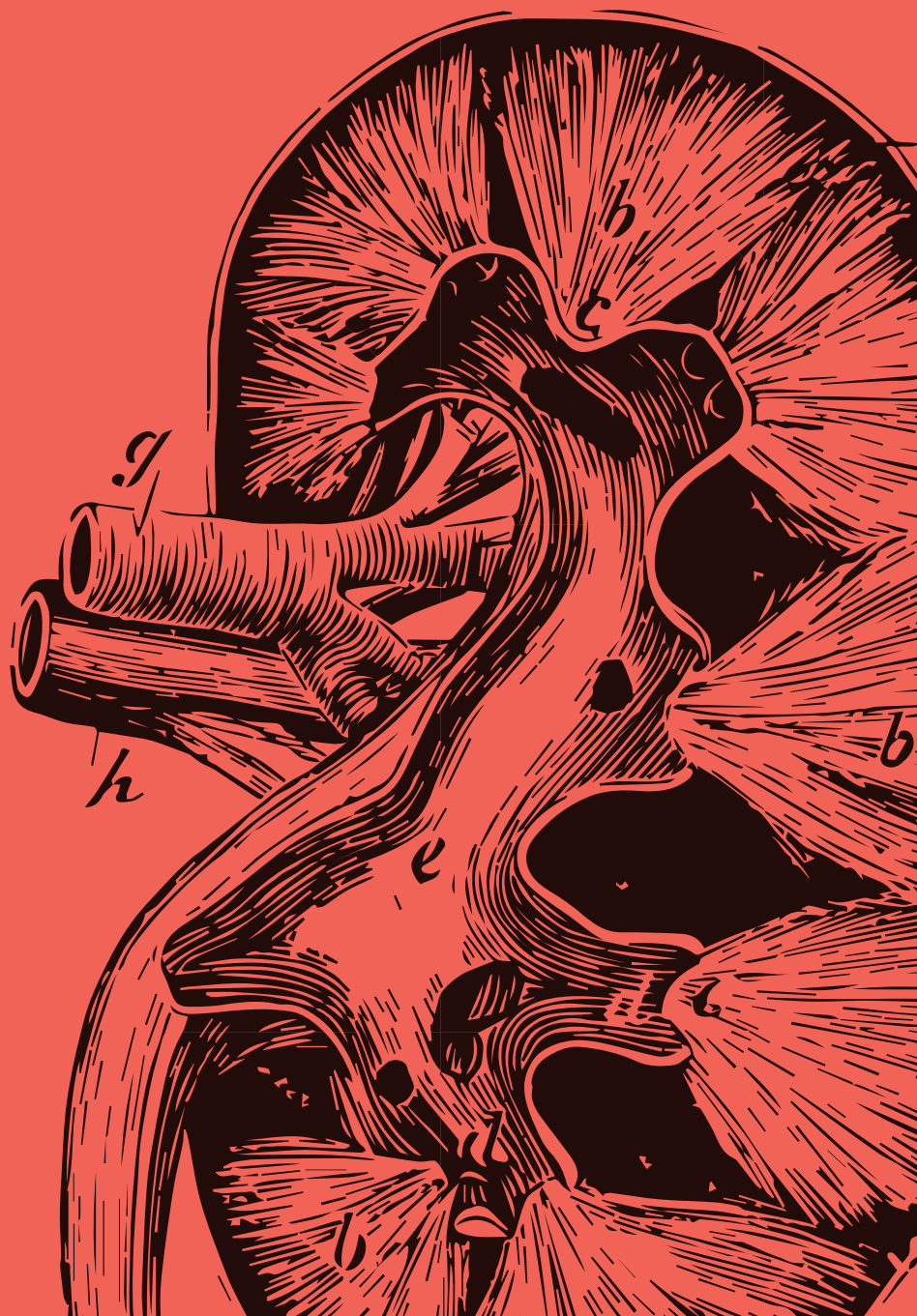
EISSN 2667-4440
https://x.com/turkjnephrol

Turkish Journal of Nephrology

Volume 34
Issue 4
October 2025



AVES turkjnephrol.org

Turkish Journal of Nephrology

TURKISH SOCIETY of NEPHROLOGY 1970

AVES

General Manager
İbrahim KARA

Publications Director
Deniz KAYA

Publications Coordinators
Nisanur ATICI
Şeref Mert GÜCÜN
Lütfiye ÇETİN
Şevval AKKAYA
Tabita TOPARLAK

Web Coordinator
Ayça Nur SEZEN

Web Assistants
Ozan ŞAHİN
Batuhan KARA

Finance Coordinator
Gözde DOĞAN

Editor in Chief: Rümeyza Kazancıoğlu
Address: Division of Nephrology, Bezmialem Vakif University School of Medicine, İstanbul, Türkiye
E-mail: info@turkjnephrol.org

Publishing Services: AVES
Address: Büyükdere Cad. 199/6, 34394, Şişli, İstanbul, Türkiye
Phone: +90 212 217 17 00
E-mail: info@avespublishing.com
Web page: avespublishing.com

Turkish Journal of Nephrology

About the Turkish Journal of Nephrology

Turkish Journal of Nephrology is a peer reviewed, open access, online-only journal published by the Turkish Society of Nephrology.

Turkish Journal of Nephrology is a quarterly journal that is published in English in January, April, July, and October.

Journal History

As of January 2019, the journal has changed its title to Turkish Journal of Nephrology.

Current Title (2019-)

Turkish Journal of Nephrology
EISSN: 2667-4440

Previous Title (1995-2018)

Turkish Nephrology, Dialysis and Transplantation Journal
ISSN: 1300-7718

Abstracting and Indexing

Turkish Journal of Nephrology is covered in the following abstracting and indexing databases; Web of Science-Emerging Sources Citation Index, Scopus, DOAJ, EBSCO, Gale, CNKI, TUBITAK ULAKBIM TR Index.

All content published in the journal is permanently archived in Portico.

Aims, Scope, and Audience

Turkish Journal of Nephrology aims to publish studies of the highest scientific and clinical value, and encourages the submission of high-quality research that advances the understanding and treatment on the fields of nephrology, dialysis and transplantation.

Turkish Journal of Nephrology covers a wide range of topics related to etiology, pathogenesis and treatment of kidney diseases, hypertension, acid-base and electrolyte disorders, dialysis therapies, kidney transplantation. In addition, studies focusing on socioeconomic aspects of kidney diseases and their treatments are also of interest to the journal.

Turkish Journal of Nephrology publishes original articles, reviews, letters to the editor, editorial comments, opinion articles, and images in nephrology that are prepared in accordance with the ethical guidelines.

Turkish Journal of Nephrology also contributes to the literature by publishing summaries from the Annual Registry Report of the Turkish Society of Nephrology. The society has been collecting data on end-stage kidney disease since 1990 that has turned into the most comprehensive regional archive. Turkish Journal of Nephrology aims to share this regional data with the international community.

The target audience of the journal includes specialists and professionals working and interested in all disciplines of nephrology and kidney care.

Open Access Policy

Turkish Journal of Nephrology is an open access publication.

Starting on January 2019, all content published in the journal is licensed under the Creative Commons Attribution (CC BY) 4.0 International License which allows third parties to use the content for non-commercial purposes as long as they give credit to the original work. This license allows for the content to be shared and adapted for non-commercial purposes, promoting the dissemination and use of the research published in the journal.

The content published before January 2019 was licensed under a traditional copyright, but the archive is still available for free access.

All published content is available online, free of charge at https://turkjnephrol.org/EN.

Copyright Policy

A Copyright Agreement and Acknowledgement of Authorship form should be submitted with all manuscripts. By signing this form, authors agree that the article, if accepted for publication by the Turkish Journal of Nephrology, will be licensed under a Creative Commons Attribution (CC BY) 4.0 International License which allows third parties to read, copy and redistribute the material in any format and adapt the material for any purpose immediately upon publication by giving the appropriate credit to the original work.

Publication Fee Policy

Turkish Journal of Nephrology is funded by the Turkish Society of Nephrology. Authors are not required to pay any fees during the evaluation and publication process.

You can find the current version of the Instructions to Authors at https://turkjnephrol.org/en/instructions-to-authors-1013

Turkish Journal of Nephrology

Contents

10.5152/turkjnephrol.2025.24733

Review Article

Turkish Journal of Nephrology

Management of Rapidly Progressive Autosomal Dominant Polycystic Kidney Disease

İsmail Koçyiğit[1], Emre Aydın[2], Özgür Akın Oto[3], Kadir Gökhan Atılgan[4], Tevfik Ecder[5]

[1]Divison of Nephrology, Erciyes University, Faculty of Medicine, Kayseri, Türkiye
[2]Divison of Nephrology, Dicle University, Faculty of Medicine, Diyarbakır, Türkiye
[3]Divison of Nephrology, İstanbul University, Faculty of Medicine, İstanbul, Türkiye
[4]Divison of Nephrology, Etlik City Hospital, Ankara, Türkiye
[5]Divison of Nephrology, İstinye University, Faculty of Medicine, İstanbul, Türkiye

ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease. In this disease, multiple cysts develop and grow over time in both kidneys. As a result, kidney function decreases over the years, patients develop end stage renal disease, and they need kidney replacement therapy. The search for drugs that can slow the growth of cysts in ADPKD has been going on for many years. Experimental and clinical studies conducted to date have demonstrated that, "tolvaptan," a vasopressin receptor antagonist has beneficial effects. There is no specific treatment other than tolvaptan currently used worldwide for rapidly progressive polycystic kidney disease. However, physicians experience difficulties in various processes with tolvaptan, such as identifying the appropriate patient group, planning the treatment process, determining the ideal dosage, and managing complications. For this reason, we decided to prepare a practical treatment guide to help supporting clinicians in the management of ADPKD patients in clinical practice.

Keywords: Community health services, primary care, public health

Corresponding author: Emre Aydın ✉ emreaydin83@hotmail.com

Received: February 20, 2024 **Revision requested:** June 4, 2024
Last revision received: July 3, 2024 **Accepted:** July 29, 2024 **Publication Date:** October 1, 2025

Cite this article as: Koçyiğit İ, Aydın E, Oto ÖA, Atılgan KG, Ecder T. Management of rapidly progressive autosomal dominant polycystic kidney disease. *Turk J Nephrol.* 2025;34(4):233-239.

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease. Multiple cysts develop in both kidneys; over time, these cysts can grow and damage the kidneys. For this reason, some ADPKD patients may develop kidney failure and need kidney transplantation or dialysis.[1,2] As a result, ADPKD is the fourth most common global cause of end-stage kidney disease.

It is known that lifestyle changes and management of blood pressure can have positive effects on the progression of the disease in patients. Therefore, all patients should be advised to avoid tobacco use, eat a salt-restricted diet, exercise, and achieve an ideal body weight. These lifestyle changes and blood pressure control are also of great importance in terms of reducing cardiovascular problems that are common in this disease.

The search for drugs that can slow the growth of cysts in ADPKD has been going on for many years. Experimental and clinical studies conducted have shown that "tolvaptan," a vasopressin receptor antagonist, has beneficial effects. Tolvaptan binds selectively to vasopressin V2 receptors in the collecting duct cells of the kidneys, thereby blocking the binding of vasopressin. Water diuresis occurs due to the elimination of the effects of vasopressin. Tolvaptan also reduces cyclic AMP (cyclic adenosine monophosphate, cAMP) levels, which reduces both fluid secretion into cystic formations and

cell proliferation. As a result of these effects, the growth of cysts slows down.[3]

Two large studies have demonstrated the beneficial effect of tolvaptan in ADPKD patients. The Tolvaptan Efficacy and safety in Management of Polycystic kidney disease and its Outcomes (TEMPO) study included patients between the ages of 18 and 50 with total kidney volumes (TKV) larger than 750 mL and creatinine clearances greater than 60 mL/min. In these early-stage patients, tolvaptan was shown to reduce cyst growth by 49% and the decline in glomerular filtration rate (GFR) by 26%.[4] The Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in ADPKD (REPRISE) study included patients with estimated GFR (eGFR) between 25 and 65 mL/min/1.73 m^2 in the 18 to 55 age range and between 25 and 44 mL/min/1.73 m^2 in the 56 to 65 age range.[5] In these late-stage patients, tolvaptan was demonstrated to reduce the decline in eGFR by 35%. As a result of these studies, tolvaptan treatment has received approval for managing ADPKD in many countries, including Türkiye. This paper will discuss recommendations for the clinical use of tolvaptan therapy in ADPKD patients.

CONFIRMATION OF THE DIAGNOSIS OF AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

In individuals with a familial history, diagnosis is simple and primarily relies on imaging techniques. There are diagnostic criteria based on ultrasonographic imaging according to age (Table 1).[6] Furthermore, in individuals younger than 30 years of age, the detection of more than 10 kidney cysts via magnetic resonance imaging (MRI) offers a sensitivity and specificity of 100% for diagnosis.[7] These criteria are for patients with PKD1 or PKD2 mutations. In individuals without a family history, PKD gene mutation analysis is also helpful for diagnosis. However, it should be kept in mind that other gene mutations may also be present.

MAIN POINTS

- Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease. Kidney function decreases over the years in ADPKD patients; end-stage kidney disease develops, and kidney replacement therapy is needed.
- The Mayo imaging classification provides a simple clinical scale that employs age and height-adjusted total kidney volumes to identify patients at risk for rapid progression, independent of kidney function.
- There is no specific treatment other than tolvaptan currently used worldwide for rapidly progressive polycystic kidney disease.
- Early therapy with tolvaptan initiation is especially beneficial for young individuals whose disease is still in its early stages.
- The therapeutic efficacy of tolvaptan increases gradually with increasing dose. Therefore, it is appropriate to increase it to the highest tolerable dose.

Table 1. Diagnostic Criteria with Ultrasonography in a Person with a Family History of ADPKD

Age	Imaging
15-39	≥ 3 cysts (unilateral or bilateral)
40-59	≥ 2 cysts (both kidneys)
≥ 60%	≥ 4 cysts (both kidneys)

CONFIRMATION OF THE DIAGNOSIS OF RAPIDLY PROGRESSIVE DISEASE

The Food and Drug Administration (FDA) has approved tolvaptan for slowing the decline in glomerular filtration rate (GFR) in patients with rapidly progressive ADPKD. Therefore, it is critical to identify patients with rapidly progressing ADPKD. Clinical Parameters for the assessment of Rapidly Progressive Disease are shown in Table 2. The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) study showed a significant relationship between TKV and the rate of GFR decline.[8] Height-adjusted TKV (HtTKV) can also predict GFR decline. Moreover, the Mayo imaging classification is a simple clinical scale that uses age and HtTKV to identify patients at risk for rapid progression, independent of kidney function (Figure 1). Based on their predicted yearly growth rate (< 1.5%, 1.5-3%, 3-4.5%, 4.5-6%, and > 6%), patients are divided into five classes (A-E).[9] The patient's age and a theoretical starting HtTKV of 150 mL/m are the basis for this evaluation. About 95% of ADPKD patients have diffuse cystic spread, which is the typical form of the disease (class 1). However, about 5% of patients have atypical kidney imaging, and HtTKV measurement cannot predict GFR decline in these patients (class 2). In addition to this categorization, a model utilizing eGFR can somewhat accurately forecast future GFR reduction. The preferred method for determining TKV is computed tomography (CT) (contrast-enhanced imaging for patients with eGFR > 60 mL/min/1.73 m^2) or contrast-free MRI.

Patients in class 1A exhibit slow progression and do not require tolvaptan therapy. Those in class 1B should undergo re-evaluation to confirm their slow progression rate, and their HtTKV should be measured again after 2-3 years. Patients in class 1C, class 1D, or class 1E demonstrate a rapidly progressive phenotype and benefit from treatment. Early therapy initiation is especially beneficial for young patients whose disease is still in its early stages.

The European Renal Association (ERA) consensus report on the use of tolvaptan in ADPKD emphasizes the importance of age-indexed eGFR values in initiating treatment. The report suggests that age-indexed eGFR values are effective in distinguishing rapidly progressive disease from slowly progressive disease in most patients. Patients are specifically classified as having slowly progressive disease if their eGFR is > 90 mL/min/1.73 m^2 at ages 40-44, > 75 mL/min/1.73 m^2 at ages 45-49, and > 60 mL/min/1.73 m^2 at ages 50-55. There is no need to treat these patients with tolvaptan.[11,12]

Table 2. Basic Clinical Parameters for Rapid Progressive Disease Assessment

Parameter	Assessment of Rapid Progression
Age-adjusted assessment of eGFR	Is eGFR unexpectedly low (or elevated) for the patient's age?
Kidney volume/Mayo classification	Class 1D/1E: Rapidly progressive Class 1C: Individual assessment
If not possible, kidney length by ultrasonography	> 16.5 cm ≤ 46 years
PROPKD score[10]	> 6: Rapidly progressive
Genetic	"Truncating" PKD1 mutation: Rapidly progressive
Early onset of urological symptoms	Macrohematuria, cyst hemorrhage, flank pain, and cyst infection before age 35
Early onset of arterial hypertension	Before age 35
Family history	Have most affected family members reached kidney failure? < 58 years old?

It is important to note that each criterion used to define rapidly progressive disease has some advantages and limitations. Considering these limitations, we conclude that the Mayo classification is simpler and more easily implemented in clinical practice.

IMPLEMENTATION OF BASIC KIDNEY PROTECTIVE MEASURES

In Figure 2, the recommended blood pressure goals, preferred anti-hypertensive medications (ACE inhibitors or AT II receptor blockers), and lifestyle adjustments for patients with ADPKD is demonstrated. In addition to tolvaptan therapy, it is crucial for clinicians to also consider other easy interventions that can significantly influence the long-term outcomes of ADPKD.[11]

INFORMING THE PATIENT ABOUT TREATMENT

The potential benefits and risks of tolvaptan therapy should be individualized to the patient, taking into account the patient's current eGFR value, age, and ability to tolerate the drug. Tolvaptan primarily slows the rate of eGFR decline and the rate of cyst growth.

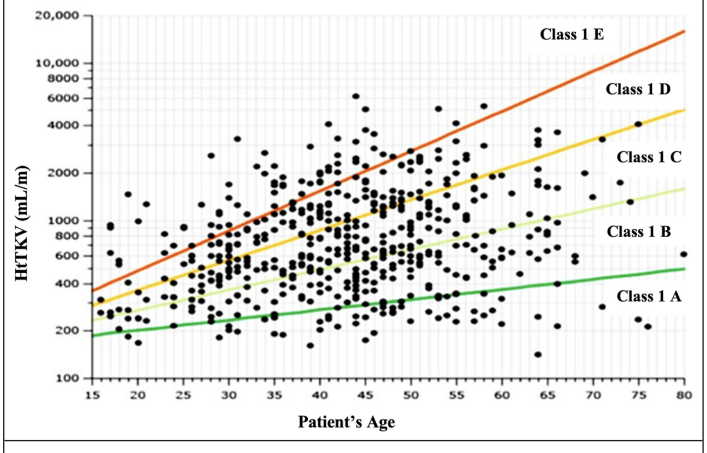


Figure 1. The subclassification of patients initially diagnosed with class 1 ADPKD according to age and HtTKV limits.

In the analysis of the TEMPO 4 : 4 study, which tracked patients from the TEMPO 3 : 4 study in an open-label format, tolvaptan treatment cumulatively and continuously reduced the annual rate of eGFR decline by about 1 mL/min/1.73 m^2.[13] Moreover, tolvaptan has been shown to reduce the frequency of kidney pain, nephrolithiasis, and hematuria with urinary tract infections, and it has also led to a slight decrease in average blood pressure.

Tolvaptan's most common side effects (polyuria, thirst, in some cases fatigue, nocturia, and increased urinary frequency) are related to the drug's aquaretic effect. An important adverse event associated with tolvaptan is idiosyncratic liver injury. In the TEMPO 3 : 4 and TEMPO 4 : 4 studies, 3-month follow-up of liver function tests (LFTs) were performed, and the incidence of at least one transaminase increase more than three times the upper limit of normal was 4.4%; this rate was found to be 1% in the placebo arm. The effects and side effects of tolvaptan treatment are summarized in Table 3.

CONDITIONS TO AVOID TREATMENT

The following conditions are contraindications to tolvaptan treatment: pregnancy, lactation, a history of severe liver damage unrelated to polycystic liver disease, hypovolemia, uncorrected hypernatremia, urinary tract obstruction, and inability to feel or respond to thirst. In addition to the above, drug interactions should be considered. Tolvaptan should not be used concomitantly with strong CYP3A inhibitors (e.g., itraconazole, ketoconazole, lopinavir, clarithromycin, indinavir, and ritonavir). Since the half-life of tolvaptan will be prolonged in combination with weak and moderate CYP3A inhibitors (e.g., erythromycin, amiodarone, fosamprenavir, diltiazem, fluconazole, verapamil, imatinib, grapefruit), the tolvaptan dose may need to be reduced. The use of tolvaptan in combination with diuretics can increase the decrease in eGFR.

PATIENT EDUCATION ON AQUARESIS AND EXPECTED OUTCOMES

Tolvaptan blocks the effects of vasopressin on the collecting ducts and distal nephron through V2 receptors, including the concentration of urine, inhibition of tubuloglomerular

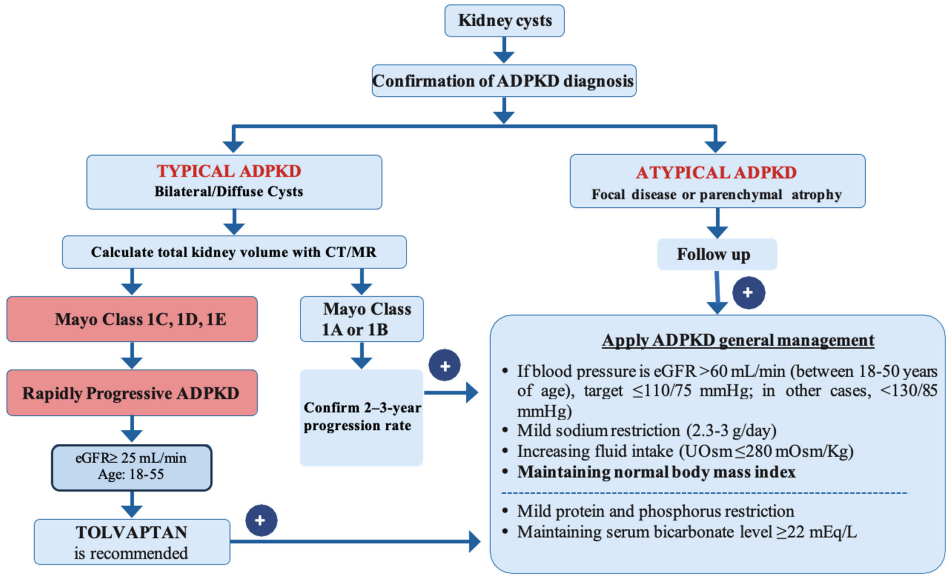


Figure 2. Treatment modality for a patient diagnosed with ADPKD.

feedback, and induction of sodium reabsorption. As a result, tolvaptan increases aquaresis and stimulates tubuloglomerular feedback; it creates afferent arteriolar vasoconstriction and lowers intraglomerular pressure and eGFR.

Patients should be well informed that tolvaptan treatment will result in severe polyuria and lead to a decrease in eGFR, which may be less noticeable in advanced CKD patients, and that this condition may return after the drug is discontinued. If the eGFR decrease exceeds 20%, the drug dose should be reduced, or the drug should be discontinued for a later restart at a lower dose. It depends on the individual approach of the attending physician. Close eGFR monitoring should be performed during the patient's tolvaptan use.

STARTING, TITRATING, AND OPTIMIZING TOLVAPTAN TREATMENT

The goal of tolvaptan treatment is to suppress the effect of vasopressin on the kidneys 24 hours a day, every day. To optimize this effect and reduce the incidence of nocturia, tolvaptan is administered in divided doses daily: the first dose is taken early in the morning, and the second dose is taken 8 hours later in the afternoon. During clinical studies, the starting dosage was usually 45 mg in the morning and 15 mg in the afternoon. Depending on the patient's tolerance, the dose was then titrated to 60/30 and 90/30 mg. The therapeutic efficacy of tolvaptan increases with higher doses, therefore, making it advisable to escalate the dosage to the maximum level that patients can tolerate.

However, another opinion is that tolvaptan should be titrated to the dose required to permanently suppress the effect of vasopressin on the kidneys. It is desirable for the urine to be hypotonic compared to plasma; i.e., the osmolality of the first urine sample before the morning dose should be below 280 mOsm/kg.

Tolvaptan treatment is recommended to be started when the disease is found to be progressing rapidly in patients over the age of 18. Tolvaptan treatment should be discontinued when the patient approaches end-stage kidney disease. Tolvaptan treatment is recommended to be started in ≤ 55-year-old adult ADPKD patients with eGFR ≥ 25 mL/min/1.73 m^2 who have shown or are likely to show signs of the disease rapidly.

Table 3. Possible Effects/Side Effects of Tolvaptan Treatment

Efficacy	Side Effect
Kidney growth slows down	Polyuria, pollakiuria, and nocturia
GFR loss slows down	Thirst and fatigue
May delay initiation of kidney replacement therapy	Increased uric acid, rarely gout
Reduces the frequency of pain, hematuria, stones, and urinary tract infections	Elevated liver function tests and severe liver toxicity
Slight drop in blood pressure	Increased cost because of close monitoring of liver function tests and drug (CYP3A inhibitor) interactions

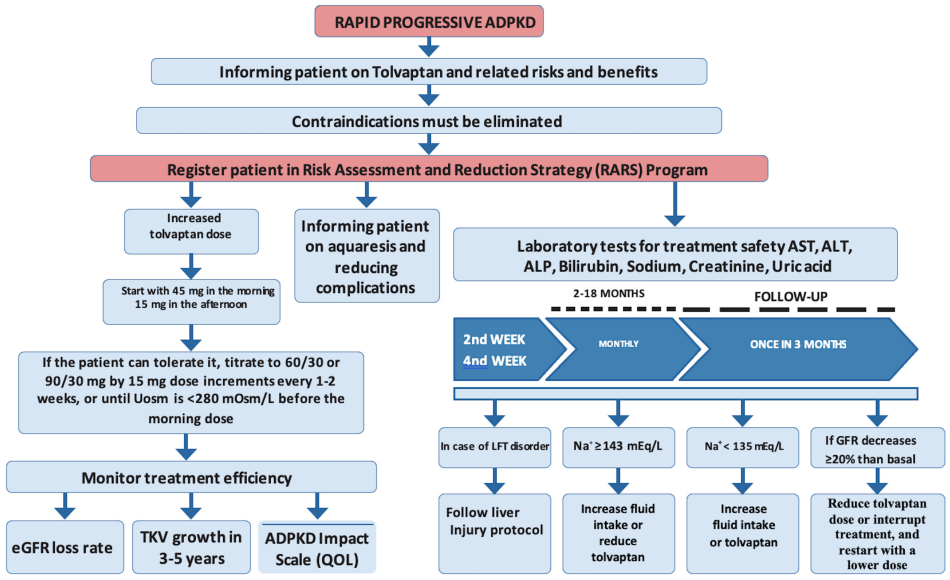


Figure 3. Tolvaptan treatment and follow-up algorithm.

Close monitoring of plasma osmolality and/or plasma sodium is essential for safety and efficacy, to ensure that a patient taking tolvaptan is drinking enough water to prevent dehydration and maintain adequate hydration. Optimal plasma sodium concentration should be maintained between 135-143 mEq/L. It is recommended to monitor plasma sodium 2-4 weeks after the start of treatment, then once a month for 18 months, and then every 3 months while evaluating liver function. It's important to be properly hydrated to avoid an increase in the levels of vasopressin in the blood, which can activate V1 receptors and have negative effects including vasoconstriction. There is not enough research on plasma copeptin measurements to predict this increase. Finally, serum uric acid levels can rise with tolvaptan treatment. This can also trigger a gout attack, and medical treatment is recommended when uric acid rises above 10 mg/dL. In general, the tolvaptan treatment algorithm is summarized in Figure 3.

PREVENTION OF COMPLICATIONS ASSOCIATED WITH AQUARESIS

It is advisable to initiate tolvaptan treatment on a day when the patient does not have work commitments, allowing them to adapt to the rapid aquaretic response induced by the medication. Patients should be counseled to drink fluids to prevent thirst and dehydration, or at the very first indication of thirst. Patients should be recommended to consume at least 2 to 3 liters of fluid during the day regardless of thirst perception, additional water before bed, and additional fluid intake after each urination at night.

Patients should be advised to track their weight every day and notify their physician if it fluctuates by more than 3% on a weekly basis. The aquaretic effect of the treatment typically becomes more tolerable after the first week.

Tolvaptan treatment should be temporarily discontinued during conditions that can cause dehydration or hinder proper hydration, such as food poisoning and gastroenteritis. It is also advisable to discontinue the treatment temporarily when there is an increased risk of insensible water loss, for example, during activities in hot weather, or when access to water might be restricted, such as when traveling or attending social events. In addition, tolvaptan must be stopped 24 to 48 hours before any elective surgery.

ASSESSMENT AND MANAGEMENT OF ELEVATED LIVER ENZYMES

When giving tolvaptan, the US FDA mandates close monitoring of liver tests as part of the "Risk Evaluation and Mitigation Strategy" (REMS) program. Patients and treatment teams should be vigilant for signs or symptoms of liver damage, such as right upper quadrant pain, abdominal tenderness, nausea, fatigue, vomiting, jaundice, rash, and fever.

If there are any symptoms or indicators of liver impairment, or if the patient's baseline level of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) is more than three times the upper limit of normal, tolvaptan treatment should be stopped right away. The protocol for managing abnormalities in liver function tests during treatment is summarized in Figure 4.

MONITORING THE EFFICACY OF TREATMENT

There is no perfect method to monitor the effectiveness of individual tolvaptan treatments. Routine annual measurement of TKV is not recommended for assessing the drug's efficacy. However, MRI or CT imaging may be useful to measure TKV every 3-5 years in comparison with initial imaging to assess the rate of TKV increase. Additionally, to confirm that the pace of

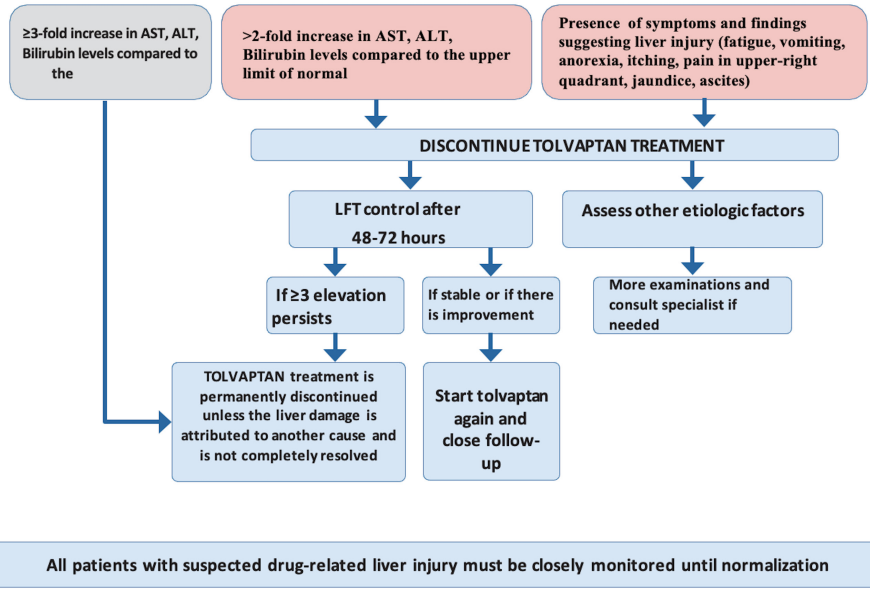


Figure 4. Tolvaptan treatment-related liver injury protocol.

loss in kidney function is slower than anticipated based on the Mayo classification, monitoring of the eGFR during tolvaptan treatment can be used.

SOCIAL SECURITY INSTITUTION ON HEALTH PRACTICES REIMBURSEMENT STATUS

Tolvaptan treatment is started in patients aged 18 (18.0)-55 (excluding 55.0), who have been diagnosed with ADPKD and have a GFR of 25 mL/min or higher, meeting all the following criteria:

The following GFR value calculated by the CKD-EPI formula is sought at the end of two measurements made within the last month:

1. Ages 18-40: eGFR criterion is not required
2. Ages 40-44: GFR < 90
3. Ages 45-49: GFR < 75
4. Ages 50-55: GFR < 60

The case must be rapidly progressing as defined below.

1. The average annual decline in estimated glomerular filtration rate (eGFR) should be greater than 3 mL/min/1.73 m^2, based on at least five measurements obtained annually over a 4-year period.

Or

2. Total kidney volume consistent with Mayo classification class 1D or 1E, as measured by MRI or CT.

The maximum dose in tolvaptan treatment should not exceed 120 mg per day. Treatment should be discontinued when eGFR is < 25 mL/min.

Previously, in patients who started tolvaptan treatment in accordance with the criteria before the age of 55, the treatment was discontinued after the age of 55. As a new development, tolvaptan treatment can now be continued in these patients after the age of 55.

CONCLUSION

There is currently no specific treatment other than tolvaptan for polycystic kidney disease, which is progressing rapidly worldwide. Early treatment with tolvaptan is particularly beneficial for young individuals whose disease is still in its early stages. The therapeutic efficacy of tolvaptan increases gradually with increasing dose. Therefore, it is appropriate to increase to the highest tolerated dose. The difficulties related to tolvaptan, such as identifying the appropriate patient group, planning the treatment process, determining the ideal dose and managing complications, are discussed in this review.

Availability of Data and Materials: The data that support the findings of this study are available on request from the corresponding author.

Peer-review: Externally peer reviewed.

Author Contributions: Concept – I.K., E.A.; Design – I.K., T.E.; Supervision – T.E.; Resources – O.A.O., K.G.A.; Materials – E.A., O.A.O.; Data Collection and/or Processing – I.K., E.A.; Analysis and/or Interpretation – I.K., E.A., T.E.; Literature Search – I.K., T.E.; Writing Manuscript – I.K., E.A., T.E.; Critical Review – I.K., T.E.; Other – K.G.A.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. Ong ACM, Devuyst O, Knebelmann B, Walz G, ERA-EDTA Working Group for Inherited Kidney Diseases. Autosomal dominant polycystic kidney disease: the changing face of clinical management. *Lancet*. 2015;385(9981):1993-2002. [CrossRef]
2. Chapman AB, Devuyst O, Eckardt KU, et al. Autosomal dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int*. 2015;88(1):17-27. [CrossRef]
3. Baur BP, Meaney CJ. Review of tolvaptan for autosomal dominant polycystic kidney disease. *Pharmacotherapy*. 2014;34(6):605-616. [CrossRef]
4. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med*. 2012;367(25):2407-2418. [CrossRef]
5. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in later-stage autosomal dominant polycystic kidney disease. *N Engl J Med*. 2017;377(20):1930-1942. [CrossRef]
6. Pei Y, Obaji J, Dupuis A, et al. Unified criteria for ultrasonographic diagnosis of ADPKD. *J Am Soc Nephrol*. 2009;20(1):205-212. [CrossRef].
7. Pei Y, Hwang YH, Conklin J, et al. Imaging-based diagnosis of autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 2015;26(3):746-753. [CrossRef]
8. Yu ASL, Shen C, Landsittel DP, et al. Baseline total kidney volume and the rate of kidney growth are associated with chronic kidney disease progression in autosomal dominant polycystic kidney disease. *Kidney Int*. 2018;93(3):691-699. [CrossRef]
9. Irazabal MV, Rangel LJ, Bergstralh EJ, et al. Imaging classification of autosomal dominant polycystic kidney disease: A simple model for selecting patients for clinical trials. *J Am Soc Nephrol*. 2015;26(1):160-172. [CrossRef]
10. Cornec-Le Gall E, Audrézet MP, Rousseau A, et al. The PROPKD score: a new algorithm to predict renal survival in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 2016;27(3):942-951. [CrossRef]
11. Chebib FT, Perrone RD, Chapman AB, et al. A practical guide for treatment of rapidly progressive ADPKD with tolvaptan. *J Am Soc Nephrol*. 2018;29(10):2458-2470. [CrossRef]
12. Müller R-U, Messchendorp AL, Birn H, et al. An update on the use of tolvaptan for autosomal dominant polycystic kidney disease: consensus statement on behalf of the ERA Working Group on Inherited Kidney Disorders, the European Rare Kidney Disease Reference Network and Polycystic Kidney Disease International. *Nephrol Dial Transplant*. 2022;37(5):825-839. [CrossRef]
13. Torres VE, Chapman AB, Devuyst O. CKD to ESRD transition: does assessment of kidney function matter? *Nephrol Dial Transplant*. 2017;32(1):1-3. [CrossRef]

10.5152/turkjnephrol.2025.25981

Review Article

Turkish Journal of Nephrology

The Dual Role of Microbiota as a Therapeutic Target in Lupus Nephritis

Ramesa Shafi Bhat

Department of Biochemistry, Science College of King Saud University, Riyadh, Saudi Arabia

ABSTRACT

Lupus nephritis, a severe manifestation of systemic lupus erythematosus (SLE), involves kidney inflammation driven by immune dysregulation. Emerging evidence highlights gut microbiota as a key factor in lupus nephritis pathogenesis, with dysbiosis contributing to inflammation, tissue damage, and disease progression. In lupus nephritis, alterations in the gut microbiome have been observed, including an increased abundance of pathogenic bacteria and a decrease in beneficial microbes. These imbalances can trigger immune system dysregulation, leading to inflammation, tissue damage, and worsening disease symptoms. Research has shown that the gut microbiota influences systemic inflammation and autoimmunity through mechanisms such as the modulation of immune cell activation, regulation of cytokine production, and interactions with the intestinal epithelial barrier. Thus, targeting the gut microbiota has gained attention as a potential therapeutic strategy for lupus nephritis. Fiber-rich foods support gut health and may reduce inflammation, offering protective benefits for kidney function. Therapeutic strategies targeting the microbiome, including probiotics, fecal microbiota transplantation, and dietary interventions, are gaining attention as potential treatments. Probiotics may restore microbial balance, enhance intestinal barrier function, and modulate immune responses to alleviate lupus nephritis symptoms. Fecal microbiota transplantation, while promising in animal models, requires further investigation in humans. Targeting the microbiota represents a promising therapeutic approach for lupus nephritis, and ongoing research may lead to microbiota-based therapies as a crucial component of lupus nephritis management.

Keywords: Lupus nephritis, inflammation, microbiome, leaky gut

Corresponding author: Ramesa Shafi Bhat ✉ rbhat@ksu.edu.sa **Received:** February 6, 2025 **Revision requested:** March 16, 2025 **Last Revision Received:** March 24, 2025 **Accepted:** April 29, 2025 **Publication Date:** July 3, 2025

Cite this article as: Bhat RS. The dual role of microbiota as a therapeutic target in lupus nephritis. *Turk J Nephrol.* 2025;34(4):240-252.

INTRODUCTION

Autoimmune diseases are characterized by an extreme immune response, high inflammation, and the accumulation of immune complexes in tissues and organs, affecting approximately 6-8% of the global population.[1] These diseases are marked by immune system abnormalities that lead to inappropriate reactions of B and T cells against body tissues.[2] The etiology of these chronic and systemic conditions is complex and involves immunological dysregulation, genetic factors, and environmental influences such as diet, lifestyle, medication, and gut microbiota.[3] Most of the time, the exact triggers for the immune system's response to self-molecules remain unclear. These disorders can affect virtually any organ system and can occur in individuals of all ages, though they are significantly more common in women.[4] While certain underlying mechanisms link these conditions, the clinical presentations can be highly diverse. Symptoms can range from acute and life-threatening organ failure to subtle laboratory changes that might go unnoticed. Autoimmune diseases can be classified as a diverse group of disorders where the immune system attacks the body's own tissues, ranging from organ-specific conditions (e.g., Hashimoto's thyroiditis, type 1

diabetes) to systemic diseases like systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and multiple sclerosis (MS). While these conditions share common features such as immune dysregulation and inflammation, they have distinct pathophysiological mechanisms, with varying immune cell involvement and organ targets.[5] The role of gut microbiota in autoimmune diseases is increasingly recognized, particularly in SLE and lupus nephritis, where it may influence immune responses and disease progression. However, the significance of gut microbiota in other autoimmune diseases depends on their specific underlying mechanisms. Despite advances in diagnostic techniques and treatment options, early detection and targeted therapies for autoimmune diseases remain significant challenges.[6] Autoimmune diseases not only profoundly affect individuals and their families but also pose significant challenges for society and healthcare costs. The prevalence of autoimmune diseases is rising significantly in various regions worldwide, likely due to changes in environmental exposures, including significant shifts in diet, exposure to xenobiotics, air pollution, infections, lifestyle choices, stress, and climate change.[6-7]

Systemic lupus erythematosus is a chronic autoimmune condition marked by inflammation and immune-related damage to various organ systems, including the mucocutaneous, musculoskeletal, hematologic, and kidney systems.[8] Around 3.4 million people globally have been diagnosed with SLE, which predominantly affects women, with a global prevalence ranging from 30 to 60 cases per 100 000 in the UK and the USA.[9,10] The pathogenesis of SLE involves genetic and environmental factors, such as viral infections, impaired apoptosis, and exposure to ultraviolet-B radiation. Regarding immune response, autoantibodies primarily target nuclear and cytoplasmic antigens.[11] Around 50% of patients with SLE develop kidney damage, presenting symptoms such as hematuria, proteinuria, edema, or reduced kidney function, a condition referred to as lupus nephritis.[12] It is a critical and serious manifestation of SLE associated with a high mortality rate.[13] "Lupus," derived from the Latin meaning "wolf," refers to the distinctive facial rash associated with SLE, which resembles a wolf's bite.[14] Lupus nephritis is characterized by immune dysregulation and kidney inflammation developed within 3-5 years after the onset of SLE. Approximately, 10% of individuals with lupus nephritis may progress to end-stage kidney disease (ESKD) within 5 years of diagnosis (Figure 1). Given the high morbidity associated with lupus nephritis, effective treatment is crucial in preventing progression to ESKD.[15] Traditional laboratory biomarkers used in the clinical evaluation of lupus nephritis include immune serology tests like anti-double-stranded (ds) DNA antibodies and complement levels, as well as kidney function indicators such as proteinuria (measured via 24-hour urinary protein excretion or the urine protein-to-creatinine ratio [uPCR]), urinary sediment analysis, and glomerular filtration rate (GFR). While these parameters are well-established, they have demonstrated limited ability to detect lupus nephritis flare-ups early and often lack sufficient sensitivity and specificity to distinguish between active disease and chronic kidney damage. This distinction is critical for guiding treatment decisions.

