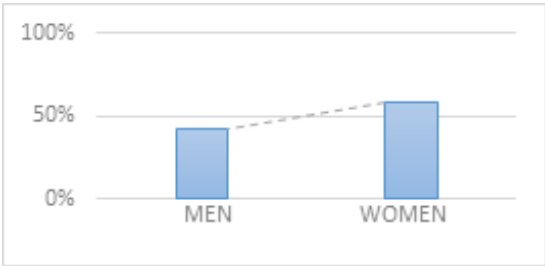


CHART 3: Distribution by residence (we have an equal distribution of subjects, both in rural and urban areas)

CHART 4: Distribution by level of education (in our population, a predominance of secondary education is observed with about 26%)

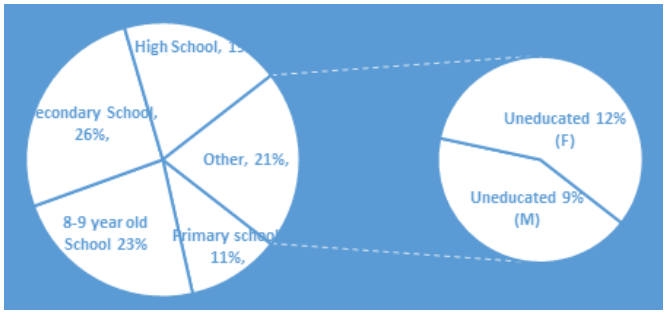


CHART 5: Distribution by marital status (highest participation of individuals with married civil status, worth around 59%)

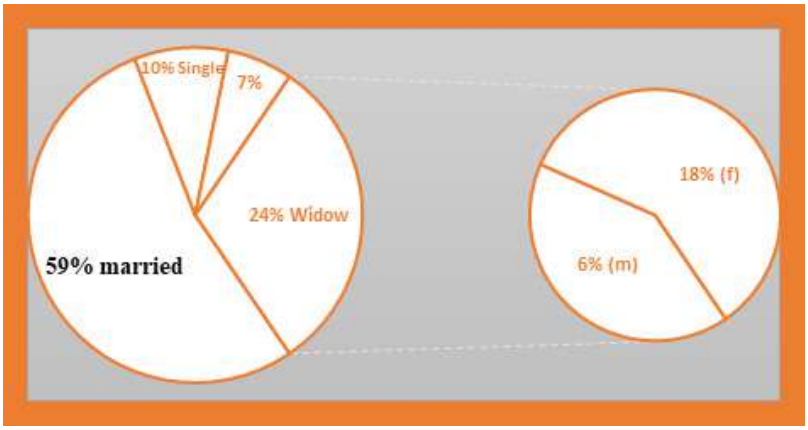


CHART 6: Distribution by employment status

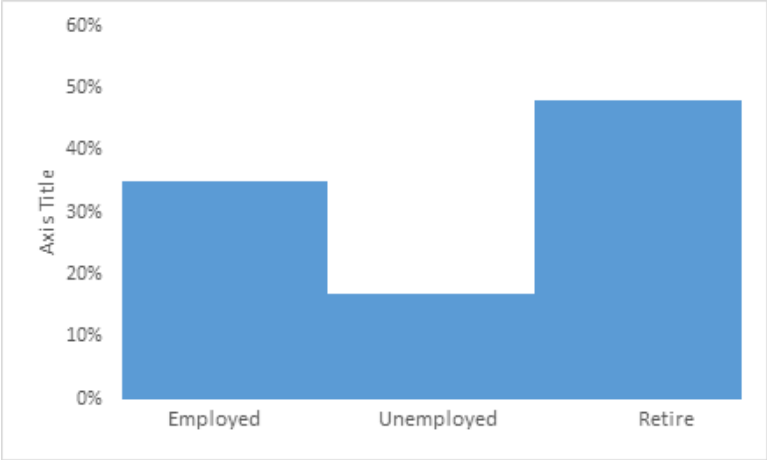
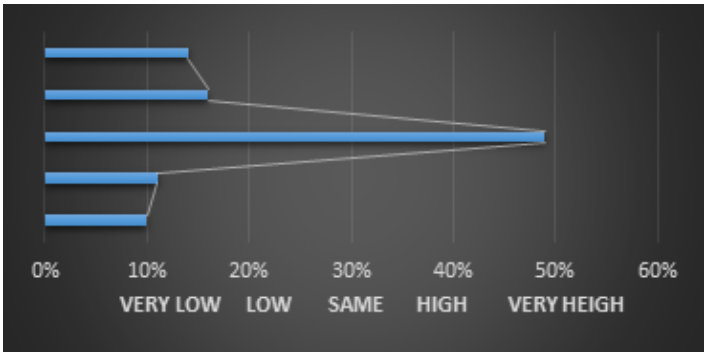


CHART 7: Distribution by economic income (compared to the average household economic income in Albania)



Based on the graphs, we can conclude that the majority of the study population is retired, approximately 48%. On the other hand, judging again from the graphical data, we can state that the study population generally has an average (moderate) income level, around 49%.

CHART 8: Regardless of the presence or absence of any disease, how is your overall health?

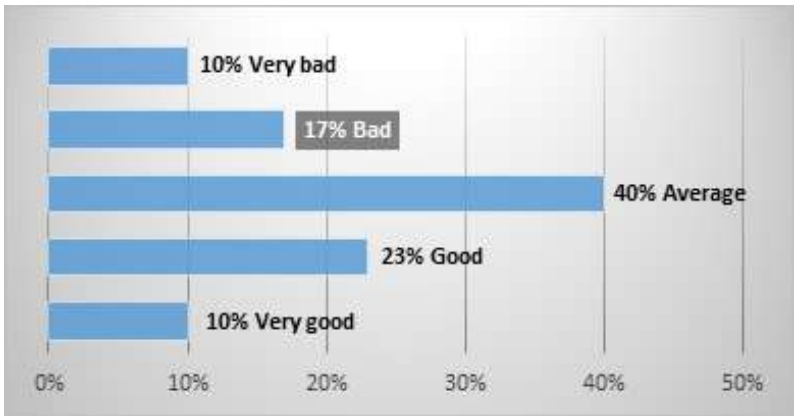


CHART 9: Have you used medications recently or have you used them before?

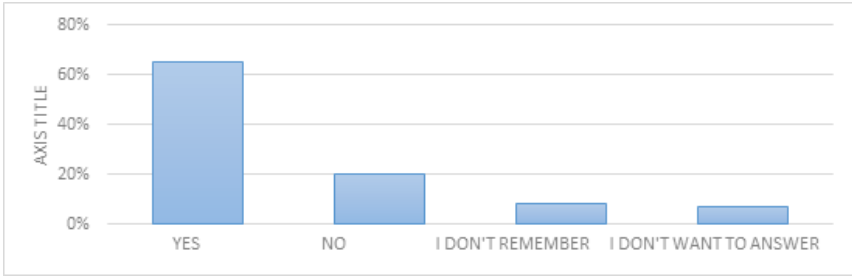


CHART 10: How often do you make a routine visit to your health center?

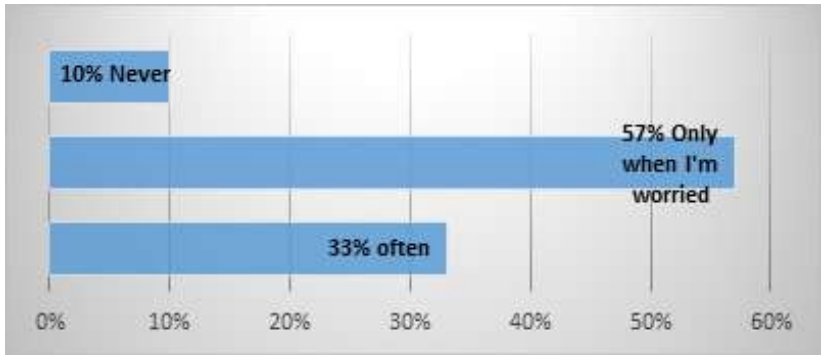


CHART 11: Number of visits to health centers, ambulances and polyclinics

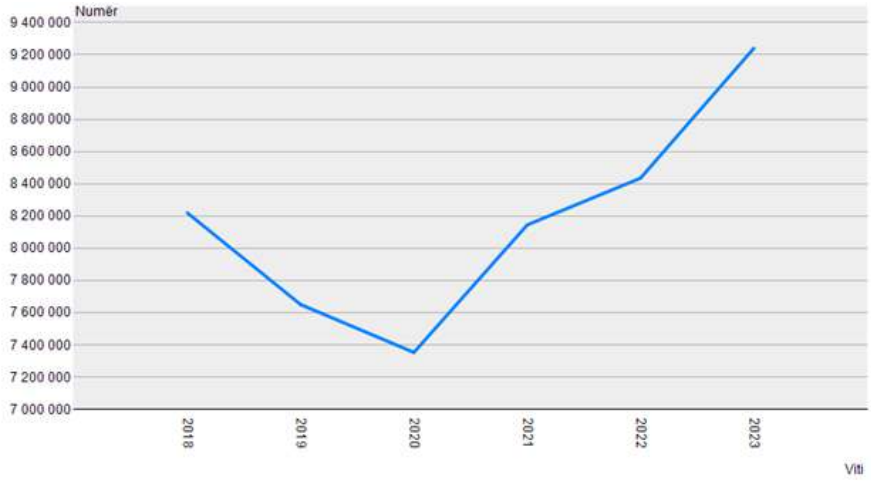
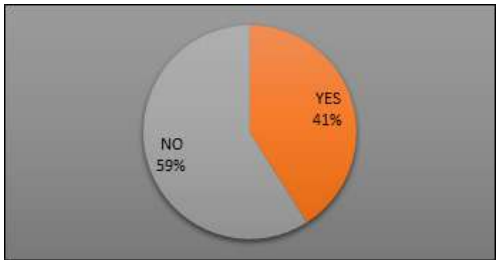


CHART 12: Do you do physical activity?