Recent research suggests that gut microbiota may play a key role in worsening lupus by promoting immune complex deposition, activating the complement system, and increasing macrophage infiltration, all of which contribute to kidney inflammation.[16] Conditions like "leaky gut" can allow harmful bacteria to enter the bloodstream and form immune complexes that accumulate in the kidneys.[17] The harmful microbial products, such as lipopolysaccharides (LPS), translocate into the bloodstream, triggering systemic inflammation. These products can activate the innate immune system, including toll-like receptors (TLRs), which in turn stimulate the production of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL)-6. The imbalance in microbiota may also contribute to the generation of autoantibodies, such as anti-dsDNA, by influencing B-cell activation. This triggers a pro-inflammatory response mediated by lymphocytes and macrophages, resulting in kidney inflammation. There is growing evidence supporting the role of intestinal dysbiosis in the development of lupus. Recently, researchers have increasingly focused on the role of the gut microbiota in lupus nephritis as gut health is significantly affected. Individuals with lupus nephritis may experience gastrointestinal issues such as diarrhea, dysbiosis (an imbalance in gut microbiota), and abdominal pain. This dysbiosis can influence the activity and severity of the disease, as the gut is vital for immune regulation.[18] However, the relationship between gut microbiota and autoimmune diseases remains an evolving field. Some research has failed to establish a significant connection between microbiota imbalances and autoimmune disease onset or progression. Factors such as genetics, diet, and medication use can influence the findings related to

MAIN POINTS

- Emerging evidence highlights the gut microbiota as a key factor in lupus nephritis, with dysbiosis (microbial imbalance) contributing to inflammation, tissue damage, and disease progression.
- Patients with lupus nephritis often show an increased abundance of pathogenic bacteria and a decrease in beneficial microbes, which can trigger immune system dysregulation and worsen symptoms.
- The gut microbiota influences systemic inflammation and autoimmunity by modulating immune cell activation, cytokine production, and interactions with the intestinal barrier.
- Probiotics, FMT, and dietary interventions are being explored as potential treatments for lupus nephritis, aiming to restore microbial balance and reduce inflammation.
- While FMT shows promise in animal models, further investigation is needed in humans. Targeting the microbiota may become an important part of lupus nephritis management in the future.

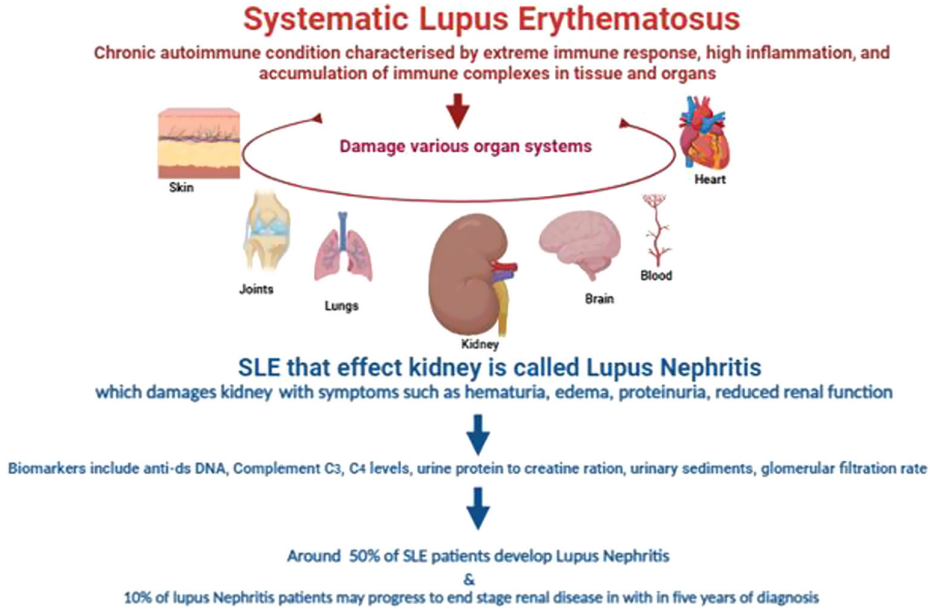


Figure 1. Systemic lupus erythematosus and lupus nephritis: organ involvement and kidney disease progression.

lupus nephritis. Genetic factors, such as immune-related gene polymorphisms, contribute to autoimmune disease susceptibility, while hormonal influences, particularly estrogen, play a key role in the higher prevalence of lupus in women. Epigenetic changes, like DNA methylation and histone modifications, can affect gene expression and contribute to immune dysfunction. A thorough understanding of lupus nephritis requires considering the interplay of these factors alongside the gut microbiota, as they collectively impact disease onset and progression. The microbiomes, predominantly bacteria, and their microbial products play a crucial role in regulating the development and function of the immune system in the human body. These microorganisms inhabit various sites, including the gut, skin, vagina, and oral cavity.[19] Types and abundance of microbes can vary between different organs and among individuals. Factors such as diet, environmental conditions, host genetics, and mode of delivery contribute to this wide microbial diversity.[20] A complex interaction between the host immune system and commensal microbiota is essential for maintaining gut homeostasis. In this symbiotic relationship, the microbiota aids in carbohydrate fermentation and digestion, vitamin synthesis, and the development of gut-associated lymphoid tissue while also preventing the colonization of harmful pathogens. In return, the host provides a suitable environment and nutrients for the survival of these microbes.[21] However, when this mutually beneficial relationship is disrupted and the interaction between immune cells and bacteria, the gut microbiota triggers autoimmune disorders. Researchers are working to clarify the microbiota's role in discovering new therapeutic strategies to maintain immune balance and homeostasis in SLE.[22] Probiotics are live microorganisms that provide a health benefit to the host when administered in sufficient quantities. Probiotics can influence systemic immune responses, maintain the balance of healthy microbiota in the intestinal mucosa, and potentially serve as adjunctive therapy for immune-mediated diseases.[23] The proposed mechanisms for these effects include promoting mucus secretion, producing antimicrobial peptides, supporting the integrity of the gastrointestinal epithelial barrier, facilitating interactions between gut microbiota and mucosal immune cells, and aiding the host immune system in response to harmful pathogens.[24] Despite these associations, the causes of gut microbiota imbalances and the pathways leading to lupus nephritis flares remain poorly understood. This review emphasizes the role of the gut microbiota in developing lupus nephritis, clarifying the regulatory mechanisms that affect inflammation and autoimmunity. While factors such as genetic predisposition, hormonal influences, and epigenetic modifications contribute to disease progression, the focus of this review will be specifically on the gut microbiota. Furthermore, it aims to detect probiotics as targeted treatment strategies for lupus. Therapeutic approaches that regulate gut microbiota composition to enhance or complement existing treatments for lupus nephritis are also discussed.

Altered Gut Microbiota in Lupus Nephritis

Gut microbiota interact with the immune system and play a crucial role in developing SLE.[25] Although, these microbiotas have the potential to serve as diagnostic and prognostic biomarkers, paving the way for new therapeutic strategies, the clinical utility remains uncertain as microbiome-based diagnostics are not widely used due to variability in microbiome data and the high cost of sequencing. Also, specific microbial compositions unique to lupus nephritis remain to be fully identified. It's important to note that gut microbiota composition can vary significantly based on factors such as diet, geography, genetics, and medication use. Thus, certain microbial profiles linked to

lupus nephritis might not be universally applicable across all populations. The variation in study methodologies, including differences in sequencing techniques, sample sizes, and patient selection criteria, can also lead to inconsistent results, making it challenging to compare findings across studies.

Biomarkers within gut microbiota may correlate with disease activity in such patients and could act as indicators for monitoring disease. Numerous studies have revealed significant changes in gut microbiota among lupus patients compared to healthy individuals.[15] *Bacteroidetes* and *Firmicutes* are the primary components of the human gut microbiota, yet a notable decrease in the *Firmicutes/Bacteroidetes* (F/B) ratio has been observed in lupus patients across various countries.[26] However, it should be noted that shifts in the F/B ratio are not specific to lupus nephritis and have been observed in multiple diseases, which may limit the specificity of this ratio as a diagnostic or monitoring tool for lupus nephritis. Active lupus patients exhibit a significantly lower F/B ratio than those with inactive disease, depending on ethnic background, lifestyle, or disease stage. Additionally, the gut microbiota composition varies between lupus patients with depression and those without.[26] To assess disease severity in lupus nephritis, several biomarkers are commonly used, including the SLE Disease Activity Index (SLEDAI), anti-dsDNA antibodies, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and complement C3 levels. Research has also linked specific gut microbiota biomarkers to disease activity in lupus nephritis. For example, circulating immunoglobilin G (IgG) antibodies to *Enterococcus gallinarum*, a gram-positive commensal gut bacterium, are elevated in lupus patients and significantly associated with higher levels of anti-ribosomal P (RP), anti-dsDNA, and anti-Sm (Smith antibodies) autoantibodies as described in Figure 2. *Ruminococcus gnavus*, a gram-positive anaerobic bacterium, is found to be 5 times more abundant in SLE patients, especially in those with lupus nephritis.[27] Anti-RP antibodies correlate positively with anti-dsDNA levels and SLEDAI scores while showing negative correlations with complement C3 and C4 levels. Patients with active nephritis, particularly those with Class III and IV, have the highest serum levels of anti-RP strain-specific antibodies. Furthermore, the abundance of genera such as *Acholeplasma*, *Capnocytophaga*, and *Leptotrichia* is negatively correlated with SLEDAI scores, while *Bacteroides*, *Ruminococcus*, and *Akkermansia* exhibit an inverse relationship with serum complement C3 levels. The genus *Streptococcus* has also been associated with lupus activity. Recent studies have shown that lupus nephritis patients exhibit an increased abundance of *Enterobacteriaceae* and *Enterococcaceae*, alongside a decreased abundance of *Ruminococcaceae* in their gut microbiota, confirming the presence of dysbiosis. Additionally, *Actinobacteria*, *Bacillales*, *Coprobacter*, and *Lachnospira* are inversely correlated with the risk of SLE, whereas *Bacilli*, *Eggerthella*, *and Lactobacillales* may serve as risk factors for the disease.[28]

Possible Onset of Lupus Nephritis via Diet versus Gut Microbiota

To regulate immune tolerance within the gut, dietary practices are vital for maintaining proper gut function. Metabolic profile can serve as a valuable indicator of microbial activity in lupus patients. Fiber, a non-digestible edible carbohydrate polymer, resists digestion and is fermented into short-chain fatty acids (SCFAs), primarily acetate, propionate, and butyrate in the gut. Inadequate dietary fiber, leading to low levels of SCFAs, can cause inflammation and disrupt both innate and adaptive immunity. However, it is important to recognize that other factors, such as genetics, medications, and overall microbial

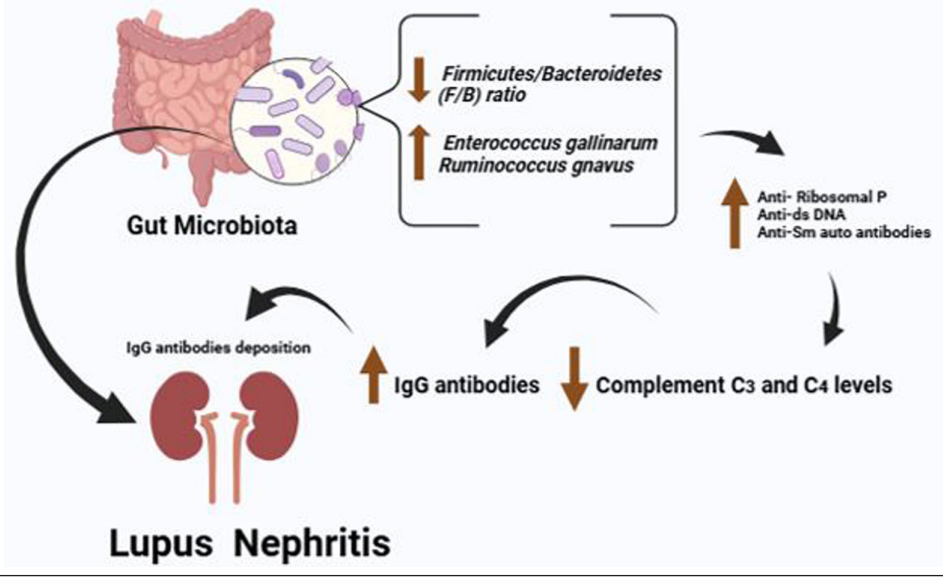


Figure 2. Gut microbial contribution to lupus pathogenesis: immunoglobilin G antibodies to gut pathobiont deposited in the kidney correlated with elevated anti-ribosomal P, anti-double stranded DNA, and anti-Sm autoantibodies.

diversity, also play crucial roles in shaping the microbiome and influencing disease progression. The relationship between fiber intake and inflammation contributes to alterations in gut microbiota that may promote the development of autoimmune disorders.[29] Short-chain fatty acids also serve as an energy source for gut microbiota, so changes in fiber intake can lead to reduced populations of gut microbes, a condition known as dysbiosis. This phenomenon is frequently observed in patients with lupus nephritis and can be partly attributed to insufficient dietary fiber intake.[30] While fiber and SCFAs are known to have beneficial effects on gut health and immune regulation, their precise role in the treatment of lupus nephritis remains uncertain. Patients with lupus nephritis often experience gastrointestinal issues, including bloating, diarrhea, or abdominal discomfort, which can complicate their ability to tolerate a high-fiber diet. These factors should be considered when evaluating dietary interventions as a potential treatment strategy for lupus nephritis. Therefore, while dietary fiber may offer benefits in terms of immune modulation and gut health, further clinical research is needed to establish its effectiveness and safety in the context of lupus nephritis treatment.

Short-chain fatty acids have several immunoregulatory functions, including anti-inflammatory effects and modulation of T cell activity through epigenetic pathways. Propionate is produced by *Bacteroides* and *Negativicutes* via the succinate pathway, acetate through the Wood-Ljungdahl pathway by *Blautia*, *Clostridium* spp., and *Streptococcus* spp., and butyrate is mainly generated by *Firmicutes* through the acetate CoA-transferase pathway. Adequate dietary fiber intake in lupus nephritis patients can help reduce disease activity by lowering serum levels of autoantibodies and inflammatory cytokines, as shown in Figure 3. Butyrate has been shown to alleviate kidney disease through G-protein-coupled receptor signaling and plays a critical role in maintaining gut homeostasis by activating PPAR-γ signaling. This activation suppresses the production of inducible nitric oxide synthase (iNOS) and prevents the overgrowth of nitrate-dependent microbes in the gut. Treatment with butyrate in lupus-prone mice has improved kidney damage by enhancing the *Firmicutes*-to-*Bacteroidetes* (F/B) ratio and increasing microbial diversity. Additionally, in NZB/W mice, histone deacetylase (HDAC) 6 inhibitors significantly reduced symptoms of lupus nephritis by inhibiting B-cell activation pathways. This evidence emphasizes the significant relationship between SCFAs and HDACs, suggesting that SCFAs may function as important immunomodulators in lupus nephritis. It is important to recognize that individual responses to these factors can differ significantly due to genetic, environmental,

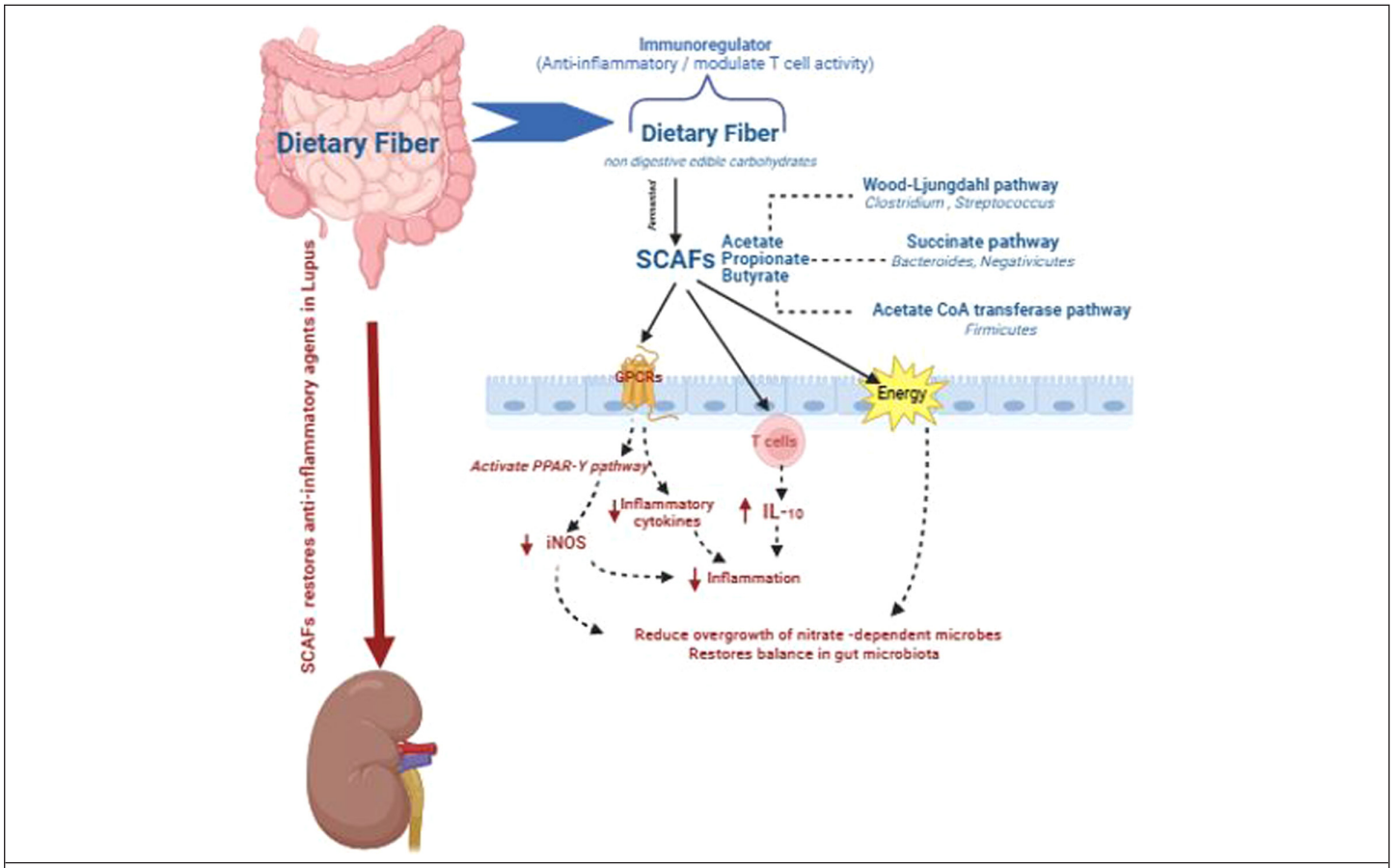


Figure 3. Dietary fibers as therapeutic agents for kidney inflammation by modulating the gut microbiome and restoring the balance between pro-inflammatory and anti-inflammatory factors in lupus nephritis patients.

and microbial variations. Additionally, understanding the interplay between regulatory pathways, such as cytokine signaling, immune cell activation, and other epigenetic mechanisms with HDACs and SCFAs, is critical for elucidating the pathogenesis of lupus nephritis and developing more targeted therapeutic strategies. Thus, microbial metabolites are crucial in the immune regulatory interactions between diet and gut microbiota. A low-fiber diet can promote immune dysregulation, leading to the deposition of immune complexes in kidney glomeruli. In contrast, lupus symptoms were significantly reduced in Lyn tyrosine kinase-deficient ($Lyn^{-/-}$) mice fed a high-fiber diet, indicating a potential link between high-fiber diets and immune modulation.[31] Few other dietary factors may also have significant effects on the gut microbiome and can influence disease progression in lupus nephritis. For example, high-fat diets have been shown to promote inflammation and alter gut microbiota composition, whereas certain micronutrients, such as vitamin D, play key roles in immune regulation.

Research on SLE rodent models indicates that resistant starch in the diet can suppress the growth of *Lactobacillus reuteri* by producing SCFAs, decreasing plasmacytoid dendritic cells (pDCs), and interferon pathways, thereby reducing lupus symptoms. This evidence suggests that resistant starch may inhibit the interferon pathway activated by gut pathobionts, which is particularly relevant to the pathogenesis of lupus nephritis. Elevated levels of fecal kynurenic acid, a metabolite derived from tryptophan, have been observed in some SLE patients, yet the exact role of tryptophan in lupus nephritis remains unclear. In certain rodent models of lupus nephritis, the gut microbiota has been shown to initiate immune responses through the degradation of tryptophan. A high-tryptophan diet has been associated with increased levels of *Lactobacillus* spp. and *Bacteroides dorei*, promoting pro-inflammatory effects. Conversely, a low-tryptophan diet has been found to improve lupus characteristics by regulating T-cell function and CD25 expression.[32] These effects are influenced by the broader dietary context, including factors such as protein intake, gut permeability, and host metabolism, all of which shape tryptophan metabolism and contribute to lupus nephritis pathogenesis. This highlights the need for a more comprehensive understanding of tryptophan's role in this condition. Rodent models are often used to investigate disease mechanisms because they provide insights into the pathophysiology. However, rodents differ from humans in various aspects, such as immune system function, metabolic pathways, and gut microbiome composition. For example, rodents typically have a simpler microbiome, which can lead to different interactions between the microbiota and host. Furthermore, differences in the genetic makeup and immune response mechanisms between species can limit the direct applicability of findings to humans. These models offer valuable preliminary data, but human studies are essential to establish more precise cause-and-effect relationships and to better understand how these interactions occur in human physiology. Similarly, diet-based interventions for lupus nephritis are still largely theoretical, and extensive research, especially in human studies, is needed to determine their practical applicability. Further clinical investigations are critical to evaluate the safety, efficacy, and feasibility of these interventions in real-world settings before specific dietary recommendations can be made for patients.

Microbial Imbalance Induced Leaky Gut in Lupus Nephritis

Modifying the host's microbiota and gut integrity could provide valuable insights for developing new treatments for lupus. The intestinal epithelium serves as the initial barrier against pathogens in the gastrointestinal tract. This epithelium comprises a single layer of various cell types essential for absorbing nutrients and water, defending against microbes, and modulating immune responses to sustain a balanced gut environment.[33] Tight junction (TJ) complexes formed between adjacent epithelial cells maintain the structural integrity of the gut barrier and regulate the passage of substances between cells. The functionality of TJs can be influenced by genetic and environmental factors, such as imbalances in gut microbiota and dietary elements.[33] Increased permeability in the gut barrier has been linked to the onset, advancement, and recurrence of lupus nephritis. Microbial imbalance in the gut can affect the gut barrier integrity through harmful bacterial growth and their byproducts, disrupting gut immune homeostasis. Research shows that restoring microbial balance can reduce gut permeability, highlighting the microbiota's crucial role in maintaining gut integrity. The presence of microbial components in the bloodstream of lupus patients indicates that microorganisms and their products may enter systemic circulation due to increased intestinal permeability.[34] Evidence from lupus patients with autoimmune hepatitis reveals the translocation of *E. gallinarum* into systemic organs, as bacterial DNA has been found in the liver. *E. gallinarum* can migrate from the gut to the liver, triggering the production of anti-dsDNA antibodies through TLR-7/8 activation in lupus patients, which is reversed by antibiotic treatment that inhibits the growth of *E. gallinarum* in tissues and eliminates pathogenic autoantibodies and T cells shown in Figure 4. TLR7 is primarily expressed on B cells and pDCs that produce type I interferons (IFNs), while TLR8 is predominantly found on monocytes, macrophages, and neutrophils. Activation of TLR7/8 triggers MyD88/IRAK/TRAF6 signaling pathways, leading to the activation of monocytes and B cells through nuclear factor (NF)-κB, or of pDCs through IRF7. Both TLR7- and TLR8-expressing cells are implicated in a variety of autoimmune diseases, with a particularly strong genetic association between TLR7 and lupus nephritis. Toll-like receptor 7 is also overexpressed in the peripheral blood mononuclear cells (PBMCs) of SLE patients. A negative correlation is found between *Synergistetes*, a phylum of anaerobic bacteria in the gut, and plasma anti-dsDNA antibodies and IL-6. Interleukin 6 is known to enhance the differentiation of T-helper (Th) 17 cells and increase the production of IL-17a, a key factor in driving autoimmunity in lupus.[35] Furthermore, various bacterial components have been identified in the blood of individuals with

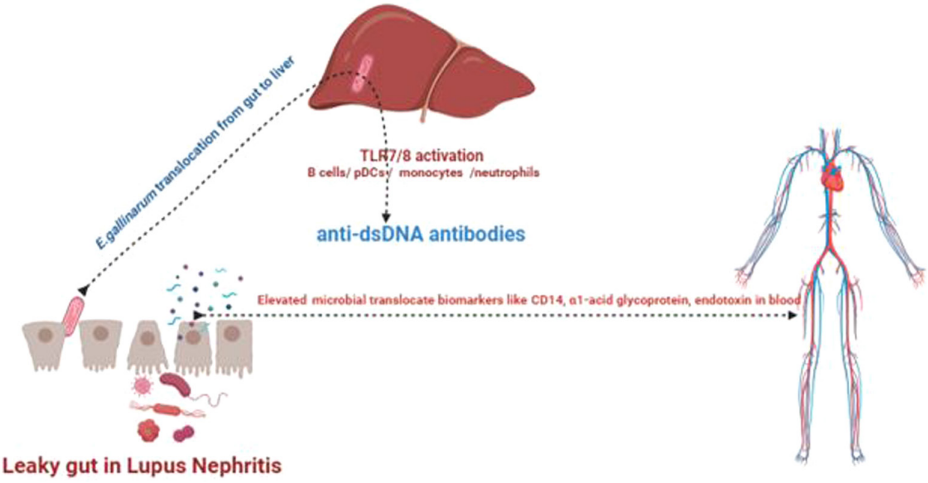


Figure 4. Microbial imbalance leads to leaky gut in lupus nephritis, compromising gut barrier integrity, which allows harmful bacterial growth and byproducts to pass through the intestinal wall, entering the liver and systemic circulation.

lupus nephritis, suggesting leakage from the gut. Elevated levels of biomarkers for microbial translocation, such as soluble CD14 and α1-acid glycoprotein, endotoxin from bacterial products, and fungal cell wall components have been detected in the serum of active lupus nephritis patients. However, there is limited understanding of the mechanisms behind losing gut barrier integrity in lupus nephritis. However, many rodent model studies provide clues about how dysbiosis could contribute to a leaky gut in lupus nephritis.

Certain bacteria can enhance gut integrity, suggesting that the development of a leaky gut may be linked to their absence. Microbial metabolites can enter the bloodstream through the gut epithelium, where they can influence immune activation and contribute to systemic autoimmunity. Toll-like receptor signaling in the intestine plays a crucial and distinct role in regulating commensal microbiota, triggering inflammatory responses, and balancing tolerance. The expression and interaction of TLRs, particularly TLR2, TLR6, TLR7, TLR8, and TLR9, play critical roles in the development of SLE. Pathogens typically contain ligands for various TLRs, activating multiple signaling pathways during infections or inflammatory conditions. Toll-like receptor expression can be localized to specific cell types and regions within the gut, with different TLR-induced cytokine responses, like TLR6 promoting the production of IL-10.[36] This complex regulation allows for precise adjustments in immune responses based on specific TLR interactions. Commensal microbiota can manipulate these levels through TLR ligands to facilitate colonization, enhance tolerance, and limit inflammatory diseases. Stimulation of intestinal epithelial cells with TLR-2 ligands prompted the redistribution of TJ proteins, which enhanced monolayer integrity. Toll-like receptor-2 is expressed in intestinal epithelial cells to recognize bacterial components and affect gut integrity. Lipoteichoic acid, a predominant surface glycolipid of gram-positive bacteria and a TLR2 ligand, increased mucin expression and reduced inflammation and gut leakage, suggesting beneficial bacteria's role in restoring gut barrier function. Toll-like receptor-7 is a disease-promoting factor, while TLR8 and TLR9 generally have more regulatory roles. Understanding these interactions is crucial for identifying therapeutic targets to modulate immune responses in lupus and other autoimmune diseases. Additionally, the relationship between TLRs and immune cells, such as ABCs, is important for disease pathogenesis. Since some TLRs, like TLR9, also have tolerogenic functions, such as establishing central B-cell tolerance, targeting them may help restore B-cell tolerance in autoimmune diseases. However, dual inhibitors targeting both TLR7 and TLR8 or TLR9 may be less effective than those focused solely on TLR7. Therefore, further research into the specific roles of each TLR is essential to refine therapeutic strategies. *Lactobacillus plantarum* enhances the expression of TJ proteins like ZO-1 and Occludin in humans.[37] When Caco-2 cell monolayers were exposed to *L. plantarum*, intestinal integrity improved by facilitating the translocation of ZO-1 to TJs.[37] However, blocking TLR2 with neutralizing antibodies negated this protective effect, indicating that *L. plantarum* likely activates TLR2 to confer its benefits. An anti-inflammatory molecule produced by *Faecalibacterium prausnitzii* and *Akkermansia muciniphila* has been shown to restore gut barrier function and increase ZO-1 expression in rodents, suggesting its direct role in maintaining gut integrity. *Lactobacillus salivarius* restores barrier function in epithelial cell monolayers through the relocation of TJs to improve integrity. *Bacteroides fragilis* increased levels of SCFAs and IL-22, as well as the number of regulatory T cells, which likely contributed to enhanced TJ integrity and reduced inflammation.[38] The overgrowth of pathogenic *Bacteroides* and *Prevotellaceae_UGG-001* in experimental autoimmune rodents disturbs gut integrity, which can be improved by administrating broad-spectrum antibiotics. The commensal bacterium *Bacteroides fragilis* has been shown to decrease

colitis development. Enterotoxigenic *B. fragilis* showed increased intestinal permeability and damage to epithelial E-cadherin due to a metalloprotease toxin produced by *B. fragilis*, which degrades TJs in rodents. This highlights the importance of maintaining microbial balance for health. For example, *B. fragilis* can be beneficial in reducing colitis under normal conditions, but when it overgrows, it can disrupt gut integrity and potentially exacerbate disease outcomes. Similarly, *Clostridium difficile* produces toxins A and B, *Clostridium perfringens* produces enterotoxin, *E. coli* produces cytotoxic necrotizing factor 1, *Helicobacter pylori* produces vacuolating toxin, *Listeria monocytogenes* produces internalin, and *Vibrio cholerae* produces Zonula occludens toxin. Furthermore, *Pseudomonas fluorescens* can trigger zonulin secretion, which negatively regulates TJs, leading to changes in the cytoskeleton and disassembly. For instance, *B. fragilis* may act as beneficial in reducing colitis under normal conditions, but when overgrown, it can disrupt gut integrity and potentially worsen disease outcomes. This underscores the importance of microbial balance in maintaining health.

Additionally, infections with protozoans like *Giardia intestinalis* and *Blastocystis hominis* have increased rodent intestinal permeability. Rotavirus can also affect gut barrier function by altering the positioning of the TJ protein occludin. Thus, various microorganisms can either positively or negatively impact gut barrier integrity, and understanding their roles in the context of lupus may be crucial for restoring gut barrier function in patients.

The Potential Role of Microbiomes Beyond the Gut in Triggering Lupus

While the intestinal microbiome has been the primary focus of research, other microbial communities, such as those in the oral, skin, and genital tracts, may also exacerbate lupus nephritis. Imbalances in these microbiomes can influence immune responses, potentially triggering autoimmune reactions and disease flare-ups. Oral bacteria and their metabolites may interfere with genes related to autoimmune disease. Studies have shown a potential link between oral microbial DNA and nucleic acid sensing, suggesting that oral bacteria could influence systemic diseases, including lupus. The composition of the oral microbiome is highly variable, influenced by factors such as diet, smoking, poor oral hygiene, periodontitis, and salivary issues. The oral microbiota maintains a symbiotic relationship with the host in healthy individuals. However, an imbalance in the microbial population can lead to periodontal damage and increased systemic inflammation, which may contribute to the onset or worsening of Lupus nephritis symptoms. Oral mucosal lesions contribute to systemic disease exacerbation through autoantibody production triggered by oral microbial products in 5-40% of Lupus patients.[38] The oral microbiota of lupus patients differs significantly from that of healthy individuals, with an increased presence of species like *Fretibacterium, Prevotella,* and *Selenomonas.* Gum diseases such as Periodontitis also tends to develop earlier in lupus patients and is often worsened by co-existing infections. Elevated cytokine levels (especially IL-1β and IL-6) and inflammation in the oral mucosa of lupus patients suggest systemic cytokine responses by subgingival bacteria.[39] The microbiota of the genital tract, particularly in women, is dynamic and can influence autoimmune diseases. Changes in vaginal microbiota occur naturally due to hormonal fluctuations, sexual activity, and aging, with lupus nephritis development most frequent during reproductive years. Research on genital dysbiosis in lupus patients is still limited but shows that microbial imbalances in this area could contribute to disease progression. *Ureaplasma urealyticum*, the more prevalent pathogen found in active cases of lupus nephritis, is potentially linked to steroid use as the majority of patients are treated with prednisone.[40] Additionally, women with lupus have a higher risk of urinary tract infections, which can influence disease exacerbation. Active SLE patients with urinary tract infections had a distinct urinary microbiome compared to healthy individuals. The skin acts as a vital defense against pathogens, but in lupus, it is often compromised by skin lesions, which affect up to 80% of patients and can sometimes be the first visible symptom of the disease.[40] Studies have shown that the microbial composition of skin with lesions differs from that of unaffected skin in these patients. For example, *Pelagibacterium* and *Novosphingobium* are more abundant in lesioned areas, while *Curvibacter* is less prevalent. When comparing patients in remission with those experiencing active lupus, the presence of *Caulobacteraceae* was positively correlated with disease activity and negatively associated with complement C3 levels. In contrast, *Aerococcaceae* negatively correlated with disease activity and immunoglobulin G levels.[40] These findings suggest that the microbiota other than the gut play a role in modulating lupus activity, underscoring the need for further research into its contribution to disease development and progression.

Microbial Molecular Mimicry Triggers Lupus Nephritis

Molecular mimicry between bacterial antigens and self-components is implicated as a pivotal mechanism by which lupus nephritis is triggered.[41] This phenomenon occurs when molecular structures of microorganisms resemble the host's self-antigens, leading to an immune response that targets the body's tissues mainly by activating T and B cells. In the case of lupus, certain bacteria that share epitope sequences with self-antigens can trigger the production of cross-reactive autoantibodies. For instance, antigens from *Burkholderia* bacteria could bind to dsDNA antibodies in the serum of lupus patients, suggesting a link between *Burkholderia* molecular mimicry and the production of anti-dsDNA antibodies, a key marker of lupus nephritis.[41] Similarly, glycolipids from the mycobacterial cell wall could interact with anti-dsDNA autoantibodies in patients. These findings support the idea that bacterial infections may drive the formation of autoantibodies in lupus nephritis through molecular mimicry. The formation of anti-dsDNA antibodies is critical in the pathogenesis of lupus nephritis, as these antibodies are often found in higher concentrations in kidney

tissue compared to systemic circulation.[41] Their levels may also rise before lupus flares, making them a valuable diagnostic and monitoring tool for disease activity. Furthermore, recent research has shown that peptides from intestinal bacteria such as *Odoribacter splanchnicus* and *A. muciniphila* resemble the epitopes of self-antigens like the anti-Smith antigen and the Fas antigen. YLYDGRIFI peptide from the IS66 family of *O. splanchnicus* transproteases can influence the secretion of IL--γ and IL-17A from PBMCs in a subset of anti-Smith antibody-positive lupus patients due to the similarity between this bacterial peptide and the YLYDGRIFI autoepitope of human small nuclear ribonucleoprotein-associated proteins B and B', which are presented to T cells by the HLA-DR isotype. Additionally, the DGQFCM peptide from *A. muciniphila* is found at higher levels in lupus patients and shares similarities with the extracellular DGQFCG region of the human Fas ligand, potentially influencing its binding to IgG antibodies produced by memory B cells in patients. The HLA-DR3 allele is a key lupus susceptibility locus, and T cells play a central role in Lupus Nephritis development. T-cell epitopes on *Clostridium tetani* mimic human autoantigens, such as a DR3-restricted bacterial epitope (ABC247-261), and activate autoreactive T cells to induce autoantibody production, highlighting the potential of bacterial mimicry in triggering autoimmunity in DR3-susceptible individuals.[41] Similarly, the Ro60 antigen, associated with anti-Ro/SSA antibodies in lupus, shows cross-reactivity with Epstein–Barr virus nuclear antigen 1 (EBNA-1). Fecal samples from patients with active lupus promoted lymphocyte activation and the differentiation of naïve CD4+ cells into Th17 lymphocytes in vitro. An imbalance between Th17 cells and Tregs may contribute to the exacerbation of lupus nephritis, increasing antibody production and kidney deposition. Enriching patient stool samples with Treg-inducing bacteria, such as certain *Clostridia* strains, reduced the Th17/Th1 balance, and *Bifidobacterium bifidum* prevents excessive CD4+ lymphocyte activation.

Potential Therapy for Lupus Nephritis through Modulating Gut Microbiota

Modulating the gut microbiota as a treatment for lupus nephritis is still in its early stages, but its link to dysbiosis offers valuable insights for developing future therapeutic approaches. The therapeutic approaches, such as probiotics, prebiotics, dietary interventions, and microbiota transplants, show promise in promoting a healthy microbiota and restoring gut integrity. However, these approaches are still under investigation, and more research is needed to determine their efficacy and safety in lupus nephritis (Figure 5).

Probiotics as a Management Strategy for Lupus Nephritis through Restoring the Gut Flora

Probiotics are live microorganisms taken as supplements to promote the growth of beneficial bacteria, leading to positive health outcomes when consumed in appropriate amounts. Recent studies have highlighted several health benefits associated with probiotics. Probiotics may regulate gut microbial functions and impact metabolic processes in lupus nephritis patients. Specific strains, especially from the *Bifidobacteria* and *Lactobacillus* families, have shown promise in protecting against autoimmune diseases. Research indicates that the depletion of *Lactobacillus* and *Bifidobacterium* in the gut microbiota of rodent models with SLE suggests that bacterial supplementation with various *Lactobacillus* strains, known to benefit

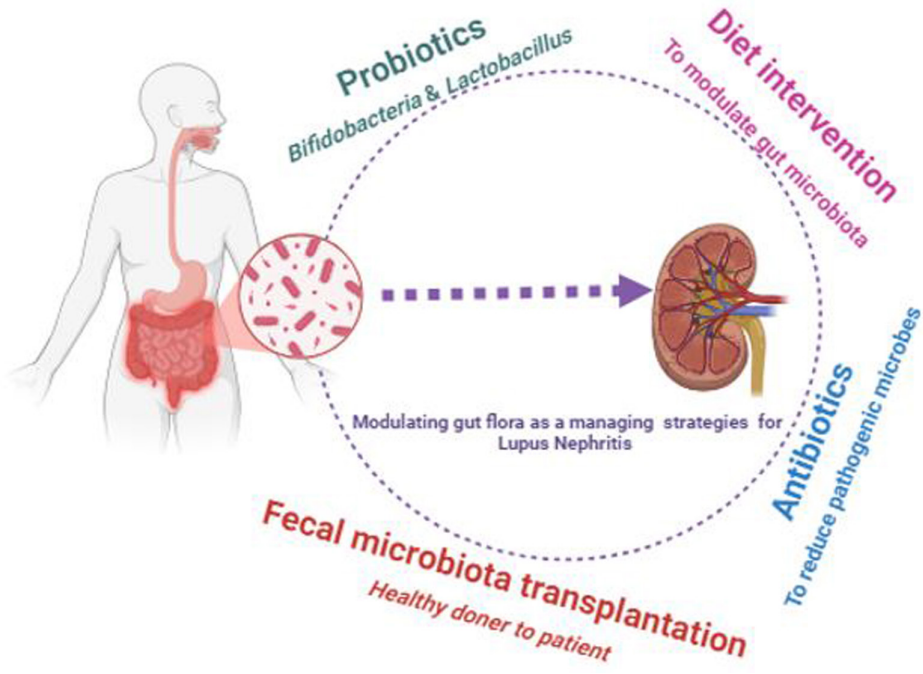


Figure 5. Approaches for modulating the gut microbiome in managing lupus nephritis.

other autoimmune conditions, might help alleviate symptoms in lupus patients. In rodent models, *Lactobacillus* spp. significantly reduced lupus nephritis and improved survival rates by lowering plasma levels of anti-dsDNA antibodies. Probiotic treatment is closely linked to lupus nephritis as it can regulate alterations in gut microbiota and metabolites. Studies have provided insights into the improvements in lupus nephritis patients and highlighted the potential of microecological therapies with probiotics as treatment options. Studies have focused on how bioactive synbiotic mixtures like dietary prebiotics enhance fecal microbiota, while probiotic supplementation increases intestinal hydrolytic enzymes and boosts immune function. Synbiotics can help restore lactobacilli populations, improve barrier function, and reduce colonic oxidative stress. Notably, synbiotic supplementation has decreased systemic inflammation and lupus disease activity while altering gut microbiota composition and function. Recently, Zhu et al.[42] investigated the impact of probiotics on gut microbiota and their metabolites in patients with new-onset lupus nephritis. The study found a reduction in pathogenic bacteria (such as *Prevotella*, *Bacteroides*, *and Enterobacteriaceae*) and an increase in beneficial bacteria (*Actinobacteria and Firmicutes*), leading to an overall rise in the *F/B* ratio. Probiotic treatment also influenced metabolic pathways, including amino acid biosynthesis and purine metabolism. Furthermore, bacterial taxa like *Negativicutes* and *Enterobacteriaceae* were identified as key predictors of treatment response. In healthy individuals, the gut microbiota and its metabolites are well-regulated, typically comprising about 20% *Bacteroides*, 80% *Firmicutes*, 1% *Proteobacteria*, and 3% other bacteria. *Firmicutes* and *Bacteroidetes* are the primary phyla involved in carbohydrate metabolism and the F/B ratio is a key indicator of gut flora balance. *Firmicutes* are the dominant phylum in the gut microbiome, primarily producing butyrate, an anti-inflammatory energy source for colonic epithelial cells. *Bacteroides* can also promote inflammation by secreting LPSs and toxic peptides. As the authors discussed above, lupus nephritis patients have significantly lower levels of *Firmicutes* compared to healthy individuals, while *Bacteroidetes* levels are increased, leading to a decreased F/B ratio. A rise in *Firmicutes* following probiotic treatment points to a potential anti-inflammatory effect. Probiotics can reduce the growth of pathogenic bacteria such as *Bacteroides*, *Prevotella*, *Faecalibacterium*, and *Parabacteroides* in the gut.[42] Probiotics also decreased the abundance of *Proteobacteria*. All *Proteobacteria* are gram-negative and primarily consist of LPSs, mainly pathogenic bacteria like *Escherichia coli* and *Salmonella.*[107] An increase in *Proteobacteria* has been reported in kidney disease, suggesting a pathogenic role for *Proteobacteria* in lupus nephritis.[42] LEfSe (linear discriminant analysis effect size) analysis identified 35 biomarkers in the lupus group before and after probiotic treatment. *Prevotellaceae* scored the highest followed by *Bacteroides.* ROC (Receiver-operating characteristic curve) analysis revealed that *Negativicutes* and *Enterobacteriaceae* are the strongest predictors in the lupus group during prebiotic treatment.[42] All these findings revealed that the composition of the intestinal flora and dysbiosis in lupus nephritis patients is implicated in the pathogenesis of this disease.