Assessment of different body systems affected by diet

CHART 13: Distribution of GI system diseases

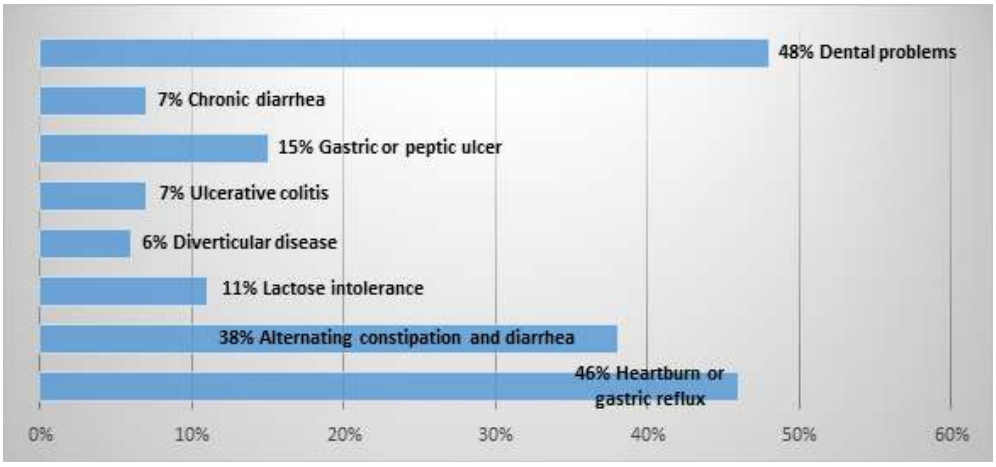


CHART 14: Distribution of diseases of the hepatic/pancreatic system

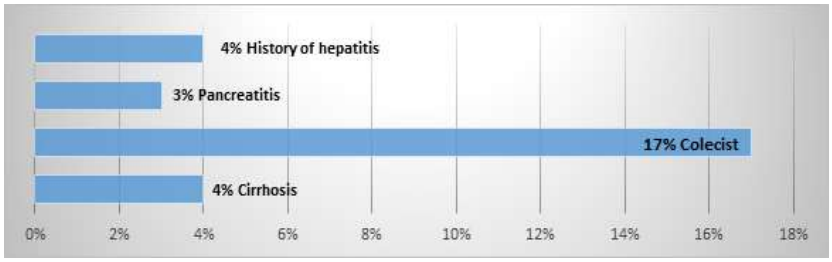


CHART 15: Distribution of diseases of the musculoskeletal system

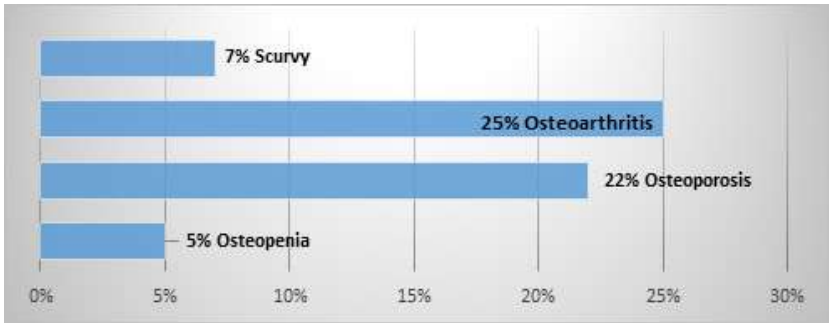


CHART 16: Distribution of metabolic/endocrine system diseases

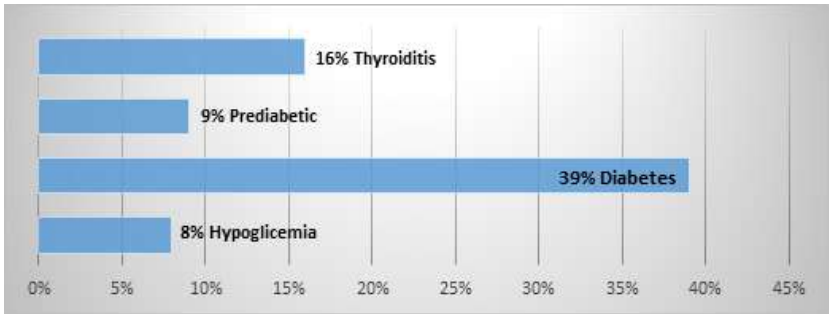


CHART 17: Distribution of diseases of the CVD system

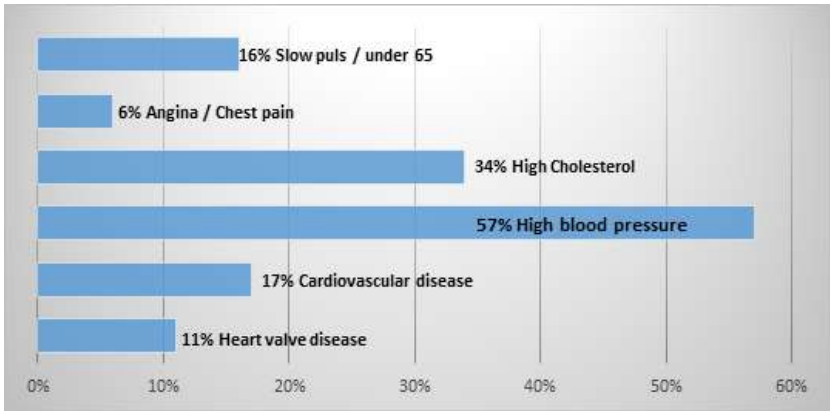


CHART 18: Distribution of diseases of the hematological / blood system

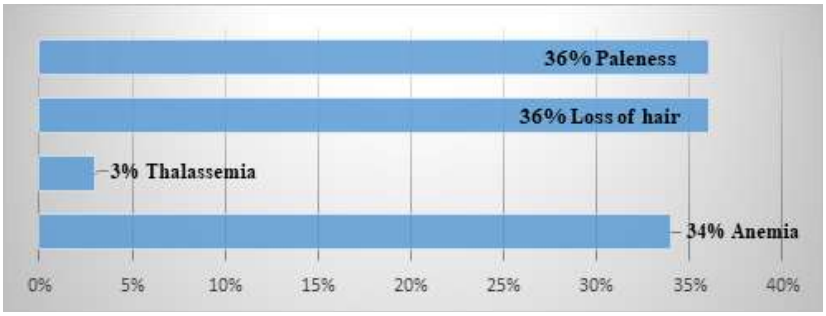


CHART 19: Distribution of urinary/renal system diseases

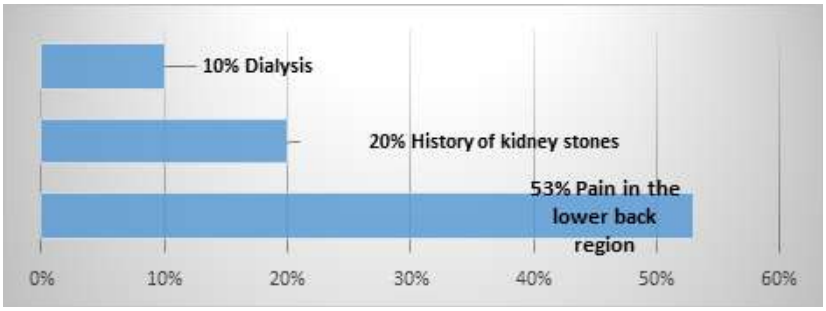


CHART 20: Distribution of neurological system diseases

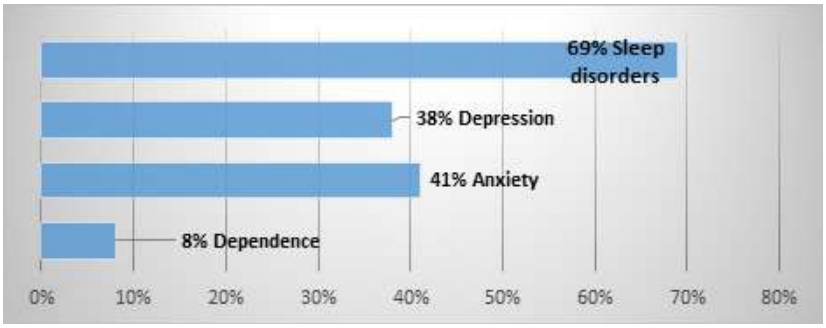


CHART 21: Eating disorders

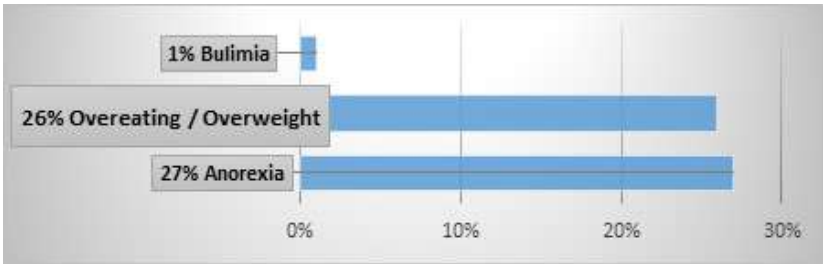
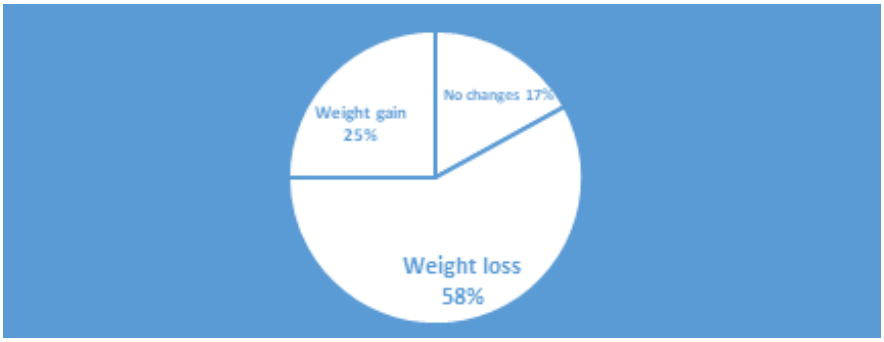


CHART 22: How has the COVID-19 pandemic affected your diet?



Nutrition History

CHART 23: Have you ever received information about nutrition?

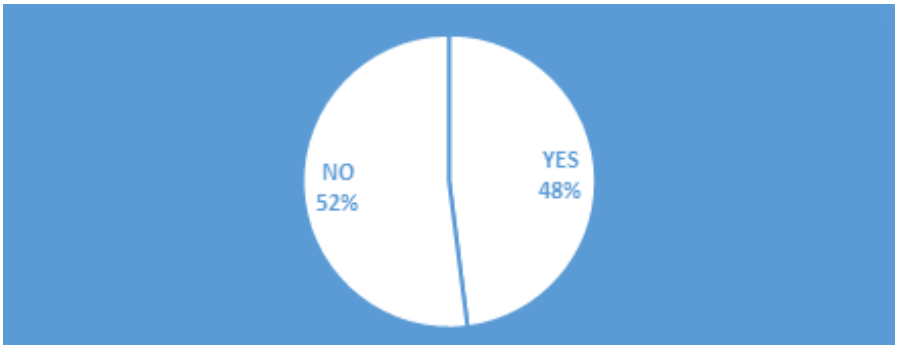


CHART 24: Do you think you eat healthily?

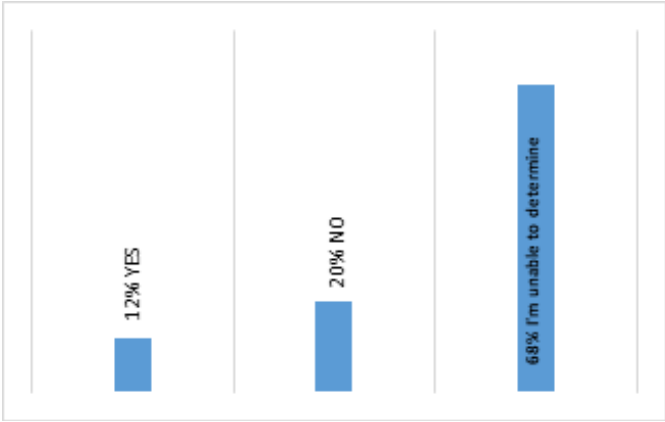


CHART 25: How do you classify your eating habits?

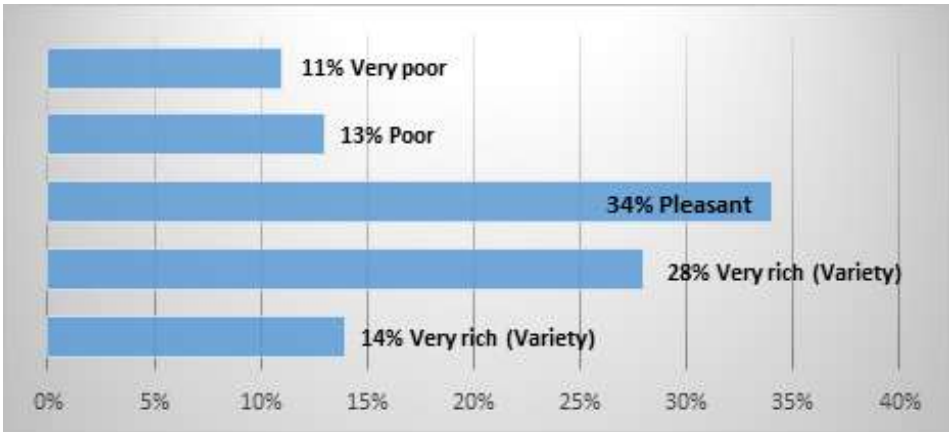


CHART 26: Have you made any changes to your eating habits due to your health?

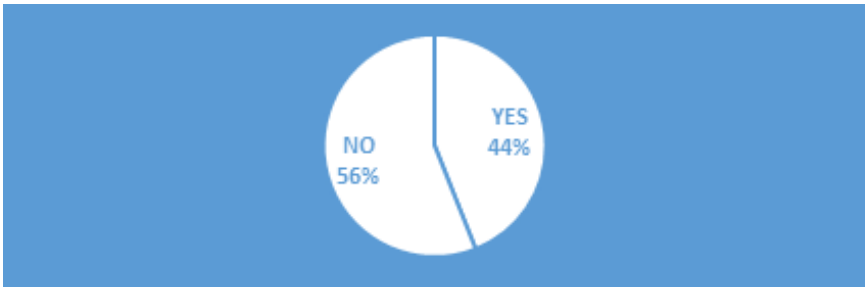


CHART 27: Have you had a recent history of weight loss or weight gain?

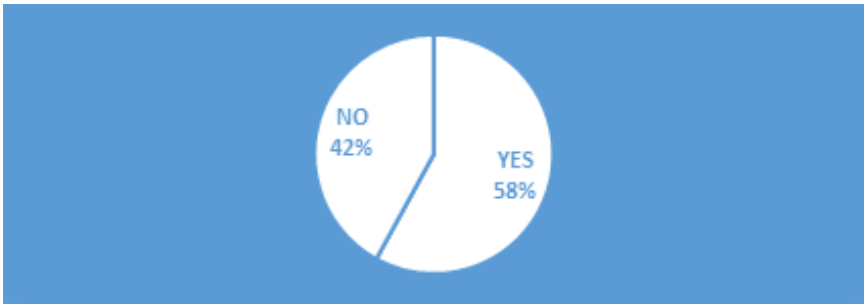


CHART 28: Distribution by consumption of fats, pastries, fruits, vegetables and salt

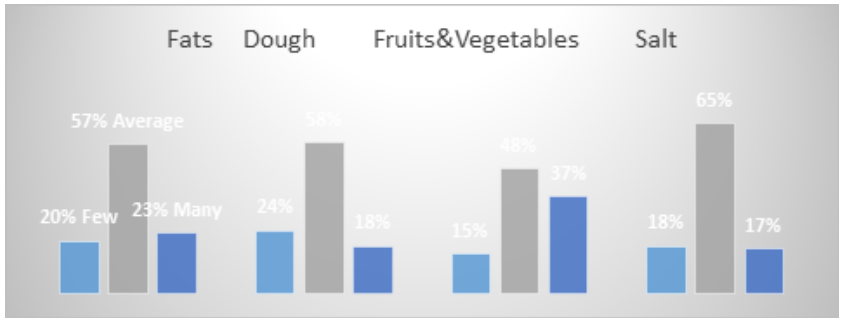


TABLE 3: Statistical data for grouped BMI

Gender	Underweight (BMI<=18.5)	Normal weight (18.5<BMI<=24.9)	Overweight (24.9<BMI<=29.9)	Preobesity (24.9<BMI<=34.9)	Obesity (BMI>34,9)
M	1%	7%	17%	7%	10%
F	26%	20%	7%	4%	1%

TABLE 4: Nutritional status & gender

Nutritional Status	The percentage
Underweight (BMI<=18.5)	
Normal weight (18.5<BMI<=24.9)	
Overweight (24.9<BMI<=29.9)	
Preobesity (24.9<BMI<=34.9)	
Obesity (BMI>34.9)	
Total	100%

TABLE 5: Nutritional status & education

Education	Underweight (BMI<=18.5)	Normal weight (18.5<BMI<=24.9)	Overweight (24.9<BMI<=29.9)	Preobesity (24.9<BMI<=34.9)	Obesity (BMI>34.9)
Primary school	4%	2%	3%	1%	1%
8-9 year old school	7%	8%	3%	3%	2%
Secondary school	7%	4%	14%	1%	0%
High School	3%	6%	2%	3%	5%
Uneducated	6%	7%	2%	3%	3%

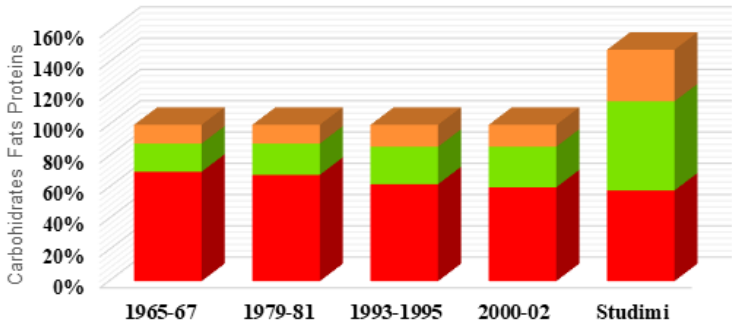
TABLE 6: Nutritional status & economic income

Economic Income	Underweight (BMI<=18.5)	Normal weight (18.5<BMI<=24.9)	Overweight (24.9<BMI<=29.9)	Preobesity (24.9<BMI<=34.9)	Obesity (BMI>34.9)
Very low	3%	5%	1%	1%	3%
Low	5%	6%	5%	1%	0%
Same	13%	11%	8%	7%	8%
High	4%	2%	5%	1%	0%
Very high	2%	3%	5%	1%	0%

TABLE 7: Distribution of major body systems based on age groups

	35-45 vjeç	46-55 vjeç	56-65 vjeç	66-75 vjeç	76-85 vjeç
SYSTEM GASTRO-INTESTINAL	16%	27%	4%	43%	52%
HEPATIC/PANCREATIC SYSTEM	0%	4%	6%	8%	10%
SYSTEM MUSCULO-SKELETAL	4%	12%	12%	15%	16%
METABOLIC/ENDOCRINE SYSTEM	11%	14%	14%	17%	18%
CARDIOVASCULAR SYSTEM	14%	22%	27%	38%	40%
URINARY/RENAL SYSTEM	1%	17%	16%	19%	21%

CHART 29: Distribution of protein, fat and carbohydrate intake in the Albanian population vs. our study population



Discussion

The findings of the study clearly show that dietary habits and nutritional status directly influence the health of the adult population. The high prevalence of unhealthy eating behaviors, particularly the elevated consumption of fried foods and sugars, represents a major risk factor for the development of chronic diseases in the studied sample.

Differences between genders (higher underweight prevalence among females and overweight among males) suggest that health interventions should be personalized according to gender and socio-demographic factors.

Compared to international literature, the results align with global WHO trends, which identify malnutrition as an important risk factor for non-communicable diseases. Another important observation is the low level of readiness among the population to change dietary behaviors, which complicates the implementation of preventive programs.

Conclusions

- The studied population shows a high prevalence of unhealthy dietary habits.
- There is a clear relationship between nutritional status, socio-demographic factors, and the occurrence of chronic pathologies.
- Males show a higher prevalence of overweight/obesity, while females more frequently present underweight.
- Cardiovascular and metabolic diseases are directly linked to dietary patterns.
- The low level of readiness for behavioral change calls for new health education strategies.

Recommendations

- Reduce the consumption of sugars, saturated fats, and salt (<5 g/day).
- Increase the intake of fruits and vegetables (≥400 g/day).
- Promote regular physical activity.
- Provide continuous nutritional education at the community level.
- Integrate nutritional counseling into primary health care.
- Focus on vulnerable groups: the elderly, low-income individuals, and people with chronic diseases

References

1. (n.d.). Retrieved from http://evolve.elsevier.com/Williams/basic/
2. (n.d.). Retrieved from Diabetes.com: www.diabetes.com
3. (n.d.). Retrieved from Lipids in Health and Disease: www.lipidworld.com
4. (2011, September 22). Retrieved September 2011, from What we eat in America: https://www.ars.usda.gov/northeast-area/beltsville-md-bhnrc/beltsville-human-nutrition-research-center/food-surveys-research-group/docs/temp-wweia-key-points-and-factsheets-overview/
5. Alan Titchenal, Skylar Hara, Noemi Arceo Caacbay, William Meinke-Lau, Ya-Yun Yang, Marie Kainoa Fialkowski Revilla, Jennifer Draper, Gemady Langfelder, Cheryl Gibby, Chyna Nicole Chun, and Allison Calabrese. (2020). *Human Nutrition.* (U. o. Program, Ed.) Hawai'i: Creative Commons Attribution 4.0 International Licence.

6. *American Dental Association.* (n.d.). Retrieved from www.ada.org/fluoride.aspx
7. Ann M. Coulston, C. J. (2017). *Nutrition In The Prevention And Treatment Of Disease* (Vol. 4). United Kingdom: Nikky Levy.
8. Associates, N. I. (2021). *Nutritional Assessment Questionnaire.* Retrieved from INVESEO: https://www.nihadc.com/forms/naq.PDF
9. *Centers For Disease Control and Prevention.* (2011, October 16). Retrieved from 1988-2008 no leisure-time physical activity trend chart: https://www.cdc.gov/nccdphp/dnpa/physical/stats/leisure_time.htm
10. Council, N. R. (Ed.). (n.d.). NIH-National Library of Medicine. *Recommendations on Diet, Chronic Diseases, and Health*. Retrieved from Dietary Recommendations.
11. *diet-nutrition-greenfacts-level2.pdf.* (2021). Retrieved from Scientific Facts on Diet and Nutrition Prevention of Chronic Diseases: https://www.greenfacts.org/en/index.htm
12. *Food and Nutrition Information Center*. (n.d.). Retrieved from http:// fnic.nal.usda.gov
13. GRENADINES, S. V. (2015). *NATIONAL HEALTH & NUTRITION SURVEY.* The Government of St. Vincent and the Grenadines. European Union 10th European Development Fund .
14. Health, N. C. (n.d.). Retrieved from www.ncemch.org
15. *Healthy People 2020*. (2020). Retrieved from http://healthypeople.gov/2020/
16. INSTAT. (1990-2020). *Numri i vizitave në qendrat shëndetësore, ambulanca dhe poliklinika sipas Lloji, Variabla dhe Viti*. Retrieved from http://databaza.instat.gov.al/pxweb/sq/DST/START__HE__KSH/HE0160/?rxid=b5069c81-9c75-4560-905a-2cb719af3ada
17. *International Foundation for Functional Gastrointestinal Disorders.* (n.d.). Retrieved from www.iffgd.org
18. KaiserL, A. (2008). *Position of the academy of nutritionand dietetics: nutrition and lifestyle for a healthy pregnancy outcome.*
19. National Cancer Institute. (n.d.). Retrieved from www.cancer.gov
20. *National Center for Chronic Disease Prevention and Health Promotion.* (n.d.). Retrieved from Heart disease prevention: what you can do: www.cdc.gov/HeartDisease/prevention.htm
21. *National Council on Aging.* (n.d.). Retrieved from www.ncoa.org
22. *National Institute of Diabetes and Digestive and Kidney Diseases.* (n.d.). Retrieved from www.niddk.nih.gov
23. *National Institute on Aging.* (n.d.). Retrieved from www.nof.org
24. Nix, S. (2013). *Williams'Basic Nutrition and Diet Therapy* (Vol. 14). Missouri, Canada: Elsevier Mosby.
25. Press, N. A. (Ed.). (2002). Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids. *Food and Nutrition Board, Institute of Medicine.* Washington, DC. Retrieved from Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids.
26. Smakaj, E. (2019, Korrik). *Etleva SMAKAJ 2016* . Retrieved from Dizertacion: http://umed.edu.al/wp-content/uploads/2019/07/Dizertacioni-1.pdf
27. Staci Nix, M. R. (2013). Williams's Basic Nutrition and Diet Therapy. In S. Nix, *INTRODUCTION TO BASIC PRINCIPLES OF NUTRITION SCIENCE* (Vol. 14). Salt Lake City, Utah, Canada: Elsevier Mosby.
28. *U.S Departament of Agriculture, Center for Nutrition Policy and Promotion.* (2011, August 23). Retrieved from USDA's myplate home page: https://www.myplate.gov/
29. *U.S Department of Agriculture, Food Safety and Inspection Service food safety publications.* (n.d.). Retrieved from www.fsis.usda.gov/fact_ sheets/index.asp