Probiotics as Immune Modulates in Lupus Nephritis

Lactobacillus Probiotics have the potential to modulate the immune system. Probiotics rapidly initiate anti-inflammatory responses by producing anti-inflammatory cytokines such as IL-4, IL-10, IL-11, and IL-13, while inhibiting pro-inflammatory cytokines like IL-1, IL-6, and TNF-α. This process involves regulatory T cells (Tregs) and T helper cells (Th cells). Notably, several strains, including *L. plantarum*, *Lactobacillus rhamnosus, Lactobacillus casei, Lactobacillus reuteri, Bifidobacterium longum*, and *Bifidobacterium breve*, have been identified as effective probiotics for addressing a range of symptoms in SLE. Probiotics induce immune shifts that decrease inflammation, alleviating lupus nephritis symptoms by modulating the numbers of Th17 and regulatory T (Treg) lymphocytes. For instance, oral administration of the probiotic *Lactobacillus delbrueckii subsp.* improved disease symptoms in a pristane-induced SLE mouse model by decreasing Th17 cell counts and the expression of IL-17a, a cytokine that promotes inflammation. Another probiotic, *Lactobacillus rhamnosus*, has been shown to influence the retinoic acid receptor-related orphan receptor gamma (RORγ), a transcription factor crucial for Th17 cell maturation, which may explain its role in reducing Th17 levels.[43] Both probiotics also decreased Th1 cell counts and the production of IFN-γ, a cytokine associated with inflammatory responses. *Lactobacillus reuteri* increased the expression of Treg lymphocytes and elevated levels of the transcription factor forkhead box P3 (FoxP3), essential for regulating pro-inflammatory lymphocytes and enhancing anti-inflammatory responses. Moreover, the probiotic treatment led to a reduction in pathogen-associated molecular pattern (PAMP) receptors like TLR-4, TLR-5, TLR-7, and TLR-9 in the liver, which are involved in the inflammatory process. *Lactobacillus paracasei* and *L. reuteri* were shown to decrease hepatic pro-inflammatory cytokines IL-1β, TNF-α, and IL-6 by inhibiting the nuclear factor-kB (NF-κB) and mitogen-activated protein kinase signaling pathways.[44] Notably, *Lactobacillus paracasei* treatment also reduced left ventricular hypertrophy in the lupus model. Chronic consumption of *Lactobacillus fermentum* increased *Bifidobacterium* counts in the guts of female lupus nephritis mouse models, with symptoms including immune complex deposition in glomeruli, the presence of dsDNA autoantibodies, albuminuria, and notably, endothelial dysfunction and hypertension. *Lactobacillus fermentum* effectively reduced lupus disease activity and enhanced gut barrier integrity, leading to decreased plasma levels of LPSs, which in turn diminished immune activation by lowering T and B cell counts in the mesenteric lymph nodes (MLN) and reducing pro-inflammatory cytokines such as IL-17a, IFN-γ, TNF-α, and IL-21 in plasma. By preventing the development of the pro-inflammatory response, *L. fermentum* also prevented complications associated with SLE, including cardiac and kidney hypertrophy. *Lactobacillus fermentum* prevents high blood pressure

and improves endothelial function by reducing phosphorylation of endothelial nitric oxide synthase (eNOS) at the inhibitory site.

Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT) involves transferring fecal bacteria from healthy donors into a patient's gut to restore microbial balance. This approach has gained attention as a potential treatment for autoimmune diseases, including SLE, due to its ability to address gut dysbiosis.[45] Microbiota-based therapies, including FMT, have gained increasing attention as potential novel treatments. FMT, in particular, is well-established for treating recurrent *C. difficile* infections and is emerging as a promising option for patients with inflammatory bowel disease and other autoimmune disorders. While the precise mechanisms behind the interaction between the gut microbiome and the host in autoimmune diseases remain unclear, FMT has demonstrated the ability to restore disrupted gut microbiota, rebuild the intestinal ecosystem, and modulate both innate and adaptive immune responses, leading to therapeutic benefits.[45] Studies in lupus animal models have demonstrated promising results with FMT as a therapeutic intervention. Although FMT has been studied in other autoimmune diseases, clinical trials investigating its use in lupus are still limited. Clinical trials of FMT for the treatment of SLE have been underway since 2020.[46] In a 12-week pilot study, 20 patients with active lupus received FMT as an adjunctive treatment. Over 3 consecutive weeks, patients were given encapsulated fecal microbiota. At the final evaluation, there was a notable reduction in SLE Disease Activity Index (SLEDAI-2K) scores and serum anti-dsDNA antibody levels, with no significant serious adverse events observed compared to baseline. The treatment also resulted in a significant increase in the abundance of bacteria that produce SCFAs and a decrease in bacteria associated with inflammation. The elevated SCFA levels in the gut led to reduced cytokine levels related to inflammation and a shift in the ratio of CD4+ memory cells to naive cells in peripheral blood. Single-cell analysis of peripheral blood post-treatment revealed a reduction in T cells and an increase in natural killer (NK) cells. Furthermore, subcluster analysis showed increased expression of IL7R and CD28 in CD4+ T cells and elevated granzyme H (GZMH) and NK cell granule protein 7 (NKG7) in CD8+ T cells. Additionally, there was a decrease in the expression of interferon-related genes in CD4+, CD8+, double-positive (DP), NK, and B cells.[47] Interestingly, patients who did not respond to FMT exhibited a higher abundance of interferon-related pathways. The study found that the efficacy of FMT was negatively associated with the expression of interferon-related genes in lymphocytes and myeloid cells. This preliminary trial offers promising evidence that FMT could be a safe and effective novel treatment for active SLE.

Antibiotic Therapy to Reduce Pathogenic Bacteria

The use of antibiotics in treating lupus is still controversial. Antibiotics can reduce pathogenic bacteria, enrich beneficial microbes, and improve gut permeability, which may slow disease progression. However, there are practical limitations in using antibiotics for lupus nephritis patients. Antibiotics may interfere with the therapeutic effects of prednisone, a commonly used medication for lupus. Furthermore, the overuse of antibiotics could lead to the development of antibiotic-resistant infections, which pose a significant risk, especially in patients who are already immunocompromised. [48] Therefore, more research is needed to refine antibiotic treatment strategies for lupus to target pathogenic bacteria without disrupting the gut microbiota balance. In recent years, various studies have explored the use of antibiotics as a potential treatment for lupus in mouse models. For example, treatment with broad-spectrum antibiotics or vancomycin in lupus-prone MRL/lpr mice, initiated after disease onset, has been shown to reduce harmful gut bacteria, promote the growth of beneficial probiotics, and restore intestinal barrier function, leading to improved lupus symptoms.[49] Additionally, antibiotic therapy has been found to correct the Treg/Th17 imbalance in these mice and mitigate hypertension caused by Th17 cell infiltration.[49] Similarly, vancomycin treatment in NZB/WF1 lupus mice led to the elimination of *E. gallinarum*, a gut pathogen, enhanced intestinal barrier integrity, and delayed lupus However, other studies have reported contradictory results. For instance, one study found that antibiotic treatment had no significant effect on the gut microbiota or the progression of SLE in NZB/WF1 mice, and the underlying mechanisms for this outcome remain unclear. Antibiotic treatment worsened the disease in MRL/lpr mice, potentially due to the short duration and insufficient dosage of antibiotics administered before disease onset. Moreover, while vancomycin therapy generally improved lupus symptoms in pregnant and postpartum MRL/lpr mice but worsened lupus in these mice, vancomycin treatment reduced Treg cell expression by inhibiting indoleamine 2,3-dioxygenase (IDO) and increased interferon-gamma (IFN-γ).[50]

CONCLUSION

Lupus nephritis represents a complex and growing global health challenge, affecting many individuals worldwide. This condition is characterized by dysregulated immune responses that lead to systemic inflammation, kidney damage, and significant morbidity. While genetic, environmental, and immunological factors all contribute to the development and progression of lupus nephritis, the emerging role of the gut microbiota offers new insights into its pathogenesis and potential therapeutic avenues. The gut microbiota plays a critical role in maintaining immune homeostasis, and disruptions in this balance may influence the onset and severity of lupus nephritis. Emerging evidence suggests that interventions aimed at restoring microbial balance, such as probiotics, prebiotics, FMT, and dietary changes, could modulate immune responses, reduce inflammation, and potentially slow disease progression. Long-term antibiotic use can disrupt the gut microbiota and lead to unintended consequences, including the development of antibiotic resistance and an increased risk of secondary infections.

Therefore, while antibiotics may offer short-term benefits in addressing microbial imbalances, the potential risks should be carefully considered. These risks highlight the need for more targeted therapeutic approaches that can balance microbial modulation with the preservation of gut health and immune function.

Despite these promising findings, much remains to be understood about the mechanisms linking the gut microbiota to lupus nephritis. Ongoing research is crucial for identifying specific microbial factors that may exacerbate disease progression and elucidating the pathways through which the microbiota influences immune dysregulation in lupus. Targeting the gut microbiota presents a promising therapeutic strategy for managing lupus nephritis. However, more work is needed to understand the underlying mechanisms fully and to translate these insights into effective microbiota-based treatments as part of a comprehensive approach to managing this disease.

Data Availability Statement: All data generated during this study are included in this published article.

Peer-review: Externally peer reviewed.

Acknowledgment: This article is dedicated to my beloved mother, who battled lupus nephritis. Though she is no longer with me, her journey has deeply motivated me to understand the etiological processes behind this disease.

Declaration of Interests: The author has no conflict of interest to declare.

Funding: The author declared that this study has received no financial support.

REFERENCES

1. Pisetsky DS. Pathogenesis of autoimmune disease. *Nat Rev Nephrol*. 2023;19(8):509-524. [CrossRef]
2. Xiang Y, Zhang M, Jiang D, Su Q, Shi J. The role of inflammation in autoimmune disease: a therapeutic target. *Front Immunol*. 2023;14:1267091. [CrossRef]
3. Choi MY, Costenbader KH. Understanding the concept of pre-clinical autoimmunity: prediction and prevention of systemic lupus erythematosus: identifying risk factors and developing strategies against disease development. *Front Immunol*. 2022;13:890522. [CrossRef]
4. Ahsan H. Origins and history of autoimmunity—A brief review. *Rheumatol Autoimmun*. 2023;3(1):9-14. [CrossRef]
5. Koppala SN, Guruprasad V. Overview of autoimmunity: classification, disease mechanisms, and etiology. *Turk J Immunol.* 2023;11(3):93-105. [CrossRef]
6. Miller FW. The increasing prevalence of autoimmunity and autoimmune diseases: an urgent call to action for improved understanding, diagnosis, treatment, and prevention. *Curr Opin Immunol*. 2023;80:102266. [CrossRef]
7. Martinelli S, Nannini G, Cianchi F, Coratti F, Amedei A. The impact of microbiota–immunity–hormone interactions on autoimmune diseases and infection. *Biomedicines*. 2024;12(3):616. [CrossRef]
8. Siegel CH, Sammaritano LR. Systemic lupus erythematosus: a review. *JAMA*. 2024;331(17):1480-1491. [CrossRef]. Erratum in: *JAMA*. 2024;331(24):2136. 10.1001/jama.2024.10468
9. Tian J, Zhang D, Yao X, et al. Global epidemiology of systemic lupus erythematosus: a comprehensive systematic analysis and modelling study. *Ann Rheum Dis*. 2023;82:351-356.
10. Yen EY, Singh RR. Lupus — an unrecognized leading cause of death in young females: a population- based study using nationwide death certificates, 2000–2015. *Arthritis Rheumatol*. 2018;70:1251-1255.
11. Lee YH, Choi SJ, Ji JD, Song GG. Overall and cause-specific mortality in systemic lupus erythematosus: an updated meta-analysis. *Lupus*. 2016;25(7):727-734. [CrossRef]
12. Sutanto H, Yuliasih Y. Disentangling the pathogenesis of systemic lupus erythematosus: close ties between immunological, genetic and environmental factors. *Medicina (Kaunas)*. 2023;59(6):1033. [CrossRef]
13. Parikh SV, Almaani S, Brodsky S, Rovin BH. Update on lupus nephritis: core curriculum 2020. *Am J Kidney Dis*. 2020;76(2):265-281. [CrossRef]
14. Pelechas E, Kaltsonoudis E, Voulgari PV, Drosos AA. Systemic lupus erythematosus. In: *Illustrated Handbook of Rheumatic and Musculo-Skeletal Diseases*. Cham: Springer; 2019:141-166. [CrossRef]
15. Roveta A, Parodi EL, Brezzi B, et al. Lupus nephritis from pathogenesis to new therapies: an update. *Int J Mol Sci*. 2024;25(16):8981. [CrossRef]
16. Mohd R, Chin SF, Shaharir SS, Cham QS. Involvement of gut microbiota in SLE and lupus nephritis. *Biomedicines*. 2023;11(3):653. [CrossRef]
17. Chancharoenthana W, Kamolratanakul S, Schultz MJ, Leelahavanichkul A. The leaky gut and the gut microbiome in sepsis - targets in research and treatment. *Clin Sci (Lond)*. 2023;137(8):645-662. [CrossRef]
18. Heravi S, Gut F. Microbiota and autoimmune diseases: mechanisms, treatment, challenges, and future recommendations. *Curr Clin Micro Rpt*. 2024;11(1):18-33. [CrossRef]
19. Aggarwal N, Kitano S, Puah GRY, Kittelmann S, Hwang IY, Chang MW. Microbiome and human health: current understanding, engineering, and enabling technologies. *Chem Rev*. 2023;123(1):31-72. [CrossRef]
20. De Luca F, Shoenfeld Y. The microbiome in autoimmune diseases. *Clin Exp Immunol*. 2019;195(1):74-85. [CrossRef]
21. Yoo JY, Groer M, Dutra SVO, Sarkar A, McSkimming DI. Gut microbiota and immune system interactions. *Microorganisms*. 2020 ;8(10):1587. [CrossRef]. Erratum in: *Microorganisms*. 2020;8(12):2046. 10.3390/microorganisms8122046
22. Wang X, Yuan W, Yang C, et al. Emerging role of gut microbiota in autoimmune diseases. *Front Immunol*. 2024;15:1365554. [CrossRef]
23. Maftei NM, Raileanu CR, Balta AA, et al. The potential impact of probiotics on human health: an update on their health-promoting properties. *Microorganisms*. 2024;12(2):234. [CrossRef]
24. Azzouz DF, Chen Z, Izmirly PM, et al. Longitudinal gut microbiome analyses and blooms of pathogenic strains during lupus disease flares. *Ann Rheum Dis*. 2023;82:1315-1327.
25. Pan Q, Guo F, Huang Y, et al. Gut microbiota dysbiosis in systemic lupus erythematosus: novel insights into mechanisms and

promising therapeutic strategies. *Front Immunol*. 2021;12:799788. [CrossRef]
26. Yao H, Yang H, Wang Y, Xing Q, Yan L, Chai Y. Gut microbiome and fecal metabolic alteration in systemic lupus erythematosus patients with depression. *Front Cell Infect Microbiol*. 2022;12: 1040211. [CrossRef]
27. Crost EH, Coletto E, Bell A, Juge N. Ruminococcus gnavus: friend or foe for human health. *FEMS Microbiol Rev*. 2023;47(2):fuad014. [CrossRef]
28. Xiang K, Wang P, Xu Z, et al. Causal effects of gut microbiome on systemic lupus erythematosus: a two-sample Mendelian randomization study. *Front Immunol*. 2021;12:667097. [CrossRef]
29. Zhang F, Fan D, Huang J-L, Zuo T. The gut microbiome: linking dietary fiber to inflammatory diseases. *Med Microecol*. 2022;14:100070. [CrossRef]
30. Islam MA, Khandker SS, Kotyla PJ, Hassan R. Immunomodulatory effects of diet and nutrients in systemic lupus erythematosus (SLE): A systematic review. *Front Immunol*. 2020;11:1477. [CrossRef]
31. Gottschalk T, Tsantikos E, Hibbs M. 35 A diet high in fibre diet can moderate inflammation and kidney pathology in a model of systemic lupus erythematosus. *Lupus Sci Med*. 2017;4:A17.
32. Choi SC, Brown J, Gong M, et al. Gut microbiota dysbiosis and altered tryptophan catabolism contribute to autoimmunity in lupus-susceptible mice. *Sci Transl Med*. 2020;12(551):eaax2220. [CrossRef]
33. Takiishi T, Fenero CIM, Câmara NOS. Intestinal barrier and gut microbiota: shaping our immune responses throughout life. *Tissue Barriers*. 2017;5(4):e1373208. [CrossRef]
34. Di Vincenzo F, Del Gaudio A, Petito V, Lopetuso LR, Scaldaferri F. Gut microbiota, intestinal permeability, and systemic inflammation: a narrative review. *Intern Emerg Med*. 2024;19(2):275-293. [CrossRef]
35. Mousa WK, Chehadeh F, Husband S. Microbial dysbiosis in the gut drives systemic autoimmune diseases. *Front Immunol*. 2022;13: 906258. [CrossRef]
36. Jin B, Sun T, Yu XH, Yang YX, Yeo AET. The effects of TLR activation on T-cell development and differentiation. *Clin Dev Immunol*. 2012;2012:836485. [CrossRef]
37. Anderson RC, Cookson AL, McNabb WC, et al. Lactobacillus plantarum MB452 enhances the function of the intestinal barrier by increasing the expression levels of genes involved in tight junction formation. *BMC Microbiol*. 2010;10:316. [CrossRef].
38. Sofi MH, Wu Y, Ticer T, et al. A single strain of Bacteroides fragilis protects gut integrity and reduces GVHD. *JCI Insight*. 2021;6(3):e136841. [CrossRef]
39. Pessoa L, Aleti G, Choudhury S, et al, host. Host-Microbial Interactions in Systemic Lupus Erythematosus and Periodontitis. *Front Immunol*. 2019;10:2602. [CrossRef]
40. Zhou HY, Cao NW, Guo B, et al. Systemic lupus erythematosuspatients have a distinct structural and functional skin microbiota compared with controls. *Lupus*. 2021;30(10):1553-1564. [CrossRef]
41. Suliman BA. Potential clinical implications of molecular mimicry-induced autoimmunity. *Immun Inflamm Dis*. 2024;12(2):e1178. [CrossRef]
42. Zhu Q, Cui J, Liu S, Wei S, Wu Q, You Y. Synbiotic regulates gut microbiota in patients with lupus nephritis: an analysis using metagenomic and metabolome sequencing. *Front Microbiol*. 2024;15:1295378. [CrossRef]
43. Mardani F, Mahmoudi M, Esmaeili SA, Khorasani S, Tabasi N, Rastin M. In vivo study: Th1-Th17 reduction in pristane-induced systemic lupus erythematosus mice after treatment with tolerogenic Lactobacillus probiotics. *J Cell Physiol*. 2018;234(1):642-649. [CrossRef]
44. Hu WS, Rajendran P, Tzang BS, et al. Lactobacillus paracasei GMNL-32 exerts a therapeutic effect on cardiac abnormalities in NZB/W F1 mice. *PLoS One*. 2017;12(9):e0185098. [CrossRef]
45. Yang R, Chen Z, Cai J. Fecal microbiota transplantation: emerging applications in autoimmune diseases. *J Autoimmun*. 2023 December;141:103038. [CrossRef]
46. Huang C, Yi P, Zhu M, et al. Safety and efficacy of fecal microbiota transplantation for treatment of systemic lupus erythematosus: an Explorer trial. *J Autoimmun*. 2022;130:102844. [CrossRef]. Erratum in: *J Autoimmun*. 2022;131:102862. 10.1016/j.jaut.2022.102862
47. Zheng M, Zhou W, Huang C, et al. A single-cell map of peripheral alterations after FMT treatment in patients with systemic lupus erythematosus. *J Autoimmun*. 2023;135:102989. [CrossRef]
48. Fanouriakis A, Kostopoulou M, Cheema K, Bertsias G, Jayne D, Boumpas D. Update of the joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of lupus nephritis. *Ann Rheum Dis*. 2020;79:713-723. [CrossRef]
49. de la Visitación N, Robles-Vera I, Toral M, et al. Gut microbiota contributes to the development of hypertension in a genetic mouse model of systemic lupus erythematosus. *Br J Pharmacol*. 2021;178(18):3708-3729. [CrossRef]
50. Mu Q, Cabana-Puig X, Mao J, et al. Pregnancy and lactation interfere with the response of autoimmunity to modulation of gut microbiota. *Microbiome*. 2019;7(1):105. [CrossRef]

10.5152/turkjnephrol.2025.251067

Original Article

Turkish Journal of Nephrology

Analysis of Body Composition Distribution in Different Stages of Chronic Kidney Disease

Srimam Murali[1], Sridevi Sankaranarayanan[1], Senthil Kumar Thillaigovindarajan[1], Yogeswari Raman[1], Venkatesh Natarajan[1], Ramprasad Ramprasad[2]

[1]Department of Cardiopulmonary Physiotherapy, Sri Ramachandra Institute of Higher Education and Research Faculty of Physiotherapy Chennai, India
[2]Department of Nephrology, Sri Ramachandra Institute of Higher Education and Research, Chennai, India

ABSTRACT

Background: Alterations in fluid balance and body composition are hallmark features of chronic kidney disease (CKD) progression, contributing to functional decline and poor outcomes. This study aimed to compare fluid compartments, body composition, muscle strength, fatigue, and quality of life between patients with CKD G3 and G4 without kidney replacement therapy (KRT) and CKD G5D (dialysis).

Methods: Eighty-six patients (43 with CKD G3-G4 without KRT and 43 with CKD G5D) were assessed in this cross-sectional study. Body composition and fluid distribution were evaluated through the use of bioelectrical impedance analysis. Parameters assessed were protein mass, fat free mass, segmental muscle/fat mass, total body water, intracellular water (ICW), extracellular water (ECW). Physical performance was evaluated using handgrip strength and 4-meter gait speed. Fatigue was measured using the Fatigue Severity Scale, and health-related quality of life was evaluated using the Kidney Disease Quality of Life questionnaire.

Results: Patients with CKD G5D exhibited significantly lower ICW and ECW and a higher extracellular water ratio ($P < .05$). They also had reduced skeletal muscle mass, fat-free mass, and segmental muscle mass ($P < .05$). Handgrip strength and gait speed were markedly lower, while fatigue scores were significantly higher ($P < .001$). Both physical and mental quality of life scores were poorer in the dialysis group, despite similar comorbidity burdens.

Conclusion: Chronic kidney disease G5D is associated with fluid imbalance, muscle wasting, and functional impairment. Early identification and intervention in CKD without KRT may mitigate decline and improve clinical outcomes.

Keywords: Body composition, chronic kidney disease, health, muscle mass

Corresponding author: S Sridevi devibsmoorthy@sriramachandra.edu.in **Received:** May 8, 2025 **Revision Requested:** June 2, 2025 **Last Revision Received:** June 29, 2025 **Accepted:** July 1, 2025 **Publication Date:** September 28, 2025

Cite this article as: Murali S, Sridevi S, Senthil Kumar T, Yogeswari R, Venkatesh N, Ramprasad E. Analysis of body composition distribution in different stages of chronic kidney disease. *Turk J Nephrol.* 2025;34(4):253-258.

INTRODUCTION

A substantial global health burden, chronic kidney disease (CKD) affects approximately 10% of the world's population and significantly raises morbidity and mortality rates.[1] Its rising prevalence is primarily driven by the global increase in diabetes mellitus, hypertension, and an aging population, leading to progressive kidney function decline and systemic metabolic disturbances. Among these, changes in body composition specifically, sarcopenia, or the loss of skeletal muscle mass and strength have been identified as important factors that contribute to poor clinical outcomes in CKD.[2,3]

Sarcopenia in CKD is multi-factorial, resulting from chronic inflammation, metabolic acidosis, hormonal imbalances, and physical inactivity. It is more prevalent and severe in patients receiving dialysis, where it contributes to frailty, reduced physical function, and increased mortality.[3] Early stages of CKD G1-G3 without kidney replacement therapy (KRT), however, often go under-recognized in clinical practice despite early signs

of muscle wasting and nutritional compromise, suggesting the need for sensitive diagnostic approaches beyond traditional kidney markers.[4]

In CKD, bioelectrical impedance analysis (BIA) has gained popularity as a useful, non-invasive technique for determining fluid status and body composition. It is particularly effective in detecting fluid distribution abnormalities, such as elevated extracellular water (ECW) and decreased intracellular water (ICW), which not only reflect poor nutritional status but are also associated with cardiovascular risk and diminished functional performance.[4]

Physical performance assessments, including handgrip strength and gait speed, are now considered essential clinical tools in CKD care, providing objective insights into frailty and overall functional capacity. These measures, along with the assessment of fatigue—a prevalent and debilitating symptom in CKD—are linked to hospitalization, an overall reduction in quality of life (QOL), and raise mortality.[5] Incorporating patient-centered outcome measures, like Kidney Disease Quality of Life (KDQOL) questionnaire, offers further value in capturing the psycho-social and functional impacts of CKD across its stages.[6]

Given the complex interplay between muscle loss, fluid shifts, physical performance, and quality of life in CKD, a comprehensive evaluation spanning the disease spectrum is essential. This study aims to compare these critical variables—body composition, hydration status, muscle strength, fatigue, and quality of life—between patients with CKD G3 and G4 without KRT and individuals with CKD G5D disease. Such an approach may help guide early interventions and improve long-term outcomes in this vulnerable population.By addressing these dimensions, including gender-specific variations in functional decline and well-being, this study supports sustainable development goal (SDG) 3 (good health and well-being) by focusing on early identification of sarcopenia and fatigue in CKD, aiming to reduce complications from chronic disease. It also aligns with SDG 5 (gender equality) by addressing gender differences in physical function, highlighting the need for equal access to care and rehabilitation.

MAIN POINTS

- Patients with chronic kidney disease (CKD) G5D (dialysis) have significantly lower skeletal muscle mass, fat-free mass, and intracellular water, indicating advanced sarcopenia and poor cellular hydration compared to CKD G3-G4 without kidney replacement therapy (KRT).
- Physical performance (handgrip strength, gait speed) and quality of life were markedly reduced, while fatigue levels were significantly higher in dialysis patients, highlighting severe functional impairment.
- Bioelectrical impedance analysis effectively identifies critical differences in body composition and fluid status across CKD stages, supporting its use for early detection and intervention in CKD G1-G4 without KRT patients.

MATERIAL AND METHODS

A cross-sectional observational study was conducted at the Department of Physiotherapy and recruited at the Department of Nephrology, in the Tertiary care Hospital, following approval from the Sri Ramachandra Institute of Higher Education and Research Institutional Ethics Committee with approval number CSP-III/25/JAN/15/18 and dated on February 10, 2025. Participant recruitment was carried out between February 2025 and April 2025. The study was propectively registered with the clinical trials registry-India. Ambulatory male and female patients between the ages of 18 and 75 years who have ensued diagnosis of CKD G3-G5 were enrolled after obtaining informed consent. All participants in the CKD G5D group were undergoing maintenance haemodialysis. Patients on peritoneal dialysis were excluded from the study. Exclusion criteria included acute infections, immunological disorders, recent major surgeries, severe comorbidities, or cognitive impairment.

A total of 86 participants were evaluated for demographic characteristics, clinical history, and body composition. Body composition was assessed using the Mediana i35 Body Composition Analyzer (InBody), a multi-frequency BIA device operating at 5, 50, 100, and 250 kHz. The device provides comprehensive body composition metrics, including total body water (TBW) and extracellular water ratio (ECWR) was obtained directly from the Mediana i35 Body Composition Analyser and is calculated automatically by the device as the ratio of extracellular water (ECW) to total body water (TBW), muscle mass, fat mass, fat-free mass, protein, mineral content, and skeletal muscle mass, visceral to subcutaneous fat ratio (VSR), Mediana score. It also enables skeletal muscle and body fat analysis (weight, skeletal muscle mass, body fat Mass with comparative tracking), along with segmental analysis of muscle and fat distribution. The i35 has demonstrated reliable and valid estimates for sarcopenia diagnosis, with good agreement when compared to dual-energy X-ray absorptiometry (DXA), as supported by recent findings.[7] Similar findings have been reported in CKD populations, where BIA-derived measures showed significant associations with clinical outcomes, reinforcing its relevance in monitoring body composition changes associated with disease progression.[8]

Muscle strength was measured using a handheld dynamometer, following standardized testing protocols. The higher value of 2 trials was recorded to enhance reliability.[9] Physical performance was assessed using the 4-meter gait speed test, a standardized and validated measure of mobility and frailty in CKD patients.[10] Fatigue severity was assessed using the Fatigue Severity Scale (FSS), a robust tool used across chronic illness populations, including individuals with CKD, to quantify the impact of fatigue on daily living.[11] Fatigue was assessed using the Tamil version of the (FSS), suitable for evaluating fatigue in

Tamil-speaking CKD patients in this study.[12] Patient-reported outcomes were measured using the KDQOL questionnaire.[6]

Statistical Analysis

All data were analyzed using IBM SPSS Statistics version 26.0 (IBM SPSS Corp.; Armonk, NY, USA). The Shapiro–Wilk test was used to assess the normality of the data. Since the data were normally distributed, unpaired *t*-tests (independent samples *t*-tests) were used to compare continuous variables between the CKD G3 and G4 without KRT group and the CKD G5D (dialysis) group. A *P*-value < .05 was considered statistically significant.

RESULTS

The study included 86 participants in total, including 43 patients with CKD G3 and G4 without KRT and 43 patients with CKD G5D. Table 1 presents demographic data of the participants, showing that the gender distribution in the CKD G3-G4 without KRT group was 58.1% male and 41.9% female, while the CKD G5D group had 44.2% male and 55.8% female participants. The 2 groups mean ages were comparable, with 50.33 ± 11.77 years in the CKD G3-G4 without KRT group and 50.81 ± 12.97 years in group CKD G5D. The group CKD G3 and G4 without KRT had higher mean body weight (66.29 ± 12.48 kg) and body mass index (BMI) (25.95 ± 4.47 kg/m^2) compared to the CKD G5D group (57.18 ± 9.42 kg and 23.15 ± 4.35 kg/m^2). Additionally, the mean height was slightly higher in the CKD G3–G4 without KRT group (159.81 ± 8.87 cm) than in the CKD G5D group (157.64 ± 9.51 cm).

Table 2 compares the fluid compartments between the CKD G3-G4 without KRT and G5D groups. It shows that TBW was considerably greater in CKD G3 and G4 without KRT patients (*P* = .05), while ICW levels were noticeably lower in CKD G5D patients (*P* = .00072). Extracellular water was reduced in CKD G5D versus to CKD G3 and G4 without KRT (*P* = .0117). The extracellular water ratio (ECWR) was marginally higher in CKD G5D patients (*P* = .0215).

In terms of body composition, Table 3 shows that CKD G5D patients had significantly lower protein mass (*P* = .00098), mineral mass (*P* = .0274), muscle mass (*P* = .0109), skeletal muscle mass (*P* = .0021), fat-free mass (*P* = .0023) compared to CKD G3-G4 without KRT patients. Fat mass differences were not statistically significant (*P* = .0669). Additionally, the visceral

Table 1. Demographic Characteristics of Study Participants by Chronic Kidney Disease Stage

Variable	CKD G3-G4 Without KRT (n = 43)	CKD G5D (n = 43)
Gender	Male: 25	Male: 19
	Female: 18	Female: 24
Age (years)	50.33 ± 11.77	50.81 ± 12.97
Height (cm)	159.81 ± 8.87	157.64 ± 9.51
Weight (kg)	66.29 ± 12.48	57.18 ± 9.42
BMI (kg/m^2)	25.95 ± 4.47	23.15 ± 4.35
Hypertension (%)	56 (24/43)	88 (38/43)
Diabetes mellitus (%)	44 (19/43)	77 (33/43)
Right-hand grip strength (kg)	25.18 ± 3.88	20.57 ± 7.58
Left-hand grip strength (kg)	24.55 ± 3.82	20.12 ± 7.85
4-metre walking speed (sec)	4.90 ± 0.48	5.45 ± 0.76
Fatigue Severity Scale (FSS)	15.16 ± 8.46	33.74 ± 14.56
KDQOL – Physical composite score	18.73 ± 3.74	38.33 ± 9.59
KDQOL – Mental composite score	30.50 ± 6.10	41.34 ± 6.76

Data presented as mean ± SD unless otherwise indicated.
BMI, body mass index; CKD, chronic kidney disease; FSS, Fatigue Severity Scale; KDQOL, Kidney Disease Quality of Life; KRT, kidney replacement therapy; SD, standart deviation.

Table 2. Comparison of Fluid Compartments Between Chronic Kidney Disease Stages 3-4 and Stage 5

Variable	CKD G3-G4 Without KRT Mean (SD)	CKD G5D Mean (SD)	*P*
TBW (L)	31.095 (7.72)	28.291 (5.09)	.05*
ICW (L)	19.877 (3.94)	17.247 (2.92)	.00072*
ECW (L)	12.335 (2.38)	11.044 (2.25)	.0117*
ECWR	0.383 (0.008)	0.389 (0.015)	.0215*

Values are expressed as mean (SD). All fluid volumes are measured in litres (L).
CKD, chronic kidney disease; ECW, extracellular water; ECWR, extracellular water ratio (unitless); ICW, intracellular water; KRT, kidney replacement therapy, SD, standart deviation; TBW, total body water.
**P* < .05 was considered statistically significant.

Table 3. Comparison of Body Composition Between Chronic Kidney Disease Stages 3-4 and Stage 5

Variable	CKD G3-G4 without KRT Mean (SD)	CKD G5D Mean (SD)	*P*
Protein mass (kg)	8.51 (1.91)	7.29 (1.34)	.00098*
Mineral mass (kg)	2.97 (0.56)	2.64 (0.75)	.0274*
Muscle mass (kg)	40.51 (9.96)	35.77 (6.56)	.0109*
Skeletal muscle mass (kg)	24.25 (6.38)	20.34 (4.93)	.0021*
Fat mass (kg)	22.50 (9.46)	18.90 (8.49)	.0669
Fat-free mass (kg)	44.06 (9.48)	38.41 (6.96)	.0023*
Visceral to subcutaneous fat ratio	0.61 (0.26)	0.89 (0.80)	.0368*

Values are expressed as mean (SD). All mass values are in kilograms (kg).
CKD, chronic kidney disease; KRT, kidney replacement therapy; SD, standart deviation
**P* < .05 was considered statistically significant.

to subcutaneous fat ratio (VSR) was significantly higher in the group CKD G5D ($P = .0368$), indicating a shift toward central fat accumulation in CKD G5D.

Table 4 shows the segmental analysis, where segmental muscle mass was significantly low in patients with CKD G5D in the trunk, arms, and legs compared to CKD G3-G4 without KRT patients ($P < .05$ for all regions). Segmental fat mass in the trunk was significantly low in patients with CKD G5D ($P = .0461$), while fat mass in the arms and legs did not show significant differences ($P > .05$).

Table 5 compares physical performance and patient-reported outcomes between the 2 groups, revealing that handgrip strength was significantly lower in patients with CKD G5D (left hand: $P = .0013$, right hand: $P = .00064$), and the 4-meter walking speed was slower in CKD G5D ($P = .00012$). Patients with CKD G5D had significantly higher levels of fatigue severity as determined by the FSS ($P < .001$). Patients with CKD G5D had significantly lower physical and mental quality of life scores on SF-12 KDQOL (physical: $P < .001$, mental: $P < .001$). Nonetheless, there was no significant difference in the overall body composition between the groups as determined by the Mediana score ($P = .928$).

In conclusion, after adjusting for BMI, sex, and age, the differences between the CKD G3-G4 without KRT and CKD G5D groups in skeletal muscle mass, handgrip strength, walking speed, fatigue, and KDQOL scores remained statistically significant.

DISCUSSION

This study evaluated the differences in body composition, fluid compartments, physical performance, and quality of life between CKD G3 and G4 without KRT patients and patients with CKD G5D undergoing dialysis. The results demonstrate a progressive decline in multiple clinical and functional parameters with advancing disease severity, particularly in the dialysis population.

Table 4. Comparison of Segmental Analysis Between Chronic Kidney Disease Stages 3-4 and Stage 5

Variable	CKD G3-G4 without KRT Mean (SD)	CKD G5D Mean (SD)	*P*
SF left arm (kg)	1.46 (0.86)	1.20 (0.72)	.1263
SF right arm (kg)	1.46 (0.88)	1.27 (0.72)	.2696
SF left leg (kg)	3.07 (1.24)	2.59 (1.09)	.0637
SF right leg (kg)	3.11 (1.23)	2.62 (1.07)	.0519
SF trunk (kg)	11.55 (5.39)	9.30 (4.89)	.0461*
SM left arm (kg)	2.26 (0.69)	1.81 (0.56)	.0013*
SM right arm (kg)	2.22 (0.71)	1.70 (0.50)	.00017*
SM left leg (kg)	6.74 (1.59)	5.74 (1.30)	.002*
SM right leg (kg)	6.85 (1.71)	5.75 (1.29)	.0012*
SM trunk (kg)	19.42 (3.84)	17.14 (3.16)	.0035*

Values are expressed as mean (SD). All segmental masses are in kilograms (kg).
CKD, chronic kidney disease; KRT, kidney replacement therapy; SD, standart deviation; SF, segmental fat mass; SM, segmental muscle mass.
*$P < .05$ was considered statistically significant.

Table 5. Comparison of Physical Performance and Patient-Reported Outcomes Between Chronic Kidney Disease Stages 3-4 and Stage 5

Variable	CKD G3-G4 without KRT Mean (SD)	CKD G5D Mean (SD)	*P*
Mediana score	52.791 (17.9)	53.14 (17.5)	.928
Right-hand grip (Kg)	25.184 (3.88)	20.572 (7.58)	.00064*
Left-hand grip (Kg)	24.551 (3.82)	20.119 (7.85)	.0013*
4-metre walking speed (sec)	4.896 (0.48)	5.454 (0.76)	.00012*
Fatigue Severity Scale (FSS)	15.162 (8.46)	33.74 (14.56)	<.001*
SF-12 physical composite – KDQOL	18.73 (3.74)	38.329 (9.59)	<.001*
SF-12 mental composite – KDQOL	30.5 (6.1)	41.34 (6.76)	<.001*

Values are expressed as mean (SD).
CKD, chronic kidney disease; FSS, Fatigue Severity Scale; KDQOL, Kidney Disease Quality of Life; KRT, kidney replacement therapy; SD, standart deviation; SF-12, Short Form-12 Health Survey.
*$P < .05$ was considered statistically significant.

Demographic Characteristics

The absence of significant differences in age and gender between groups indicates that the observed disparities likely stem from disease progression rather than demographic variability. A slightly lower mean body weight and BMI in CKD G5D patients aligns with prior evidence from South Asia highlighting the nutritional deterioration associated with dialysis dependency.[13]

Fluid Compartments

In this study, CKD G5D patients had significantly lower intracellular and extracellular water volumes, while their elevated ECWR reflects volume overload and altered fluid homeostasis—a hallmark of dialysis populations. This elevation in ECWR is concerning, as it is linked to cardiovascular stress and adverse clinical outcomes. Reduced intracellular water, in particular, signifies diminished muscle mass and cell volume, consistent with nutritional deficits. Similar findings have established ECWR as a reliable indicator of fluid imbalance, strongly linked to morbidity and mortality in hemodialysis patients.[14] Bioimpedance metrics such as ECWR offer valuable insights into fluid shifts and are increasingly used in dialysis care for volume management.[15]

Body Composition

The present study showed a marked reduction in muscle mass, skeletal muscle, protein, mineral, and fat-free mass was observed in the advanced CKD G5D group. These changes are

representative of the multi-factorial burden of protein-energy wasting (PEW), inflammation, and metabolic derangement's commonly associated with disease progression. Similarly, Yogesh et al[16] reported a prevalence of PEW in CKD, attributing it to these multifactorial mechanism. The onset of maintenance dialysis in this cohort appeared to compound these effects, likely due to increased oxidative stress and systemic inflammation, consistent with previous findings by Pupim et al[17] although total fat mass was comparable between groups, this study identified a higher visceral to subcutaneous fat ratio in dialysis patients, suggesting central adiposity. This pattern aligns with previous evidence linking visceral fat accumulation with cardiovascular risk.[18]

Segmental Analysis

We found that the reductions in segmental muscle mass across the trunk, arms, and legs in CKD G5D patients suggest a systemic pattern of sarcopenia. This aligns with prior findings indicating that loss of regional muscle, especially in trunk and appendicular compartments, independently predicts mortality in dialysis patients.[19] Additionally, reduced trunk fat may reflect malnutrition coupled with altered hydration dynamics.

Handgrip Strength and Functional Capacity

In the present study, lower handgrip strength in both hands among CKD G5D patients met established diagnostic thresholds for sarcopenia. Moreover, reduced 4-meter gait speed provides objective evidence of functional impairment that intensifies with CKD progression. These physical performance deficits are critical prognostic indicators for hospitalization and survival. Similarly, prior research has shown that frailty and reduced physical capacity are strongly associated with poor outcomes in CKD with KRT.[20] Furthermore, these findings shows reduced handgrip strength and physical activity in CKD G5D patients aligns with previous studies that indicate impaired muscle strength and muscle mass, likely due to sarcopenia aging and associated comorbidities .[21]

Fatigue Severity Scale

This study showed that fatigue levels were significantly higher in the dialysis cohort, reflecting one of the most common and debilitating symptoms experienced by patients with CKD G5D. Recent studies confirm the high prevalence of fatigue in this group and its impact on mental and physical health.[22] Contributing factors include anemia, sleep disturbances, chronic inflammation, and reduced physical activity. Consistent with prior reports, fatigue also perpetuates sarcopenia by limiting movement and promoting deconditioning.[23] Higher fatigue levels further support previous findings identifying fatigue and dyspnea as key barriers to physical activity in CKD, affecting mobility and quality of life.[24]

Kidney Disease Quality Of Life

The present study also found that both mental and physical health domains of KDQOL were substantially lower in the CKD G5D group. This likely results from the compounded effects of fatigue, reduced muscle mass, and loss of independence. These findings echo those of previous evidence suggesting that diminished physical function and nutritional impairment are strong determinants of reduced quality of life throughout CKD progression.[25]

Taken together, these findings underscore the multifaceted deterioration seen in advanced CKD, particularly among dialysis patients. Early detection of muscle loss and functional decline during CKD G3-G4 without KRT may offer an important window for intervention. Strategies such as resistance training, nutritional supplementation, and individualized rehabilitation programs are urgently needed to preserve muscle integrity and improve quality of life in this vulnerable population.

Limitations

Several limitations must be acknowledged. First, the cross-sectional design of this study makes it impossible to draw conclusions about causality. To ascertain the course of muscle loss and functional decline across CKD stages, longitudinal studies required. Secondly, despite being a useful and non invasive technique for determining body composition, BIA may be impacted by hydration levels, particularly in dialysis patients. Third, the sample size, while sufficient for detecting significant group differences, may limit generalizability to broader CKD populations across diverse clinical settings. Finally, dietary intake and physical activity levels, which are important modifiers of muscle mass and function, were not directly measured.

This study highlights significant differences in body composition, hydration status, physical performance, and quality of life between CKD G3 and G4 without KRT patients and individuals with CKD G5D. The CKD G5D individuals was associated with reduced skeletal muscle mass, impaired physical function, higher fatigue levels, and lower quality of life, independent of age, sex, and BMI. These findings emphasize the progressive nature of sarcopenia and physical decline in CKD and underscore the need for early screening and targeted interventions—particularly in the early stages to mitigate functional loss and enhance patient outcomes. Furthermore, the study supports key SDGs, SDG 3 (good health and well-being) and SDG 5 (gender equality) by identifying functional decline in CKD and promoting early, equitable intervention across genders. Additionally, it aligns with SDG 10 (reduced inequalities) by highlighting the need for tailored rehabilitation access for vulnerable populations, and with SDG 17 (partnerships for the goals) by encouraging interdisciplinary collaboration among nephrologists, physiotherapists, and nutritionists to improve patient care in chronic disease.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Ethics committee approval was received for this study from Sri Ramachandra Institute of Higher Education and

Research Institutional Ethics Committee (Date: 10.02.2025; No.: CSP-III/25/JAN/15/18).

Informed Consent: Written informed consent was obtained from patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.M., S.S.; Design – S.M., S.S.; Supervision – S.S.; Resources – S.M., S.S.; Materials – S.M., S.S.; Data Collection and/or Processing – S.M., S.S., R.E.; Analysis and/or Interpretation – S.M., S.S.; Literature Search – S.M., S.S.; Writing Manuscript – S.M., S.S., S.K.T., Y.R., V.N., R.E.; Critical Review – S.M., S.S., S.K.T., Y.R., V.N., R.E.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2020;395(10225):709-733. [CrossRef]
2. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing*. 2019;48(1):16-31. [CrossRef]
3. Cheng TC, Huang SH, Kao CL, Hsu PC. Muscle wasting in chronic kidney disease: mechanism and clinical implications—A narrative review. *Int J Mol Sci*. 2022;23(11):6047. [CrossRef]
4. La Porta E, Faragli A, Herrmann A, et al. Bioimpedance analysis in CKD and HF patients: a critical review of benefits, limitations, and future directions. *J Clin Med*. 2024;13(21):6502. [CrossRef]
5. Gregg LP, Bossola M, Ostrosky-Frid M, Hedayati SS. Fatigue in CKD: epidemiology, pathophysiology, and treatment. *Clin J Am Soc Nephrol*. 2021;16(9):1445-1455. [CrossRef]
6. Hays RD, Kallich JD, Mapes DL, Coons SJ, Carter WB. Development of the kidney disease quality of life (KDQOL) instrument. *Qual Life Res*. 1994;3(5):329-338. [CrossRef]
7. Lee JH, Kim HJ, Han S, Park SJ, Sim M, Lee KH. Reliability and agreement assessment of sarcopenia diagnosis through comparison of bioelectrical impedance analysis and dual-energy x-ray absorptiometry. *Diagnostics (Basel)*. 2024;14(9):899. [CrossRef]
8. Bansal N, Zelnick LR, Himmelfarb J, Chertow GM. Bioelectrical impedance analysis measures and clinical outcomes in CKD. *Am J Kidney Dis*. 2018;72(5):662-672. [CrossRef] [published correction appears in *Am J Kidney Dis*. 2024;83(3):426. (https://doi.org/10.1053/j.ajkd.2023.12.007
9. Bohannon RW. Hand-grip dynamometry predicts future outcomes in aging adults. *J Geriatr Phys Ther*. 2008;31(1):3-10. [CrossRef]
10. Roshanravan B, Khatri M, Robinson-Cohen C, et al. A prospective study of frailty in nephrology-referred patients with CKD. *Am J Kidney Dis*. 2012;60(6):912-921. [CrossRef]
11. Jhamb M, Weisbord SD, Steel JL, Unruh M. Fatigue in patients receiving maintenance dialysis: a review of definitions, measures, and contributing factors. *Am J Kidney Dis*. 2008;52(2):353-365. [CrossRef]
12. Dhanish J, Kanthanathan S, Rajeswari S, Aseer PAL. Translation and validation of Tamil version of Fatigue Severity Scale (FSS) in individuals with rheumatoid arthritis. *Indian J Rheumatol*. 2024;19(3):198-204. [CrossRef]
13. Abraham G, Varughese S, Thandavan T, et al. Chronic kidney disease hotspots in developing countries in South Asia. *Clin Kidney J*. 2016;9(1):135-141. [CrossRef]
14. Dekker MJE, Marcelli D, Canaud BJ, et al. Impact of fluid status and inflammation and their interaction on survival: a study in an international hemodialysis patient cohort. *Kidney Int*. 2017;91(5):1214-1223. [CrossRef]
15. Yu SJ, Kim DH, Oh DJ, Yu SH, Kang ET. Assessment of fluid shifts of body compartments using both bioimpedance analysis and blood volume monitoring. *J Korean Med Sci*. 2006;21(1):75-80. [CrossRef]
16. Yogesh M, Nagda J, Kankhara F, Parmar PA, Mody M, Vyas SS, et al. Prevalence and Predictors of Sarcopenia, Protein-Energy Wasting, and Sarcopenic Obesity in Patients with Chronic Kidney Disease. *Indian J Nephrol*. [CrossRef]
17. Pupim LB, Himmelfarb J, McMonagle E, Shyr Y, Ikizler TA. Influence of initiation of maintenance hemodialysis on biomarkers of inflammation and oxidative stress. *Kidney Int*. 2004;65(6):2371-2379. [CrossRef]
18. Kim B, Kim GM, Oh S. Use of the visceral adiposity index as an indicator of chronic kidney disease in older adults: comparison with body mass index. *J Clin Med*. 2022;11(21):6297. [CrossRef]
19. Caetano C, Valente A, Oliveira T, Garagarza C. Body composition and mortality predictors in hemodialysis patients. *J Ren Nutr*. 2016;26(2):81-86. [CrossRef]
20. Bao Y, Dalrymple L, Chertow GM, Kaysen GA, Johansen KL. Frailty, dialysis initiation, and mortality in end-stage kidney disease. *Arch Intern Med*. 2012;172(14):1071-1077. [CrossRef]
21. Vijayalakshmi V, Sridevi S, Venkatesh N, Kumar TS. Relationship between body composition, physical activity and functional capacity. *Indian J Public Health Res Dev*. 2019;10(8):1292-1296. [CrossRef]
22. Rafiullah, Jamal Z, Iqbal J, et al. Prevalence of Fatigue among Patients with End Stage kidney Diseases with Special Emphasis on Quality of Life. *J East Asian Stud*. 2023;12:304-312.
23. Bossola M, Vulpio C, Tazza L. Fatigue in chronic dialysis patients. *Semin Dial*. 2011;24(5):550-555. [CrossRef]
24. Das A, Sridevi S, Venkatesh N, Senthil Kumar T. A study to find barriers for physical activity among chronic kidney disease patients. *Indian J Public Health Res Dev*. 2019;10(12):450-455. [CrossRef]
25. Pagels AA, Söderkvist BK, Medin C, Hylander B, Heiwe S. Health-related quality of life in different stages of chronic kidney disease and at initiation of dialysis treatment. *Health Qual Life Outcomes*. 2012;10:71. [CrossRef]

10.5152/turkjnephrol.2025.251006

Original Article

Turkish Journal of Nephrology

Low-Dose Rituximab and Calcineurin Inhibitor Combination as an Effective Treatment Strategy in Relapsed Primary Membranous Nephropathy

Ahmet Mert Yanık[1], İlay Berke[2], Mahmut Başar Aykent[1,3], Arzu Velioğlu[2], Ebru Aşıcıoğlu[2], Murat Tuğcu[2], Dilek Barutçu[2], Zübeyde Serhan Tuğlular[2], Mehmet Koç[2], İzzet Hakkı Arıkan[2]

[1]Division of Hematology, Department of Internal Medicine, Marmara University School of Medicine, İstanbul, Türkiye
[2]Divisionof Nephrology, Marmara University School of Medicine, İstanbul, Türkiye
[3]Department of Nephrology, Şişli Hamidiye Etfal Training and Research Hospital, Istanbul, Türkiye

ABSTRACT

Objective: In primary membranous nephropathy (PMN), treatment includes tailored immunosuppressive protocols to reduce progression risks, with relapse being a common challenge. Nevertheless, the existing body of literature on utilizing Rituximab (RTX) and calcineurin inhibitors (CNIs) in such cases is limited. The study aims to document the outcomes associated with the combined use of low-dose RTX and CNIs in the treatment of relapsed PMN patients with a moderate to high risk.

Methods: In this retrospective study, 22 relapsed PMN patients (22.7% female, average age 51.2 ± 12 years) were included. At the time of diagnosis, 27% (n = 6) were identified as high risk and 73% (n = 16) as moderate risk. The patients were treated with 2 doses of 500 mg RTX administered 15 days apart. Low-dose CNI was started (n = 2) or maintained (n = 20) combined with RTX therapy.

Results: The mean follow-up period was 46.9 ± 11.9 months. Initial proteinuria averaged 5.9 ± 3 g/day, decreasing to 2.1 ± 2.5 g/day at 12 months and 2 ± 2.4 g/day at 24 months post treatment. All patients achieved remission, with 41% attaining complete remission and 59% partial remission. The median time to remission was 6.68 months, and the average duration of sustained remission was 26.5 months.

Conclusion: The results suggest that the combination of low-dose RTX and CNI could be a viable and safe treatment option for relapsed PMN patients with a moderate to high risk. The synergistic impact of CNI and RTX may augment treatment effectiveness, enabling the use of reduced RTX dosages.

Keywords: Calcineurin inhibitors, clinical nephrology, immunosuppressive therapy, membranous nephropathy, Rituximab

Corresponding author: Ahmet Mert Yanık ✉ ahmetmertyanik@gmail.com **Received:** March 17, 2025 **Revision Requested:** May 14, 2025
Last Revision Received: July 05, 2025 **Accepted:** July 07, 2025 **Publication Date:** October 1, 2025

Cite this article as: Yanık AM, Berke İ, Aykent MB, et al. Low-dose rituximab and calcineurin inhibitor combination as an effective treatment strategy in relapsed primary membranous nephropathy. *Turk J Nephrol.* 2025;34(4):259-266.

INTRODUCTION

Primary membranous nephropathy (PMN) stands as the leading cause of nephrotic syndrome in non-diabetic adults globally, with its incidence rising alongside age.[1]

Primary membranous nephropathy is classified as an autoimmune disorder, and around 70%-80% of cases exhibit antibodies against phospholipase A2 receptor (PLA2R), situated in podocytes. Additionally, 2%-3% of patients possess thrombospondin type-1 domain-containing 7A antibodies, linked to cancer in roughly 20% of cases.[2-4] Prolonged identification of high serum PLA2R titers point to active PMN, signifying heightened immunological activity and reduced likelihood of spontaneous remission or a delayed and less effective response to immunosuppressive treatment.[5-7]

Immunosuppressive therapy (IST) was typically advised for PMN patients with high disease progression risk factors.[6] The Ponticelli protocol, involving alternating monthly corticosteroids and chlorambucil for 6 months, is a well-established successful treatment strategy in

PMN.[8,9] A modified version using cyclophosphamide as an alkylating agent (the modified Ponticelli protocol) was also effective with reduced toxicity.[10] However, cyclophosphamide carries potential risks such as bladder cancer and infertility, particularly concerning for young patients, along with infection risks.[10,11] Calcineurin inhibitors (CNIs) alone or in combination with low-dose prednisone have demonstrated efficacy in inducing remission, but the high risk of early relapses upon tapering or discontinuation raises concerns.[9,12]

The effectiveness of Rituximab (RTX), a monoclonal antibody targeting CD20 on mature B cells, in PMN led to comparative studies with other treatments in recent years.[10,13-15] As a result of these studies, although RTX alone has become a more commonly used and recommended treatment approach in PMN, complete remission (CR) rates is low and more than one-third of the patients remain unresponsive

In the Kidney disease improving global outcomes 2021 (KDIGO 2021) guideline PMN was categorized logically based on clinical criteria evaluating the rate of kidney function progression. Since preceding studies were conducted prior to this guideline, patient groups lacked uniform classification within certain risk categories.[15] TFor high risk patients, the KDIGO guidelines suggest a treatment regimen involving 6 months of CNI therapy followed by RTX treatment. However, studies investigating outcomes of combining CNIs and RTX from the initial treatment stages are limited.[16-19] The aim of this study was to demonstrate the efficacy of a reduced RTX dose alongside low-dose CNI therapy in relapsed moderate and high risk PMN patients.

MATERIAL AND METHODS

The study involved 22 patients diagnosed with relapsed PMN in moderate or high risk group and treated with low-dose RTX and low-dose CNI at the nephrology clinic, between 2014 and 2019. This retrospective study received approval from the Marmara University ethics committee (Approval no : 09.2019.659, Date : 26.07.2019). Written informed consent was obtained from all of the patients.

MAIN POINTS

- Primary membranous nephropathy (PMN) is the most common cause of nephrotic syndrome in non-diabetic adults, with Rituximab (RTX) and calcineurin inhibitors (CNI) being widely used in treatment.
- There is no established consensus on the dosing and administration protocols for RTX and CNI therapy.
- The combination of low-dose RTX and CNI emerges as an effective and safe treatment option for relapsed PMN patients with moderate to high risk.
- The study suggests that the synergistic effect of CNI and low-dose RTX may enhance treatment efficacy, potentially allowing for reduced RTX dosages while maintaining favorable remission outcomes.

Based on retrospective clinical data, patients were categorized according to the risk classification from the KDIGO 2021 guidelines at the time of diagnosis: 6 patients (27%) were identified as high risk and 16 patients (73%) as moderate-risk.[15] Patients were treated according to their health insurance coverage, regional guidelines, and preferences before initiating the combination therapy of low-dose RTX and CNI.

Additionally, patients with active infections and patients with secondary membranous nephropathy were also excluded.

All the patients included in the study had experienced relapses following prior treatments. Six patients (27.2%) had previously received cyclophosphamide, and at least 2 years had elapsed since the administration of cyclophosphamide for each patient.

Low-dose cyclosporine was administered to patients at a dosage of 1 mg/kg/day, targeting serum cyclosporine level of 50-70 ng/mL. One patient was treated with low-dose tacrolimus at a dosage of 0.05 mg/kg/day, targeting a serum tacrolimus level of 3-5 ng/mL. Prior to relapse, 20 patients (91%) were on low-dose cyclosporine, targeting serum cyclosporine level of 50-70 ng/mL, due to persistent proteinuria following first IST. Although CR was not achieved with the prior treatment, these patients exhibited improvements in proteinuria and serum albumin levels with ongoing CNI therapy. Following the onset of relapses, 2 patients commenced low-dose CNI therapy. In patients who achieved a CR, CNI treatment was discontinued 6 months after initiating low-dose RTX. Conversely, for patients who did not achieve CR, CNI treatment was maintained until the relapse.

The RTX was given as 2 doses of 500 mg administered 2 weeks apart. However, 1 patient only received a single dose of 500 mg RTX due to allergic side effects. Figure 1 summarizes the management of the patients.

At the time of relapse, low-dose oral methylprednisolone (4-8 mg/day) was also administered to the patients, followed by a gradual tapering over time and discontinuation within 1-2 months. One patient (4.5%) continued with a low dose of methylprednisolone (4 mg/day) for maintenance. All patients received maintenance angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers therapy.

The CD19 levels were monitored in all patients every 4-6 weeks following RTX administration, and a level of <5 cells/μL was considered indicative of appropriate immunosuppression. To assess potential infection risks, all patients underwent routine follow-up evaluations, including complete blood count, biochemical tests, and x-ray imaging. Liver and kidney functions were also closely monitored. Patients deemed at risk for hepatitis B and tuberculosis received pre-treatment prophylaxis.

Complete remission was defined as urinary protein excretion being less than 0.3 g/d as well as normal serum albumin

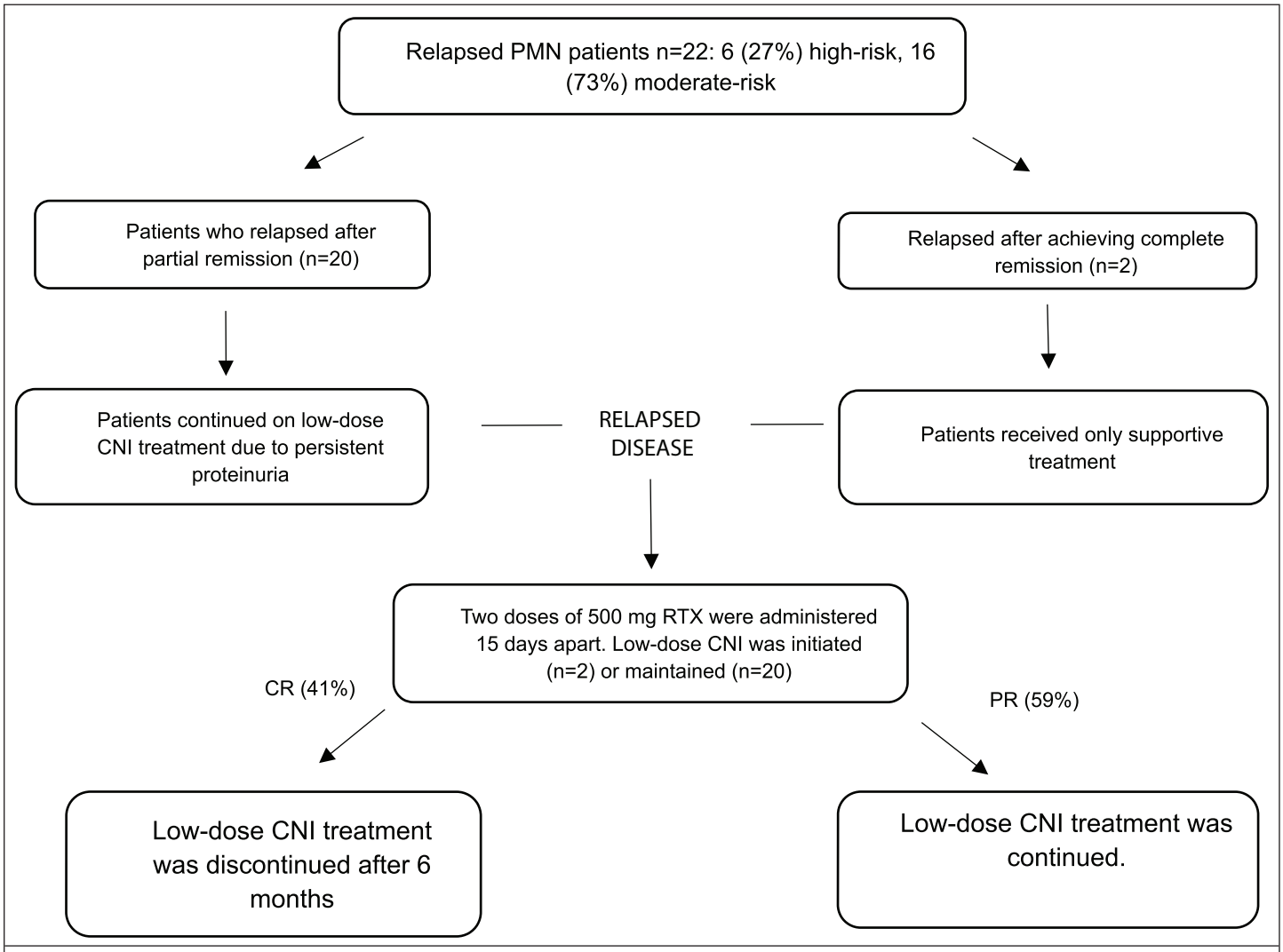


Figure 1. Patient management flow chart.

concentration and a normal serum creatinine (SCr) level. Partial remission was defined as urinary protein excretion was below 3.5 g/d with a reduction of 50% or more as well as an improvement or normalization of the serum albumin concentration and stable SCr.[15] Relapse in PMN was defined as proteinuria >3.5 g/day after CR or a >50% increase to nephrotic-range proteinuria (>3.5 g/day) after PR.

Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 20.0 (IBM SPSS Corp.; Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation (SD) if normally distributed, or as median (minimum-maximum) if not. Categorical variables were summarized using frequencies and percentages. The Shapiro–Wilk test was applied to assess the normality of distribution for continuous variables. For between-group comparisons, the independent samples *t*-test was used for normally distributed variables, and the Mann–Whitney *U* test was applied for non-normally distributed variables. For paired samples, the paired *t*-test was used when appropriate, and the Wilcoxon signed-rank test was used for non-parametric comparisons. Kaplan–Meier survival analyses were performed to evaluate both the time to remission and the duration of remission following treatment. A *P*-value of <.05 was considered statistically significant.

RESULTS

Out of the 22 patients enrolled in the study, 5 (22.7%) were female, and 17 (77.3%) were male. The mean age of the patients was 51.2 ± 12 years. Immunohistochemical analysis was conducted on kidney biopsy specimens from all participants to assess PLA-2R antigen staining, and all specimens tested positive. Among the 22 patients, 7 (31.8%) tested positive for serum anti-PLA2R, whereas 5 (22.7%) tested negative. Serum anti-PLA2R levels were only assessed in 12 patients, resulting in a mean serum titer of 57.5 ± 19.3 (range: 29-91) RU/mL. After the diagnosis, patients were followed for an average duration of 81.2 ± 43.2 months, with a mean post-treatment follow-up period of 46.9 ± 11.9 months. Hypertension was present in 15 patients (68.2%), and 8 patients (36.4%) had diabetes

mellitus. After diagnosis, thromboembolism was experienced by 2 patients (9%). Table 1 presents a summary of the patients' demographic data.

Partial response was achieved in 13 (59%) patients, and a complete response was observed in 9 (41%) patients. On average, the patients reached remission within 6.68 months, with individual cases varying between 1 and 23 months. The time to remission after treatment and remission durations by response type are depicted in Figure 2.

As shown in Table 2 among the patients, 6 (27%) were classified as high risk, while 16 (73%) were categorized as moderate risk. In the high-risk group, 2 patients (33%) achieved CR through the combination of low-dose RTX and low-dose CNI treatment. In the moderate-risk group of 16 patients, CR was attained in 6 (37.5%) cases. The laboratory data at the time of the patients' changing clinical conditions are presented in Table 2. The remaining patients in both risk groups achieved PR, with 77% in the high-risk group and 62.5% in the moderate-risk group. Initial mean proteinuria was 5.9 ± 3 g/day, decreasing to 2.1 ± 2.5 g/day by 12 months and to 2 ± 2.4 g/day by 24 months post-treatment. Table 3 summarizes the mean laboratory data for patients at baseline, as well as at 3, 6, 12, and 24 months after treatment, including the corresponding *P*-values relative to the baseline values.

Follow-Up

During follow-up, the patients were noted to sustain remission for an average duration of 26.5 (8.5-38.7) months. Remission duration for all patients and stratified by treatment response is shown in Figure 3. However, among these patients, 16 required an additional 2 doses of 500 mg of RTX due to relapse after an average duration of 20.1 (4-50) months. Among the 16 patients who received the additional RTX doses, 14 exhibited a partial response, while 2 achieved a complete response. Table 3 summarizes the mean laboratory data for patients at baseline, as well as 3, 6, 12, and 24 months following treatment, along with the corresponding *P*-values relative to the baseline values.

Table 1. Demographic Characteristics of Patients with Primary Membranous Nephropathy at Baseline (n = 22)

Variable	n (%)
Age± SD (years)	51.2 ± 12
Gender, n (female)	5 (22.7)
Hypertension, n (%)	15 (68.2)
Diabetes mellitus, n (%)	8 (36.4)
RAS blockers, n (%)	22 (100)
ACEi	11 (50)
ARB	11 (50)
Prior immunosuppressive treatment, n (%)	22 (100)
Steroid	22 (100)
Calcineurin inhibitor	22 (100)
Cyclophosphamide	6 (27.2)

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; SD, standart deviation; RAS blocker, renin-angiotensin system blockers.

Side Effects

Calcineurin inhibitor therapy was stopped in 1 patient 6 months after treatment due to acute kidney injury and hyperkalemia. Additionally, in another patient, CNI therapy was halted 8 months after treatment due to cardiac side effects, manifested as QT prolongation. Apart from 1 patient who encountered a grade 3 allergy during RTX infusion, no RTX-related side effects were noted. Furthermore, no serious infections were observed during follow-up.

DISCUSSION

The aim of the current study was to document the clinical responses of a combination therapy with low-dose RTX and low-dose CNI in 22 relapsed patients with PMN who were classified as moderate or high risk. Importantly, most patients (20 out of 22) were already undergoing low-dose CNI therapy prior to treatment initiation. All patients, except 1, received 2 doses of 500 mg of RTX administered 2 weeks apart. Clinical remission was observed in all patients, with 9 patients (40.9%) achieving CR and 13 patients (59.1%) experiencing PR.

The outcomes of our treatment protocol in patients with relapsing PMN can be discussed from 3 different perspectives.

Firstly, the study revealed that a significant proportion of patients with moderate to high-risk experienced remission through RTX therapy, without discontinuing their CNI treatment. This positive response was either observed in patients who had achieved CR but later relapsed, while in the process of reducing CNI therapy or relapsed patients when their proteinuria demonstrated some reduction under CNI treatment, yet the discontinuation of CNI and glucocorticoid therapy was not feasible due to ongoing significant proteinuria. This suggests that combining RTX with ongoing CNItherapy can be a viable strategy for managing relapsed PMN. Indeed, in 2009, Segarra A et al[20] reported achieving long-term clinical remission in 13 patients with CNI-dependent PMN despite discontinuing CNI therapy. They utilized a regimen of 4 weekly doses of RTX (375 mg/m^2). Over a 30-month follow-up period, only 3 patients experienced relapses, which were effectively managed with second course of RTX.

In a pilot study, 13 high-risk PMN patients underwent a treatment approach involving combination induction therapy with RTX and cyclosporine for a duration of 6 months. This was followed by a second cycle of RTX and a gradual reduction of cyclosporine during an 18-month maintenance phase. The study revealed that at 9-month, 92% of patients achieved either complete or PR. Specifically, 54% of the patients attained CR at 12 months. Notably, all patients with initially high anti-PLA2R

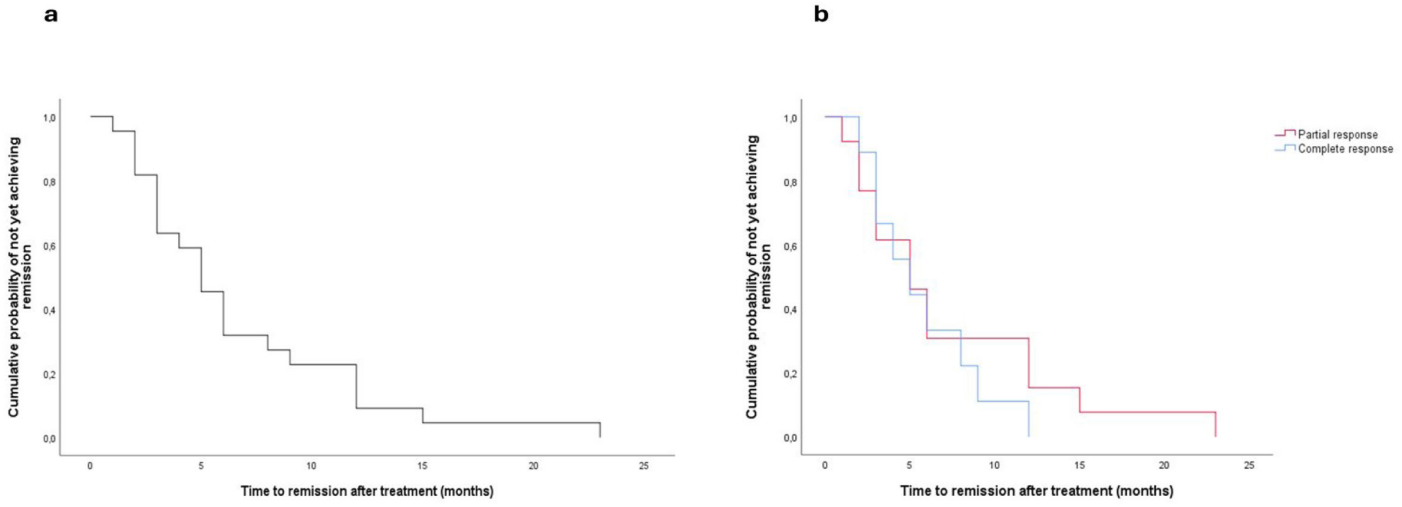


Figure 2. Time to remission following treatment. (a) Kaplan–Meier estimate of time to remission after treatment initiation. (b) Kaplan–Meier estimate of time to remission stratified by response type.

levels experienced immunological remission. Over a 24-month follow-up period, only 2 patients experienced relapses.[21]

The STARMEN (2019) trial compared 2 PMN treatments in 86 patients: a single 1 g dose of RTX after 6 months of tacrolimus, and the modified Ponticelli regimen (cyclical methylprednisolone and cyclophosphamide). After 24 months, the Ponticelli regimen showed higher remission (CR + PR at 84%, CR at 60%) compared to the tacrolimus and RTX combination (CR + PR at 58%, CR at 26%). These remission rates were lower than those reported in our study and others.[13] The differences in the treatment protocols and patients' characteristics could be the underlying reasons for this disparity. In the present study, CNI treatment was maintained for 6 months after RTX administration in patients who achieved CR, whereas patients on partially remission continued CNI treatment during follow-up. However, in the STARMEN study, CNI treatment was halted 3 months after RTX administration. Notably, during the follow-up period, 72.7% of the patients experienced relapse; however, clinical remission was successfully attained through the administration of additional RTX treatments.

Secondly, low-dose RTX in inducing and maintaining remission when combined with CNI treatment could be effective as standard RTX protocol for moderate-high risk patients with PMN. Previous studies investigated the efficacy of low-dose RTX in PMN patients.[22-24] In 2018, Bagchi et al[22] conducted a study involving 21 active PMN patients resistant to previous IST. They administered 2 doses of 500 mg RTX 1 week apart. Over an average follow-up of 13.1 months (ranging from 10 to 23.9 months), remission was achieved in 13 patients (61.9%), with 4 patients (19%) experiencing CR and 9 patients (42.9%) experiencing PR. The median time to remission after treatment was 2.7 months (ranging from 1.2 to 7 months). If CD19 levels didn't decrease, an additional dose was planned. The CD19 level reduction occurred in 20 patients (95.2%), with just 1 patient requiring an additional 500 mg RTX dose. Only 1 patient who achieved PR experienced relapse after 13 months.

In another study, 12 newly diagnosed PMN patients were given a single 375 mg/m^2 dose of RTX, with a second dose planned when ≥5 B cells/mm^3 were detected in circulation after the first dose. Only 1 patient required a second dose for full CD20 cell depletion. Except for 1 patient needing a second RTX dose, all patients achieved persistent CD20 cell depletion. Remission rates were comparable to 24 reference patients receiving the standard 4 weekly doses of 375 mg/m^2 RTX.[24] These findings suggest the potential use of relatively low-dose RTX, which could be cost-effective and may decrease the risk of developing anti-chimeric antibodies associated with adverse reactions and treatment resistance.[25,26] Similarly, in the current study, CD19 levels were monitored approximately 2 months after the last RTX dose, and all patients achieved complete CD19 depletion. However, there is evidence suggesting that lower doses of RTX may be less effective than the standard dose in patients with PMN. In a retrospective study, standard-dose RTX treatment was found to be more effective, showing higher remission rates at 6 months (64% vs. 30%, $P = .01$).[27]

On the other hand, it has been demonstrated that even with B-cell depletion achieved through low-dose RTX, B-cell recovery was faster compared to the standard RTX dose.[7,28] Furthermore, higher RTX doses appear to be more effective in patients with PMN, especially in those with higher baseline anti-PLA-2 titers.[23]

Is it possible that continuing low-dose CNI treatment in conjunction with RTX might reduce the required RTX dosage in patients with PMN? This hypothesis stems from the observation that RTX can be excreted in the urine of nephrotic patients, potentially leading to reduced treatment responsiveness. The combined effect of CNI and RTX could enhance treatment efficacy,

Table 2. Characteristics of Patients Receiving Low-Dose RTX and Low-Dose CNI Therapy

No.	Age	Gender	SCr1 (mg/dL)	SAlb1 (g/dL)	UPr1 (g/day)	Risk Group at the Time of Diagnosis	Prior Treatment	Initial Serum anti-PLA2R ab	Follow-Up After the Treatment (Years)	SCr2 (mg/dL)	SAlb2 (g/dL)	UPr2 (g/day)	Treatment Response	Time to Achieve Clinical Response After Treatment (Months)	Clinical Response Duration (Months)
1.	46	M	1.9	3.3	4.8	MR	Steroid + ACEi + CNI	NK	2	0.9	3.8	2.2	PR	6	7
2.	32	M	1.4	2.4	15	HR	Steroid + ACEi + CNI	POS	4	0.8	4.2	2.4	PR	23	26
3.	34	F	0.8	2.5	13.4	HR	Steroid + ACEi + CNI	POS	2	0.9	4.1	1.3	PR	13	13
4.	62	F	0.8	3.2	4.1	MR	Steroid + ACEi + CNI	NK	1	0.6	4.6	0.2	CR	7	8
5.	61	F	0.6	2.4	5.5	HR	Steroid + ACEi + CNI	POS	2	0.8	3.8	0.2	CR	13	15
6.	65	M	0.7	2.5	8.6	HR	Steroid+ ARB + CNI	NEG	3	0.6	4.4	0.1	CR	4	28
7.	52	F	1.8	3.2	7.7	MR	Steroid + ACEi + CNI	NEG	1	1.3	4.3	0.1	CR	11	5
8.	56	M	0.8	3.3	6.3	MR	Steroid + ARB + CNI	NK	2	0.9	4.5	0.2	CR	12	18
9.	42	M	1.7	3.1	6.7	MR	Cy + steroid + ACEi + CNI	NEG	3	1.4	3.6	2.6	PR	17	18
10.	46	M	0.9	3.4	4.1	MR	Cy + steroid + ARB + CNI	NK	2	1	4.5	0.2	CR	5	14
11.	52	M	0.9	3.1	6.3	MR	Steroid + ARB + CNI	POS	1	1	3.5	0.2	CR	5	2
12.	53	M	1	2.4	3.6	HR	Cy + steroid + ARB + CNI	NK	4	1	4.25	0.2	CR	3	30
13.[a]	49	M	1	3	4	MR	Steroid + ARB + CNI	NK	2	0.8	4	0.2	CR	2	28
14.[a]	74	F	1.1	3.3	4.2	MR	Steroid + ARB + CNI	POS	2	1.3	3.6	3.5	PR	12	14
15.	31	M	1.1	3.2	4.8	MR	Steroid + ACEi + CNI	POS	4	1.1	3.7	2.4	PR	15	3
16.	70	F	0.7	2.8	5.1	MR	Cy + Steroid + ARB + CNI	NK	2	1.1	3.5	3.1	PR	5	6
17.	53	M	1	3.2	5.6	MR	Steroid + ACEi + CNI	NEG	1	0.8	4.1	0.9	PR	1	7
18.	63	M	2.1	2.8	6.7	MR	Cy + Steroid + ARB + CNI	NK	2	2	3.9	0.6	PR	6	14
19.	39	M	0.5	3.4	3.7	MR	Steroid + ARB + CNI	NEG	3	0.6	3.8	1.6	PR	1	5
20.	52	M	1.6	3.2	4.3	MR	Steroid + ARB + CNI	NK	2	1	3.5	1.6	PR	5	12
21.	54	M	0.9	3.3	3.8	MR	Cy + Steroid + ARB + CNI	NK	3	0.9	3.7	1.5	PR	3	5
22.	39	M	0.9	2.2	3.6	HR	Steroid + ARB + CNI	POS	3	0.8	3.1	2.3	PR	3	37

ACEi, ace inhibitors; ARB, angiotensin receptor blocker; CN, calcineurin inhibitor; CR, complete remission; Cy, cyclophosphamide; F, female; HR, high risk; M, male; MR, moderate risk; NEG, negative; NK, not known; POS, positive; PR, partial remission; SCr1, baseline serum creatinine level; SCr2, serum creatinine level at the time of remission; SAlb1, baseline serum albumin level; SAlb2, serum albumin level at the time of remission; UPr1, baseline urinary protein level; UPr2, urinary protein at the time of remission.

[a]Patients number 13 and 14 discontinued CNI therapy due to side effects after 6 and 8 months respectively.

Table 3. Laboratory Parameters of the Patients at Baseline and at 3, 6, 12, and 24 Months after Treatment

	Baseline n = 22	3 Months n = 21	6 Months n = 20	12 Months n = 20	24 Months n = 20
BUN (mg/dL)	22.6 ± 12.9	18.8 ± 86.0	22.5 ± 14.2	19.9 ± 10.1	19.4 ± 10.0
Serum creatinine (mg/dL)	1.0 ± 0.4	1.0 ± 0.2	1.0 ± 0.3	1.0 ± 0.3	1.0 ± 0.2
eGFR (ml/dak/1.73 m^2)	84.4 ± 34.6	90.3 ± 27	84.4 ± 28.9	82.7 ± 27.6	86.3 ± 28.9
Serum albumin (g/dL)	3.0 ± 0.5	3.7 ± 0.4*	3.9 ± 0.4*	3.9 ± 0.8*	4.0 ± 0.5*
Proteinuria (g/day)	5.9 ± 3.0	2.6 ± 2.0**	2.3 ± 2.5**	2.1 ± 2.5**	2.0 ± 2.4**

BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.
All results are expressed as mean± standard deviation.
*Compared to baseline serum albumin ($P < .01$).
**Compared to baseline serum proteinuria ($P < .01$).

allowing for lower RTX doses to be effective. This approach may address the issue of RTX loss in nephrotic syndrome, a condition commonly associated with PMN, characterized by significant proteinuria and the potential loss of therapeutic proteins like RTX.[29] The combination of CNIs with RTX could potentially diminish the urinary loss of RTX. This is because proteinuria might decrease to a certain extent because of CNIs' antiproteinuric effects (hemodynamic and/or immunologic). This period might extend until the RTX effect initiates, potentially ensuring the maintenance of sufficient serum RTX levels. This combined approach might mitigate the issue of RTX wastage through urinary excretion and enhance its efficacy in PMN patients.

Lastly, administering RTX in conjunction with a CNI regimen may offer the potential advantage of reducing the required dosage of CNIs, thereby possibly lowering the risk of kidney toxicity. This low-dose combination strategy might help optimize therapeutic efficacy in the treatment of nephropathy, while potentially minimizing the adverse effects commonly associated with higher CNI doses.