30. U.S Government Printing Office, 2. (Ed.). (2011). National Center for Health Statistics. *Health, United States, 2010: with special feature on death and dying*. U.S.
31. *U.S. Department of Agriculture, Economic Research Service. U.S. food supply:*. (2010, February 16). Retrieved from nutrients and other food compo nents, per capita per day, 1909 to 2004: https://www.ers.usda.gov/Data/FoodConsumption/NutrientAvailIndex.htm
32. *U.S. Department of Health and Human Services. Healthy people ,Washington*. (n.d.). Retrieved from U.S. Government Printing Office: https://www.sciencedirect.com/science/refhub/B978-0-323-08347-8.00001-9/sr0010
33. *U.S. Department of Health and Human Services. Healthy people 2020, Washington, DC*. (n.d.). Retrieved from U.S. Government Printing Office; 2010.
34. *USDA Choose My plate*. (n.d.). Retrieved from https://www.myplate.gov/
35. WHO. (2000). *Nutrition for Health and Development*. In progress, WHO, France.
36. WHO. (2020, April 29). *Nutrition*. (World Health Organization) Retrieved from Health Topics/ Nutrition: https://www.who.int/health-topics/nutrition
37. WHO. (2020, April 29). *Nutrition*. Retrieved from Health Diet: https://www.who.int/news-room/fact-sheets/detail/healthy-diet
38. WHO. (n.d.). *Health Topics*. Retrieved from Food Safety: https://www.who.int/news-room/fact-sheets/detail/food-safety
39. World Health Organization. (2010, May 6). *A healthy lifestyle- WHO recommendations*. Retrieved from https://www.who.int/europe/news-room/fact-sheets/item/a-healthy-lifestyle---who-recommendations
40. *World Health Organization child growth standards*. (n.d.). Retrieved from https://www.who.int/toolkits/child-growth-standards

Minimal Change Disease and Metabolic Syndrome: A Therapeutic Challenge in a Young Adult Male

Ambra METASANA
Department of Nephrology, Dialysis and Transplantation, University Hospital Center "Mother Teresa", Tirana, Albania

Amantia IMERAJ
Department of Nephrology, Dialysis and Transplantation, University Hospital Center "Mother Teresa", Tirana, Albania

Ariana STRAKOSHA
Department of Nephrology, Dialysis and Transplantation, University Hospital Center "Mother Teresa", Tirana, Albania

Abstract

Minimal Change Disease (MCD) is a podocytopathy most commonly diagnosed in children and less frequently in adults, where the clinical course tends to be more complicated and variable. In adults, the disease often demonstrates delayed responsiveness to corticosteroids, higher relapse rates, and an increased likelihood of requiring alternative forms of immunosuppression to achieve remission. When MCD occurs together with metabolic syndrome—a cluster of metabolic abnormalities including central obesity, dyslipidemia, hypertension, and hepatic steatosis—the condition becomes even more challenging to manage. The combination creates a vicious cycle in which metabolic dysfunction aggravates glomerular injury while renal impairment worsens cardiometabolic status. In this case, we describe a 21-year-old male who presented with nephrotic-range proteinuria and severe metabolic derangements. Renal biopsy revealed MCD, and treatment required a highly individualized approach in

order to preserve renal function while avoiding the detrimental metabolic consequences associated with high-dose steroid therapy. Rituximab was introduced early as part of a steroid-sparing strategy, resulting in a favorable clinical response. This case highlights the significance of personalized immunosuppressive therapy, long-term metabolic control, and multidisciplinary care in preventing irreversible renal and cardiovascular outcomes in young adults living with both MCD and metabolic syndrome.

Introduction

Minimal Change Disease is characterized by the loss of podocyte foot processes, resulting in marked proteinuria and nephrotic syndrome. [1,2] However, because glomerular structure appears preserved on routine light microscopy, diagnosis often requires electron microscopy. [2] Although its precise pathogenesis remains incompletely understood, immune dysregulation affecting podocytes is strongly implicated. [3] Adults diagnosed with MCD frequently experience a clinical course that differs substantially from children, including delayed response to steroid therapy, higher likelihood of sustained proteinuria, and an increased overall burden of disease-related complications. [3,4] Metabolic syndrome, which includes obesity, elevated blood pressure, altered lipid metabolism, insulin resistance, and in many cases, non-alcoholic fatty liver disease—has become increasingly common among young adults as a result of changing dietary patterns and reduced physical activity. [5] When metabolic syndrome exists alongside kidney disease, each condition accelerates the progression of the other. [5-7] Glomerular hyperfiltration, lipid-mediated inflammatory damage, and increased oxidative stress contribute to podocyte dysfunction, raising concern that cases initially diagnosed as MCD may evolve into more severe forms of glomerulosclerosis if metabolic drivers remain uncontrolled. [5-7] The therapeutic challenge in this case lies not only in ensuring remission of proteinuria, but also in protecting metabolic health, preventing steroid-associated toxicity, and enabling long-term kidney preservation.

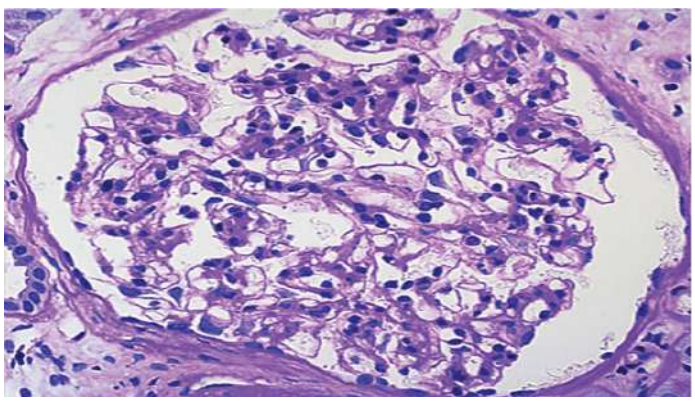
Case Presentation

A 21-year-old male presented with a gradual 5-year history of episodic occipital headaches, persistent hypertension, polyuria accompanied by excessive thirst, and chronic joint discomfort. Over this period, he gained significant body weight, particularly around the abdomen. He reported a lifestyle characterized by frequent intake of highly processed meals and the consumption of approximately two liters of sugar-sweetened beverages each day, contributing to the development of metabolic complications. He had no known family history of autoimmune disease, hereditary kidney disorders, or premature cardiovascular disease.

Initial medical evaluation in April 2024 revealed important abnormalities. Laboratory assessment showed persistent nephrotic-range proteinuria, reaching over 5 grams in 24 hours, in addition to a mildly elevated serum creatinine level that indicated an early decline in kidney function. His lipid profile demonstrated markedly elevated cholesterol and triglyceride levels, confirming severe dyslipidemia. His uric acid level was also significantly high, suggestive of metabolic overproduction or impaired renal excretion. Liver function testing detected elevations consistent with hepatocellular stress. A computed tomography scan of the abdomen confirmed Grade III hepatic steatosis, demonstrating significant fat infiltration within the liver parenchyma. At that time, however, the patient was unfortunately lost to follow-up and no specific treatment was started.

Parameter	Result	Interpretation
Urea	56 mg/dL	Mild azotemia
Creatinine	1.30–1.47 mg/dL	Early renal dysfunction
Proteinuria	4.3–5.5 g/24h	Nephrotic range
Cholesterol	264 mg/dL	Severe dyslipidemia
LDL	167 mg/dL	High cardiovascular risk
Triglycerides	360 mg/dL	Metabolic syndrome
Uric acid	12 mg/dL	Hyperuricemia
Liver enzymes	Elevated	Suggest NAFLD
Urinalysis	No hematuria	Non-inflammatory pathology

Nearly one year later, in March 2025, he returned to medical attention with visible peripheral edema, persistent hypertension, and worsening proteinuria. A renal biopsy was performed to determine the underlying cause of his nephrotic syndrome. Initially, the biopsy was mistakenly interpreted as suggesting mesangiocapillary glomerulonephritis, a condition associated with immune complex involvement. A more detailed re-evaluation, confirming Minimal Change Disease, without immune complex deposition.



Further Hospital Evaluation

He was admitted to the hospital in April 2025 due to the progression of renal dysfunction and worsening nephrotic syndrome. At that time, laboratory findings indicated proteinuria exceeding eight grams per day, accompanied by elevated urinary microalbumin levels. Kidney function remained impaired, though stable, while liver enzymes were significantly higher than before, indicating progression of hepatic steatosis. Extensive immunological testing—including markers for autoimmune, viral, and neoplastic diseases—returned negative results. Cardiac function and renal Doppler ultrasonography were normal, ruling out secondary hemodynamic causes of kidney injury.

Test	Result
Proteinuria	8.4 g/24 h
Microalbuminuria	6.6 g/24 h
Creatinine	1.27 mg/dL
Urea	49 mg/dL
Triglycerides/LDL	351/156 mg/dL
ALT/AST/GGT	141/47/209 U/L

The confirmed final diagnosis included:

- Minimal Change Disease causing severe proteinuric nephropathy
- Chronic kidney disease, stage G2/A3
- Metabolic syndrome with hypertension, dyslipidemia, hyperuricemia, and obesity
- Grade III non-alcoholic fatty liver disease

Therapeutic Intervention

Management required addressing both nephrotic syndrome and the systemic metabolic burden. To reduce glomerular pressure and protein loss, an angiotensin-converting enzyme inhibitor was initiated. In addition, an SGLT2 inhibitor was introduced to improve metabolic control by reducing glucose reabsorption and to provide additional kidney-protective benefits such as lowering intraglomerular hyperfiltration. A statin was added to attenuate lipid toxicity and reduce long-term cardiovascular risk.

For immunosuppression, a low-dose steroid regimen was started. Unlike standard recommendations, high-dose corticosteroids were intentionally avoided to prevent further deterioration of hepatic steatosis, minimize body fat accumulation, and reduce the risk of steroid-induced diabetes. Rituximab was selected as a steroid-sparing agent due to its demonstrated efficacy in achieving remission in adults with MCD. The patient received two 1-gram infusions of rituximab spaced 14 days apart. This allowed suppression of B-cell-mediated immune activity while minimizing systemic metabolic consequences.

Supportive therapy included:

- ACE inhibitor - reduction of intraglomerular hyperfiltration and proteinuria
- SGLT2 inhibitor - dual benefit in renal protection and weight/metabolic control
- Statin therapy - management of persistent dyslipidemia to reduce renal lipotoxicity
- Sodium restriction and structured weight-loss program

Immunosuppressive strategy:

- Methylprednisolone 0.5 mg/kg/day (32 mg) - lower dose to reduce metabolic toxicity
- Rituximab 1 g IV on days 1 and 14 - selected for steroid-sparing effect and durable remission potential

Clinical Progress and Follow-Up

Over the following months, the patient demonstrated noticeable improvement. His proteinuria decreased substantially, though it had not yet reached complete remission. Kidney function also stabilized, indicating a halt in the progression of chronic kidney disease. Importantly, he achieved meaningful weight loss (-10kg) through lifestyle changes and dietary counseling, which contributed to improvements in blood pressure control and liver enzyme normalization. Edema resolved completely, and his physical functioning improved.

Date	Creatinine (mg/dL)	Urea (mg/dL)	Proteinuria (g/24h)	Microalbuminuria (g/24h)
30/07/2025	1.54	86.9	2.7	2.7
21/08/2025	1.48	73.9	3.7	-
08/10/2025	1.20	78	3.1	2.7

While he did not yet reach full remission of nephrotic syndrome, his gradual progress reflected a positive response to rituximab therapy. The stabilization of renal function and slowing of proteinuria progression suggest the potential to avoid progression to more permanent glomerular scarring.

Discussion

This case illustrates several important lessons in the management of Minimal Change Disease in an adult with metabolic syndrome. First, diagnosis required careful histological review, emphasizing that MCD cannot be reliably confirmed without electron microscopy. [4,5] Second, the metabolic abnormalities present in this patient likely contributed both to the severity of his disease and to reduced responsiveness to standard steroid therapy. [3-5] Obesity and dyslipidemia are known to cause harmful mechanical and inflammatory stress on podocytes, potentially leading to more complex glomerular pathology resembling early focal segmental glomerulosclerosis — a condition that may develop if MCD is not adequately controlled. [3-5]

The avoidance of high-dose steroids in this case was crucial. [4,5] Corticosteroids, while highly effective in many patients, can worsen insulin resistance, promote visceral fat accumulation, and accelerate liver steatosis. [4,5,8] These metabolic side effects would only further impair kidney recovery. [8] Rituximab therefore represented a more appropriate immunosuppressive choice, with evidence supporting its ability to induce remission and prevent relapses while maintaining a favorable metabolic safety profile. [9-14]

Long-term monitoring remains essential. Although the patient's progress is promising, persistent proteinuria indicates ongoing podocyte vulnerability. [9,10] If remission is not achieved or if proteinuria worsens, a repeat kidney biopsy may be necessary to evaluate whether irreversible glomerulosclerosis has begun to develop. [9-14]

Conclusion

This case highlights the complex interaction between podocyte-driven renal disease and systemic metabolic dysfunction in a young adult. Early investigation, accurate renal biopsy interpretation, and rapid initiation of appropriate immunotherapy were vital to improving this patient's prognosis and preventing further kidney damage. Rituximab allowed for effective immunosuppression while reducing steroid exposure, ultimately improving both renal and metabolic outcomes.

Equally important, lifestyle modification and weight reduction provided essential support in halting disease progression. Continued follow-up is required to ensure sustained remission, prevent renal decline, and avoid severe cardiovascular and hepatic complications that often accompany metabolic syndrome.

This case demonstrates that kidney disease cannot be treated in isolation. Successful care requires a multidisciplinary approach that addresses the full spectrum of metabolic risk factors, especially in young adults whose long-term health and organ function can still be preserved through timely, coordinated intervention.

References

1. KDIGO 2023 Clinical Practice Guideline for Glomerular Diseases.
2. Vivarelli M, et al. Rituximab in minimal change disease and FSGS. JASN. 2022.
3. Ponticelli C, Glassock RJ. Pathophysiology of MCD and FSGS. N Engl J Med. 2019.
4. Rovin BH, et al. Management strategies for adult nephrotic syndrome. Kidney Int. 2021.
5. Choudhury D, et al. Interaction of metabolic syndrome and renal disease. CJASN. 2020.
6. Fogo AB. Causes and mechanisms of FSGS progression. Nat Rev Nephrol. 2015.
7. Jefferson JA, et al. Podocyte biology and clinical implications. Kidney Int. 2020.
8. Fassett RG, et al. Lipid nephrotoxicity and CKD progression. Kidney Int. 2018.
9. Kari J, et al. Adult steroid-resistant MCD and rituximab outcomes. Clin Nephrol. 2021.
10. Rista, E., Cadri, V., Duni, A., Musa, J., Hyseni, F., Guy, A., ... & Idrizi, A. (2021). Rituximab Treatment of Membranous Nephropathy after Failure of other Therapies-A Case report. *Archives of Clinical and Medical Case Reports*, *5*(2), 234-239.
11. Yabu JM, et al. Role of obesity in podocyte dysfunction. CJASN. 2017.
12. Targher G, et al. NAFLD in CKD — mechanisms and outcomes. Nat Rev Nephrol. 2020.
13. Garofalo C, et al. SGLT2 inhibitors in CKD beyond diabetes. Clin Kidney J. 2022.
14. RISTA, Elvana, Kristi SALIAJ, and Vilma CADRI. "Chronic Kidney Disease: Old challenges and New Perspectives." 236.

Dog Bites in Humans: Current Insights into Causative Microorganisms and Associated Infections

Ermira MUCO
Infectious Diseases Service, University Hospital Center "Mother Teresa" Tirana, Albania. MD, PhD.
Corresponding author: ermiramuco@yahoo.com

Amarildo BLLOSHMI
Department of Imaging Sciences, University Hospital Center 'Mother Theresa', Tirana, Albania

Ornela CELA
Dermatology & Venerology Service, University Hospital Center "Mother Theresa", Tirana, Albania

Najada KALLASHI (JAHIQI)
University Hospital of Trauma,
Tirana, Albania, - Associate Professor

Abstract

Introduction: Although dogs are considered humans' best friends, they often bite and cause wounds that may become complicated with life-threatening infections. Various Gram-positive and Gram-negative microorganisms can lead to conditions such as sepsis, septic shock, multiorgan failure, tetanus, rabies, and others. The cornerstone of management is appropriate wound care, immunoprophylaxis, and treatment with selected antibiotics and other necessary symptomatic therapies.

Methods: A review of the literature was conducted to identify studies addressing the microbial agents, infectious syndromes or nosologies caused by dog bites, and the antibiotic and immunoprophylactic measures aimed at preventing secondary infectious complications. Diagnostic and therapeutic approaches in these patients were also evaluated, as well as the role of clinical microbiology laboratories in isolating microorganisms from wound or blood cultures.

Results: Dog bites carry a significant risk of infectious diseases such as tetanus and rabies. Despite the availability of vaccination, tetanus remains a global threat and a serious public health issue in our country, with mortality rates reaching up to 40%. These patients may also present with clinical manifestations of meningitis, endocarditis, fasciitis, septic arthritis, osteomyelitis, and other conditions caused by diverse microbial pathogens.

Conclusions: Dog bites are common incidents worldwide and in our region, leading to physical impairment, psychological trauma, secondary wound infections, and potentially life-threatening infectious diseases, as well as considerable economic costs. Proper and timely management of these patients requires strong and professional interdisciplinary collaboration.

***Keywords**: dog bite wound, bite, microorganisms, immunization status, antibiotic therapy, tetanus vaccination, epidemiology, treatment.*

Introduction

Dogs, often called humankind's four-legged friends, trace their origins back more than 100,000 years.[1] They are believed to be the first animal domesticated by humans around 10,000 years ago, leading to a long history of coexistence. Both domestic and wild or stray dogs constitute a global population of approximately 900 million.[2] Dogs make the world a better place, performing multiple roles within human society — as companions, aids to people with disabilities, and partners of law enforcement agencies, among others.[3] As Victor Hugo once said, "Look into the eyes of a dog and try again to assert that animals have no soul."

However, when provoked or frightened, dogs may react defensively and bite. Those at risk of dog bites include children, adults, the elderly, and specific occupational groups such as veterinarians, animal handlers, and agricultural workers. The lifetime probability of experiencing a dog bite is estimated at around 50%, and dog bite injuries account for approximately 1% of all emergency department visits.[4] These bites often lead to infections ranging from mild to life-threatening.

The routes of infection include direct inoculation of microorganisms into the damaged skin or tissues, secondary superinfection, or transmission through food

or close contact with the dog. The most common causative agents are Pasteurella multocida, Capnocytophaga canimorsus, Streptococcus species, Staphylococcus species, Bergeyella zoohelcum, and Alcaligenes faecalis, among others.

Local bacterial infections typically manifest with redness, swelling, and pain at the bite site and may progress to cellulitis, abscess formation, septic arthritis, or fasciitis. Systemic infections may include sepsis, septic shock, and multiorgan failure. These severe forms are more frequently observed in high-risk groups such as the elderly (due to reduced immunity and increased dog ownership), and individuals with asplenia, diabetes, cirrhosis, or chronic alcoholism.[5][6][7]

Post–dog bite management consists of meticulous wound care, the use of appropriate antibiotics and supportive symptomatic therapy, and the application of immunoprophylaxis — including administration of tetanus antitoxin (particularly in those not up to date with vaccination) and anti-rabies serum when indicated.

Methods

A literature review was conducted to identify studies addressing the microbial agents and infectious syndromes or nosologies caused by dog bites. We also identified studies discussing antibiotic and immunoprophylactic strategies aimed at minimizing subsequent infectious complications. A summary of the literature on the diagnosis and treatment of infections in patients with dog bite wounds was presented. Furthermore, we evaluated the work of clinical microbiology laboratories that facilitate the isolation of microorganisms obtained from wound, blood, and other relevant cultures.

Results

Even a seemingly minor dog bite can lead to severe and potentially fatal infection. Dog bite wounds account for approximately 250,000 visits to emergency and urgent care units each year.[8] Pasteurella canis is the most common microorganism isolated following dog bites, although other aerobic bacteria (Streptococcus, Staphylococcus, Moraxella, Neisseria) and anaerobes (Fusobacterium, Bacteroides tectum, Porphyromonas, Prevotella heparinolytica) are also frequently involved. [9] Initially, local infection manifests as cellulitis or abscess formation resulting from soft tissue injury, laceration, microbial contamination, or secondary superinfection.[10][11]

Sepsis and fulminant sepsis can develop even in individuals without evident bite marks, scratches, or open wounds. Capnocytophaga canimorsus — a Gram-negative, facultative anaerobic bacterium that colonizes the oral cavity of dogs — is

recognized as one of the leading causes of fulminant sepsis, with a high mortality rate (26–60% following bites and approximately 24% after scratches, close contact, or licking).[12][13] Without prompt and professional intervention, sepsis may rapidly progress to septic shock, disseminated intravascular coagulation, multiorgan failure, and death.

Jun et al. reported the case of a 46-year-old man who, three months after a dog bite, developed infective endocarditis of the aortic valve caused by C. canimorsus.[14] Such patients may also develop meningitis, endocarditis, pneumonia, or osteomyelitis.[15] These clinical manifestations may also be due to fungal microorganisms; therefore, in patients unresponsive to appropriate antibiotic therapy, fungal etiology should be considered.[16] Bergeyella zoohelcum, an aerobic Gram-negative bacterium, has been implicated particularly in pediatric infectious complications.[17][18]

Albania, as a Mediterranean country with diverse flora and fauna, provides an environment that facilitates close human–dog contact. In our country, dog bite victims have included cases that developed infectious diseases such as rabies and tetanus. One notable historical episode occurred in Kaçinar in 1976, when 60.8% of dog bite victims developed rabies — manifesting as encephalitic or paralytic forms — and all of them died.[19] Tetanus remains, as globally, a serious public health concern in Albania. Pilaca et al., in a study of 64 hospitalized patients in Tirana, Shkodra, and Korça, reported a mortality rate of 38.6%, most frequently among the elderly, in those with incubation periods shorter than 11 days, and in patients with infected wounds.[20]

It is therefore essential to evaluate wounds with tetanus potential to appropriately apply immunotherapy (serum and vaccine) and prevent the occurrence of tetanus — a life-threatening infection caused by Clostridium tetani. During diagnosis, the patient's medical history and comorbidities should be carefully considered, as these may adversely affect prognosis. Reliable information on the patient's vaccination record (particularly regarding tetanus) is crucial, as well as data on the geographical site of exposure and the type of dog involved (especially concerning rabies risk). Additional diagnostic evaluations including laboratory, microbiological, serological, and imaging studies are of great importance. Microbiological diagnosis is based on identifying the causative pathogens in clinical microbiology laboratories from cultures obtained from the wound, tissue, or blood.