Similar findings have been reported in earlier studies; however, this study adds further evidence and provides additional insights within this context.[22,25] The study is also subject to several notable limitations, including a small sample size and the lack of anti-PLA2R testing in a significant portion of the patients. Due to limitations in test availability at our center during the study period and the lack of insurance coverage for this test, it could only be performed in 12 patients, and follow-up measurements were not feasible for the same reasons. Moreover, its retrospective design and the absence of a control group further constrain the robustness and generalizability of the findings. Nonetheless, this study adds value to the existing literature by focusing on a specific patient population, employing a low-dose treatment strategy, and providing long-term follow-up data.

In conclusion, the combination of low-dose RTX and CNIs may potentially exert a synergistic effect, enhancing RTX's efficacy in inducing remission in patients with relapsed moderate to high-risk PMN. However, this possible benefit should be interpreted with caution, as the treatment regimen appears to be associated with a considerable risk of relapse, often necessitating additional RTX doses during follow-up. This approach could allow for lower RTX dosages, thereby possibly reducing the likelihood of adverse effects. In high-risk patients, particularly those with elevated baseline anti-PLA2R antibody levels, a standard RTX protocol in combination with low-dose CNIs might extend remission duration.

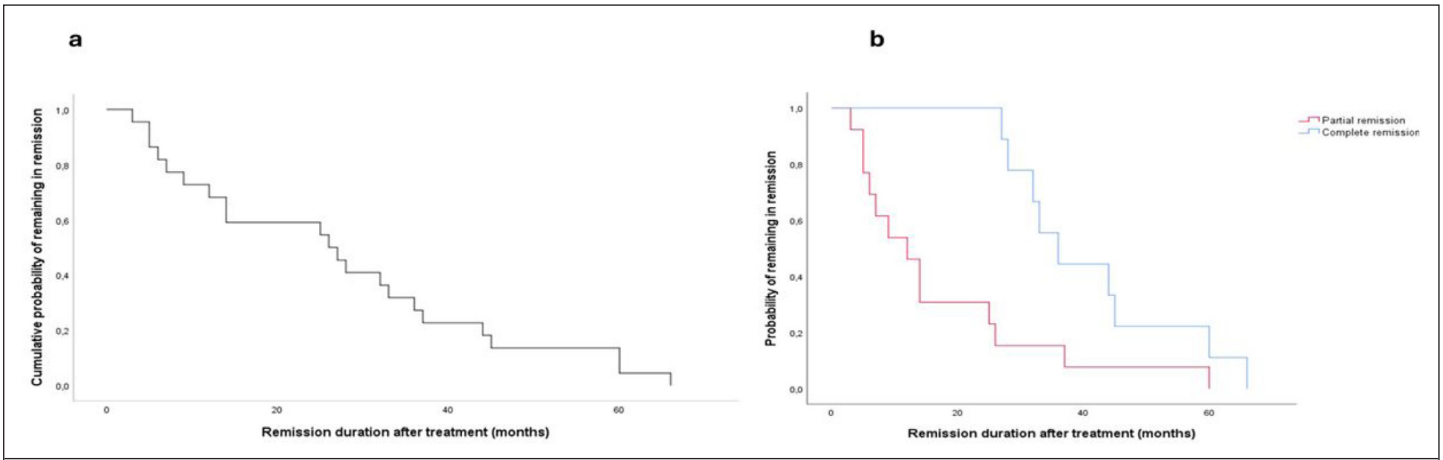


Figure 3. Remission duration after treatment. (a) Kaplan–Meier estimates of remission duration after treatment; (b) Kaplan–Meier estimates of remission duration stratified by response type.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: This study was approved by the Ethics Committee of Marmara University (Date: 26.07.2019; Approval no: 09.2019.659).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.M.Y., İ.H.A .; Design – A.M.Y.; Supervision – İ.H.A., Z.S.T., M.K. ; Resources – A.M.Y.; Materials – A.M.Y.; Data Collection and/or Processing – A.M.Y, İ.H.A.; Analysis and/or Interpretation – A.M.Y., İ.H.A.; Literature Search – A.M.Y., İ.M, M.B.A.; Writing Manuscript – A.M.Y., İ.H.A., M.K.; Critical Review –İ.H.A, M.K.; Other –A.V., E.A., M.T., D.B.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. Glassock RJ. Diagnosis and natural course of membranous nephropathy. *Semin Nephrol*. 2003;23(4):324-332. [CrossRef]
2. Tomas NM, Beck LH, Jr, Meyer-Schwesinger C, et al. Thrombospondin type-1 domain-containing 7A in idiopathic membranous nephropathy. *N Engl J Med*. 2014;371(24):2277-2287. [CrossRef]
3. Akiyama S, Imai E, Maruyama S. Immunology of membranous nephropathy. *F1000Res*. 2019;8:F1000 Faculty Rev-734. [CrossRef]
4. Alsharhan L, Beck LH, Jr. Membranous nephropathy: core curriculum 2021. *Am J Kidney Dis*. 2021;77(3):440-453. [CrossRef]
5. Müller-Deile J, Schiffer L, Hiss M, Haller H, Schiffer M. A new rescue regimen with plasma exchange and rituximab in high-risk membranous glomerulonephritis. *Eur J Clin Investig*. 2015;45(12):1260-1269. [CrossRef]
6. Kidney Disease Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of GlomerularDiseases. *Kidney Int*. 2021; 100(4S):S1-S276.
7. Ponticelli C. Membranous nephropathy. *J Clin Med*. 2025;14(3):761. [CrossRef]
8. *Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guideline for Glomerulonephritis. Kidney Inter Suppl. 2012;2:139-274.* . 2012.
9. Couser WG. Primary membranous nephropathy. *Clin J Am Soc Nephrol*. 2017;12(6):983-997. [CrossRef]
10. Angioi A, Lepori N, López AC, Sethi S, Fervenza FC, Pani A. Treatment of primary membranous nephropathy: where are we now? *J Nephrol*. 2018;31(4):489-502. [CrossRef]
11. Chen Y, Schieppati A, Cai G, et al. Immunosuppression for membranous nephropathy: a systematic review and meta-analysis of 36 clinical trials. *Clin J Am Soc Nephrol*. 2013;8(5):787-796. [CrossRef]
12. Beck L, Bomback AS, Choi MJ, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for glomerulonephritis. *Am J Kidney Dis*. 2013;62(3):403-441. [CrossRef]
13. Fernández-Juárez G, Rojas-Rivera J, Logt AV, et al. The STARMEN trial indicates that alternating treatment with corticosteroids and cyclophosphamide is superior to sequential treatment with tacrolimus and rituximab in primary membranous nephropathy. *Kidney Int*. 2021;99(4):986-998. [CrossRef]
14. Scolari F, Delbarba E, Santoro D, et al. Rituximab or cyclophosphamide in the treatment of membranous nephropathy: the RI-CYCLO randomized trial. *J Am Soc Nephrol*. 2021;32(4):972-982. [CrossRef]
15. Group KDIGOKGW. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. 2021;100:(4S).
16. Caravaca-Fontán F, Yandian F, Fervenza FC. Future landscape for the management of membranous nephropathy. *Clin Kidney J*. 2023;16(8):1228-1238. [CrossRef]
17. Chen M, Liu J, Xiong Y, Xu G. Treatment of idiopathic membranous nephropathy for moderate or severe proteinuria: a systematic review and network meta-analysis. *Int J Clin Pract*. 2022;2022:4996239. [CrossRef]
18. Chen X, Jiao S, Li S, et al. Combination of rituximab and low-dose tacrolimus in the treatment of refractory membranous nephropathy: a retrospective cohort study. *Balk Med J*. 2023;40(4):287-293. [CrossRef]
19. Mathew GG, Sundaramurthy S, Muthuperumal P, Jayaprakash V. Low-dose rituximab in the treatment of primary membranous nephropathy - A systematic review and meta-analysis. *G Ital Nefrol*. 2024;41(5):2024-vol5. [CrossRef]
20. Segarra A, Praga M, Ramos N, et al. Successful treatment of membranous glomerulonephritis with rituximab in calcineurin inhibitor-dependent patients. *Clin J Am Soc Nephrol*. 2009;4(6):1083-1088. [CrossRef]
21. Waldman M, Beck LH, Jr, Braun M, Wilkins K, Balow JE, Austin HA, 3rd. Membranous nephropathy: pilot study of a novel regimen combining cyclosporine and rituximab. *Kidney Int Rep*. 2016;1(2):73-84. [CrossRef]
22. Bagchi S, Subbiah AK, Bhowmik D, et al. Low-dose rituximab therapy in resistant idiopathic membranous nephropathy: single-center experience. *Clin Kidney J*. 2018;11(3):337-341. [CrossRef]
23. Moroni G, Depetri F, Del Vecchio L, et al. Low-dose rituximab is poorly effective in patients with primary membranous nephropathy. *Nephrol Dial Transplant*. 2017;32(10):1691-1696. [CrossRef]
24. Cravedi P, Ruggenenti P, Sghirlanzoni MC, Remuzzi G. Titrating rituximab to circulating B cells to optimize lymphocytolytic therapy in idiopathic membranous nephropathy. *Clin J Am Soc Nephrol*. 2007;2(5):932-937. [CrossRef]
25. Gauckler P, Shin JI, Alberici F, et al. Rituximab in membranous nephropathy. *Kidney Int Rep*. 2021;6(4):881-893. [CrossRef]
26. Teisseyre M, Boyer-Suavet S, Crémoni M, Brglez V, Esnault V, Seitz-Polski B. Analysis and management of rituximab resistance in PLA2R1-associated membranous nephropathy. *Kidney Int Rep*. 2021;6(4):1183-1188. [CrossRef]
27. Seitz-Polski B, Dahan K, Debiec H, et al. High-dose rituximab and early remission in PLA2R1-related membranous nephropathy. *Clin J Am Soc Nephrol*. 2019;14(8):1173-1182. [CrossRef]
28. Fenoglio R, Baldovino S, Sciascia S, et al. Efficacy of low or standard rituximab-based protocols and comparison to Ponticelli's regimen in membranous nephropathy. *J Nephrol*. 2021;34(2):565-571. [CrossRef]
29. Jacobs R, Langer-Jacobus T, Duong M, et al. Detection and quantification of rituximab in the human urine. *J Immunol Methods*. 2017;451:118-121. [CrossRef]

10.5152/turkjnephrol.2025.251103

Original Article

Turkish Journal of Nephrology

Economic Benefit of Anti-PLA2R Antibody Testing in the Diagnosis of Membranous Nephropathy: A Single-Center Cost Analysis

Asil Demirezen[1], Nuri Alperen Malkoç[2], Ömer Faruk Akçay[1], Saliha Yıldırım[3], Emre Yaşar[4], Sena Türkmen[5], Özlem Gülbahar[5], Betül Öğüt[6], İpek Işık Gönül[6], Galip Güz[1], Ülver Derici[1], Yasemin Erten[1], Kadriye Altok[1], Özant Helvacı[1]

[1]Division of Nephrology, Gazi University Faculty of Medicine, Ankara, Türkiye
[2]Department of Internal Medicine, Gazi University Faculty of Medicine, Ankara, Türkiye
[3]Divisionof Nephrology, Sincan Training and Research Hospital, Ankara, Türkiye
[4]Department of Nephrology, Etlik City Hospital, Ankara, Türkiye
[5]Department of Medical Biochemistry, Gazi University Faculty of Medicine, Ankara, Türkiye
[6]Department of Pathology, Gazi University Faculty of Medicine, Ankara, Türkiye

ABSTRACT

Background: This study aimed to evaluate the financial impact of using anti-phospholipase A2 receptor antibody testing instead of kidney biopsy for diagnosing membranous nephropathy.
Methods: A retrospective cross-sectional study was conducted at Gazi University Faculty of Medicine Hospital between November 2022 and January 2024. Seventy adult patients with nephrotic syndrome underwent anti-phospholipase A2 receptor antibody testing using an enzyme-linked immunosorbent assay. The costs of diagnosis based on serology and kidney biopsy were compared.
Results: Among 70 patients, 18 tested positive for anti-phospholipase A2 receptor antibodies. Of these, 13 were diagnosed without a kidney biopsy, leading to a cost reduction of approximately 52 000 Turkish Liras (1300 American Dollars). The total expense for anti-phospholipase A2 receptor antibody testing was significantly lower than that of kidney biopsy, which required hospitalization and procedural costs. If all antibody-positive patients had been diagnosed without a biopsy, the potential savings would have reached 24 000 Turkish Liras (600 American Dollars).
Conclusion: Anti-phospholipase A2 receptor antibody testing provides a cost-effective, non-invasive alternative to kidney biopsy for diagnosing membranous nephropathy. Implementing a serology-first approach in selected cases may significantly reduce healthcare expenditures while maintaining diagnostic accuracy.
Keywords: Cost analysis, diagnosis, membranous nephropathy, nephrotic syndrome, phospholipase A2 receptor

Corresponding author: Asil Demirezen ✉ demirezenasil@gazi.edu.tr
Received: June 12, 2025 **Revision Requested:** June 28, 2025
Last Revision Received: July 3, 2025 **Accepted:** July 5, 2025 **Publication Date:** October 1, 2025

Cite this article as: Demirezen A, Malkoç NA, Akçay ÖF, et al. Economic benefit of anti-PLA2R antibody testing in the diagnosis of membranous nephropathy: A single-center cost analysis. *Turk J Nephrol.* 2025;34(4):267-271.

INTRODUCTION

Nephrotic syndrome is characterized by proteinuria exceeding 3.5 g/day, hypoalbuminemia, edema, and hyperlipidemia.[1] Kidney biopsy remains the gold standard in the diagnosis of glomerular diseases causing nephrotic syndrome. However, it carries risks such as bleeding, pain, hematuria, and the need for hospitalization, thereby increasing both the overall cost and the burden patient.[2,3] In contrast, in certain types of nephritis (e.g.anti neutrophilic cytoplasmic antibody(ANCA)-associated patient burden glomerulonephritis), a diagnosis can often be established with high accuracy using serological markers, without the need for a kidney biopsy.[4]

One of the most common causes of nephrotic syndrome in adults is membranous nephropathy (MN).[5] Membranous nephropathy can be associated with malignancies, drugs, infections, and systemic diseases; however, approximately 80% of cases occur primarily.[6] In the pathogenesis of primary MN, M-type phospholipase A2 receptors located on the podocyte surface and the anti-phospholipase A2 receptor (PLA2R) antibodies formed against them play a crucial role.[7] Anti-PLA2R antibodies are detectable in 50%-80% of patients with primary MN.[8]

Bobart et al[3] demonstrated that in patients with an estimated glomerular filtration rate (eGFR) ≥60 mL/min/

1.73 m^2 and no identifiable secondary causes of MN, a positive anti-PLA2R antibody test provided sufficient diagnostic certainty to forgo a kidney biopsy, as the biopsy results did not alter clinical management.

Consistent with this, the 2021 Kidney Disease: Improving Global Outcomes (KDIGO) guideline for the management of glomerular diseases states that in patients with preserved kidney function who present with nephrotic syndrome and test positive for anti-PLA2R antibodies, kidney biopsy may not be necessary to confirm the diagnosis of MN.[9]

Building on this diagnostic shift, a retrospective cohort study was conducted to assess the economic impact of biopsy-based versus enzyme-linked immunosorbent assays (ELISA)-based diagnosis in MN. By comparing real-world diagnostic costs, the aim was to determine whether a serology-first strategy provides a meaningful financial advantage in clinical practice.

MATERIAL AND METHODS

Study Design

This retrospective cross-sectional study included 70 patients with nephrotic syndrome who presented to the Nephrology Clinic at Gazi University Faculty of Medicine Hospital between November 2022 and January 2024. All patients had anti-PLA2R antibody levels measured at presentation.

Inclusion criteria for the study were: age ≥18 years, availability of complete clinical and laboratory data at both presentation and follow-up visits, and documented serum anti-PLA2R measurements at initial evaluation.

Patients who did not continue care at the institution were excluded.

Data Collection

Patient records provided data on demographic characteristics (age, gender), comorbid conditions, anticoagulant and antiplatelet medication usage, and relevant laboratory parameters, including creatinine levels, estimated glomerular filtration rate (eGFR) calculated via the CKD-EPI 2021 equation, albumin and lipid profiles, quantitative proteinuria, and anti-PLA2R antibody measurements. Complete data were available for all variables specified in the analysis. Anti-PLA2R antibody quantification was performed using ELISA methodology with EUROIMMUN commercial assay kits. Interpretation of anti-PLA2R antibody titers followed standardized cutoffs: values <14 RU/mL were classified as negative, 14-19 RU/mL as borderline, and ≥20 RU/mL as positive.[10]

The cost of anti-PLA2R antibody testing at the center was approximately 400 Turkish Liras (TL)/10 American Dollars ($) per patient during the study period. The overall expense of an uncomplicated percutaneous renal biopsy in Türkiye was around 4000 TL ($100), including 450 TL for single-day hospitalization and 3550 TL for the procedure itself.

A cost analysis was conducted between 2 patient cohorts diagnosed with MN, either by kidney biopsy or ELISA-based serology.

The Gazi University Ethics Committee approved this study on September 5, 2023 (Approval number: E-77082166-604.01.02-813550). The research was conducted according to the Declaration of Helsinki principles. Due to the nature of this study, informed consent was waived by the ethics committee.

This study followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Statistical Analysis

Data were analyzed using SPSS version 22.0 (IBM SPSS Corp.; Armonk, NY, USA). Descriptive statistics for demographic and clinical characteristics, means and SDs, medians and interquartile ranges for continuous variables, and frequencies and percentages for categorical variables were calculated. The normality of the distribution was assessed using the Shapiro-Wilk test. Normally distributed data were given as mean, and non-normally distributed data were given as median (interquartile range [IQR]).

RESULTS

We enrolled 70 patients presenting with nephrotic syndrome who underwent anti-PLA2R antibody testing. The mean age was 54 ± 17 years. Thirty-seven were male and 33 were female. Anti-PLA2R antibodies were detected in 18 patients (25.7%) (Table 1). Five of the anti-PLA2R antibody-positive patients had diabetes mellitus. None of the patients with positive anti-PLA2R antibodies were considered false positives. Among seropositive individuals, the median serum creatinine was 0.94 mg/dL, and the median estimated glomerular filtration rate (eGFR) was 74.5 mL/min. Median serum albumin and 24-hour proteinuria were 2.8 g/dL and 8650 mg/day, respectively. Comprehensive laboratory parameters are summarized in Table 2.

Among the 18 anti-PLA2R antibody-positive patients, 13 received a diagnosis of MN without the need for kidney biopsy. The remaining 5 underwent kidney biopsy due to suspected

MAIN POINTS

- Anti-phospholipase A2 receptor (PLA2R) test enables non-invasive diagnosis of membranous nephropathy.
- Cost analysis shows significant savings with anti-PLA2R-based diagnosis.
- Adopting antibody testing may reduce the healthcare burden without accuracy loss.

Table 1. General Characteristics of Patients with Nephrotic Syndrome

Age, mean ± SD (years)	54 ± 17
Sex (female/male), (n [%])	33 (47.1%) / 37 (52.9%)
Anti-PLA2R antibody-positivity (n [%])	18 (25.7%)
Presence of diabetes mellitus (n [%])	19 (27.1%)

PLA2R, phospholipase A2 receptor. SD; standart deviation

Table 2. Laboratory Characteristics of Anti-Phospholipase A2 Receptor Antibody–Positive Patients

Creatinine (mg/dL), median (IQR)	0.94 (0.70)
eGFR (CKD-EPI 2021, mL/min/1.73 m^2), median (IQR)	74.50 (59.00)
Albumin (g/dl), median (IQR)	2.80 (0.60)
Anti-PLA2R antibody level (RU/mL), median (IQR)	99.47 (398.03)
Total cholesterol (mg/dL), median (IQR)	278.50 (97.00)
LDL cholesterol (mg/dL), median (IQR)	180.00 (64.25)
Proteinuria (mg/day), median (IQR)	8650.00 (2475.00)

CKD-EPI, chronic kidney disease epidemiology collaboration; eGFR, glomerular filtration rate; IQR, interquartile range; LDL, low density lipoprotein; PLA2R, phospholipase A2 receptor.

concomitant rheumatologic disease (n = 2) or delayed serological results (n = 3) (Figure 1). No post-procedural complications were observed, and all patients were discharged following 24 hours of monitoring. Biopsy confirmed the diagnosis of MN in all 5 cases.

Among the 52 patients with negative serum anti-PLA2R antibody results, 10 did not undergo biopsy due to small kidney size, mandatory anticoagulant or antiplatelet use, presumed chronic disease, or patient refusal. The remaining 42 underwent biopsy, and 12 were diagnosed with serum anti-PLA2R-negative MN (Figure 1).

The total cost of testing 70 patients for anti-PLA2R antibodies was approximately 28 000 TL ($700). The cost of the 5 biopsies performed on anti-PLA2R antibody-positive patients was approximately 20 000 TL ($500). Since 13 patients were diagnosed with MN without biopsy, the avoidance of biopsy costs saved approximately 52 000 TL ($1300), resulting in a net savings of 4000 TL ($100) (Figure 2). If the 5 antibody-positive patients had been diagnosed without performing a kidney biopsy, this economic benefit could have increased by 20 000 TL ($500), reaching 24 000 TL ($600).

DISCUSSION

This study hypothesized that the use of anti-PLA2R antibodies for the diagnosis of membranous nephropathy is more cost-effective than kidney biopsy. According to the literature review, this study is the first to conduct a cost analysis of anti-PLA2R antibodies and kidney biopsy in the diagnosis of MN and demonstrates that anti-PLA2R antibodies are cost-effective compared to kidney biopsy in the diagnosis of MN. Using anti-PLA2R antibodies in the diagnosis of MN has provided with approximately 4000 TL ($100) in economic benefit. If a biopsy had not been performed on patients for whom it was conducted despite a positive antibody test, the economic benefit would have increased even more. This finding demonstrates the significant cost advantage of anti-PLA2R antibodies in the diagnosis of MN.

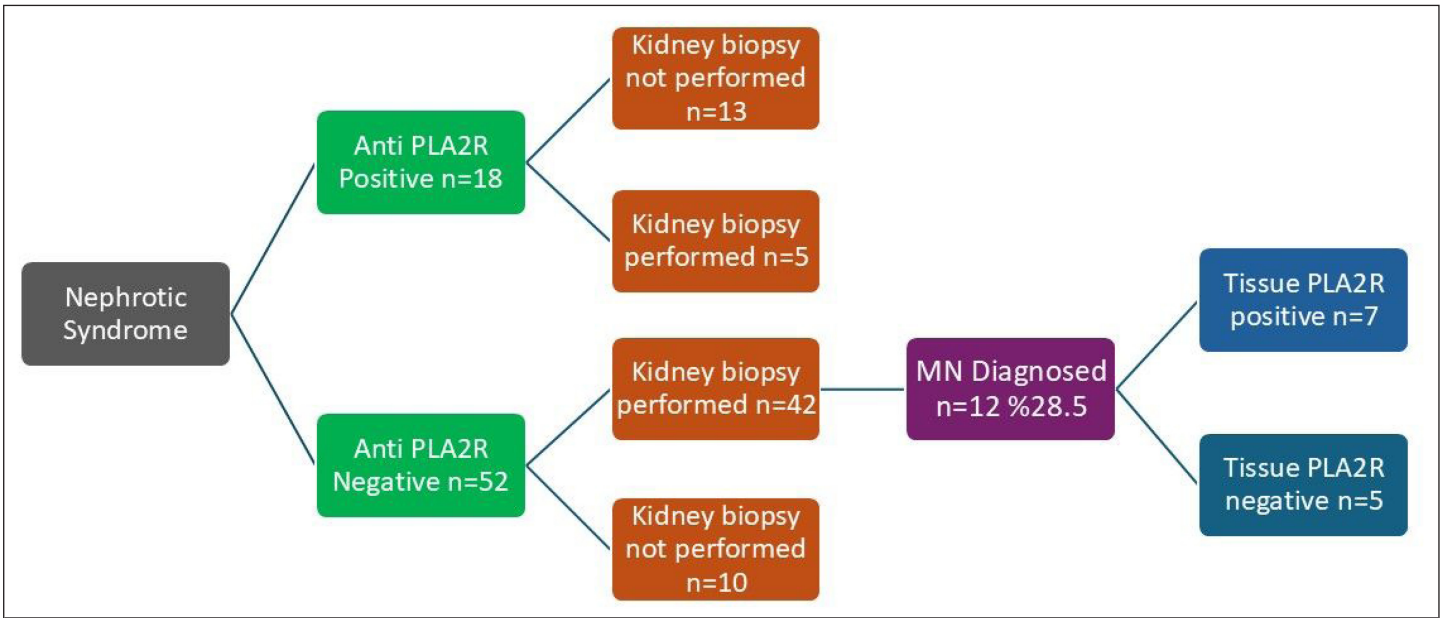


Figure 1. Anti-PLA2R antibody and kidney biopsy analysis. PLA2R, phospholipase A2 receptor.

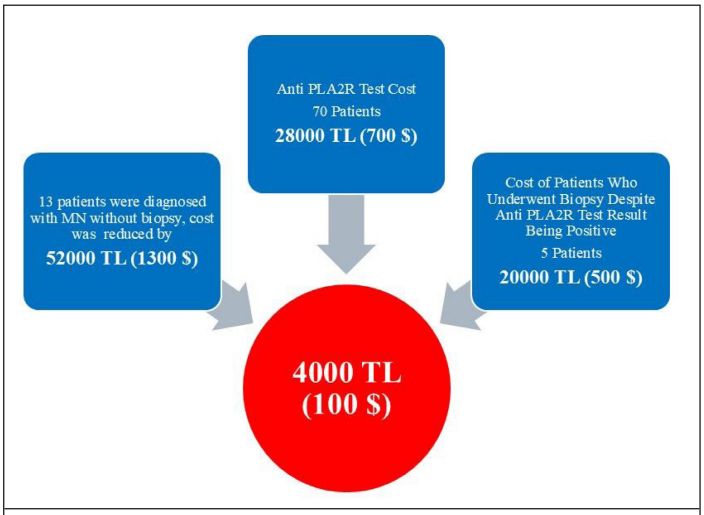


Figure 2. Anti-PLA2R test and kidney biopsy cost analysis. PLA2R, phospholipase A2 receptor; TL, Turkish Lira; $, American Dollar.

Serum anti-PLA2R antibodies are generally detected using immunofluorescence assays (IFA) and ELISA methods. Immunofluorescence assay is a more sensitive method than ELISA. Its sensitivity has been reported as 83% and its specificity as 100%.[11] In a study conducted by Jurubiță and colleagues,[12] using the ELISA method with a cut-off value of 20 RU/mL, the sensitivity of anti-PLA2R antibodies in diagnosing MN was found to be 64%, specificity 94%, positive predictive value 91%, and negative predictive value 75%. In another study conducted by Li and colleagues,[13] again with a cut-off value of 20 RU/mL, the sensitivity of anti-PLA2R antibodies in diagnosing MN was reported as 62.2% and specificity as 91.5%. Although prioritizing the IFA method in diagnosis is necessary, these studies also demonstrate that measuring serum anti-PLA2R antibodies using the ELISA method is highly specific in diagnosing MN.

There is no direct study in the literature regarding the cost analysis of anti-PLA2R antibodies. Ragy and colleagues reported in their study that the average cost of anti-PLA2R antibody measurement in the United Kingdom was £27.[14] In our clinic, the cost of anti-PLA2R antibody measurement is 400 TL ($10). The elimination of the need for hospitalization by the test prevents loss of workforce for both the patient and the caregivers. The repeatability of the test and its ability to show response to treatment also provide indirect economic benefit by reducing unnecessary use of immunosuppressive therapy.[15] All these factors provide a significant economic advantage. The cost analysis conducted in this study also demonstrates that the use of anti-PLA2R antibodies in diagnosis is significantly more cost-effective compared to kidney biopsy.

Kidney biopsy is accepted as the gold standard method for MN diagnosis.[16] In addition to diagnosing the disease, kidney biopsy also provides information on the severity and chronicity of the disease. The measurement of anti-PLA2R antibodies is highly specific for diagnosis,[17] but it cannot provide information on disease severity and chronicity, which biopsy offers. Despite the positive contributions of biopsy in diagnosis and treatment, its disadvantages include being an invasive procedure and the possibility of complications such as post-procedure bleeding.[16] Additionally, kidney biopsy is a costly procedure.[17] In a study conducted by Ragy and colleagues, the cost of an uncomplicated biopsy procedure in England was reported as an average of £774, whereas in Türkiye, it is on average 4000 TL ($100).[14,18] In cases where complications develop after kidney biopsy, these costs can further increase. The hospitalization of patients for the kidney biopsy procedure and their temporary absence from working life also impose additional burdens on the national economy.

The fact that anti-PLA2R antibodies provide a non-invasive diagnostic method protects patients from possible complications associated with biopsy. In patients who are hesitant about kidney biopsy due to potential complications, the measurement of PLA2R antibodies enables accurate diagnosis and the planning of appropriate post-diagnosis treatment.[19] Additionally, anti-PLA2R antibodies can also be used in disease monitoring after diagnosis.[20] The test has several disadvantages. These include its inability to provide information about the chronicity of the disease—unlike kidney biopsy—the relatively low sensitivity of the ELISA method, and the potential for false-negative or false-positive results. Indeed, false-positive results have been reported in diabetic patients in the literature.[20] A false-negative result obtained by the ELISA method may delay the diagnosis and treatment process of MN. In cases where the test result is suspected to be falsely positive or negative, it is recommended to evaluate antibody levels using the indirect immunofluorescence test or to include a kidney biopsy in the diagnostic process.[21] In such cases, the economic benefit provided by the test may also be limited. Although the cost of the IFA method is higher compared to ELISA, it may offer a more meaningful economic advantage in certain patients due to its higher diagnostic accuracy and its ability to eliminate the need for an invasive procedure.

The study supports that anti-PLA2R antibodies are cost-effective in the diagnosis of MN. Furthermore, the fact that the pathology results of all patients who underwent kidney biopsy despite having positive anti-PLA2R antibodies were reported as MN indicates the high specificity of the test. In the literature review, there were no similar studies conducting a comparative cost analysis of anti-PLA2R antibodies and kidney biopsy in the diagnosis of MN, making this study significant in this regard.

This study has several limitations. The first is that its single-center and retrospective design limits the generalizability of the findings to institutions with different clinical practices or cost structures. Multicenter prospective studies are needed to validate the results in more diverse healthcare settings. Another limitation is that evaluating the cost analysis solely based on

procedure and test fees excludes the economic losses due to workforce absenteeism of patients and caregivers, as well as additional expenses incurred due to access to hospital services during hospitalization. Additionally, establishing the diagnosis of MN without performing a biopsy allows the medical team and pathologists to allocate more time to other procedures not included in the cost analysis; not including this gain in the analysis is another limitation of this study. The economic benefit identified in this study is modest; however, considering the limitations in future similar studies and including workforce-related losses in the analysis will enable a more effective cost evaluation. As a result, in such a case, the economic benefit obtained from such analyses may be on a larger scale.

Our study demonstrates that anti-PLA2R antibodies should be included as a cost-effective, non-invasive diagnostic method in the diagnosis of primary MN. The widespread implementation of anti-PLA2R antibody measurements in diagnosis will provide significant benefits for healthcare economics.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Gazi University (Date: 05.09.2023; No.: E-77082166-604.01.02-813550).

Informed Consent: Due to the retrospective nature of this study, informed consent was not obtained from the patients.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.D., G.G., U.D., Y.E., K.A., O.H.; Design – A.D., G.G., U.D., Y.E., K.A., O.H.; Supervision – O.F.A., G.G., U.D., Y.E., K.A., O.H.; Resources – A.D., N.A.M., S.Y., E.Y., S.T., O.G., B.O., I.I.G.; Materials – A.D., N.A.M., S.Y., E.Y., S.T., O.G., B.O., I.I.G.; Data Collection and/or Processing – A.D., N.A.M., S.Y., E.Y., S.T., O.G., B.O., I.I.G.; Analysis and/or Interpretation – A.D., N.A.M., S.Y., E.Y.; Literature Search – A.D., O.F.A.; Writing Manuscript – A.D., O.F.A.; Critical Review – O.F.A., S.Y., E.Y., O.G., B.O., I.I.G., G.G., U.D., Y.E., K.A., O.H.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. Zabala Ramirez MJ, Stein EJ, Jain K. Nephrotic syndrome for the internist. *Med Clin North Am*. 2023;107(4):727-737. [CrossRef]
2. Poggio ED, McClelland RL, Blank KN, et al. Systematic review and meta-analysis of native kidney biopsy complications. *Clin J Am Soc Nephrol*. 2020;15(11):1595-1602. [CrossRef]
3. Bobart SA, Han H, Tehranian S, et al. Noninvasive diagnosis of PLA2R-associated membranous nephropathy: a validation study. *Clin J Am Soc Nephrol*. 2021;16(12):1833-1839. [CrossRef]
4. Guchelaar NAD, Waling MM, Adhin AA, van Daele PLA, Schreurs MWJ, Rombach SM. The value of anti-neutrophil cytoplasmic antibodies (ANCA) testing for the diagnosis of ANCA-associated vasculitis, a systematic review and meta-analysis. *Autoimmun Rev*. 2021;20(1):102716. [CrossRef]
5. Sethi S, Fervenza FC. Membranous nephropathy-diagnosis and identification of target antigens. *Nephrol Dial Transplant*. 2024;39(4):600-606. [CrossRef]
6. Couser WG. Primary membranous nephropathy. *Clin J Am Soc Nephrol*. 2017;12(6):983-997. [CrossRef]
7. Beck LH Jr, Bonegio RGB, Lambeau G, et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. *N Engl J Med*. 2009;361(1):11-21. [CrossRef]
8. Du Y, Li J, He F, et al. The diagnosis accuracy of PLA2R-AB in the diagnosis of idiopathic membranous nephropathy: a meta-analysis. *PLoS One*. 2014;9(8):e104936. [CrossRef]
9. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int*. 2021;100(4S):S1-S276. [CrossRef]
10. EUROIMMUN. IFU EA 1254-9601. EUROIMMUN website. Available at: https://www.euroimmun.co.jp/fileadmin/Subsidiaries/Japan/Documents/IFU/IFU_EA_1254-9601_G.pdf Accessed April 1, 2025.
11. Ronco P, Plaisier E, Debiec H. The role of PLA2R antibody monitoring: what we know and what we do not know. *Nephrol Dial Transplant*. 2023;38(4):826-833. [CrossRef]
12. Jurubiță R, Obrișcă B, Achim C, et al. Anti-phospholipase A2 receptor antibody screening in nephrotic syndrome may identify a distinct subset of patients with primary membranous nephropathy. *Int Urol Nephrol*. 2022;54(7):1713-1723. [CrossRef]
13. Li X, Wei D, Zhou Z, et al. Anti-PLA2R antibodies in Chinese patients with membranous nephropathy. *Med Sci Monit*. 2016;22:1630-1636. [CrossRef]
14. Ragy O, Rautemaa V, Smith A, Brenchley P, Kanigicherla D, Hamilton P. Can use of the serum anti-PLA2R antibody negate the need for a renal biopsy in primary membranous nephropathy? *PLoS One*. 2023;18(2):e0281726. [CrossRef]
15. Wei SY, Wang YX, Li JS, et al. Serum anti-PLA2R antibody predicts treatment outcome in idiopathic membranous nephropathy. *Am J Nephrol*. 2016;43(2):129-140. [CrossRef]
16. Bobart SA, De Vriese AS, Pawar AS, et al. Noninvasive diagnosis of primary membranous nephropathy using phospholipase A2 receptor antibodies. *Kidney Int*. 2019;95(2):429-438. [CrossRef]
17. Bobart SA, Fervenza FC. Kidney biopsy is required for nephrotic syndrome with PLA2R+ and normal kidney function: the con view. *Kidney360*. 2020;1(9):890-893. [CrossRef]
18. Social Security Institution (SGK). Healthcare implementation Communiqué (SUT). SGK Website. Published January 28, 2025. Available at: https://www.sgk.gov.tr/Download/DownloadFile?f=0b10f530-cb28-4769-87ee-672663b03397.zip. Accessed April 1, 2025.
19. McDonnell T, Wu HHL, Sinha S, Chinnadurai R. The role of PLA2R in primary membranous nephropathy: do we still need a kidney biopsy? *Genes (Basel)*. 2023;14(7):1343. [CrossRef]
20. Song EJ, Jeong KH, Yang YA, et al. Anti-phospholipase A2 receptor antibody as a prognostic marker in patients with primary membranous nephropathy. *Kidney Res Clin Pract*. 2018;37(3):248-256. [CrossRef]
21. Damle A, Wu HHL, Kanigicherla DAK, Chinnadurai R. The significance of anti-PLA2R in diabetic kidney disease: truly a false positive? *Glomerular Dis*. 2024;4(1):91-94. [CrossRef]

10.5152/turkjnephrol.2025.25996

Original Article

Turkish Journal of Nephrology

Empagliflozin Decreased Proteinuria in Patients with Glomerulonephritis without Diabetes: A Randomized Clinical Trial

Shahram Taheri[1], Mojgan Mortazavi[1], Shiva Seirafian[1], Abdolamir Atapour[1], Firouzeh Moeinzadeh[1], Javad Golpayegani[2]

[1]Department of Nephrology, Kidney Diseases Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
[2]Department of Nephrology, Isfahan University of Medical Sciences, Isfahan, Iran

ABSTRACT

Objective: Empagliflozin (EMPA) is a new class of hypoglycemic drugs acting as a sodium glucose co-transporter 2 inhibitor. In addition to reducing blood sugar, cardiovascular complications, and mortality rate, EMPA also has kidney protective properties (such as reducing proteinuria, progression of albuminuria, and the rate of estimated glomerular filtration rate (eGFR) decline). Therefore, this study aimed at investigating the effect of EMPA on proteinuria in non-diabetes mellitus (non-DM) patients with glomerulonephritis.

Methods: A randomized double-blind clinical trial was conducted on 60 non-DM patients with glomerulonephritis that were assigned into 2 groups of 30. All patients received their usual treatment. Patients in the first group received EMPA 10 mg tablets daily (EMPA group), while patients in the control group received placebo daily (placebo group) for 3 months.

Results: The results of the present study showed that the mean change weight decreased in the EMPA group and increased in the control group (−0.25 kg vs. +0.10 kg; $P < .001$). Although eGFR decreased over time, there was not any significant difference between the EMPA and control groups at either the start or the end of study (−2.72 mL/min/1.73m^2 vs. −1.89 mL/min/1.73m^2, $P = .767$). Proteinuria decreased and increased significantly in EMPA and control groups, respectively (−118.06 mg/24h vs. +233.69 mg/24h, $P = .013$).

Conclusion: According to the results of the present study, it seems that EMPA administration can play an effective role in reducing proteinuria in patients with glomerulonephritis.

Keywords: Empagliflozin, proteinuria, glomerulonephritis

Corresponding author: Javad Golpayegani ✉ javad62golpayegani@gmail.com **Received:** March 2, 2025 **Revision Requested:** March 26, 2025 **Last Revision Received:** July 13, 2025 **Accepted:** July 13, 2025 **Publication Date:** October 1, 2025

Cite this article as: Taheri S, Mortazavi M, Seirafian S, Atapour A, Moeinzadeh F, Golpayegani J. Empagliflozin decreased proteinuria in patients with glomerulonephritis without diabetes: A randomized clinical trial. *Turk J Nephrol.* 2025;34(4):272-280.

INTRODUCTION

Glomerulonephritis is a kind of kidney disease, characterized by inflammation of glomeruli or small blood vessels in the kidneys, and may be with or without hematuria and proteinuria.[1] Recently, some researchers have indicated that sodium-glucose cotransporter 2 inhibitor (SGLT2i), as a new class of antidiabetic drugs, may reduce proteinuria in diabetic nephropathy patients by reducing podocyte apoptosis. In fact, SGLT2i can repair the damage of proximal tubular cells, reduce podocytes shedding by inhibiting kidney oxidative stress, and further relieve proteinuria.[1,2]

Some of SGLT2i drugs include canagliflozin, dapagliflozin, and empagliflozin (EMPA), which inhibit the SGLT2i transport pump in the kidney, increase the excretion of glucose in the urine, and reduce the serum glucose level.[3] Although the primary purpose of these drugs was to improve the control of blood sugar indicated by reducing glycosylated hemoglobin A1c (HbA1c) by 0.8-0.5%,[4] some additional benefits comprised weight loss,

blood pressure reduction, and decreased the length of hospitalization, and lower cardiovascular mortality rate.[5,6]

The mechanisms of kidney protection by SGLT2i are not yet fully understood; however, its beneficial effects on the kidney may be mediated by sodium excretion, which leads to systemic and intrarenal hemodynamic changes. In particular, SGLT2i increases the delivery of distal tubular sodium and chloride to the macula densa, which increases the tubuloglomerular feedback and causes arteriolar vasoconstriction. As a result, SGLT2i causes an acute decrease in intraglomerular pressure and estimated glomerular filtration rate (eGFR). This effect is particularly observed in patients with type II diabetes (T2DM) that do not exhibit hyper-filtration.[7,8]

Empagliflozin is hypothesized to reduce the risk of cardiovascular mortality, improve outcomes in septic patients, and decrease hospitalization for heart failure. Furthermore, findings suggest promising potential for reducing complications and mortality rates in patients with kidney damages as well.[5,9,10] Moreover, EMPA reduces the rate of eGFR decline, decreases the development of albuminuria, and reduces the rate of cardiovascular mortality in patients with albuminuria.[11] Besides, dapagliflozin has some effects on proteinuria in non-diabetic patients with chronic kidney disease. Although the mentioned effect was not significant, it has caused not only body weight loss but also an acute and reversible decrease in eGFR.[12,13]

As stated, it seems that additional clinical studies should be conducted to determine whether SGLT2i such as EMPA differ from other SGLT2is in its effect. Moreover, no studies have specifically evaluated the effect of EMPA on patients with glomerulonephritis. Therefore, the present study aimed at investigating the effect of EMPA on proteinuria in non-DM patients with glomerulonephritis during 2020-2024.