The cornerstone of management remains proper wound care (thorough cleaning and debridement), antibiotic use to reduce the risk of secondary infections, and immunoprophylaxis (serum and vaccination). The "golden key" is timely antibiotic prophylaxis.[21] Treatment is often empirical; combinations such as imipenem/cilastatin, clindamycin, or beta-lactamase inhibitors are consistently effective and may be recommended for all types of infection.[22][23]

Nevertheless, dogs bring such joy to our lives that it is difficult to imagine life without them — a reminder that we must care for them responsibly, while also safeguarding our own health.

Conclusion

Stray dogs, often aggressive, remain a serious concern for local residents — including children, adults, and the elderly — as well as for the growing number of foreign tourists, given that Albania has become a popular tourist destination. Dog bites are common occurrences both globally and locally, leading to consequences such as physical injury, psychological trauma, wound superinfection, and potentially life-threatening infectious complications including sepsis, tetanus, and rabies, in addition to the economic costs of disability and treatment.

Proper and timely management of these patients requires strong and professional interdisciplinary collaboration.

References

1. C Vilà, P Savolainen, J E Maldonado. Multiple and ancient origins of the domestic dog. Science. 1997 Jun 13;276(5319):1687-9. doi: 10.1126/science.276.5319.1687.
2. Nicole Cosgrove. How Many Dogs Are There? US & Worldwide Statistics 2025. Updated on March 6, 2025. https://www.dogster.com/statistics/how-many-dogs-are-there-statistics.
3. Oskarsson M. Analysis of Origin and Spread of the Domestic Dog Using Y-Chromosome DNA and MtDNA Sequence Data. KTH Royal Institute of Technology, School of Biotechnology, Gene Technology; Stockholm, Sweden: 2012.
4. Sheraz Yaqub, Jørgen V Bjørnholt, Kjell B Hellum. Bite wound infections. Tidsskr Nor Laegeforen. 2004 Dec 16;124(24):3194-6.
5. James P Wilson, Kalman Kafetz, Douglas Fink. Lick of death: Capnocytophaga canimorsus is an important cause of sepsis in the elderly. BMJ Case Rep. 2016 Jun 1;2016: bcr2016215450. doi: 10.1136/bcr-2016-215450.
6. Butler T. Capnocytophaga canimorsus: an emerging cause of sepsis, meningitis, and post-splenectomy infection after dog bites. Eur J Clin Microbiol Infect Dis 2015;34: 1271–80. 10.1007/s10096-015-2360-7.
7. Ahmad Ahsen. Capnocytophaga canimorsus Infection in a 38-Year-Old Male after a Dog Bite. Case Reports in Infectious Diseases. 16 October 2023 https://doi.org/10.1155/2023/9917898.
8. Finn E. Role of prophylactic antibiotics in treating patients presenting to emergency care with dog bites. Emerg Nurse. 2025 Mar 4;33(2):21-27. doi: 10.7748/en.2024. e2208. Epub 2024 Aug 29.
9. D A Talan, D M Citron, F M Abrahamian. Bacteriologic analysis of infected dog and cat bites. Emergency Medicine Animal Bite Infection Study Group. N Engl J Med. 1999 Jan 14;340(2):85-92. doi: 10.1056/NEJM199901143400202.

10. Lin WR, Chen YS, Liu YC. Cellulitis and bacteremia caused by Bergeyella zoohelcum. J Formos Med Assoc. 2007; 106: 573–576.
11. Shukla SK, Paustian DL, Stockwell PJ, et al. Isolation of a fastidious Bergeyella species associated with cellulitis after a cat bite and a phylogenetic comparison with Bergeyella zoohelcum strains. J Clin Microbiol. 2004; 42:2 90–293.
12. James P Wilson, Kalman Kafetz, Douglas Fink. Lick of death: Capnocytophaga canimorsus is an important cause of sepsis in the elderly. BMJ Case Rep. 2016 Jun 1; 2016: bcr2016215450. doi: 10.1136/bcr-2016-215450
13. Low SC, Greenwood JE. Capnocytophaga canimorsus: infection, septicaemia, recovery and reconstruction. J Med Microbiol 2008;57(Pt 7):901–3. 10.1099/jmm.0.47756-0.
14. Jun Sakai, Kazuhito Imanaka, Masahiro Kodana. Infective endocarditis caused by Capnocytophaga canimorsus; a case report. BMC Infect Dis. 2019 Nov 4;19(1):927. doi: 10.1186/s12879-019-4492-3.
15. James P Wilson, Kalman Kafetz, Douglas Fink. Lick of death: Capnocytophaga canimorsus is an important cause of sepsis in the elderly. BMJ Case Rep. 2016 Jun 1;2016:bcr2016215450. doi: 10.1136/bcr-2016-215450.
16. Silvia Di Bari, Francesca Gavaruzzi, Daniele De Meo et al. Candida parapsilosis osteomyelitis following dog bite: a case report and review of the literature. J Mycol Med. 2022 Mar;32(1):101208. doi: 10.1016/j.mycmed.2021.101208.
17. Bracis R, Seibers K, Julien RM. Meningitis caused by group II J following a dog bite. West J Med. 1979; 131:438–440.
18. Reina J, Borrell N. Leg abscess caused by Weeksella zoohelcum following a dog bite. Clin Infect Dis. 1992; 14:1162–1163.
19. Dh. Kraja, N. Gjermei, N. Como et al. "Identikiti i nje shperthimi Rabik, Kacinar 1976" Konferenca Kombetare Infeksionet nga kafshimet, gervishtjet dhe pickimet. Libri abstrakteve, fq.16-17. 6 Tetor 2012. Tirane.
20. A S Pilaca, A I Beqiri, A H Ndreu et al. Factors affecting the prognosis of Albanian adult patients with generalized tetanus. G Chir. 2012 Apr;33(4):105-9.
21. Finn E. Role of prophylactic antibiotics in treating patients presenting to emergency care with dog bites. Emerg Nurse. 2025 Mar 4;33(2):21-27. doi: 10.7748/en.2024.e 2208.
22. Anne Jolivet-Gougeon, Jean-Louis Sixou, Zohreh Tamanai-Shacoori et al. Antimicrobial treatment of Capnocytophaga infections. Int J Antimicrob Agents. 2007 Apr;29(4):367-73.
23. D A Talan, D M Citron, F M Abrahamian. Bacteriologic analysis of infected dog and cat bites. Emergency Medicine Animal Bite Infection Study Group. N Engl J Med. 1999 Jan 14;340(2):85-92. doi: 10.1056/NEJM199901143400202.

Synergistic Effects of Physiotherapy and Pharmacological Treatment in Chronic Pain

Xhejni KURTI
Department of Nursing and Physiotherapy, Aldent University,Tirana Albania.
(xhejni.kurti@ual.edu.al)

Dorina DERVISHI
https://orcid.org/0000-0003-3693-0878
Department of Nursing and Physiotherapy, European University,Tirana Albania.

Abstract

Purpose: The study aims to examine the synergistic effects produced by combining physiotherapy interventions with pharmacological treatment in the management of chronic pain, with a focus on improving functional outcomes and enhancing overall quality of life.

Design/methodology/approach: A narrative synthesis of current evidence was conducted, drawing on clinical studies, systematic reviews and guidelines related to multimodal chronic pain interventions. The approach evaluates the interaction between physiotherapeutic techniques—such as therapeutic exercise, manual therapy, neuromodulation and electrotherapy—and commonly used pharmacological agents, including NSAIDs, muscle relaxants and neuropathic pain medications.

Findings: Evidence indicates that integrating physiotherapy with pharmacological treatment provides enhanced analgesic effects, facilitates functional recovery and reduces long-term medication dependence. Synergistic benefits include improved neuromuscular performance, modulation of central sensitization and increased

patient adherence to rehabilitation. The combination appears especially effective in conditions such as chronic low back pain, osteoarthritis, cervical pain syndromes and neuropathic disorders.

Research limitations/implications: The heterogeneity of study designs and variations in treatment protocols limit direct comparability. Further controlled research is needed to identify optimal modality pairings and dosage–exercise combinations.

Practical implications: Combined interventions may support more efficient clinical decision-making, reduce pharmacological side effects and promote sustainable long-term outcomes in rehabilitation settings.

Originality: The study highlights the growing importance of synergistic multimodal strategies in chronic pain management and offers a consolidated analysis of current interdisciplinary evidence.

***Keywords**: chronic pain, physiotherapy, pharmacological treatment, multimodal therapy, rehabilitation, synergistic effects*

Structure

Current literature consistently supports the use of combined therapeutic modalities for chronic pain management. Physiotherapy plays a key role in restoring joint mobility, improving muscular balance and reducing mechanical load through targeted exercise, manual therapy, postural re-education and electrotherapy techniques. Parallel to this, pharmacological agents—such as non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, muscle relaxants and neuropathic pain medications—provide biochemical modulation of pain pathways.

Literature Review

"Multimodal interventions have demonstrated superior outcomes compared to monotherapy, particularly in chronic musculoskeletal and neuropathic conditions, where both functional and sensory mechanisms must be addressed collaboratively."

Physiotherapy modalities in evidence

Therapeutic exercise, manual therapy, neural mobilization, stabilization training and electrotherapy all contribute to reducing pain perception and enhancing movement efficiency.

Pharmacological contributions

Pharmacological treatment supports central and peripheral modulation of nociceptive pathways, reducing inflammation, muscle hypertonicity and neuropathic signaling.

Synergy between Approaches

The literature indicates that the interaction between physiotherapy and pharmacological treatment enhances adherence to rehabilitation, reduces long-term drug dependence and promotes functional recovery.

Methodology

A narrative review methodology was adopted for this study. Scientific articles, clinical trials, systematic reviews and guideline documents published within the past 15 years were examined using major databases including PubMed, Scopus and Google Scholar.

Inclusion criteria focused on adult populations with chronic musculoskeletal or neuropathic pain, studies evaluating combined physiotherapy and pharmacological interventions and outcomes related to pain intensity, function and quality of life. Exclusion criteria included acute pain studies, surgical interventions, pediatric populations and articles lacking outcome data.

Results

The synthesis of evidence revealed consistent improvements in pain reduction, range of motion and functional capacity when physiotherapy and pharmacological interventions were used together. Programs combining analgesics or anti-inflammatory drugs with exercise-based rehabilitation produced superior results compared to pharmacological treatment alone. Patients undergoing combined treatment showed increased adherence rates, decreased recurrence of symptoms and reduced reliance on long-term medication.

Study	Population	Intervention	Outcome Measures	Key Findings
Study 1 (2020)	Adults with chronic low back pain (n=120)	Physiotherapy (exercise + manual therapy) + NSAIDs	Pain intensity (VAS), ROM, functional disability	Combined treatment improved VAS by 45% vs. 22% in pharmacology alone.
Study 2 (2019)	Patients with cervical pain syndrome (n=85)	Electrotherapy + muscle relaxants	Pain, cervical mobility, patient satisfaction	Significant improvement in mobility; reduced drug dosage after 4 weeks.
Study 3 (2021)	Osteoarthritis knee patients (n=150)	Strengthening exercises + NSAIDs	Pain, walking distance, quality of life (SF-36)	Improved function and lower long-term medication use.
Study 4 (2018)	Chronic neuropathic pain individuals (n=60)	Neural mobilization + gabapentinoids	Neuropathic pain scale, daily function	Combined approach superior in reducing neuropathic symptoms.
Study 5 (2022)	Chronic musculoskeletal pain (n=200)	Stabilization training + analgesics	Functional performance, recurrence rates	Lower recurrence and higher adherence to therapy program.

Figure 1. Conceptual model illustrating the bidirectional synergy between physiotherapy interventions and pharmacological treatment in chronic pain management. The figure demonstrates how physiotherapy contributes to improved biomechanics, increased mobility, neuromuscular re-education and reduction of mechanical stress. Parallel to this, pharmacological treatment modulates nociceptive pathways, reduces inflammation, decreases muscle hypertonicity and influences central sensitization. The combined pathway shows enhanced patient participation in rehabilitation, amplified analgesic effects, improved functional outcomes and reduced long-term medication reliance.

Discussion

The findings of this review highlight that the integration of physiotherapy and pharmacological treatment creates a therapeutic synergy that is not merely additive but often multiplicative, producing outcomes that are superior to those achieved by either approach alone. This synergy becomes particularly evident when examining how each modality influences different but interconnected aspects of the pain experience—biomechanical, neurophysiological and psychosocial.

From a biomechanical standpoint, physiotherapy interventions such as therapeutic exercise, manual therapy and stabilization training directly target movement impairments, muscular imbalances and joint dysfunction. These interventions reduce mechanical loading on painful structures and improve neuromuscular control, enabling patients to move with less pain and greater efficiency. When combined with pharmacological agents—such as NSAIDs, muscle relaxants or neuropathic pain medications—the reduction in pain sensitivity and inflammation provides an optimal physiological environment for rehabilitation,

allowing patients to tolerate higher exercise intensity, greater range of motion and more consistent participation.

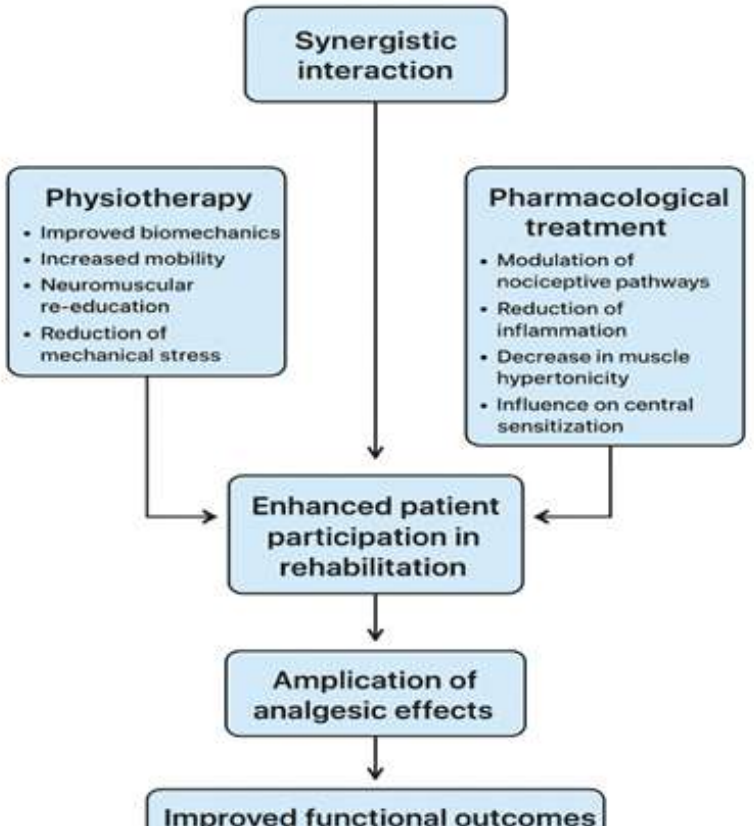
Neurophysiologically, the synergistic effects can be attributed to the dual modulation of nociceptive pathways. Pharmacological therapies act on peripheral inflammation, spinal neurotransmission and supraspinal pain processing, while physiotherapy techniques such as neural mobilization, electrotherapy and progressive loading influence central sensitization and promote endogenous analgesia. The interaction between these mechanisms appears to accelerate the normalization of pain processing, especially in chronic conditions where neuroplastic changes contribute to persistent symptoms. Several included studies reported that patients receiving combined care demonstrated faster reductions in pain scores, improved sensory thresholds and reduced reliance on long-term medication—suggesting that multimodal treatment may help interrupt the chronic pain cycle more efficiently than monotherapy.

Furthermore, the combined approach shows important implications for patient adherence and long-term outcomes. Pain relief obtained through pharmacological treatment often enhances the patient's willingness and ability to engage actively in exercise-based therapy, which is crucial for functional restoration. Conversely, the functional gains achieved through physiotherapy reduce the burden on pharmacological management, decreasing the risk of drug dependency, tolerance and side effects. This bidirectional reinforcement was consistently observed across multiple studies, with patients reporting higher satisfaction, greater autonomy in daily activities and reduced recurrence of symptoms.

The review also highlights that the synergistic model may be particularly effective in conditions characterized by mixed pain mechanisms, such as chronic low back pain, osteoarthritis and cervical pain syndromes. These disorders involve both nociceptive and neuropathic components, as well as psychosocial factors, making a single treatment modality insufficient. Multimodal interventions allow for a more holistic approach that aligns with modern biopsychosocial perspectives on chronic pain. By addressing mechanical dysfunction, biochemical inflammation and maladaptive neural processing simultaneously, clinicians may achieve more stable and sustainable improvements.

Despite these promising findings, methodological variability among studies remains a limiting factor. Differences in treatment duration, dosage of medications, intensity of physiotherapy interventions and patient characteristics reduce the comparability of results. Moreover, few studies explore long-term outcomes beyond six or twelve months, leaving uncertainty about the durability of synergistic effects. Future research should focus on identifying optimal combinations—such as specific dosage-exercise pairings, sequencing of interventions and individualized treatment algorithms—to maximize clinical results while minimizing medication use.

Overall, the evidence suggests that the integration of physiotherapy and pharmacological treatment represents an evolving and highly effective paradigm in chronic pain management. By leveraging the complementary strengths of both therapeutic domains, clinicians can facilitate faster pain reduction, promote functional recovery and support long-term self-management. This synergistic approach not only enhances clinical outcomes but also aligns with contemporary goals in rehabilitation: reducing dependency on medication, empowering patient participation and promoting sustainable health improvements.



Limitations

The narrative review design limits the ability to make definitive causal claims. The heterogeneity of intervention protocols, duration of treatment and pharmacological dosage reduced comparability across studies. Additionally, some included studies had small sample sizes or lacked long-term follow-up.

Conclusions

The integration of physiotherapy and pharmacological treatment demonstrates strong potential to enhance clinical outcomes in chronic pain management. The synergistic interaction between biomechanical rehabilitation and pharmacological modulation promotes improved functional capacity, reduced pain intensity and better long-term maintenance. Further controlled research is recommended to establish standardized combined treatment protocols and identify patient profiles that benefit most from multimodal approaches.

References (APA 6th Edition)

Book with one author

Loeser, J. D. (2013). Bonica's management of pain (4th ed.). Philadelphia, PA: Lippincott Williams & Wilkins.

Book chapter in an edited book

Smith, T. R. (2019). Physiotherapy interventions for chronic musculoskeletal pain. In L. A. Johnson (Ed.), Contemporary rehabilitation strategies (pp. 112–135). New York, NY: Springer.

Journal articles

Arnold, L. M., Rosen, A., Pritchett, Y. L., Jacobs, H., & Ramadan, N. (2019). A randomized, double-blind trial of duloxetine in chronic pain conditions. Pain Medicine, 20(4), 623–631. https://doi.org/10.1093/pm/pnz012.

Bialosky, J. E., Bishop, M. D., & George, S. Z. (2018). The mechanism of manual therapy in pain modulation. Journal of Manual & Manipulative Therapy, 26(1), 1–10. https://doi.org/10.1080/10669817.2017.1396541

Chou, R., & Huffman, L. H. (2017). Non-pharmacologic therapies for chronic low back pain. Annals of Internal Medicine, 167(7), 493–505. https://doi.org/10.7326/0003-4819-147-7-200710020-00007

Geneen, L. J., Moore, R. A., Clarke, C., Martin, D., Colvin, L., & Smith, B. H. (2017). Physical activity and exercise for chronic pain in adults: An overview of Cochrane reviews. Cochrane Database of Systematic Reviews, 4, CD011279. https://doi.org/10.1002/14651858.CD011279.pub3

Kamper, S. J., Apeldoorn, A. T., Chiarotto, A., Smeets, R. J., Ostelo, R. W., Guzman, J., & van Tulder, M. W. (2015). Multidisciplinary biopsychosocial rehabilitation for chronic low back pain. The Cochrane Library, 9, 1–102. https://doi.org/10.1002/14651858.CD000963.pub3

Kolt, G. S., & Snyder-Mackler, L. (2018). Exercise-based rehabilitation for chronic pain conditions. Journal of Orthopaedic & Sports Physical Therapy, 48(5), 357–364. https://doi.org/10.2519/jospt.2018.7842

Online report

World Health Organization. (2021). Chronic pain: A major global health issue. Retrieved from https://www.who.int/publications/chronic-pain-report

Conference paper

Martinez, P. R., & Allen, K. D. (2020). Combined physiotherapy and pharmacological interventions in chronic pain management. In Proceedings of the International Conference on Rehabilitation Medicine (pp. 89–96). Vienna, Austria: ICRM Press.

The Impact of Ibuprofen on Acute Kidney Injury in Brucellosis: A Case Report

Klejda ÇOLLAKU
Regional Hospital of Peshkopi, Albania
Corresponding Author klejda.collaku@yahoo.com

Neada HOXHA
Regional Hospital of Peshkopi, Albania

Armanda SARACI
Hospital of Kruja, Albania

Olta ZENELI
Regional Hospital of Peshkopi, Albania

Abstract

Purpose: To report a case of acute kidney injury (AKI) in a patient with brucellosis, highlighting the role of nephrotoxic medications, particularly ibuprofen, in its development. Brucellosis is a systemic zoonotic infection with diverse clinical manifestations, while renal involvement remains an uncommon but recognized complication [1–3,6].

Methodology: A 65-year-old male with poorly controlled type 2 diabetes mellitus presented with fever, anemia, hepatosplenomegaly, and bilateral pleural and pericardial effusions, consistent with severe systemic brucellosis [1,3]. Serological testing confirmed the diagnosis (Wright agglutination test 1:320, positive). The patient was treated with rifampicin and doxycycline, in accordance with recommended

therapy for brucellosis [2,5], along with supportive medications including ibuprofen, spironolactone, and furosemide. Clinical course, laboratory findings, and therapeutic adjustments were carefully reviewed.