MATERIALS AND METHODS

Study Design

This study was a randomized double-blind clinical trial and was approved by the Ethics Committee of Isfahan University of Medical Sciences (Approval no: IR.MUI.MED.REC.1400.419; Date: 2021-09-01 and the Clinical Trial Code: IRCT20090127001598N6v).

MAIN POINTS

- The obtained results showed that the 3-month administration of EMPA with a low dosage (10 mg) had no adverse effects on the patients' hemodynamic parameters and blood factors.
- The obtained results indicated that EMPA administration slightly and non-significantly reduced eGFR.
- The obtained results revealed that EMPA administration significantly reduced proteinuria. Hence its prescription may be considered safe in this category of patients.

Setting and Participants

The sample size in each group was estimated to be 36 at the confidence level of 95%, the test power of 80%, and considering the results of previous studies[11] with regard to the SD values of eGFR in 2 groups with and without kidney problems treated with EMPA equal to 21 and 7.5, respectively, and the mean difference of 12.

The inclusion criteria in the study comprised patients over 18 years old, with a history of proteinuria and glomerulonephritis, and with eGFR ≥ 30 mL/min/1.73 m^2. The patients were excluded from the study and replaced with another sample in case of allergic reaction to EMPA drug, change of drug or drug dosage affecting proteinuria, decrease of patients' fasting blood sugar (FBS) from the normal range during the study, unwillingness to continue cooperation in the study, or failure to refer for further follow-ups. It should be noted that the diagnosis of glomerulonephritis was confirmed by a pathologist through kidney biopsy.

After obtaining written consent from eligible patients to enter the study, 72 patients with glomerulonephritis that referred to Nephrology Clinics in Isfahan during 2020-2024 were randomly selected. Then, the patients were divided into 2 groups of 36 using random allocation software.

Intervention

All patients continued their usual drugs including angiotensin-II receptor blockers (ARBs), calcineurin inhibitors (CNIs), etc. In addition, patients in the first group received EMPA 10 mg tablets (Gloripa®; Abidi Pharmaceutical Company, Tehran, Iran) daily for 3 months (EMPA group). The second group, as a control group, received placebo tablets from the same Pharmaceutical Company daily for 3 months. Furthermore, FBS and creatinine (Cr) were checked by the patients monthly to control hypoglycemia or the incidence of acute kidney injury (AKI).

Empagliflozin and placebo were provided by Prof. Abidi pharmaceutical company. It is worth mentioning that in order to comply with blinding conditions, matching placebo tablets, identical in color, shape, and prescription protocol to the active EMPA tablets, were prepared and given to the researcher. Therefore, the study employed double-blinding, and the data analyst also did not know the grouping categorization of the 2 groups.

Outcomes

At the beginning of the study, the patients' basic information such as age, gender, duration of glomerulonephritis, systolic blood pressure (SBP), diastolic blood pressure (DBP), and their clinical parameters including blood urea nitrogen (BUN), Cr, albumin (Alb), sodium (Na), potassium (K), FBS, HbA1c, triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol (Tch), alanine transaminase (ALT), aspartate transaminase (AST), 24-hour proteinuria, eGFR, 24-hour creatinine, and 24-hour urine volume were recorded.

After completing the treatment period (3 months), the patients' clinical parameters including SBP, DBP, BUN, Cr, Na, K, FBS, HbA1c, Alb, TG, HDL, LDL, Tch, ALT, AST, 24-hour proteinuria, eGFR, 24-hour Cr, and the 24-hour urine volume were recorded.

Data Analysis

At the level of descriptive statistics, indicators such as mean, SD, frequency, and frequency percentage were used. At the level of inferential statistics, chi-squared test was used to compare the frequency distribution of qualitative variables between 2 groups. Moreover, independent samples *t*-tests and univariate analysis (with control of the base value) were used to compare the mean of quantitative variables between 2 groups. Furthermore, paired *t*-tests were applied to compare the mean of the quantitative variables after the intervention, as compared to before the intervention. The significance level was considered less than .05 in all analyses. Data analysis was done using SPSS statics software version 25.

RESULTS

Six patients from the control group (3 patients due to vomiting, 3 patients due to skin rash) and 6 patients from the EMPA group (4 patients due to vomiting and 2 patients due to skin rash) were excluded from the study. Ultimately, 30 patients remained in the EMPA group and 30 in the control group for final analyses (Figure 1).

The EMPA group consisted of 15 (50%) men and 15 (50%) women with a mean age of 44.37 ± 11.21 years, while the control group comprised 20 (66.7%) men and 10 (33.3%) women with a mean age of 43.63 ± 10.69 years (*P*-value = .295 and .796, respectively). Moreover, the mean change weight after the intervention, compared to before the intervention, decreased in the EMPA group and increased in the control group (mean difference: −0.25 ± 1.56 kg vs. +0.10 ± 1.71 kg; *P*-value < .001) (Table 1).

Examination of laboratory factors also found that none of the blood factors including BUN, Cr, Alb, Na, K, FBS, HbA1c, TG, HDL, LDL, Tch, ALT, and AST showed a significant difference between the 2 groups, either before and 3 months after the intervention (*P* > .05). Moreover, these factors did not change significantly after the intervention, as compared to before the intervention (*P* > .05) (Table 2).

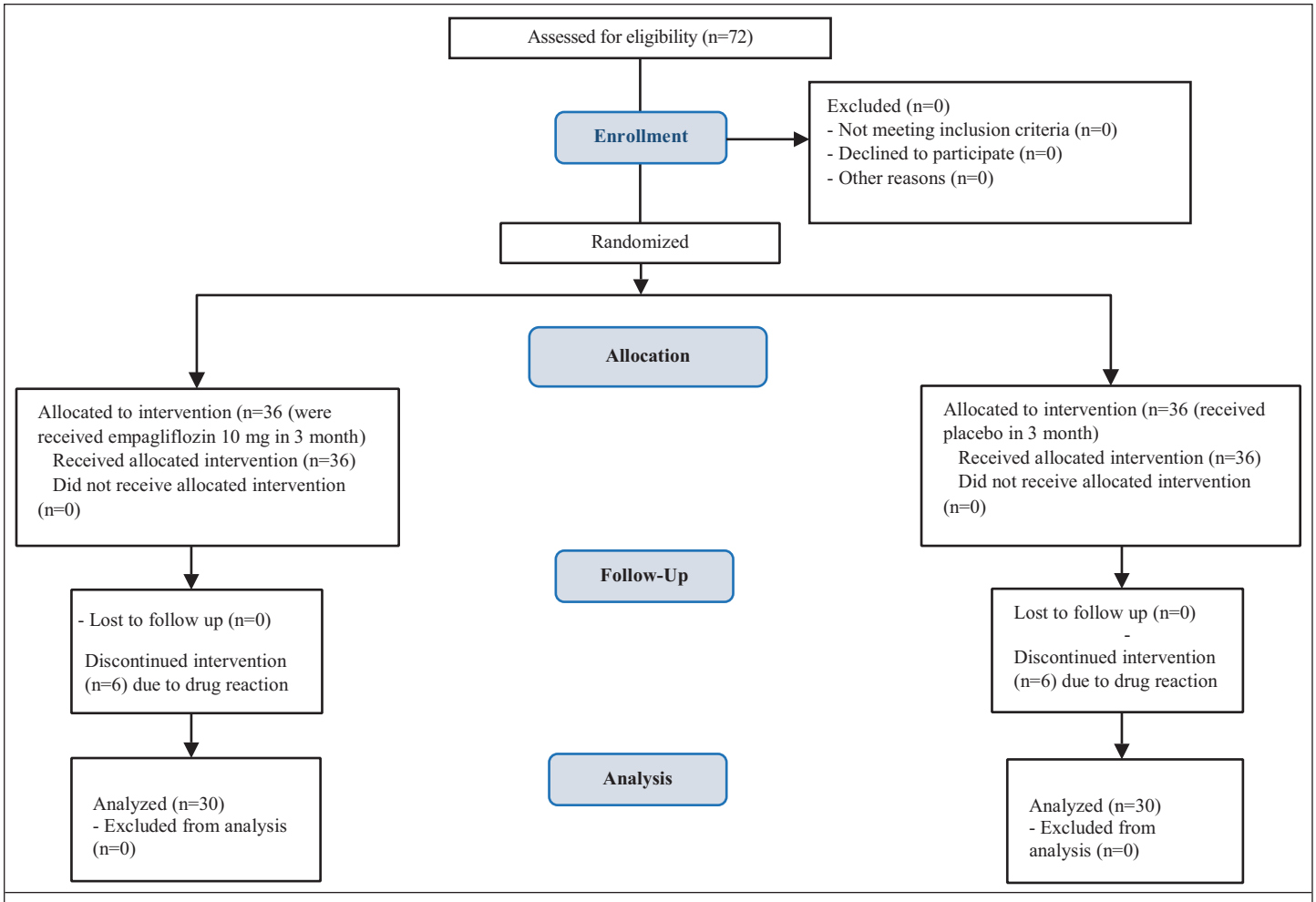


Figure 1. Consort flowchart of patients.

Table 1. Patients' Basic and Clinical Characteristics in the 2 Groups

Characteristics		EMPA Group (n = 30)	Control Group (n = 30)	*P*
Sex	Male	15 (50.0%)	20 (66.7%)	.295*
	Female	15 (50.0%)	10 (33.3%)	
Age±SD (years)		44.37 ± 11.21	43.63 ± 10.69	.796**
Duration of glomerulonephritis±SD (years)		8.05 ± 5.13	8.31 ± 4.80	.844**
Weight changes±SD (kg)		−0.25 ± 1.56	+0.10 ± 1.71	<.001**
Type of pathology	MGN	10 (33.3%)	11 (36.7%)	.143*
	MPGN	1 (3.3%)	0 (0%)	
	IgAN	7 (23.5%)	4 (13.3%)	
	FSGS	10 (33.3%)	11 (36.7%)	
	SLE	1 (3.3%)	3 (10%)	
	MCD	1 (3.3%)	1 (3.3%)	
SBP±SD (mmHg)	Baseline	82.17 ± 10.39	82.03 ± 8.50	.957**
	Third month	81.21 ± 7.63	80.26 ± 6.19	.614**
*P****		.445	.088	
DBP±SD (mmHg)	Baseline	82.17 ± 10.39	82.03 ± 8.50	.957**
	Third month	81.21 ± 7.63	80.26 ± 6.19	.614**
*P****		.610	.327	

DBP, diastolic blood pressure; EMPA, Empagliflozin; FSGS, focal segmental glomerulosclerosis; IgAN, immunoglobulin A nephropathy; MCD, minimal change disease MGN, membranous glomerulonephritis; MPGN, membranoproliferative glomerulonephritis; SBP, systolic blood pressure; SD, standart deviation; SLE, systemic lupus erythematous.
*The significance level obtained from the chi-square test comparing the 2 groups' distribution frequency of variables.
**The significance level obtained from the independent samples t-test comparing the 2 groups' mean of variables.
***The significance level obtained from the paired t-test comparing the mean of the variables after the intervention compared to before the intervention in each of 2 groups.

The eGFR in the EMPA (−2.72 mL/min/1.73m^2) and control (−1.89 mL/min/1.73m^2) groups decreased after the intervention, as compared to before the intervention, although this decrease was not statistically significant (*P* = .767). Proteinuria in the EMPA group was significantly lower after the intervention with a mean of 1326.73 ± 980.39 mg/24 h as compared to before the intervention with a mean of 1444.79 ± 897.18 mg/24h (Mean difference: −118.06 mg/24h; *P* = .008). However, proteinuria in the control group was significantly higher after the intervention with the mean of 1564.86 ± 380.13 mg/24h, as compared to before the intervention with the mean of 1331.17 ± 956.98 mg/24 h (mean difference: +233.69 mg/24 h; *P* = .003). Therefore, the level of proteinuria in the EMPA group was significantly lower than its level in the control group after 3 months (*P* = .022). Creatinine and 24-hour urine volume also increased insignificantly in both groups (*P* > .05), with no significant difference between the 2 groups (*P* > .05) (Table 3 and Figure 2).

DISCUSSION

The results of the present study conducted on 60 patients with glomerulonephritis revealed that none of the patients' laboratory factors and hemodynamic parameters had significant changes by prescribing EMPA for 3 months; however, the patients' weight decreased significantly during this prescription period.

In line with the results of the present study, Neeland et al[14] and Ridderstrale et al[15] have indicated that EMPA, as compared to placebo, significantly reduced body weight, waist circumference, and total and visceral adiposity indices in T2DM patients. Therefore, it seems to have promising potential for improving cardiometabolic risk in T2DM patients. In fact, this drug has diuretic effects, and SGLT-2i reduces blood sugar and body weight by inhibiting the absorption and transfer of glucose in the kidney.[16,17]

Furthermore, EMPA leads to the reduction of arterial stiffness, which is associated with the improvement of blood pressure control. Empagliflozin exerts a consistent weight loss, and which has been demonstrated to reduce blood pressure through various mechanisms including anti-inflammatory effects.[18,19] In the present study, the SBP and DBP slightly reduced, and finally the patients' hemodynamic stability was reported following 3 months of EMPA administration.

Besides, eGFR had a slight and non-significant decrease in both EMPA and control groups after the intervention. Creatinine and 24-hour urine volume also increased slightly

Table 2. Comparison of the Patients' Mean Laboratory Factors before and after the Intervention in the 2 Groups

Variables	Follow-up Time	EMPA Group (n = 30)	Control Group (n = 30)	*P*[1]
BUN (mg/dL)	Baseline	23.91 ± 11.67 20.00 [15.72-31.00]	22.42 ± 9.48 20.00 [16.05-28.00]	.593
	Third month	21.79 ± 10.31 21.00 [14.15-28.25]	21.62 ± 10.67 19.54 [11.97-29.92]	.951
P[2]		.100	.721	
Cr (mg/dL)	Baseline	1.25 ± 0.42 1.07 [0.97-1.55]	1.28 ± 0.42 1.19 [0.95-1.55]	.640
	Third month	1.27 ± 0.45 1.12 [0.95-1.43]	1.30 ± 0.47 1.20 [0.99-1.50]	.786
P[2]		.364	.956	
Na (mEq/L)	Baseline	139.22 ± 2.13 139.20 [137.75-140.77]	139.01 ± 4.42 138.75 [136.00-140.00]	.813
	Third month	140.10 ± 2.95 140.00 [138.00-142.25]	138.96 ± 2.29 138.90 [137.00-140.00]	.099
P[2]		.137	.956	
K (mmol/L)	Baseline	4.36 ± 0.59 4.30 [3.97-4.65]	4.33 ± 0.41 4.25 [3.99-4.62]	.845
	Third month	4.39 ± 0.50 4.30 [4.09-4.52]	4.34 ± 0.46 4.27 [3.97-4.72]	.699
P[2]		.640	.811	
FBS (mg/dL)	Baseline	94.57 ± 11.26 93.50 [85.00-101.75]	95.20 ± 13.23 96.00 [87.50-101.25]	.448
	Third month	93.00 ± 8.57 91.50 [86.75-98.25]	93.53 ± 15.62 89.50 [85.00-99.50]	.774
P[2]		.326	.346	
HbA1C (%)	Baseline	5.38 ± 0.46 5.20 [5.20-5.40]	5.37 ± 0.55 5.40 [5.13-5.65]	.938
	Third month	5.35 ± 0.59 5.15 [5.10-5.40]	5.36 ± 0.93 5.40 [5.10-5.90]	.188
P[2]		.727	.100	
Alb (g/dL)	Baseline	4.13 ± 0.55 4.20[3.80-4.52]	4.29 ± 0.42 4.40 [3.90-4.58]	.234
	Third month	4.12 ± 0.50 4.10 [3.80-4.47]	4.19 ± 0.35 4.30 [3.90-4.45]	.579
P[2]		0.954	0.145	
TG (mg/dL)	Baseline	155.62 ± 83.58 134.00 [93.50-190.00]	152.65 ± 50.59 127.00 [90.50-179.00]	.885
	Third month	149.03 ± 85.63 134.00 [85.00-183.00]	151.43 ± 99.29 140.5 [92.50-172.00]	.862
P[2]		.162	.986	
Tch (mg/dL)	Baseline	170.23 ± 51.99 163.00 [134.00-187.25]	156.86 ± 44.07 148.00 [137.50-173.00]	.292
	Third month	164.07 ± 42.95 163.00 [134.00-188.00]	156.10 ± 28.02 157.00 [140.50-174.00]	.406
P[2]		.244	.772	

(*Continued*)

Table 2. Comparison of the Patients' Mean Laboratory Factors before and after the Intervention in the 2 Groups (*Continued*)

Variables	Follow-up Time	EMPA Group (n = 30)	Control Group (n = 30)	*P*[1]
LDL (mg/dL)	Baseline	90.83 ± 37.84 85.50 [66.00-107.50]	80.74 ± 31.54 73.00 [57.00-101.25]	.287
	Third month	89.03 ± 31.92 89.50 [64.25-106.75]	78.68 ± 22.05 76.00 [65.50-94.50]	.154
P[2]		.696	.343	
HDL (mg/dL)	Baseline	48.80 ± 16.82 43.50 [35.77-63.00]	51.89 ± 15.15 50.00 [41.00-61.75]	.467
	Third month	45.89 ± 14.42 39.00 [35.00-58.00]	48.17 ± 11.68 48.50 [38.75-55.25]	.515
P[2]		.138	.169	
ALT (IU/L)	Baseline	26.40 ± 13.06 22.50 [17.75-34.25]	25.50 ± 13.64 21.00 [18.50-28.50]	.795
	Third month	25.60 ± 12.86 22.00 [14.75-34.00]	22.21 ± 8.72 20.00 [17.00-26.00]	.242
P[2]		.704	.232	
AST (IU/L)	Baseline	22.30 ± 8.96 18.00 [16.75-28.00]	23.30 ± 9.72 20.00 [17.75-26.25]	.680
	Third month	23.90 ± 9.68 22.00 [18.00-27.50]	19.76 ± 6.26 19.00 [15.50-22.00]	.057
P[2]		.281	.080	

Data shown mean ± SD and median [IQR]. Alb, albumin; ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; Cr, creatinine; EMPA, Empagliflozin; FBS, fasting blood sugar; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; K, potassium; LDL, low-density lipoprotein; Na, sodium; TG, triglyceride; Tch, total cholesterol.
[1]The significance level obtained from the independent samples t-test comparing the 2 groups' mean of variables in each of the follow-up times.
[2]The significance level obtained from the paired t-test comparing the mean of the variables after the intervention compared to before the intervention in each of the 2 groups.

and non-significantly in both groups. In contrast, the patients' proteinuria decreased significantly following the EMPA administration. The level of proteinuria in the EMPA group was significantly lower than that of the control group after 3 months.

Sodium glucose co-transporter 2 inhibitors may protect the kidney through mechanisms similar to hyperglycemia-dependent pathways, potentially benefiting proteinuria from various causes characterized by hyperfiltration (e.g., obesity-related chronic kidney disease (CKD), focal segmental glomerular (FSGS), immunoglobulin A nephropathy (IgAN)).[20] Clinical trials showed that SGLT2is like empagliflozin significantly reduced albumin–creatinine ratio and preserved eGFR while lowering kidney/cardiovascular mortality.[17,21] Some other studies have reported that SGLT2i either have no adverse effects on kidney function[3] or may exert non-protective effects.[22,23]

Large-scale clinical trials on SGLT2i have revealed that although initial eGFR decreases rapidly, eGFR improves in SGLT2i users after 192 weeks of follow-up.[6,17] Another study also revealed that the cumulative reduction of more than 40% in eGFR <60 mL/min/1.73 m^2 of body surface area, kidney disease progression, or death due to kidney or cardiovascular causes occurred less frequently with dapagliflozin use, as compared to placebo.[24]

In fact, EMPA reduces the rate of eGFR decline, the progress of albuminuria, and the rate of cardiovascular mortality in albuminuric individuals.[17] Considering these results obtained from the EMPAREG trial, the recommended drug regimen was modified in patients with T2D and established cardiovascular disease.[25]

In addition, a significant decrease in urinary albumin-to-creatinine ratio has been observed in SGLT2i-treated patients, as compared to control patients, especially those with CKD after a certain follow-up period.[21,24]

Cherney et al[18] demonstrated that SGLT2i dapagliflozin did not reduce proteinuria in non-DM CKD patients after 6 weeks, despite causing transient eGFR reduction and weight loss. Although the findings of the mentioned study were contrary to those of the current study, in which EMPA had a significant role in reducing proteinuria, it may be stated that the difference of the studied sample can be the source of this variation in findings. Moreover,

Table 3. Comparison of the Patients' Mean Kidney Factors before and after the Intervention in the 2 Groups

Variables	Follow-up Time	EMPA Group (n = 30)	Control Group (n = 30)	P^1
eGFR mL/min/1.73 m^2	Baseline	69.73 ± 22.89	70.45 ± 27.68	.922
	Third month	67.01 ± 21.71	68.56 ± 23.27	.809*
eGFR difference		−2.72 −4.00 [−11.20 ± 4.62]	−1.89 −2.00 [−6.92 ± 4.00]	.767
P^2		0.224	0.417	
Proteinuria mg/24 h	Baseline	1444.79 ± 897.18	1331.17 ± 956.98	.637
	Third month	1326.73 ± 980.39	1564.86 ± 380.13	.022*
Proteinuria difference		−118.06 −248.00 [−524.25 ± 162.25]	233.69 −223.00 [−789.00 ± 135.12]	.013
P^2		.008	.003	
Cr mg/24 h	Baseline	1155.23 ± 411.26	1080.07 ± 290.86	.600
	Third month	1397.23 ± 330.64	1214.14 ± 446.79	.754*
Cr difference		242.00 −67.00 [−285.00 ± 213.00]	134.07 −83.00 [−378.00 ± 209.00]	.261
P^2		.461	.055	
Urine volume mL/24 h	Baseline	1681.00 ± 693.31	1705.86 ± 642.09	.887
	Third month	1711.17 ± 758.17	1755.00 ± 620.39	.861*
Urine volume difference		30.17 100.00 [−275.00 ± 325.00]	49.14 0.00 [−285.00 ± 425.00]	.997
P^2		.786	.730	

Data shown mean ± SD or median [IQR]. Cr, creatinine; eGFR, estimated glomerular filtration rate; EMPA, Empagliflozin; IQR, interquartile range; SD, standard deviation.
[1]The significance level obtained from the independent samples *t*-test comparing the 2 groups' mean of variables in each of the follow-up times.
[2]The significance level obtained from the paired *t*-test comparing the mean of the variables after the intervention compared to before the intervention in each of the 2 groups.
*Univariate analysis test comparing variables after the intervention between 2 groups while controlling the baseline value, sex, age, duration of glomerulonephritis, and type of pathology.

EMPA, as compared to dapagliflozin, may have a different effect on proteinuria, which highlights the necessity of conducting further studies in this respect.

In line with the present study, Hammad et al[26] presented that the administration of 25 mg of EMPA once a day for 3 months as a supplement to the usual treatment protocol (RAAS blockers

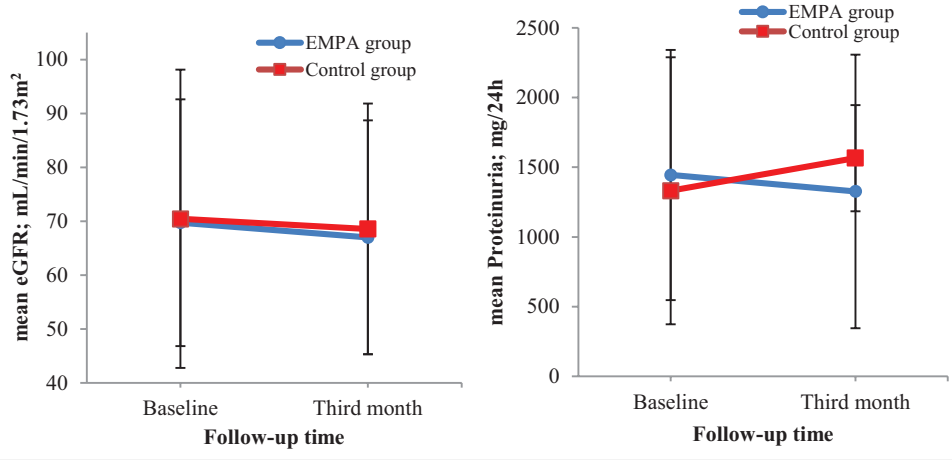


Figure 2. Changes in eGFR and proteinuria before and after the intervention in the 2 groups.

and immuno-suppressants) had a satisfactory effect on the improvement of proteinuria in patients with glomerulonephritis. Empagliflozin, as compared to placebo, has tended to preserve kidney function in patients with glomerulonephritis.[26]

Likewise, the results of another study have addressed the possible role of SGLT2i in reducing proteinuria and delaying the progression of chronic kidney disease in patients with nephrotic-range proteinuria.[27]

Some studies have reported very rare genital infections as well as urinary tract and asymptomatic bacteriuria after treatment with EMPA;[28,29] however, none of these complications were observed in the present study.

In addition to the small size of the sample, the lack of long-term follow-up can be considered as one of the other limitations of this study. Therefore, it is recommended to conduct further clinical trials with a larger sample size and a longer treatment duration evaluating the trend of changes in kidney and inflammatory factors, body weight, visceral fat, and waist size. In addition, the comparative evaluation of the effect of different doses of EMPA or the effect of different SGLT2i drugs on proteinuria as well as hemodynamic and metabolic stability of patients with various diabetic and non-diabetic diseases or type of pathology of glomerulonephritis such as (membranoproliferative glomerulonephritis (MPGN), IgAN, FSGS, systemic lupus erythematous (SLE), etc) can be fascinating.

CONCLUSION

According to the results of the present study, the 3-month administration of EMPA with a low dosage (10 mg) had no adverse effects on the patients' hemodynamic parameters and blood factors. Furthermore, the rate of decline in eGFR, and increase in Cr and urinary output was not significant, while it was associated with a significant decrease in proteinuria in patients with glomerulonephritis. Therefore, in this patient population, prescribing this drug may be considered a safe therapeutic option for reducing selective proteinuria.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author, J.G. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Isfahan University of Medical Sciences (Approval no: IR.MUI.MED.REC.1400.419 Date: 01.09.2021).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer reviewed.

Author Contributions: Concept – J.G., S.T.; Design – J.G., S.T., M.M.; Supervision – J.G., S.T.; Resources – J.G., S.T.; Materials – J.G., S.T.; Data Collection and/or Processing – J.G., S.T., M.M.; Analysis and/or Interpretation – A.A., F.M., S.T.; Literature Search – J.G., S.T.; Writing Manuscript – J.G., S.T.; Critical Review – A.A., F.M., S.T.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. Ponticelli C, Glassock RJ, eds. *Treatment of Primary Glomerulonephritis*. Oxford University Press; 2019.
2. Tian Y, Chen XM, Liang XM, Wu XB, Yao CM. SGLT2 inhibitors attenuate nephrin loss and enhance TGF-β1 secretion in type 2 diabetes patients with albuminuria: a randomized clinical trial. *Sci Rep*. 2022;12(1):15695. [CrossRef]
3. Klimontov VV, Korbut AI, Taskaeva IS, et al. Empagliflozin alleviates podocytopathy and enhances glomerular nephrin expression in db/db diabetic mice. *World J Diabetes*. 2020;11(12):596-610. [CrossRef]
4. Mikhail N. Place of sodium-glucose co-transporter type 2 inhibitors for treatment of type 2 diabetes. *World J Diabetes*. 2014;5(6):854-859. [CrossRef]
5. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117-2128. [CrossRef]
6. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644-657. [CrossRef]
7. Cherney DZI, Perkins BA, Soleymanlou N, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation*. 2014;129(5):587-597. [CrossRef]
8. van Bommel EJM, Muskiet MHA, van Baar MJB, et al. The renal hemodynamic effects of the SGLT2 inhibitor dapagliflozin are causedby post-glomerular vasodilatation rather than pre-glomerular vasoconstriction in metformin-treated patients with type 2 diabetes in the randomized, double-blind RED trial. *Kidney Int*. 2020;97(1):202-212. [CrossRef]
9. Maayah ZH, Ferdaoussi M, Takahara S, Dyck J. Empagliflozin suppresses inflammation and protects against acute septic renal injury. Inflammopharmacology. 2021;29(1):269- 79. [CrossRef]
10. Soni S, Dyck JRB. The multiple effects of SGLT2 inhibitors suggest potential benefit in COVID-19 patients. *Can J Cardiol*. 2020;36(10):1691.e3. [CrossRef]
11. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med*. 2016;375(4):323-334. [CrossRef]
12. Cherney DZI, Dekkers CCJ, Barbour SJ, et al. Effects of the SGLT2 inhibitor dapagliflozin on proteinuria in non-diabetic patients with chronic kidney disease (DIAMOND): a randomised double blind cross-over trial. *Lancet Diabetes Endocrinol*. 2020;8(7):582-593. [CrossRef]
13. Wanner C, Inzucchi SE, Zinman B, et al. Empa-Reg Outcome Investigators. Consistent effects of empagliflozin on cardiovascular and kidney outcomes irrespective of diabetic kidney disease categories: insights from the EMPA-REG Outcome trial. *Diabetes Obes Metab*. 2020;22(12):2335-2347. [CrossRef]
14. Neeland IJ, McGuire DK, Chilton R, et al. Empagliflozin reduces body weight and indices of adipose distribution in patients with

type 2 diabetes mellitus. *Diab Vasc Dis Res*. 2016;13(2):119-126. [CrossRef]
15. Ridderstråle M, Andersen KR, Zeller C, et al. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial. *Lancet Diabetes Endocrinol*. 2014;2(9):691-700. [CrossRef]
16. Sano H, Kudo E, Yamazaki T, Ito T, Hatakeyama K, Kawamura N. Efficacy of sodium-glucose cotransporter 2 inhibitor with glucagon-like peptide-1 receptor agonist for the glycemic control of a patient with Prader-Willi syndrome: a case report. *Clin Pediatr Endocrinol*. 2020;29(2):81-84. [CrossRef]
17. Farinha JB, Weinert LS, Costa LP, Costa MZ, de Peres PP, Lorea CF. Efficacy of empagliflozin for weight and glycemic control of a patient with Prader-Willi syndrome, systemic lymphedema and extreme obesity: a case report. *Int J Diabetes Dev Ctries*. 2022;42(4):787-790. [CrossRef]
18. Cherney DZI, Cooper ME, Tikkanen I, et al. Pooled analysis of Phase III trials indicate contrasting influences of renal function on blood pressure, body weight, and HbA1c reductions with empagliflozin. *Kidney Int*. 2018;93(1):231-244. [CrossRef]
19. Cherney DZ, Perkins BA, Soleymanlou N, et al. The effect of empagliflozin on arterial stiffness and heart rate variability in subjects with uncomplicated type 1 diabetes mellitus. *Cardiovasc Diabetol*. 2014;13:28. [CrossRef]
20. Cherney DZ, Odutayo A, Aronson R, Ezekowitz J, Parker JD. Sodium glucose cotransporter-2 inhibition and cardiorenal protection: JACC review topic of the week. *J Am Coll Cardiol*. 2019;74(20):2511-2524. [CrossRef]
21. Cherney DZI, Zinman B, Inzucchi SE, et al. Effects of empagliflozin on the urinary albumin-tocreatinine ratio in patients with type 2 diabetes and established cardiovascular disease: an exploratory analysis from the EMPA-REG OUTCOME randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2017;5(8):610-621. [CrossRef]
22. Škrtić M, Cherney DZI. Sodium-glucose cotransporter-2 inhibition and the potential for renal protection in diabetic nephropathy. *Curr Opin Nephrol Hypertens*. 2015;24(1):96-103. [CrossRef]
23. Andrianesis V, Glykofridi S, Doupis J. The renal effects of SGLT2 inhibitors and a mini-review of the literature. *Ther Adv Endocrinol Metab*. 2016;7(5-6):212-228. [CrossRef]
24. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2018;380(4):347-357.
25. Piepoli MF, Hoes AW, Agewall S, et al. European guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J*. 2016;37(29):2315-2381. [CrossRef]
26. Hammad H, Shaaban A, Philips MV, Fayed A, Abdelaziz TS. Effect of sodium–glucose transporter 2 inhibitor empagliflozin on proteinuria and kidney function progression in patients with non-diabetic glomerulonephritis: a pilot superiority randomized controlled trial. *Int Urol Nephrol*. 2023;55(9):2321-2326. [CrossRef]
27. Kalay Z, Sahin OE, Copur S, et al. SGLT-2 inhibitors in nephrotic-range proteinuria: emerging clinical evidence. *Clin Kidney J*. 2023;16(1):52-60. [CrossRef]
28. Jensen J, Omar M, Kistorp C, et al. Effects of empagliflozin on estimated extracellular volume, estimated plasma volume, and measured glomerular filtration rate in patients with heart failure (Empire HF Renal): a prespecified substudy of a double-blind, randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2021;9(2):106-116. [CrossRef]
29. Herrington WG, Preiss D, Haynes R, et al. The potential for improving cardio-renal outcomes by sodium-glucose co-transporter-2 inhibition in people with chronic kidney disease: a rationale for the EMPA-KIDNEY study. *Clin Kidney J*. 2018;11(6):749-761. [CrossRef]

10.5152/turkjnephrol.2025.251024

Original Article

Turkish Journal of Nephrology

Leptospirosis-Associated Acute Kidney Injury—Still a Major Burden in Tropical Countries?

Indhumathi Elayaperumal[1], Kevin T John Keeppallil[2], Nisha Jose[3], Jayakumar Matcha[4]

[1]Division of Nephrology, Saveetha Medical College, Chennai, India
[2]Division of Nephrology, Seha Kidney Care, Abu Dhabi, United Arab Emirates
[3]Department of Nephrology, Christian Medical College and Hospital, Vellore, India
[4]Department of Nephrology, Sri Ramachandra Institute of Higher Education and Research, Porur, India

ABSTRACT

Background: Leptospirosis is a common condition that affects people from the tropics. This disease is known to cause severe morbidity and mortality. Acute kidney injury (AKI) is commonly observed in leptospirosis patients. It was previously thought to occur only in severe forms of the disease, also known as Weil's disease. The current study was conducted to evaluate kidney involvement in leptospirosis in the era of early diagnosis and widespread antibiotic use.
Methods: A retrospective study was conducted over a period of 5 years, including all patients with a proven diagnosis of leptospirosis. The clinical characteristics and kidney involvement were noted in detail. Analysis was done to evaluate the frequency of complications and recovery characteristics of the patients with this disease.
Results: Acute kidney injury was common with leptospirosis and was present in 26.7% of patients; however, hypokalemia and other electrolyte abnormalities were seen only in 17.05% of the total patient population. There appears to be significant progression to chronic kidney disease (CKD) in patients with leptospirosis with 80% of patients who require dialysis during the AKI episode going on to varying stages of kidney failure in the future and 33.3% of patients requiring continuing KRT. Patients with AKI had an increased mortality compared to patients without AKI in leptospirosis.
Conclusion: Leptospirosis continues to be a significant contributor to mortality and morbidity even today. Abnormal electrolytes previously believed to be common in this disease, need not always be present. In view of a high rate of AKI to CKD transition, screening of all patients with AKI and leptospirosis may be recommended.
Keywords: Leptospirosis, acute kidney injury, progression to chronic kidney disease, hypokalemia, non-oliguric AKI

Corresponding authors: Indhumathi Elayaperumal and Nisha Jose ✉ drindhusrmc@yahoo.com or josenisha2000@gmail.com

Cite this article as: Elayaperumal I, Keeppallil KTJ, Jose N, Matcha J. Leptospirosis-associated AKI—still a major burden in tropical countries?. *Turk J Nephrol.* 2025;34(4):281-288.

INTRODUCTION

Leptospirosis is an important zoonotic disease that occurs worldwide and is more common in warm and humid environments. Humans with occupational exposure to animals such as sewage workers, veterinarians, or those in contact with contaminated water from infected animal urine during floods following heavy rainfall are at high risk for leptospirosis. Clinical manifestations vary from mild flu-like symptoms to acute severe illness with multiorgan dysfunction and associated mortality. A triad of fever, jaundice, and acute kidney injury (AKI) should raise the suspicion of leptospirosis.[1]

Acute kidney injury occurs in 40-87% of patients with leptospirosis. It can vary from mild pre-renal azotemia to severe dialysis requiring AKI in 10-60% of patients.[2] Acute interstitial nephritis is the most common kidney lesion observed in leptospirosis, with tubular dysfunction causing hypokalemia and hypomagnesemia. Acute kidney injury occurs either because of direct injury by the organism or indirectly via hypovolemia, hypotension, hyperbilirubinemia, endothelial injury, and rhabdomyolysis. Mortality from leptospirosis is high, occurring in up to 20% of patients, despite the widespread availability of antibiotics. Data on the risk factors

for the development of AKI and mortality in leptospirosis are scarce. Hence, the current study aimed to identify the prevalence, clinical presentation, risk factors associated with the development of AKI, immediate outcomes of AKI, and impact of various clinical and laboratory features on mortality in the current era of widespread antibiotic therapy.

MATERIAL AND METHODS

This retrospective observational study was conducted at a single tertiary care center in South India. All consecutive patients who were found to have a positive ELISA for leptospirosis and were admitted between January 2015 and November 2020 were included in the study. Data were collected using the hospital's electronic system. The study was approved by Sri Ramachandra Institutional Ethics Committee (Approval No: IEC-NI/21/FEB/77/51 Date: 08.03.2021). Patients with incomplete data and pediatric patients were excluded from the study. In view of the retrospective nature of the study, informed consent was not mandated by the ethics committee of the institution.

A total of 258 adult patients were included in this study. Patients were divided into two groups: those with AKI (group) and those without AKI (non-AKI group), based on the KDIGO (Kidney Disease: Improving Global Outcomes) definition of AKI. Sixty-nine (26.7%) and 189 (73.3%) patients were included in the AKI and non-AKI groups, respectively.

Demographic factors such as age, sex, duration of hospital stay, clinical data such as the presence of fever, myalgias, jaundice, oliguria, bleeding diathesis, altered sensorium, and conjunctival suffusion and laboratory data such as complete blood count, presence of leucocytosis, thrombocytopenia, BUN, creatinine, electrolytes, liver function tests, coagulation profile, creatine phosphokinase (CPK), requirement of dialysis, kidney recovery, and patient survival were collected. The presence of comorbidities, such as diabetes and hypertension, was also noted.

Statistical Analysis

Data analysis was performed using SPSS version 17 (SPSS Inc.; Chicago, IL, USA). All categorical variables are expressed as numbers and percentages, and continuous variables are expressed as mean ± SD. Values between the AKI and non-AKI groups, survivors, and non-survivors were compared using Student's *t*-test or the Mann–Whitney test, as appropriate. The chi-square test was used to compare the categorical variables. Univariate Cox regression analyses were performed, with mortality as the outcome variable. All statistical tests were performed two-tailed, and a significance level of *P*-value of <.05 was considered statistically significant.

MAIN POINTS

- Leptospirosis is still associated with significant organ involvements such as the kidney, lung, and liver.
- All patients with kidney involvement need not follow that typically described, such as with hypokalemia and hypomagnesemia.
- Acute kidney injury is seen in 26.7% of patients and is associated with poor long-term recovery of kidney function.
- It can lead to chronic kidney disease and long term requirement for dialysis.

RESULTS

After screening the hospital online database over a period of 5 years, 258 patients who met the inclusion criteria were identified. The baseline characteristics are listed in Table 1. The mean age of the study population was 44 ± 16.67 years. More men were noted in this study. Diabetes mellitus was also observed in 25.2% of patients (Table 1).

The mean liver enzymes and creatinine-phosphokinase (CPK) were elevated. The mean sodium level was low, while the mean potassium level was normal (Table 1). The most common laboratory abnormality was metabolic acidosis (51.2%), followed by liver enzyme abnormalities (39.1%) (Figure 1). Hypokalemia was noted in 17.1% of the patients.

Almost all the patients (98.4%) had fever, as shown in Figure 2. The second most common symptom among patients was gastrointestinal (GI) disturbances, such as nausea, diarrhea, and vomiting. Myalgia was noted in 23.6% of the patients. Oliguria and conjunctival suffusion were rarely noted in 6.2% and 0.15% of patients, respectively.

The most common organ involved in leptospirosis was the kidney, which was observed in 41% of all patients (Figure 3). Shock, central nervous system, and lung involvement were observed in less than 20% of patients. Multi-organ involvement was noted in 12% of the patients.

Acute kidney injury was present in 26.7% of patients (Table 2). Proteinuria was noted in 18.2% of the patients. Only 5.8% of the patients required KRT (kidney replacement therapy). Among those who required KRT, complete recovery (i.e., return to baseline kidney function or normal kidney function) was seen only in 20%; 33.3% of patients with AKI who were on KRT, required persistent KRT, while the remaining patients had varying degrees of persistent kidney dysfunction. The mean duration of hospital stay due to leptospirosis was 1 week. Most patients recovered (93.8%), with mortality in only 6.2% of patients (Table 1).

The entire study cohort was divided into two groups, AKI and non-AKI, to facilitate comparison. The mean age of the patients in the AKI group was higher than that in the non-AKI group ((52.01 ± 15.01 years vs 41.33 years ±16.10, *P* < .001) (Table 3). Diabetes mellitus (n = 29,42%, P < .001) and hypertension (n = 21, 30.4%; *P* < .001) were significantly associated with AKI.

Table 1. Baseline Characteristics of the Study Population

Characteristics	Frequency (percentage) or mean (SD), N = 258
Age, years	44.19 (2SD 16.67)
Male: Female	163 (63.2%): 95 (36.8%)
Diabetes mellitus	65 (25.2%)
Hypertension	36 (14%)
Baseline laboratory data	
Hemoglobin (g/dL)	11.48 ± 2.41
Total leucocyte count (cells/cu.mm)	9954.84 ± 5777.13
Platelet count (×10^5/μL" or "Lakhs/μL" (should be standardized))	1.93 ± 1.26
SGOT (U/L)	119.60 ± 295.79
SGPT (U/L)	87.95 ± 251.24
Total bilirubin (mg/dL)	2.09 ± 3.44
CPK (mcg/L)	1014.20 ± 2223.22
Serum creatinine (mg/dL) (Admission)	1.35 ± 1.36
Serum creatinine (mg/dL) (Peak)	1.63 ± 1.73
Serum creatinine (mg/dL) (Discharge)	1.17 ± 1.11
Serum sodium (mEq/L)	133.87 ± 5.59
Serum potassium (mEq/L)	3.97 ± 0.66
Serum bicarbonate (mEq/L)	21.25 ± 4.00
Serum calcium (mg/dL)	8.22 ± 1.00
Serum magnesium (mg/dL)	1.79 ± 0.51
Prothrombin time (seconds)	14.85 ± 4.04
Activated partial thromboplastin time (seconds)	31.45 ± 10.96
International normalized ratio	1.25 ± 0.41
Outcome variables	
Recovered from leptospirosis	242 (93.8%)
Duration of hospital stay, days	7.43 (2SD6.94)
Death from leptospirosis	16 (6.2%)

SD, standart deviation.

Leucocytosis (n = 35, 50.7%; $P < .009$), hyperbilirubinemia (n = 22, 31.8%; $P < .005$), coagulation profile abnormalities, proteinuria, hypotension, and bleeding diathesis were more common in the AKI group. The AKI group had a greater number of patients with rhabdomyolysis than the non-AKI group ($P < .01$). Patients with multi-organ dysfunction (n = 17, 24.6%, $P < .001$), requiring mechanical ventilation (n = 13, 18.8%, $P < .001$), and inotropic support (n = 21, 30.4%, $P < .001$) seemed to develop AKI more frequently than patients without these conditions. Central nervous system involvement was more common in the AKI group (n = 9, 13%; $P < .005$). Hospital stay was more prolonged in patients with AKI than without AKI (10.32 ± 10.17 vs. 6.37± 4.93 days, $P < .001$). Mortality was more common among patients with AKI (n = 13, 18.8%; $P < .001$) (Figure 4).

DISCUSSION

Leptospirosis is a common condition that affects people from endemic regions. These regions are generally hot and humid, such as sub-Saharan Africa, India, Malaysia, the Caribbean, and South-east Asia.[3] Disease morbidity due to leptospirosis is very high resulting in 102,000 years lived with living with disability and 2.8 million years of life lost due to the disease.[4] Kidney involvement in leptospirosis is seen in 10-60% of patients.[2] Kidney disease occurs in various forms in leptospirosis, ranging from acute tubular necrosis to tubule-interstitial nephritis, and later progression to chronic kidney disease (CKD). The current study shows the type of renal involvement and current mortality rate in leptospirosis in an endemic region.

Clinical Characteristics of Leptospirosis

As in this study and worldwide, males have been more affected by this disease than females. The reasons contributing to this appear to be exposure-related (at workplaces such as walking through paddy fields or sewer water) and behavioral (associated with perceived severity of the disease).[5] This is also the same reason why the age group most affected by this disease is 10-39 years.[6] In this study, the mean age of patients affected by leptospirosis was 44.19 years. Fever was the most common manifestation of leptospirosis observed in this study. This is a common finding corroborated by several other cohorts worldwide where leptospirosis is endemic. Fever is usually accompanied by severe myalgia, back and calf pain. This was also a common finding in this cohort of patients, where myalgia was noted in 23.6% of the patients. In other cohorts, bleeding manifestations were commonly recorded in leptospirosis[7] however, in this study, bleeding manifestations were uncommon in only 2.7% of patients. Abnormal platelet counts were observed in 25.2% of patients, while abnormal bleeding tests were noted in 7% of patients. The reason for this is not certain; it may be due to an early presentation to the hospital and early initiation of treatment. Jaundice was noted in 6.9% of the patients and was associated with multi-organ involvement. In other studies, liver involvement generally varied widely between less than 20% and >80%.[8]

Kidney Involvement in Leptospirosis

The most common organ affected in this study was the kidney, which was affected to varying degrees in 39% of the patients. In leptospirosis from the tropics, the kidney is the primary organ affected, with involvement varying from between 40% and 60% of cases.[9] In known leptospirosis data, the triad of fever and liver and kidney involvement points to a diagnosis of leptospirosis. The Leptospira outer membrane protein (OMP) triggers inflammation and injury via TLR receptor (toll-like receptor) proteins.[10] This results in tubulointerstitial involvement during the early stages, which can later progress to interstitial fibrosis. Other indirect kidney insults, such as hypovolemia, hypoxemia, and

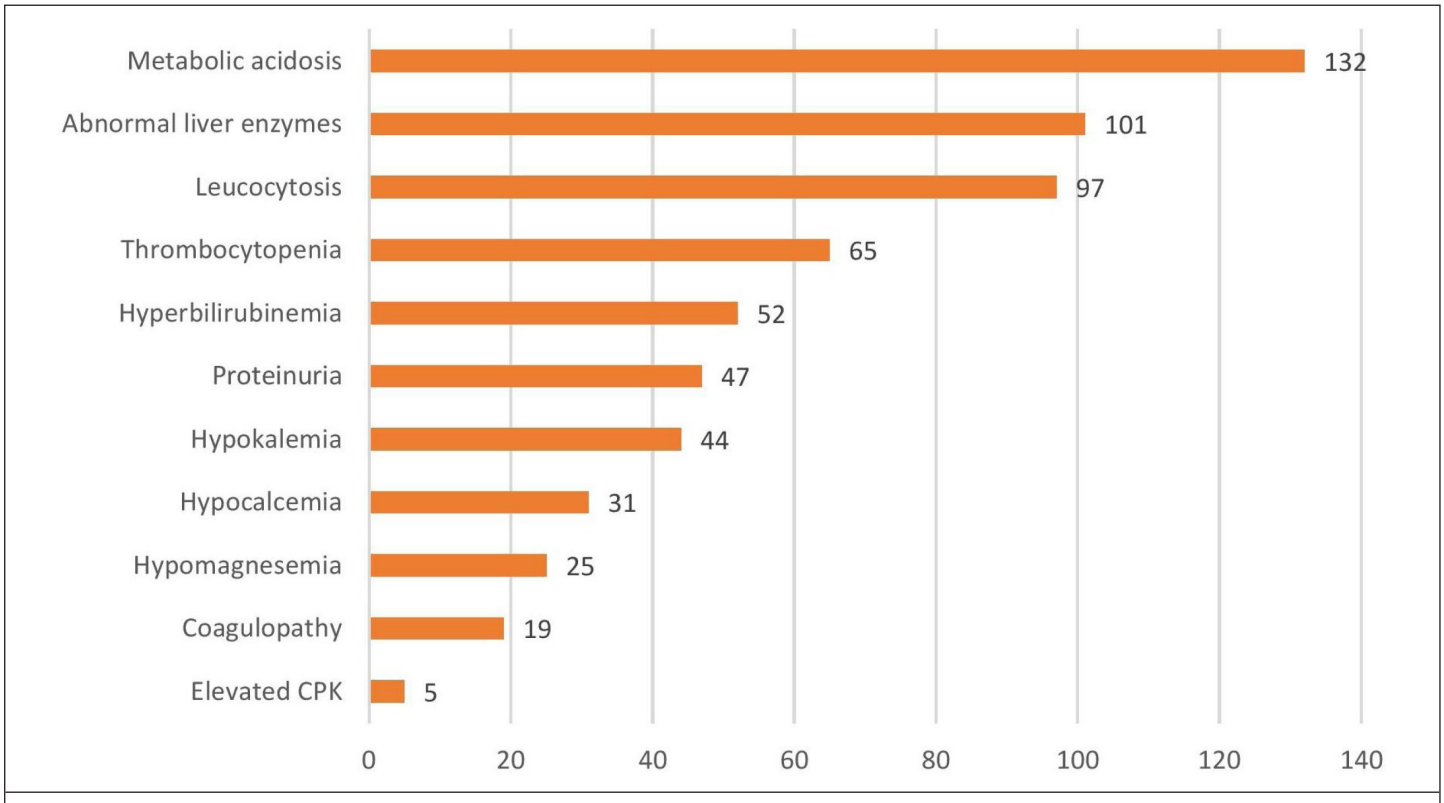


Figure 1. The frequency abnormal laboratory values in leptospirosis.

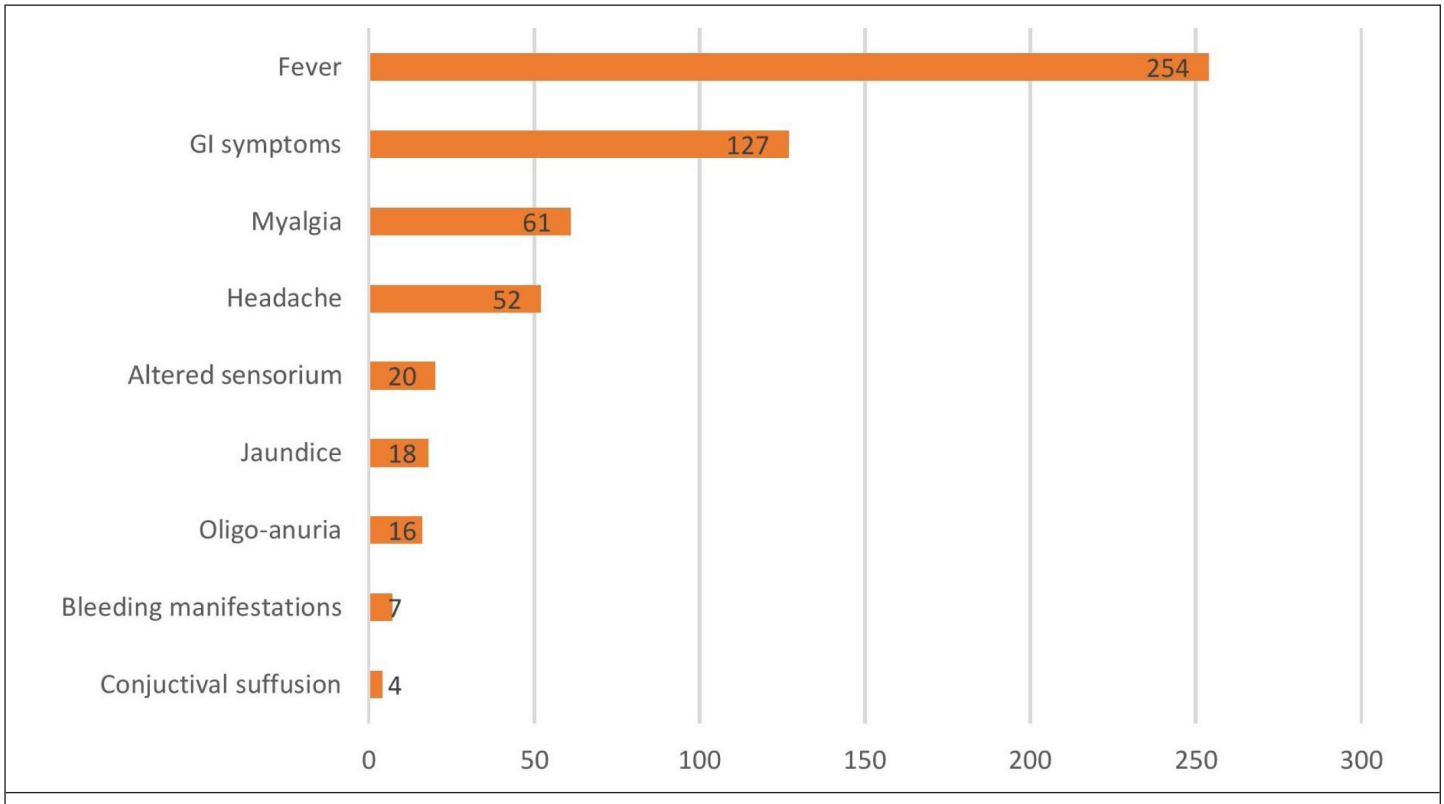


Figure 2. The frequency of clinical characteristics in leptospirosis.

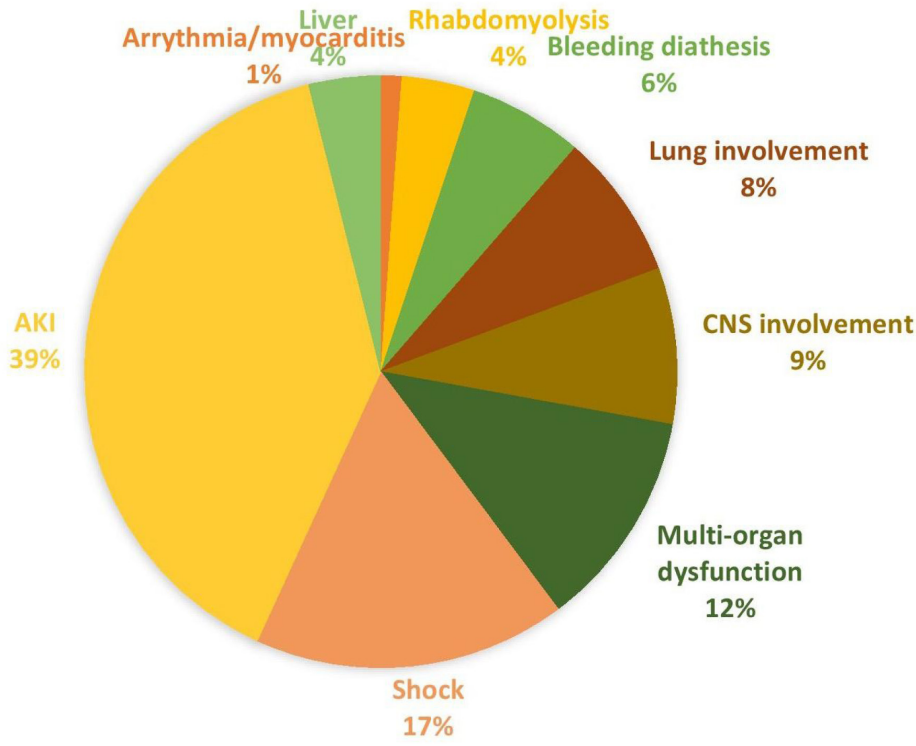


Figure 3. The frequency of organ involvement in leptospirosis.

rhabdomyolysis, also contribute to AKI.[11] The pathognomonic type of kidney involvement in leptospirosis is a non-oliguric AKI with hypokalemia.[12] In fact, certain serovars of leptospirosis are known to cause polyuria due to their effect on the NKCC2 (Na^+-K^+-Cl^- co-transporter) channel in the TAL (thick ascending limb) segment of the loop of Henle.[13] In keeping with data from abroad, in this study, oligo-anuria was uncommon, seen in only 6.2% of patients, and hypokalemia was noted in 17.08% of patients. Among those with AKI only a small proportion—5.8%, required KRT. About one-third of patients who required KRT remained dialysis-dependent after the infection was cleared. This is probably due to interstitial fibrosis and inflammatory pathways triggered by Leptospira. Originally, it was thought that only Weil's disease would have severe AKI requiring dialysis; however, this study adds to the growing body of evidence that even anicteric leptospirosis (a milder form of leptospirosis without major end-organ involvement) can often trigger severe AKI[14] since very few patients in this cohort had jaundice.

Table 2. Characteristics of Kidney Involvement in Leptospirosis

Variables	Frequency (percentage)
AKI present	69 (26.7%)
Stage of AKI	
AKI stage 1	30 (11.6%)
AKI stage 2	21 (8.1%)
AKI stage 3	18 (7.0%)
Proteinuria more than 1+ urine analysis	47 (18.2%)
Kidney replacement therapy (KRT)	
KRT required	15 (5.8%)
SLED	4 (1.6%)
CRRT	1 (0.4%)
IHD	10 (3.9%)
Kidney recovery after AKI	
No recovery	12 (80%)
Recovered	3 (20%)
Persistent KRT required	5 (33.3%)

AKI, acute kidney injury; CRRT, continuous renal replacement therapy; IHD, intermittent hemodialysis; KRT, Kidney replacement therapy; SLED, sustained low-efficiency dialysis.

Hypokalemia was previously thought to occur commonly in leptospirosis, often seen in 35-70% of patients with AKI;[15] however, in this cohort, it was observed in only 17% of patients with leptospirosis. Other electrolyte abnormalities known to occur in leptospirosis include hyponatremia, hypomagnesemia, hypophosphatemia, hypocupremia, hypozincemia, and hypocalcemia.[16] This is usually due to the increased urinary excretion of these compounds. Some of these also occur due to diarrheal illness, which may be part of leptospirosis. In the current study, other electrolytes were also found to be low in keeping with worldwide data; however, the frequency of these manifestations appears to be low (12% and 9.6% for hypocalcemia and hypomagnesemia, respectively).

Table 3. Association between Various Clinical and Laboratory Variables and Acute Kidney Injury

Parameters	AKI		*P*
	AKI GROUP (n, %) (69, ...%)	Non- AKI GROUP (n,%) (189, ...%)	
Age (years)	52.01 ± 15.78	41.33 ± 16.10	<.001
Age			.076
<65 years	55 (79.7%)	167 (88.3%)	
>65 years	14 (20.3%)	22 (11.6%)	
Gender			<.001
Male	60 (86.9%)	103 (54.4%)	
Female	9 (13.0%)	86 (45.5%)	
Diabetes mellitus	29 (42%)	36 (19%)	<.001
Hypertension	21 (30.4%)	15 (7.9%)	<.001
Fever	68 (98.5%)	186 (98.4%)	1.000
Jaundice	6 (8.6%)	12 (6.3%)	.5803
Conjunctival suffusion	3 (75.0%)	1 (25.0%)	.0583
Hemoglobin (g/dL)	10.67 ± 2.73	11.77 ± 2.21	<.001
Total leucocyte counts (/cu.mm)	13042.03 ± 7083.44	8827.78 ± 4764.58	<.00
Leukocytosis	35 (50.7%)	62 (32.8%)	.009
Platelet count (Lacs/cu.mm)	1.77 ± 1.46	1.99 ± 1.18	.052
Thrombocytopenia	23 (33.3%)	42 (24.8%)	.069
Hyperbilirubinemia	22 (31.8%)	30 (15.8%)	.005
Creatine phosphokinase	978.26 ± 1976.88	1051.77 ± 2501.82	.518
S. Creatinine (mg/dL) (Admission)	2.79 ± 1.97	0.83 ± 0.31	<.001
S. Creatinine (mg/dL) (Peak)	3.70 ± 2.26	0.87 ± 0.30	<.001
S. Creatinine (mg/dL) (Discharge)	2.34 ± 1.59	0.75 ± 0.27	<.001
Hypokalemia	15 (21.7%)	29 (15.3%)	.227
Metabolic acidosis	46 (66.6%)	86 (45.5%)	.003
PT (s)	15.77 ± 4.01	14.52 ± 4.01	<.001
aPTT (s)	35.16 ± 14.59	30.10 ± 8.96	<.001
INR	1.36 ± 0.45	1.22 ± 0.38	<.001
Coagulopathy	12 (17.4%)	7 (3.7%)	<.001
Proteinuria	35 (50.7%)	12 (6.3%)	<.001
Hypotension	21 (30.4%)	9 (4.7%)	<.001
Bleeding diathesis	9 (13%)	2 (1.05%)	<.001
Arrhythmias/myocarditis	1 (1.4%)	1 (0.5%)	.464
Rhabdomyolysis	5 (7.2%)	2 (1.05%)	.016
MODS	17 (24.6%)	4 (2.1%)	<.001
Mechanical ventilation	13 (18.8%)	6 (3.1%)	<.001
Inotropic support	21 (30.4%)	7 (3.7%)	<.001
Pulmonary manifestations	4 (0.5%)	10 (5.3%)	1.000
CNS involvement	9 (13%)	6 (3.1%)	.005
Length of hospital stay (days)	10.32 ± 10.17	6.37 ± 4.93	<.001
Mortality	13 (18.8%)	18 (9.5%)	<.001

AKI, acute kidney injury. PT, Prothrombin time, APTT, activated prothrombin time, INR, International normalised ratio, MODS, Multi-organ dysfunction syndrome, CNS, Central nervous system

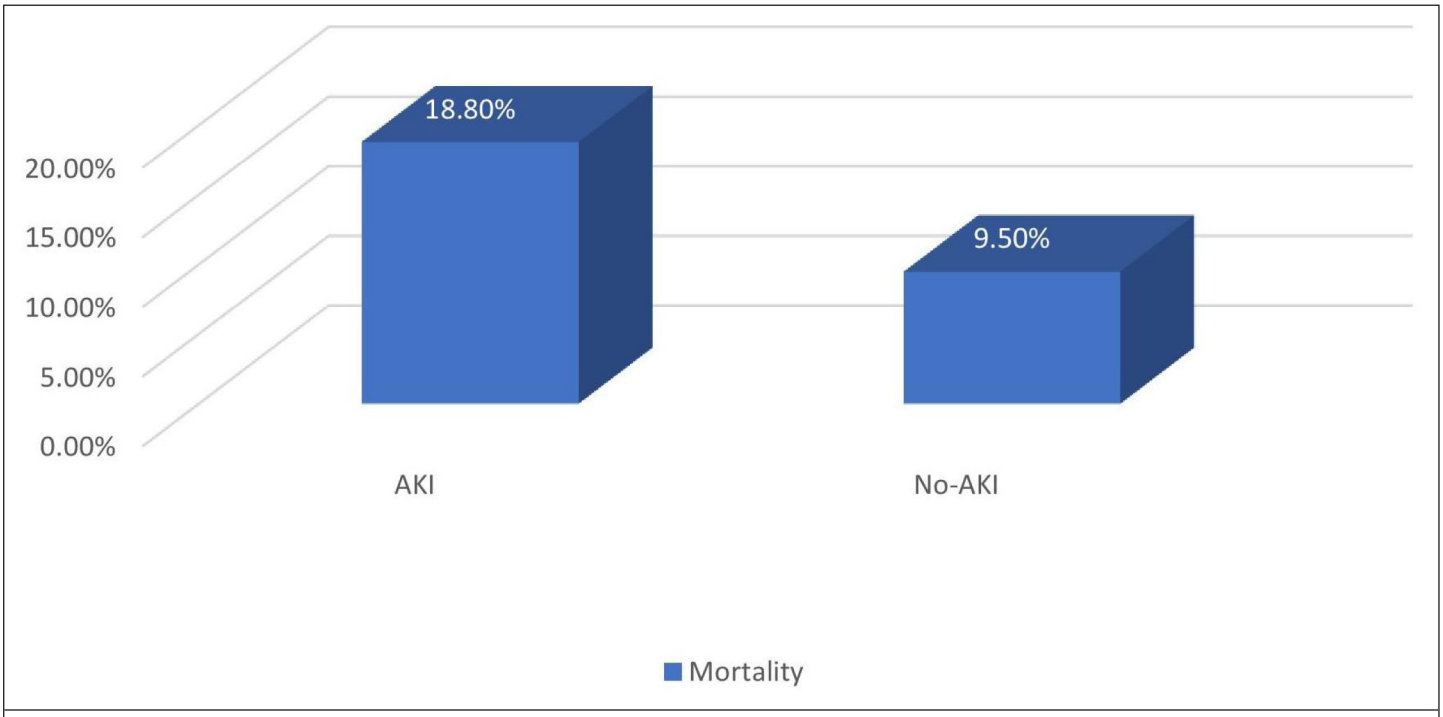


Figure 4. Comparison of mortality in patients with acute kidney injury vs. those without acute kidney injury.

Table 3 showed the association between various clinical risk factors and AKI development. As with other infections that trigger AKI, more severe disease in terms of multi-organ dysfunction, requirement of mechanical ventilation and inotropic support, and severe coagulopathy were significantly associated with the development of AKI. Pre-existing comorbidities such as diabetes seem to influence the development of AKI. One difference from other studies on AKI[17] is that myoglobinuria was not significantly associated with the development of AKI. The mean CPK level was also not very high in this cohort. Acute kidney injury is associated with increased mortality in most infections. Early KRT is believed to decrease mortality in patients with leptospirosis. This could not be proven in this cohort, because the timing of initiation was not recorded in most patient files. Figure 4 showed the difference in mortality between patients with AKI and those without AKI.

Kidney recovery is uncommon in patients with leptospirosis. Multiple studies have delineated pathogenic mechanisms that link the loss of nephrons due to AKI or trigger transcription molecules such as STAT-3 and profibrotic molecules to signal maladaptive repair within the kidney, leading to progression to CKD among those who survive AKI.[2]

The strength of this study was that it is one of the largest single-center studies on the epidemiology and clinical characteristics of leptospirosis in the Indian subcontinent. All significant factors associated with AKI were identified. The limitations of this study were its retrospective nature and single-center design.

Severe kidney involvement in leptospirosis occurs even in the absence of liver injury. Acute kidney injury is frequently non-oliguric. Hypokalemia may be seen even without overt AKI in leptospirosis and may not be as common in AKI as was previously believed. Kidney recovery was observed in only 20% of the patients with leptospirosis and AKI. Acute kidney injury is significantly associated with leptospirosis-related mortality.

Data Availability Statement: Research data supporting this publication is available within this manuscript.

Ethics Committee Approval: Ethical committee approval was received from Sri Ramachandra Institutional Ethics Committee (Approval No: IEC-NI/21/FEB/77/51 Date: 08.03.2021).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – I.E., K.J., J.M.; Design – I.E., K.J., N.J.; Supervision – I.E., J.M.; Resources – N.J., K.J.; Materials – K.J., N.J.; Data Collection and/or Processing – K.J., N.J., I.E.; Analysis and/or Interpretation – N.J., I.E., J.M.; Literature Search – N.J., K.J., I.E.; Writing Manuscript – I.E., N.J.; Critical Review – I.E., N.K., J.M.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. Ricaldi JN, Vinetz JM. Leptospirosis in the tropics and in travelers. *Curr Infect Dis Rep*. 2006;8(1):51-58. [CrossRef]
2. Chou LF, Yang HY, Hung CC, Tian YC, Hsu SH, Yang CW. Leptospirosis kidney disease: evolution from acute to chronic kidney disease. *Biomed J*. 2023;46(4):100595. [CrossRef]

3. Antima BS, Banerjee S. Modeling the dynamics of leptospirosis in India. *Sci Rep*. 2023;13(1):19791. [CrossRef]
4. Torgerson PR, Hagan JE, Costa F, et al. Global burden of leptospirosis: estimated in terms of disability adjusted life years. *PLoS Negl Trop Dis*. 2015;9(10):e0004122. [CrossRef]
5. Delight EA, de Carvalho Santiago DC, Palma FAG, et al. Gender differences in the perception of leptospirosis severity, behaviours, and Leptospira exposure risk in urban Brazil: a cross-sectional study. medRxiv. 2024;2024.04.28.24306445. Published 2024 Apr 30. [CrossRef]
6. Klement-Frutos E, Tarantola A, Gourinat AC, Floury L, Goarant C. Age-specific epidemiology of human leptospirosis in New Caledonia, 2006-2016. *PLoS One*. 2020;15(11):e0242886. [CrossRef]
7. Haake DA, Levett PN. Leptospirosis in humans. *Curr Top Microbiol Immunol*. 2015;387:65-97. [CrossRef]
8. Leptospirosis - an overview. *Sciencedirect Topics* [Internet]. Available at: https://www.sciencedirect.com/topics/nursing-and-health-professions/leptospirosis. Accessed March 24, 2025.
9. Sitprija V. Renal dysfunction in leptospirosis: a view from the tropics. *Nat Clin Pract Nephrol*. 2006;2(12):658-659. [CrossRef]
10. Yang CW. Leptospirosis renal disease: understanding the initiation by toll-like receptors. *Kidney Int*. 2007;72(8):918-925. [CrossRef]
11. *Asian Pacific Journal of Tropical Medicine* [Internet]. Available at: https://journals.lww.com/aptm/fulltext/2018/11100/acute_kidney_injury_in_leptospirosis__overview_and.1.aspx. Accessed March 24, 2025.
12. Andrade L, de Francesco Daher E, Seguro AC. Leptospiral nephropathy. *Semin Nephrol*. 2008;28(4):383-394. [CrossRef]
13. Lin CL, Wu MS, Yang CW, Huang CC. Leptospirosis associated with hypokalaemia and thick ascending limb dysfunction. *Nephrol Dial Transplant*. 1999;14(1):193-195. [CrossRef]
14. Hurst FP, Neff RT, Katz AR, et al. Acute kidney injury requiring hemodialysis in patients with anicteric leptospirosis. *Clin Nephrol*. 2009;72(3):186-192. [CrossRef]
15. Daher Ede F, de Abreu KL, da Silva Junior GB. Leptospirosis-associated acute kidney injury. *Braz J Nephrol*. 2010;32(4):400-407.
16. Sitprija V. Altered fluid, electrolyte and mineral status in tropical disease, with an emphasis on malaria and leptospirosis. *Nat Clin Pract Nephrol*. 2008;4(2):91-101. [CrossRef]
17. Osorio-Rodríguez E, Rodelo-Barrios D, Rebolledo-Maldonado C, et al. Acute kidney injury associated with severe leptospirosis: fatal re-emerging disease in Latin America. *Kidney Dial*. 2024;4(2):78-92.

10.5152/turkjnephrol.2025.251046

Original Article

Turkish Journal of Nephrology

Post-Earthquake Realities: A Study on the Challenges of Relocated Hemodialysis Patients Following the Kahramanmaraş Earthquake

Murat Tuğcu[1], Mustafa Keleş[2], Murat Duranay[3], Bülent Hüddam[4], Raziye Yazıcı[5], Yavuz Ayar[6], Fatma Betül Güzel[7],Zehra Eren[8], Sultan Özkurt[9], Ebru Gök Oğuz[10], Tuncay Şahutoğlu[11], İrem Pembegül[12], İdris Şahin[13], Zafer Ercan[14], Melike Betül Öğütmen[15], Rümeyza Kazancıoğlu[16], Zübeyde Serhan Tuğlular[1]

[1]Division of Nephrology, Department of Internal Medicine, Marmara University School of Medicine, İstanbul, Türkiye
[2]Department of Nephrology, Tarsus MMT American Hospital, Mersin, Türkiye
[3]Department of Nephrology, Ankara City Health Practice Research Center, Health Sciences University, Ankara, Türkiye
[4]Division of Nephrology, Department of Internal Medicine, Muğla Sıtkı Koçman University Faculty of Medicine, Muğla, Türkiye
[5]Division of Nephrology, Department of Internal Medicine, Konya Beyhekim Training and Research Hospital, Konya, Türkiye
[6]Division of Nephrology, Department of Internal Medicine, Bursa City Health Practice Research Center, Health Sciences University, Bursa, Türkiye
[7]Division of Nephrology, Department of Internal Medicine, Kahramanmaraş Sütçü İmam University Faculty of Medicine, Kahramanmaraş, Türkiye
[8]Division of Nephrology, Department of Internal Medicine, Alanya Training and Research Hospital, Alanya Alaaddin Keykubat University, Antalya, Türkiye
[9]Division of Nephrology, Department of Internal Medicine, Eskişehir Osmangazi University Faculty of Medicine, Eskişehir, Türkiye
[10]Division of Nephrology, Department of Internal Medicine, Dışkapı Yıldırım Beyazıt Education and Research Hospital, University of Health Sciences, Ankara, Türkiye
[11]Division of Nephrology, Department of Internal Medicine, Mehmet Akif İnan Training and Research Hospital, Şanlıurfa, Türkiye
[12]Division of Nephrology, Department of Internal Medicine, Malatya Training and Research Hospital, Turgut Özal University, Malatya, Türkiye
[13]Division of Nephrology, Department of Internal Medicine, İnönü University Faculty of Medicine, Malatya, Türkiye
[14]Division of Nephrology, Department of Internal Medicine, Sakarya University Faculty of Medicine, Sakarya, Türkiye
[15]Division of Nephrology, Department of Internal Medicine, Haydarpasa Numune Training and Research Hospital, University of Health Sciences, İstanbul, Türkiye
[16]Division of Nephrology, Department of Internal Medicine, Bezmialem Vakif University Faculty of Medicine, İstanbul, Türkiye

ABSTRACT

Background: In February 2023, Türkiye experienced 2 significant earthquakes, measuring 7.4 and 7.3 on the Richter scale and impacting 11 provinces. This study was performed to investigate the experiences of patients undergoing hemodialysis treatment in earthquake-affected areas who were relocated to alternative centers, with a focus on assessing the medical challenges that emerged thereafter.

Methods: This study included 181 hemodialysis patients (71 females, 110 males) from 11 earthquake-affected provinces who were transferred to different dialysis centers because of infrastructure and superstructure damage at their original treatment facilities.

Results: The predominant reason for relocation was damage to personal residences, reported by 77.4% of patients. Notably, 59.4% resumed hemodialysis with a delay of at least 1 day. Emergency complications were observed in 24.6% of patients, with hypervolemia (11.7%) being the most common. At the time of reporting, 23.1% of patients continued treatment at the relocated centers, while 78.8% expressed intent to return to their original facilities. Importantly, only 1 patient was reported to have died during the study period, highlighting the overall resilience of this population.

Conclusion: Hemodialysis patients are particularly vulnerable to the impacts of earthquake-related disruptions. Dialysis centers in high-risk regions must adhere to construction standards that ensure operational resilience. Additionally, prioritizing the transfer and medical coordination of hemodialysis patients during disasters is essential to maintaining continuity of care and minimizing health risks.

Keywords: Disaster, earthquake, hemodialysis, dialysis

Corresponding author: Murat Tuğcu ✉ drmrttgc@hotmail.com **Received:** May 2, 2025 **Revision Requested:** May 22, 2025 **Last Revision Received:** July 4, 2025 **Accepted:** July 8, 2025 **Publication Date:** October 1, 2025

Cite this article as: Tuğcu M, Keleş M, Duranay M, et al. Post-earthquake realities: A study on the challenges of relocated hemodialysis patients following the Kahramanmaraş earthquake. *Turk J Nephrol.* 2025;34(4):289-296.

INTRODUCTION

Major disasters—both natural and man-made—have devastating effects that disrupt every aspect of life, with particularly severe consequences for individuals with chronic illnesses requiring continuous treatment. Studies show that 25-40% of people in disaster-affected regions, such as those impacted by Hurricanes Katrina and Rita, have at least one chronic condition.[1] Among these, patients undergoing hemodialysis are especially vulnerable because of their dependence on specialized treatment centers and the risk of life-threatening complications if timely care is interrupted.[2] Natural disasters, such as Hurricane Katrina in 2005, have been shown to significantly disrupt dialysis schedules, with patients missing sessions at rates five to seven times higher than usual.[3] Such interruptions increase the risk of serious conditions—including hyperkalemia, hypervolemia, and metabolic acidosis—which can develop rapidly without regular access to dialysis.[4] Man-made disasters, such as armed conflicts, present similarly complex challenges for patients dependent on chronic hemodialysis because of infrastructure damage, transportation barriers, and disruptions in electricity and clean water supplies.[5]

On February 6, 2023, Türkiye experienced the devastating Pazarcık–Elbistan earthquake, measuring 7.4 and 7.3 on the Richter scale. Affecting 11 provinces, the disaster exemplifies the significant challenges healthcare systems face in the aftermath of such events. Official figures estimate that 14 013 196 people—16.4% of the national population—were affected, with more than 50 783 lives lost and more than 122 000 injured. The earthquake caused extensive infrastructure damage across 350 000 km^2, with more than 35 000 buildings destroyed, approximately 300 000 damaged, and more than 2 million households facing housing problems. The disaster also triggered more than 40 000 aftershocks, further compounding the impact and leading to the displacement of over 2 million individuals.[6]

Given the scale of disruption caused by disasters, understanding the extent to which hemodialysis treatments are affected is critical. The field of "disaster nephrology" has emerged in response to these challenges, offering strategies to mitigate the risks faced by patients requiring chronic kidney replacement therapy.[7] This study aims to examine the disruption of dialysis services for patients in the 11 provinces affected by the Pazarcık–Elbistan earthquake. Additionally, it explores the medical complications that arose during and after the transfer of hemodialysis patients to alternative treatment centers in the disaster's aftermath.

MAIN POINTS

- **Existing Knowledge:** In the context of an earthquake or other disaster, it's crucial to recognize that the continuity of dialysis treatment may be disrupted. Establishing emergency preparedness within the dialysis community is vital to ensure the uninterrupted provision of patient care. Factors such as power outages, damaged infrastructure, and impassable roads can pose significant challenges to relocating patients to alternative facilities.
- **Novel Contribution:** While there have been some studies addressing this issue, the number of investigations about the post-earthquake experiences of patients, particularly those undergoing displacement, remains limited. Given the authors' country's susceptibility to earthquakes, this research provides valuable insights that can guide the authors' preparedness efforts for future seismic events.
- **Potential Significance:** This study contributes to the evolving field of "disaster nephrology," furnishing practical guidance for healthcare professionals and disaster response teams. This knowledge can aid in better preparing for and supporting hemodialysis patients during critical periods, enhancing overall disaster response strategies.

MATERIAL AND METHODS

Study Design

This retrospective multicenter study aimed to explore the post-earthquake experiences of hemodialysis patients who survived the Pazarcık–Elbistan Earthquake, which occurred on February 6, 2023. The study included a cohort of hemodialysis patients from the 11 provinces affected by the disaster, who were later transferred to other dialysis centers.

Participants

The study population consisted of adult hemodialysis patients aged 18 years or older who were residing in the earthquake-affected region at the time of the disaster. These patients were receiving treatment at both public and private hemodialysis centers.

Data Collection

Data collection was conducted using a questionnaire initially developed for a study on hemodialysis patients displaced from Ukraine due to the Russia–Ukraine War.[8] This questionnaire was revised and adapted for use on Google Forms platform.[9] The modified version consisted of 26 questions, included an introductory page outlining the study methods for participants. The first section of the questionnaire gathered demographic data. The second section addressed the effects of the earthquake on patients and hemodialysis facilities, including trauma, electrical disruptions, and other related issues. The third section focused on how patients relocated to other cities. The fourth section examined medical problems, complications, emotional stress, and communication challenges. The fifth and final section included questions about the patients' current status at the receiving centers. Three months after the earthquake, the survey was distributed via email to all members

of the Turkish Society of Nephrology and the Association of Dialysis Physicians. It was administered to patients through medical staff in dialysis centers. A total of 18 dialysis centers from 12 different cities participated in the study. Marmara University School of Medicine Clinical Investigation Ethics Committee approved the research project under protocol number 09.2023.584.

Statistical Analyses

All analyses were performed using the Statistical Package for the Social Sciences for Windows, version 20.0 (IBM SPSS Corp.; Armonk, NY, USA). Descriptive statistics were calculated for all numeric variables, including means, medians, standard deviations, and minimum and maximum values, along with proportions for all categorical variables.

RESULTS

This study collected information on 181 hemodialysis patients who were transferred to 18 different dialysis centers across 12 cities. Data collection occurred between 107 and 491 days after the earthquake (average of 194 days). Among all patients, 39.2% were female, and their mean age was 58.9 ± 14.6 years. The mean dialysis vintage was 55.9 ± 19.6 months (Table 1).

In total, 37.6% of patients were transferred from Hatay to other centers, followed by 18.2% from Kahramanmaraş, and 14.9% from Malatya. Among the cohort, 6.1% had been trapped under rubble and were rescued after an average of 10.9 hours. Only 1 patient sustained life-threatening injuries, requiring amputation due to crush syndrome. Additionally, 77.4% of patients reported damage to their homes, while 42.1% noted damage to the dialysis centers where they received treatment after the earthquake. Furthermore, 29.8% of patients reported experiencing power and water outages (Table 2).

Table 1. Demographic and Clinic Data

Age (years SD)		58.9 ± 14.6
Gender (Female %)		39.2
Etiology of End Stage Kidney Disease (ESKD) (%)	Diabetes	36.9
	Hypertension	33.8
	Uropathies	5.6
	Polycystic kidney disease	5.6
	Glomerulonephritis	5
	Others	13.1
City (%)	Hatay	37.6
	Malatya	18.2
	Kahramanmaraş	14.9
	Gaziantep	13.8
	Adıyaman	7.2
	Others	8.3
Hemodialysis (HD) duration (months SD)		55.9 ± 19.6
HD sesion number (%)	3 per week	87.7
	2 per week	11.1
	>3 per week	1.2
Vascular access (%)	Arteriovenous fistula	74.4
	Permanent catheter	13.8
	Transient catheter	6.1
	Arteriovenous graft	1.8

SD, standart deviation.

Table 2. Questions About the Aftermath Earthquake

	Response	%	(n)
"Has the patient been trapped under rubble?"	Yes	6.1	161
	No	93.9	
"Did the patient sustain any injuries in the aftermath of the earthquake?"	Yes	13.3	111
	No	86.7	
"What was the reason for the patient's relocation from the dialysis center in the earthquake zone?"*	Home Damage	77.4	164
	Dialysis Center Damage	42.1	
	Power Outage	15.2	
	Water Shortage	14.6	
	Staff Shortage	6.7	
	Other Reasons	14.6	
"Did any issues occur with the patient's vascular access route aftermath earthquake?"	Yes	8.6	162
	No	91.4	

*Multiple-choice question.

Transportation to other centers was facilitated by relatives for 67.7% of the patients, and 68.6% began living in their relatives' homes. A total of 60.8% were transferred to dialysis centers located in the cities where their relatives resided. Following the earthquake, 40.6% of the patients did not miss a dialysis session, while 31.9% experienced delays of three or more days. Additionally, 8.6% of patients reported problems with vascular access during this period (Table 3).