Findings: After two weeks of therapy, the patient developed AKI (urea 159 mg/dL, creatinine 3.2 mg/dL, potassium 5.5 mmol/L) with preserved urine output. Nephrotoxic agents, including NSAIDs and spironolactone, were discontinued, while anti-brucellosis therapy was maintained. Supportive management, including hydration and electrolyte correction, resulted in complete renal recovery within two weeks (urea 54 mg/dL, creatinine 1.22 mg/dL, potassium 4.5 mmol/L). No recurrence of effusions or hepatosplenomegaly was observed. These findings are consistent with previously reported cases of reversible renal involvement in brucellosis [4,6].

Conclusion: Acute kidney injury in brucellosis is rare but possible [3,6]. Its development may be influenced by a combination of infectious factors, drug-induced nephrotoxicity, and patient-related risk factors such as diabetes and hypertension, which can increase renal vulnerability [4,6].

Early recognition of AKI is essential for favorable outcomes. Careful monitoring of renal function and cautious use of potentially nephrotoxic agents, including NSAIDs or aminoglycosides, can help prevent permanent kidney damage.

Originality: This case highlights the rarely reported contribution of ibuprofen to AKI in the setting of brucellosis, underscoring the need for vigilance when prescribing potentially nephrotoxic medications in infected patients.

***Keywords**: Brucellosis; Acute kidney injury; Ibuprofen; NSAIDs; Drug-induced nephrotoxicity; Case report*

Introduction

Brucellosis is a common zoonotic infection with systemic involvement, particularly affecting the reticuloendothelial, musculoskeletal, and hepatobiliary systems [1–3]. Renal complications are relatively uncommon, reported in approximately 2–20% of cases, and most frequently manifest as membranoproliferative glomerulonephritis, tubulointerstitial nephritis, or IgA nephropathy [3,6]. Rapidly progressive glomerulonephritis (RPGN) associated with brucellosis is exceedingly rare and has been described only in isolated case reports [6].

The pathogenesis of renal involvement in brucellosis is believed to be primarily immune-mediated, with immune complex deposition playing a central role [3,6]. In addition, acute kidney injury (AKI) in patients with brucellosis may be exacerbated by contributing factors such as dehydration, systemic inflammation, hemodynamic instability, and exposure to nephrotoxic medications, including non-steroidal anti-inflammatory drugs (NSAIDs) [4,6].

This case highlights the multifactorial etiology of AKI in a patient with brucellosis, with particular emphasis on the contributory role of ibuprofen in precipitating renal injury.

Case Presentation

Patient

A 65-year-old male with a history of poorly controlled type 2 diabetes mellitus, arterial hypertension, anemia, gastritis, peptic esophagitis, sigmoid diverticulitis, non-proliferative diabetic retinopathy, and severe COPD (GOLD stage IV) presented with fever, fatigue, anorexia, unintentional weight loss of 12 kg in one month, and night sweats. Imaging revealed bilateral pleural effusion and minimal pericardial effusion.

Diagnosis

Brucellosis confirmed by serology (*Brucella abortus* / Wright agglutination test 1:320, positive).

Hospitalizations

- First admission (30 June – 16 July 2025): Brucellosis diagnosis confirmed.
- Second admission (16 July – 1 August 2025): Transferred to Infectious Diseases Department.
- Third admission (8 – 15 August 2025): Worsening renal function/AKI.

Initial therapy

- Rifampicin 600 mg/day, Doxycycline 200 mg/day
- Gentamicin 240 mg/day during initial hospitalization
- Supportive medications: Ibuprofen 600 mg/day, Spironolactone 25 mg/day, Furosemide 40 mg/day
- Antidiabetic therapy: Oral agents (Siofor 850 mg, Maninil 5 mg), later switched to insulin therapy

TABELE 1. Medications Administered During Hospitalizations and Nephrotoxicity Risk

Drug	Dose	Duration	Indication	Nephrotoxicity Risk
Rifampicin	600 mg/day	16.07 – ongoing	Standard anti-brucellosis therapy	Low
Doxycycline	200 mg/day	16.07 – ongoing	Standard anti-brucellosis therapy	Low
Gentamicin	240 mg/day	16.07 – 01.08	Short course Anti-brucellosis adjunct	High
Spironolactone	25 mg/day	17.07 – 08.08	Chronic antihypertensive	Moderate
Furosemide	40 mg/day	16.07 – 08.08	Chronic antihypertensive	Moderate
Ibuprofen	400 mg ×3/day	25.07 – 08.08	Added for inflammatory control	High
Colchicine	1 mg/day	25.07 – 08.08	Added for pericardial involvement	Low

High risk / nephrotoxic: Medications with a strong potential to cause kidney injury.
Moderate risk / potential hemodynamic impact: Medications that may affect renal function indirectly through hemodynamic changes or mild nephrotoxicity.
Low risk / considered safe: Medications generally considered safe for renal function under monitored conditions.

Results

FIGURE 1. Serum Creatinine and Urea Trend (July – October 2025)

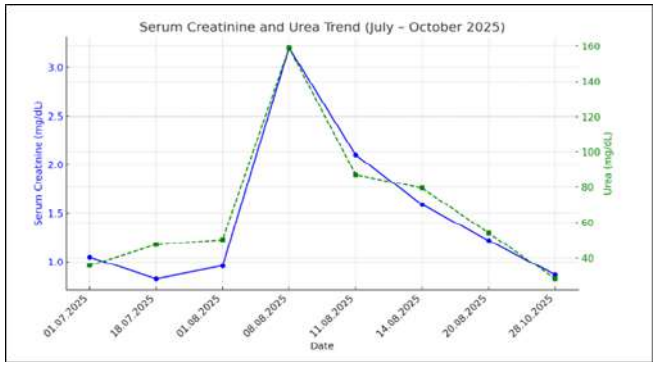


TABLE 2. Laboratory changes

Date	Creatinine (mg/dL)	Urea (mg/dL)
01.07.2025	1.05	35.6
18.07.2025	0.83	47.4
01.08.2025	0.96	50.2
08.08.2025	3.20	159.0
11.08.2025	2.10	87.1
14.08.2025	1.59	79.4
20.08.2025	1.22	54.0
28.10.2025	0.87	28.2

Evolution of Renal Function and Therapeutic Adjustments

Acute Kidney Injury (AKI)

After two weeks of therapy, the patient developed AKI with preserved urine output. Laboratory values at onset: urea 159 mg/dL, creatinine 3.2 mg/dL, potassium 5.5 mmol/L.

Therapeutic Adjustments

- NSAIDs (ibuprofen), spironolactone, and colchicine were discontinued due to nephrotoxic and hemodynamic effects.
- Anti-brucellosis therapy (rifampicin + doxycycline) was continued; gentamicin was administered only during the initial hospitalization.
- Supportive care included hydration, electrolyte correction, monitoring of urine output, renal function and hemodynamics, and nutritional support.

Renal Function Recovery

Gradual improvement was observed following discontinuation of nephrotoxic drugs. Within two weeks, renal function normalized (urea 54 mg/dL, creatinine 1.22 mg/dL, potassium 4.5 mmol/L). No recurrence of pleural or pericardial effusions; hepatosplenomegaly resolved.

Interpretation

Findings confirm multifactorial AKI due to infection, nephrotoxic medications, and possible hemodynamic factors. Early recognition and intervention led to complete renal recovery.

Discussion

AKI in this patient was multifactorial, resulting from:

1. Inflammatory effects of brucellosis [1–3,6]
2. Nephrotoxic effects of ibuprofen (NSAIDs) [4,6]
3. Potential hemodynamic factors (diuretics, spironolactone) [4]

Early recognition and discontinuation of nephrotoxic agents, along with supportive therapy led to complete renal recovery [4,6].

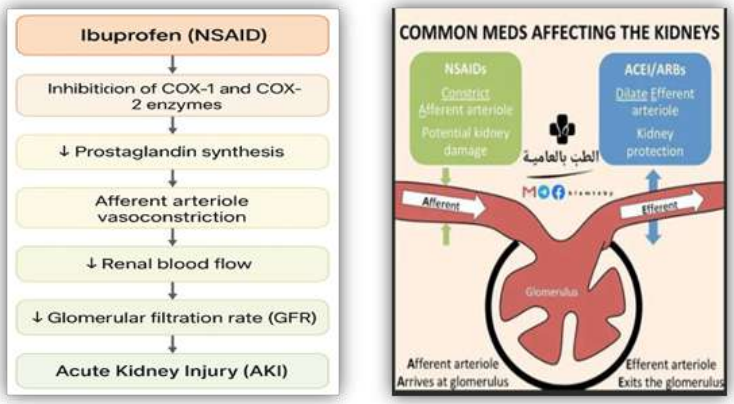
This case highlights the importance of monitoring renal function in brucellosis patients receiving potentially nephrotoxic drugs [3,6].

Mechanism of Ibuprofen-Induced AKI

Ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID), inhibits COX-1 and COX-2 enzymes, leading to decreased prostaglandin synthesis [4].

- Role of prostaglandins: Normally, prostaglandins mediate vasodilation of the afferent arteriole, maintaining adequate renal blood flow and glomerular filtration rate (GFR) [4].
- Effect of NSAID use: Reduced prostaglandin levels cause afferent arteriole vasoconstriction, resulting in decreased renal perfusion and reduced GFR, which can precipitate acute kidney injury (AKI) [4,6].

FIGURE 2. Mechanism of Ibuprofen-Induced Acute Kidney Injury



Risk factors for NSAID-induced AKI include:

- Volume depletion / dehydration [4,6]
- Congestive heart failure [4]
- Liver cirrhosis [4]
- Pre-existing kidney disease [4,6]

In this patient, *the combination of ibuprofen therapy, brucellosis-related inflammatory effects, and underlying comorbidities likely contributed to the multifactorial AKI observed. [3,4,6].* Early discontinuation of ibuprofen and supportive care facilitated complete renal recovery [4,6].

Conclusion

Acute kidney injury in brucellosis is rare but possible. Its development may be influenced by a combination of infectious factors, drug-induced nephrotoxicity, and patient-related risk factors such as diabetes and hypertension, which can increase renal vulnerability. Early recognition of AKI is essential for favorable outcomes. Careful monitoring of renal function and cautious use of potentially nephrotoxic agents, including NSAIDs or aminoglycosides, can help prevent permanent kidney damage. This highlights the importance of assessing renal risk factors during brucellosis treatment.

Research Limitations

This is a single-case report; therefore, findings are not generalizable. However, it provides insight into the contributory role of nephrotoxic drugs in brucellosis-associated AKI.

Practical Implications

Early recognition of renal dysfunction and prompt discontinuation of nephrotoxic agents are essential to prevent permanent kidney damage, particularly in patients with systemic infections [4,6].

Social Implications

Increased awareness of drug-induced renal injury may improve patient safety and reduce healthcare burden.

References

1. Pappas G, Papadimitriou P, Akritidis N, Christou L, Tsianos EV. Brucellosis. *N Engl J Med*. 2005;352(22):2325–2336.
2. Young EJ. Brucella species. In: Bennett JE, Dolin R, Blaser MJ, editors. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 8th ed. Elsevier; 2015.

3. Colmenero JD, Reguera JM, Martos F, Sanchez-De-Mora D, Delgado M, Causse M, Queipo-Ortuño MI. Brucellosis: Clinical and microbiological characteristics. *Infect Dis Clin North Am*. 2020;34(2):65–82.
4. Miao Y, Li X. Brucellosis and renal involvement: Case review. *Medicine (Baltimore)*. 2024;103(13):e37560.
5. Ariza J, Bosilkovski M, Cascio A, Colmenero JD, Corbel MJ, Falagas ME, Solera J. Perspectives for the treatment of complicated brucellosis. *PLoS Med*. 2007;4(12):e317.
6. Solís García del Pozo J, Solera J. Renal involvement in brucellosis: A systematic review. *PLoS One*. 2012;7(3):e32090.