A total of 62.3% of patients remained in contact with their primary treatment center. No emergency conditions were reported in 79.2% of patients at the centers to which they were transferred; the most common emergency condition was hypervolemia, occurring in 11.7% of patients. High dialysis session frequency was maintained for 97.5% of patients. Additionally, 63.7% of patients did not have any documentation detailing their previous treatments, and 48.4% did not have their medications with them at the time of transfer. However, 96.8% of patients reported no issues in obtaining their medications after relocation. Approximately 90% of patients indicated that their fluid intake and dietary compliance had not worsened compared with their pre-earthquake levels. Only 14.5% were receiving psychological support. Among those still receiving care at the transfer center, 23.1% intended to continue treatment there, while 78.8% planned to return to their primary center (Table 4).

DISCUSSION

Patients undergoing maintenance hemodialysis represent a particularly vulnerable population during seismic events such as earthquakes, where disruptions to infrastructure and healthcare systems pose significant challenges. In the cities affected by the February 2023 earthquake, there were approximately 8,000 hemodialysis patients, and it is estimated that approximately 1,000 were transferred to other centers due to the earthquake's impact. In this study, the authors' goal was to identify the challenges faced by patients undergoing maintenance hemodialysis who were required to relocate to different facilities, as well as to examine the clinical issues encountered during this process.

The intensity of a high-magnitude earthquake can lead to partial or complete destruction of medical facilities.[10] In this study, 42.2% of patients reported that their dialysis center was so incapacitated, it could no longer be used. Additionally, electricity and water supply systems are often disrupted following earthquakes;[11] in the authors' findings, 15.2% and 14.6% of patients experienced electricity and water outages, respectively, in the affected areas. These results highlight the critical importance of maintaining the functionality of dialysis facilities to ensure uninterrupted care for patients undergoing maintenance hemodialysis. Investments in earthquake-resistant infrastructure and the integration of backup power systems can significantly reduce disruptions caused by structural damage or power failures.[11] One of the most frequently reported reasons for dialysis units being inoperable was the toppling of water treatment tanks. In earthquake-prone areas, securing these systems may offer a simple yet effective solution.[12] Furthermore, strategically locating dialysis centers in regions less susceptible to seismic activity could improve overall resilience. In addition to facility damage, 77.4% of patients reported damage to their homes as a key reason for relocation. Recognizing the impact of home damage on patients' ability to transport essential medications is also crucial. Contingency plans should address the challenges patients face when their living environments are compromised.[13]

The prompt and secure relocation of patients undergoing maintenance hemodialysis to alternative treatment centers is a crucial element of earthquake preparedness. Planning, rescue coordination, and flexibility are essential for rapid, reliable,

Table 3. Question About Relocation Period

		%	Response (n)
"Why did the patient come to your unit?"	The city where their relatives live	60.8	158
	Referral by government	27.2	
	The nearest center	12	
"How did the patient reach your unit? Through which organizations?"	With relatives	67.7	158
	Ownself	15.8	
	Referral by government	12	
	Others	4.5	
"Where is the patient staying?"	With relatives	68.6	156
	Rent	25.6	
	Hostage	5.8	
	Hotel	0.6	
"Was there any communication or language barrier with the patient?"	Yes	6.3	160
	No	93.7	

Table 4. Questions About After Relocation

	Response	%	(n)
"Is the patient in contact with their own center?"	Yes	62.3	162
	No	37.7	
"How many days was the last dialysis session delayed?"	0	40.6	160
	1	10.6	
	2	19.6	
	3	14.4	
	4	5.6	
	5	6.3	
	>5	2.9	
"Was there a nephrological emergency when the patient arrived at your unit?"	Acidosis	1.3	154
	Hyperkalemia	0	
	Hypervolemia	11.7	
	Others	7.5	
	None	79.2	
"Has the number of dialysis sessions been reduced after the earthquake?"	Yes	2.5	162
	No	97.5	
"Did the patient have a medical report, including a dialysis prescription, when being admitted to your unit?"	Yes	36.3	157
	No	63.7	
"Did the patient have the medications when being admitted to your unit?"	Yes	51.6	155
	No	48.4	
"After being admitted to your unit, were there any issues with supplying the patient's medications?"	Yes	3.2	157
	No	96.8	
"How was the patient's diet compliance compared to before the earthquake?"	Very good	17.4	155
	Good	32.9	
	Medium	38.1	
	Bad	9	
	Very bad	2.6	
"Has the patient received or is the patient receiving psychological support?"	Yes	14.5	159
	No	85.5	
"Will the patient continue their dialysis treatment in your unit?"	Yes	23.1	160
	No	76.9	
"If not, where will the treatment continue?"*	Return to own center	78.8	118
	Another center in same city	11	
	To another city	10.2	

*Only those who answered no to the previous question answered.

and manageable patient transfers. This approach was successfully implemented during the L'Aquila earthquake in Italy (2009), where patients were moved to neighboring units and a provisional dialysis center was established.[2] Similarly, the positive outcomes following the New Zealand earthquake were attributed to well-coordinated efforts and established emergency planning guidelines.[14] In this study, when participants were asked about their means of transfer to other centers, 67.7% reported relying on relatives, 15.8% used their own transportation, and fewer than 15% were transferred via state-provided

transport. These findings highlight the need for well-defined protocols for patient relocation, including coordination with transportation services and neighboring healthcare facilities, to improve the efficiency of such transfers. Additionally, a majority of patients (68.6%) reported staying with their relatives. While the transfer process itself is essential, systematic planning for patient accomodation is equally important. From this perspective, pre-planning the use of guesthouses, school dormitories, or hotels could help meet the housing needs of patients who must relocate to another city after a disaster. It is also important to recognize that logistical challenges may make patient transfers impossible in some situations. In such cases, alternative treatment methods—such as peritoneal dialysis or portable hemodialysis machines—can be employed to provide life-sustaining care.[15,16]

Managing medical records and medications for patients transferred to other centers due to an earthquake is a significant challenge. Effective strategies are essential to ensure continuity of care and proper resource allocation during such disasters. Utilizing standardized patient encounter forms and centralized data collection points can streamline patient tracking and care coordination during emergencies.[17] Furthermore, the Health Information Services should have pre-planned strategies for retrieving and allocating medical records in disaster situations.[18] In this study, 63.7% of patients reported not having a medical report containing details of their treatment history or hemodialysis prescription. Additionally, 37.7% stated they were not in contact with their previous center. Fortunately, the authors' country has a national online database (E-Pulse system), which stores all patients' health data and is accessible to healthcare professionals with the individual's consent. This system enabled access to the necessary information regarding patients' treatment processes, ensuring the continuation of healthcare services without interruption. Remote management of hemodialysis patients has been shown to be both feasible and safe, supporting timely physician reviews and reducing the need for physical visits.[19] Telemedicine applications, which became more widespread during the coronavirus disease (COVID-19) pandemic,[20] have also emerged as important support tools in the aftermath of disasters. In fact, telemedicine has proven to be a vital means of maintaining continuity of care for hemodialysis patients by enabling remote consultations and monitoring—an approach that was especially critical during the COVID-19 pandemic, when access to physical healthcare facilities was significantly restricted.[21,22] Moreover, a telemedicine-based breastfeeding counseling program was implemented in disaster-affected regions following the earthquake in Türkiye on February 6, successfully addressing breastfeeding challenges.[23] Given the shortage of healthcare workers (including physicians) during earthquakes, these technologies allow professionals to remotely assess patients' conditions, provide guidance, and adjust treatment plans, thereby reducing the need for immediate physical transfers after seismic events.

Ensuring a consistent supply of medications and dialysis equipment is crucial for the well-being of patients undergoing maintenance hemodialysis. In this study, 48.4% of patients reported being unable to bring their medications with them during their transfer to another center. This issue can be partly attributed to the fact that 77.4% of patients had sustained damage to their homes. Understandably, in times of crisis, such details may be overlooked. Therefore, the establishment of robust contingency plans for securing and distributing essential supplies in the aftermath of earthquakes is imperative. Moreover, educating patients about emergency response plans is essential to help mitigate risks during natural disasters.[24] Encouragingly, 96.2% of patients reported no issues in obtaining medications after relocation. Immediate networking between dialysis units across Türkiye and coordination of needs through the previously established Renal Disaster Task Force of the Turkish Society of Nephrology played a key role in this positive outcome. Collaboration with pharmaceutical and medical supply companies to develop resilient supply chain strategies can help further prevent shortages during times of crisis.[25] Additionally, fostering a sense of community among patients promotes mutual support during difficult times. A collaborative approach involving healthcare professionals, emergency responders, and community stakeholders is essential to strengthen the overall resilience of patients.[25]

Additionally, the logistical challenges posed by disasters—including difficulty accessing treatment centers and missed dialysis sessions—contribute significantly to the elevated risk of medical complications.[26,27] In this study, 59.4% of patients missed at least one dialysis session, with 29.8% experiencing a lapse of three or more days in their dialysis schedule. The vulnerability of hemodialysis patients is heightened during seismic events, presenting a complex array of challenges. Disruptions in dialysis regimens due to earthquakes may lead to the accumulation of potassium, fluid overload, and acid–base imbalances, all of which carry serious risks for individuals with compromised renal function. Specifically, 11.7% of patients exhibited hypervolemia, and 1.3% experienced complications related to acidosis. Addressing the medical complexities of these conditions, along with developing strategies to reduce the impact of missed dialysis sessions, is essential for tailoring disaster-preparedness protocols to the specific needs of hemodialysis patients in earthquake-prone regions.[13] Furthermore, empowering maintenance hemodialysis patients with knowledge about earthquake preparedness is a proactive and effective strategy.[28] Providing educational resources on assembling emergency kits, understanding evacuation procedures, and recognizing early signs of medical distress equips patients to take an active role in safeguarding their health. Establishing networks for sharing best practices and lessons learned from previous seismic events can further strengthen preparedness and response efforts.[29,30] In addition, offering education and training for both healthcare providers and patients—through regular

drills and simulations—can improve familiarity with protocols and enhance performance under stressful conditions.[31]

The study has several limitations, including its retrospective design, potential recall bias, exclusion of some relocated patients, and the absence of an assessment of the long-term consequences of relocation. Despite these limitations, the study's strength lies in its ability to highlight the transfer processes and medical challenges faced by patients during the post-earthquake period, offering valuable insights and practical suggestions. With the anticipation of future earthquakes, the study's recommendations serve as a guide for strategic preparedness, promoting a tailored and rational approach to future planning.

In conclusion, safeguarding maintenance hemodialysis patients during earthquakes requires a comprehensive and multidimensional strategy. By addressing infrastructure vulnerabilities, refining patient transfer protocols, embracing telehealth solutions, ensuring a robust supply chain, promoting patient education, and fostering interdisciplinary collaboration, healthcare systems can more effectively manage the complexities of seismic events and protect the well-being of this vulnerable population. These findings underscore the importance of a thorough and adaptable approach to disaster preparedness in the context of hemodialysis care, taking into account the unique vulnerabilities and needs of patients in earthquake-prone regions.

Data Availability Statement: All relevant data was presented in the manuscript.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Marmara University School of Medicine (Approval No: 09.2023.584, Date: 05.09.2023).

Informed Consent: Informed consent was obtained from the participants who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.T., S.T., R.K. ; Design – M.T., S.T., R.K. ; Supervision – S.T., R.K.; Resources –M.T. ; Materials –M.T. ; Data Collection and/or Processing – M.T., M.K., M.D., B.H., R.Y., Y.A., F.B.D., Z.E., S.Ö., E.G.O., T.Ş., İ.P., İ.Ş., Z.E., M.B.Ö.; Analysis and/or Interpretation – M.T., S.T.; Literature Search – M.T.; Writing Manuscript – M.T., ST., R.K.; Critical Review – S.T., R.K.; Other – M.T., S.T.

Acknowledgments: The authors would like to thank all healthcare workers who have shown extraordinary dedication to the care and well-being of hemodialysis patients in the earthquake-affected region and other cities across the country.

Declaration of Interests: Rümeyza Kazancıoğlu is the Editor in Chief at Turkish Journal of Nephrology, and Zübeyde Serhan Tuğlular is a member of the Editorial Board at Turkish Journal of Nephrology; however, their involvement in the peer-review process was solely as authors. The other authors have no conflicts of interest to declare.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. Miller AC, Arquilla B. Chronic diseases and natural hazards: impact of disasters on diabetic, renal, and cardiac patients. *Prehosp Disaster Med*. 2008;23(2):185-194. [CrossRef]
2. Bonomini M, Stuard S, Dal Canton A. Dialysis practice and patient outcome in the aftermath of the earthquake at L'Aquila, Italy, April 2009. *Nephrol Dial Transplant*. 2011;26(8):2595-2603. [CrossRef]
3. Kopp JB, Ball LK, Cohen A, et al. Kidney patient care in disasters: lessons from the hurricanes and earthquake of 2005. *Clin J Am Soc Nephrol*. 2007;2(4):814-824. [CrossRef]
4. Obialo CI, Hunt WC, Bashir K, Zager PG. Relationship of missed and shortened hemodialysis treatments to hospitalization and mortality: observations from a US dialysis network. *Clin Kidney J*. 2012;5(4):315-319. [CrossRef]
5. Tuğlular S, Luyckx V, Vanholder R, et al. Lessons learned during the war in Ukraine: a report from the Renal Disaster Relief Task Force of the ERA. *Nephrol Dial Transplant*. 2023;38(9):1960-1968. [CrossRef]
6. *2023 Kahramanmaras and Hatay Earthquakes Report*. Ankara, Türkiye: Anatolian Agency; 2023. Available at: https://www.sbb.gov.tr/wp-content/uploads/2023/03/2023-Kahramanmaras-and-Hatay-Earthquakes-Report.pdf.
7. Eknoyan G. The Armenian earthquake of 1988: a milestone in the evolution of nephrology. *Adv Ren Replace Ther*. 2003;10(2):87-92. [CrossRef]
8. Pawłowicz-Szlarska E, Vanholder R, Sever MS, et al. Distribution, preparedness and management of Ukrainian adult refugees on dialysis-an international survey by the Renal Disaster Relief Task Force of the European Renal Association. *Nephrol Dial Transplant*. 2023;38(10):2407-2415. [CrossRef]
9. *Şubat 2023 Depremi ve Hemodiyaliz Anketi*. Available at: https://docs.google.com/forms/d/1NF8w6O6FY-_E0x3wP_LvMLocJwH5ItnNz-oksPQhaZY/edit.
10. Fukagawa M. Nephrology in earthquakes: sharing experiences and information. *Clin J Am Soc Nephrol*. 2007;2(4):803-808. [CrossRef]
11. Ishida K, Sawa M, Fujiwara K, et al. Study of electrical power facilities and measures for planned outages in Japanese hemodialysis clinics after the Great East Japan Earthquake. *Ther Apher Dial*. 2013;17(1):65-71. [CrossRef]
12. Ikegaya N, Seki G, Ohta N. How should disaster base hospitals prepare for dialysis therapy after earthquakes? Introduction of double water piping circuits provided by well water system. *BioMed Res Int*. 2016;2016:9647156. [CrossRef]
13. Bissell RA, Pinet L, Nelson M, Levy M. Evidence of the effectiveness of health sector preparedness in disaster response: the example of four earthquakes. *Fam Community Health*. 2004;27(3):193-203. [CrossRef]
14. Irvine J, Buttimore A, Eastwood D, Kendrick-Jones J. The Christchurch earthquake: dialysis experience and emergency planning. *Nephrology (Carlton)*. 2014;19(5):296-303. [CrossRef]
15. Tattersall JE, Richards NT, McCann M, Mathias T, Samson A, Johnson A. Acute haemodialysis during the Armenian earthquake disaster. *Injury*. 1990;21(1):25-29. [CrossRef]

16. Kimura K, Ogura M, Yokoyama K, Hosoya T. A reason for choosing peritoneal dialysis: lessons after the Japan earthquake and the Fukushima nuclear accident. *Am J Kidney Dis*. 2012;60(2):327. [CrossRef]
17. Leonard RB, Stringer LW, Alson R. Patient-data collection system used during medical operations after the 1994 San Fernando Valley-Northridge earthquake. *Prehosp Disaster Med*. [published correction appears in *Prehospital Disaster Med* 1996;11(1):80]. 1995;10(3):178-183. [CrossRef]
18. Smith E, Macdonald R. Managing health information during disasters. *Health Inf Manag*. 2006;35(2):8-13. [CrossRef]
19. Bernstein K, Zacharias J, Blanchard JF, Yu BN, Shaw SY. Model for equitable care and outcomes for remote full care hemodialysis units. *Clin J Am Soc Nephrol*. 2010;5(4):645-651. [CrossRef]
20. Shaver J. The state of telehealth before and after the COVID-19 pandemic. *Prim Care*. 2022;49(4):517-530. [CrossRef]
21. Haroon S, Voo TC, Chua H, Tan GL, Lau T. Telemedicine and haemodialysis care during the COVID-19 pandemic: an integrative review of patient safety, healthcare quality, ethics and the legal considerations in Singapore practice. *Int J Environ Res Public Health*. 2022;19(9):5445. [CrossRef]
22. Haroon S, Lau T, Tan GL, Davenport A. Telemedicine in the satellite dialysis unit: is it feasible and safe? *Front Med (Lausanne)*. 2021;8:634203. [CrossRef]
23. Basibuyuk M, Karabayir N, Celep G, et al. Telelactation support in emergency situations: experiences from the recent devastating earthquakes in turkey. *Cureus*. 2025;17(2):e79399. [CrossRef]
24. Yoo KD, Kim HJ, Kim Y, et al. Disaster preparedness for earthquakes in hemodialysis units in Gyeongju and Pohang, South Korea. *Kidney Res Clin Pract*. 2019;38(1):15-24. [CrossRef]
25. Sezer S, Tuglular S, Yildiz A. The day the earth shook. *J Nephrol*. 2023;36(3):599-600. [CrossRef]
26. Al Salmi I, Larkina M, Wang M, et al. Missed hemodialysis treatments: international variation, predictors, and outcomes in the dialysis outcomes and practice patterns study (DOPPS). *Am J Kidney Dis*. 2018;72(5):634-643. [CrossRef]
27. Anderson AH, Cohen AJ, Kutner NG, Kopp JB, Kimmel PL, Muntner P. Missed dialysis sessions and hospitalization in hemodialysis patients after Hurricane Katrina. *Kidney Int*. 2009;75(11):1202-1208. [CrossRef]
28. Sugisawa H, Shimizu Y, Kumagai T, Sugisaki H, Ohira S, Shinoda T. Earthquake preparedness among Japanese hemodialysis patients in prefectures heavily damaged by the 2011 great East Japan earthquake. *Ther Apher Dial*. 2017;21(4):334-344. [CrossRef]
29. Lameire N, Sever MS, Van Biesen W, Vanholder R. Role of the international and national renal organizations in natural disasters: strategies for renal rescue. *Semin Nephrol*. 2020;40(4):393-407. [CrossRef]
30. Sever MS, Luyckx V, Tonelli M, et al. Disasters and kidney care: pitfalls and solutions. *Nat Rev Nephrol*. 2023;19(10):672-686. [CrossRef]
31. Cartwright C, Hall M, Lee ACK. The changing health priorities of earthquake response and implications for preparedness: a scoping review. *Public Health*. 2017;150:60-70. [CrossRef]

10.5152/turkjnephrol.2025.251076

Original Article

Turkish Journal of Nephrology

Outcomes of Peritoneal Dialysis after Kidney Transplant Failure: A Single-Center Experience*

Gizem Kumru, Şayeste Akkan Eren, Şule Şengul, Kenan Ateş, Kenan Keven

Division of Nephrology, Ankara University Faculty of Medicine, Ankara, Turkiye

*The preliminary data of this study has been presented at 60th European Renal Association-European Dialysis and Transplant Association Milan & Virtual Congress (2023).

ABSTRACT

Objective: Despite advancements in graft survival, the kidney allograft failure is increasingly leading to the initiation of dialysis. While studies indicate no significant differences in survival among dialysis modalities, there are concerns about negative clinical outcomes associated with peritoneal dialysis (PD) in this population.

Methods: This retrospective study analyzed 19 patients who initiated PD following kidney transplant failure (PD-postTx) from January 2010 to June 2022, comparing them with 70 transplant-naive patients who began PD during the same time-frame (PD-noTx group). Acomparison of residual diuresis, episodes of peritonitis, time on PD therapy, and patient survival was performed between 2 groups.

Results: The PD-postTx group was younger and less likely to have diabetes than the PD-noTx group. Compared to PD-noTx patients, PD-postTx patients had more peritonitis episodes (35.7% vs. 68.4%, *P* = .011) and significant decline in urine volume at the end of the first year (*P* = .002). Residual kidney function (RKF) reduced the risk of peritonitis (OR 0.262, 95%CI 0.105-0.653; *P* = .040). -PD-postTx patients had a higher probability of transfer to hemodialysis. Three and 5-year PD survival were 81.7%, 65.4%, and 98.5%, 91.9% in PD-postTx and PD-noTx groups, respectively (*P* = .015). Multiple analysis showed a trend toward PD discontinuation in previously transplanted patients (HR 2.772, 95%CI 0.899-8.543; *P* = .076). Patient survival rates were comparable in both groups.

Conclusion: A prior history of transplantation poses a risk for PD discontinuation and peritonitis; but not for mortality in PD patients. The preservation of RKF may significantly contribute to the protection of peritonitis and the improvement of time on PD therapy.

Keywords: Kidney transplantation, peritoneal dialysis, peritoneal dialysis discontinuation, peritonitis, time on peritoneal dialysis, transplant failure

Corresponding author: Gizem Kumru ✉ gkumru@ankara.edu.tr **Received:** May 13, 2025 **Revision Requested:** June 19, 2025 **Last Revision Received:** June 23, 2025 **Accepted:** July 10, 2025 **Publication Date:** October 1, 2025

Cite this article as: Kumru G, Akkan Eren Ş, Şengul Ş, Ateş K, Keven K. Outcomes of peritoneal dialysis after kidney transplant failure: A single-center experience. *Turk J Nephrol.* 2025;34(4):297-303.

INTRODUCTION

Long-term kidney allograft survival has consistently improved over the decades.[1] However, with the rising total number of kidney transplants (KTx), the management of patients following KTx failure has become essential. In the United States, 11% of candidates waitlisted for transplantation had a prior transplant, while 10% of patients who received a transplant had a history of previous transplantation.[2] This underscores the significant burden of allograft failure in the end-stage kidney disease (ESKD) population. Preemptive transplantation is the optimal treatment for individuals with kidney failure; nonetheless, the proportion of transplants following failed allografts has declined over time.[3] Approximately, 1-2% of transplant recipients return to dialysis by the end of the first-year post-transplantation.[2,4] Therefore,

the optimal transition process, including modality counseling, should be managed with attention to transplant-related risk factors.

Kidney allograft failure leads to a 3-fold increase in mortality risk compared to patients who have a functioning transplant.[5] Nevertheless, overall patient survival rates are similar across different dialysis modalities following allograft failure.[6-8] Peritoneal dialysis (PD) is less favored compared to hemodialysis (HD) following KTx failure (3-18%).[6,7,9,10] However, evidence indicates that advanced age and comorbidities are the primary risk factors influencing outcomes, irrespective of the dialysis method employed.[7,10] Both dialysis methods provide comparable outcomes following KTx failure, making PD a viable option for these patients. Studies examining mortality, PD discontinuation, and peritonitis rates in PD patients with KTx failure vs. transplant-naive individuals have revealed inconsistent findings.[9,11-13] This study assessed outcomes in patients who initiated PD following KTx failure and those who are transplant naive, addressing the limited data available in the literature.

MATERIAL AND METHODS

Study Population

Patients who initiated PD at our center between January 2010 and June 2022 were evaluated retrospectively. The exclusion criteria included individuals under 18 years of age, those who had undergone PD for less than 6 months, patients who received more than 2 months of HD prior to PD, and individuals with a history of multiple organ transplants. Following the exclusion criteria, patients were categorized into 2 groups according to their prior KTx history: (1) 19 patients who initiated PD after kidney allograft loss (PD-postTx) and (2) 70 patients who had not received a KTx (PD-noTx).

Clinical and demographic data of patients, including age, gender, comorbidities, PD modality, and age at PD initiation, were collected from patient files. Diuresis volume was assessed based on 24-hour urine collection during the initial month of PD, at the end of the first year, and at the last follow-up visit. Loss of residual kidney function (RKF) was defined as anuria, marked by diuresis of less than 100 mL in 24 hours. The definition of immunosuppression included the prescription of prednisone at a dosage of 5 mg/day or higher and/or the administration of a calcineurin inhibitor or an antiproliferative agent. PD discontinuation was defined as transition to HD. PD–associated peritonitis was diagnosed when 2 or more of the following criteria were met: (1) consistent clinical features, (2) effluent white cell count exceeding 100/mm^3 with neutrophils comprising over 50% of the total cell count, and (3) positive effluent culture.[14] The clinical outcomes regarding diuresis volume, peritonitis, PD discontinuation, and mortality were documented until December 2024. The outcomes were evaluated by comparing patients in PD-postTx and PD-noTx groups.

The study protocol was approved by the Ethical Committee of Ankara University (Approval No: İ08-539-22, Date: 05.10.2022) and was conducted in accordance with the Declaration of Helsinki. Informed consent has not been obtained due to the retrospective design of the study.

Statistical Analysis

The variables are presented as the mean ± SD, median (minimum-maximum), or percentage (%). Comparisons between PD-postTx and PD-noTx were made using the paired student's *t*-test, Mann–Whitney *U* test, chi-square test, or Fisher's test as appropriate. Logistic regression was employed to analyze factors associated with episodes of peritonitis. Variables exhibiting a *P*-value less than .10 from univariate analyses were included as potential factors in the regression model. The final model was established using a forward stepwise elimination approach (Forward LR), with odds ratios (OR), 95% confidence intervals (CI), and Wald statistics calculated for each variable. Time on PD therapy was evaluated through Kaplan-Meier survival analysis, supplemented by the Log-Rank test. Univariate Cox analysis was employed to identify parameters affecting transfer to HD within the entire cohort. A multiple Cox regression analysis was performed to determine hazard ratios (HRs) for independent risk factors.

The statistical analysis utilized IBM Statistical Package for Social Sciences version 30.0 software (IBM SPSS Corp.; Armonk, NY, USA). A *P*-value below .05 is considered statistically significant.

MAIN POINTS

- Patients initiating PD following kidney transplant failure has an elevated risk of PD discontinuation and peritonitis relative to those without a transplantation history.
- Residual kidney function declines more rapidly in patients with a transplantation history and was predictive for peritonitis episodes irrespective of immunosuppression status.
- To achieve favorable outcomes in patients initiated PD after kidney allograft failure, complications, and comorbidities must be carefully managed and treatment must be tailored according to transplant-related factors.

RESULTS

Patient Characteristics

The demographic and clinical data of the 2 groups are presented in Table 1. The mean age at PD initiation was 47 years and patients at PD-postTx group were significantly younger (38.3 ± 12.4 vs. 48.9 ± 16.4, respectively; *P* = .004). In terms of gender, weight, PD mode, and the etiology of ESKD, the groups were comparable. Diabetes was more common in the PD-noTx group than in the PD-postTx group (5.3% vs. 28.6%, respectively; *P* = .060).

Table 1. Demographic and Clinical Data of Peritoneal Dialysis Patients, According to Transplantation Status

Parameters	PD-postTx (n = 19, 21.3%)	PD-noTx (n = 70, 78.7%)	*P*	Total (n = 89, 100.0%)
Female, n (%)gender	7 (36.8)	36 (51.4)	.259	43 (48.3)
Age, years	43.2 ± 12.6	52.7 ± 16.1	**.020**	52.6 ± 15.8
ESKD etiology, n (%)			.091	
Hypertension	5 (26.3)	21 (30.0)		22 (24.7)
Diabetic kidney disease	1 (5.3)	17 (24.3)		22 (24.7)
Glomerulonephritis	4 (21.1)	13 (18.6)		17 (19.1)
Unknown	4 (21.1)	8 (11.4)		12 (13.5)
Other	5 (26.3)	11 (15.7)		16 (18.0)
Diabetes mellitus	1 (5.3)	20 (28.6)	.060	21 (23.9)
Weight, kg	67.0 ± 14.0	71.2 ± 15.4	.305	70.3 ± 15.2
Immunosuppression, n (%)	10 (52.6)	2 (2.9)	**<.001**	12 (13.5)
PD characteristics				
Age at PD initiation, years	38.3 ± 12.4	48.9 ± 16.4	**.004**	46.6 ± 16.2
PD modality, n (%)			.052	
CAPD	15 (78.9)	38 (54.3)		53 (59.6)
APD	4 (21.1)	32 (45.7)		36 (40.4)
Initial diuresis, mL (n = 81)	1520.6 ± 1038.3	1622.8 ± 1032.3	.716	1602.6 ± 1028.2
First year diuresis, mL	293.7 ± 112.1	1108.9 ± 77.6	**<.001**	953.6 ± 685.8
First year PET, n (%)			**.046**	
Low (0.34-0.49)	0 (0.0)	15 (21.4)		15 (16.8)
Low average (0.50-0.64)	8 (42.1)	30 (42.9)		38 (42.7)
High average (0.65-0.80)	6 (31.6)	22 (31.4)		28 (31.5)
High (0.81-1.03)	5 (26.3)	3 (4.3)		8 (9.0)
Outcomes				
Time on PD therapy, months	60.0 (range:29-194)	63.0 (range:28-206)	.575	61.0 (28-206)
With residual kidney function, n (%)	4 (21.1)	52 (74.3)	**<.001**	56 (62.9)
Patients with peritonitis				
at least 1 episode	13 (68.4)	25 (35.7)	**.011**	38 (42.7)
≥2 episodes, n (%)	8 (42.1)	14 (20.0)	.070	22, (24.7)
Transfer to HD, n (%)	7 (36.8)	8 (11.4)	**.015**	15 (16.9)
Death, n (%)	5 (26.3)	17 (24.3)	1.000	22 (24.7)

The values are described as the mean ± SD, median (minimum-maximum) or number (%). Values appears in bold if *P*-value was significant (below .05). APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; ESKD, end stage kidney disease; HD, hemodialysis; kg, kilograms; PD, peritoneal dialysis; PET, peritoneal equilibration test; Tx, transplantation.

In PD-postTx group, the follow-up with a functioning graft was 117.4 ± 87.2 months. Four patients had undergone preemptive KTx and median dialysis vintage before KTx was 4.5 (0-132) months in PD-postTx group. Patients were transplanted at mean age of 28 years, 78.9% from living donor. Among the patients, 6 experienced biopsy-proven rejection, comprising 3 cases of T-cell–mediated rejection, 1 case of mixed rejection, 1 borderline rejection, and 1 case of chronic active T-cell–mediated rejection. Patients diagnosed with acute rejection (n = 5) and recurrent glomerulonephritis (n = 1) were administered additional immunosuppression, which includes anti-thymocyte globulin, steroids, and plasmapheresis based on their diagnosis; however, PD was initiated no sooner than 6 months following these interventions. The causes of graft loss in the cohort were chronic allograft nephropathy in 12 patients (63.2%), acute rejection in 4 patients (21.1%), chronic active rejection in 1 patient (5.3%), malignancy in 1 patient (5.3%), and recurrent glomerulonephritis in 1 patient (5.3%). The mean time on PD and total dialysis vintage was similar in PD-postTx and PD-noTx groups (*P* = .575 and *P* = .163, respectively). Five (26.3%) patients in the PD-postTx group administered 5 mg/day of prednisone after transplant failure, and 5 (26.3%) patients received prednisone plus a calcineurin inhibitor or azathioprine. Two patients (2.9%) in the PD-noTx group received 5 mg/day of prednisone

for extrarenal manifestations of sistemic lupus erythematosus and vasculitis.

Peritonitis and Other Complications

Peritonitis and other PD-associated complications, such as exit-site infection, tunnel infection, and catheter malfunction, were more common in PD-postTx group compared with PD-noTx group (73.7% vs. 37.1%, respectively; *P* = .039). Thirteen patients (68.4%) from the PD-postTx group encountered at least one episode of peritonitis, in contrast to 25 patients (35.7%) in the PD-noTx group (*P* = .011). The PD-postTx group exhibited a greater incidence of peritonitis than the PD-noTx group (0.33 vs. 0.13 episodes per patient per year, respectively). Among culture positive peritonitis episodes, the highest prevalence was *Staphylococcus aureus* (34.8%), followed by coagulase-negative *Staphylococcus* (13.0%), other gram-positive Cocci (21.7%), gram-negative Bacilli (26.2%), and fungi (4.3%). The evaluation of patients who experienced at least 1 episode of peritonitis revealed a higher prevalence among younger PD initiation (*P* = .033), individuals with no history of diabetes mellitus (*P* = .028), those with a longer PD duration (*P* = .018), patients with KTx history (*P* = .011), and among patients with no residual diuresis (*P* = .004). In the multivariate model, the presence of RKF was independently preventive for peritonitis (OR 0.262, 95% CI 0.105-0.653; *P* = .040) and KTx history was not a risk factor (*P* = .209).

Initial diuresis volume was similar between PD-postTx and PD-noTx groups (*P* = .716). However, the decline in the diuresis volume was much greater in the PD-postTx group at the end of the first year (*P* = .002) (Figure 1A) and no difference was observed in the PD-postTx group concerning immunosupression usage (*P* = .513) (Figure 1B). At the end of approximately 5 years of follow-up, 4 patients (21.1%) in PD-postTx, and 52 (74.3%) in PD-noTx group had RKF (*P* < .001).

Final Outcomes

Fifteen patients (16.9%) were transferred to HD during the follow-up. The causes of PD discontinuation were dialysis inadequacy and/or ultrafiltration failure (n = 6, 40.0%), peritonitis (n = 4, 26.7%), catheter disfunction (n = 2, 13.3%), patient's preference or psychosocial causes (n = 2, 13.3%), and diaphragmatic leak (n = 1, 6.7%). Patients who were transferred to HD had at least 1 peritonitis episode (73.3% vs. 36.5%, *P* = .009). Three and 5-year PD survivals in patients who had 3 or more peritonitis episodes or not were 90.9%, 72.7%, 95.9%, 79.7%, respectively (*P* = .076) (Figure 2A). Patients with transplantation history experienced a higher rate of PD discontinuation compared with transplant-naive patients (36.8% vs. 11.4%). Three and 5-year PD survivals in PD-postTx and PD-noTx group were 81.7%, 65.4%, and 98.5%, 91.9%, respectively (*P* = .015) (Figure 2B). In multiple analysis, a trend toward a higher risk for PD discontinuation in patients with a history of KTx was observed (HR 2.772, 95% CI 0.899-8.543; *P* = .076). Mortality rate was similar between the groups (PD-postTx 26.3% vs. PD-noTx 24.3%).

DISCUSSION

The current research demonstrated that patients initiating PD following KTx failure had an elevated risk of PD discontinuation and peritonitis relative to those without a transplantation history. However; the 2 groups exhibited no difference in patient survival. An increased number of peritonitis episodes and KTx failure was associated with a trend indicating a higher risk for PD discontinuation.

A previous study in Turkiye assessed 34 PD patients with a history of failed KTx and compared them to 82 PD patients without prior transplantation.[15] Duman et al[15] demonstrated that previous KTx did not negatively impact patient survival and time on PD therapy; nonetheless, it was linked to a higher occurrence

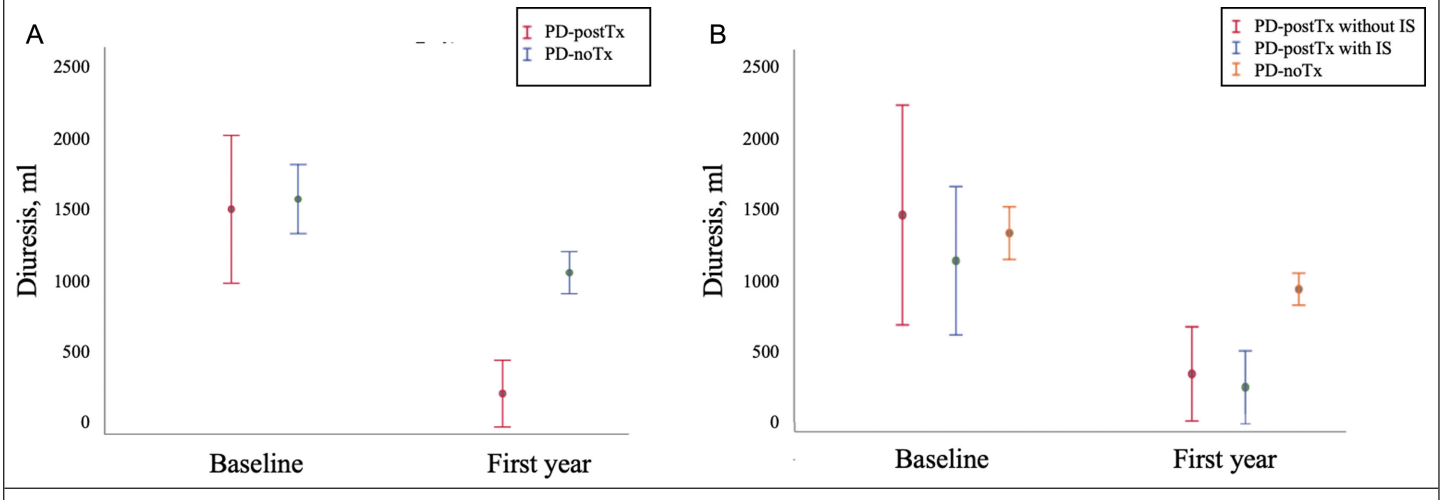


Figure 1. Diuresis volume at baseline, and at the end of the first year of peritoneal dialysis. (A) According to transplantation history status, decline in diuresis volume PD-postTx 1321.9 ± 882.2 mL vs. PD-noTx 528.0 ± 891.0 mL; *P* = .002. (B) According to immunosupression status, decline in diuresis volume PD-postTx without IS 1492.8 ± 915.3 mL, PD-postTx with IS 1188.9 ± 886.3 mL vs. PD-noTx 528.0 ± 891.0 mL; Group 1-2 *P* = .512; Group 1-3 *P* = .008; Group 2-3 *P* = .040. Symbols and lines represent the mean and SD of the mean. IS, immunosupression; PD, peritoneal dialysis; Tx, transplantation.

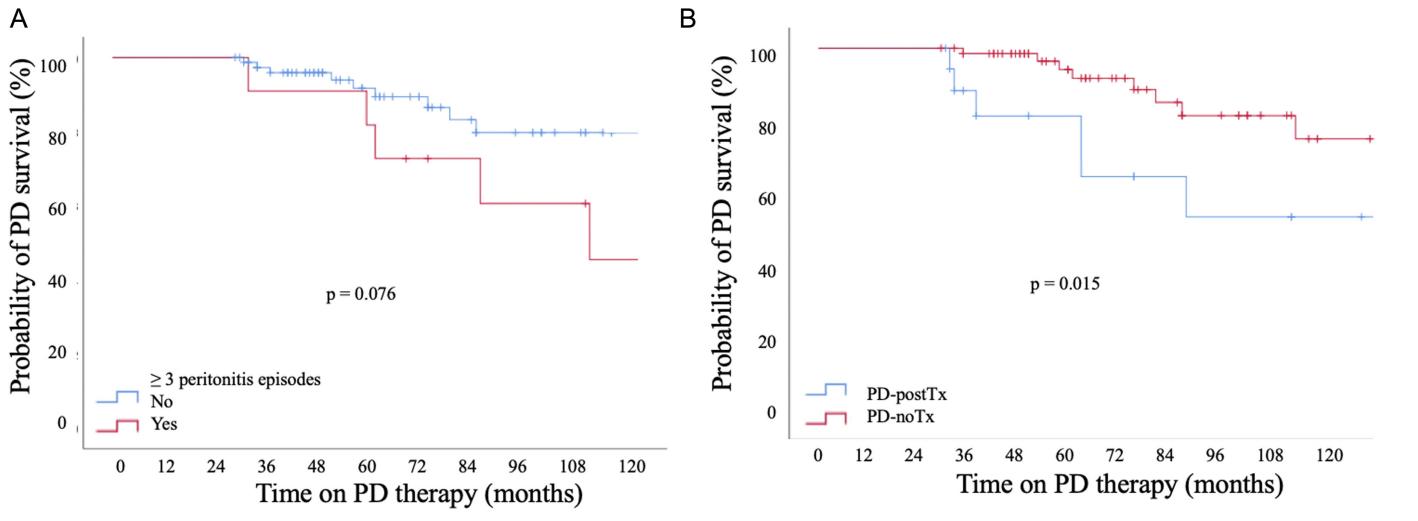


Figure 2. Kaplan-Meier plot showing PD survival. (A) According to experience of ≥3 peritonitis episodes. (B) According to transplantation history status. IS, immunosupression; PD, peritoneal dialysis; Tx, transplantation.

of peritonitis episodes. The survival rates of the technique at 1, 3, and 5 years were 83%, 77%, and 60% for the transplantation group, and 91%, 64%, and 48% for the no-transplantation group, respectively. Our study found that the time on PD therapy in the PD-postTx group were similar to those reported by Duman et al.; however, the survival rates in the tranplant-naive group were markedly superior.

Some small studies indicated adverse outcomes in patients with failed transplantation.[12,13,16] Nonetheless, further research revealed contrary findings. In comparison to 13 638 transplant-naive patients, 309 individuals returning to PD after failed KTx in Australia and New Zealand from 1991 to 2004 were younger and exhibited a lower incidence of diabetes mellitus, as in this study.[11] The rates of mortality, death-censored PD discontinuation, and peritonitis-free survival were comparable between the 2 groups. A study comparing patients who began PD after failed KTx with case-matched groups of transplant-naive patients starting on PD, as well as patients transitioned from HD to PD, found similar survival rates.[17] Transplantation rates were lower among patients who began PD following failed KTx compared to those with no transplantation history, yet comparable to rates of patients transferred to PD from HD. The French Language Peritoneal Dialysis Registry reported one of the largest cohorts in this population.[9] In a study of 328 patients who returned to PD following prior KTx, patient survival and peritonitis rates were comparable to those of 656 matched transplant-naive patients initiating PD over the same timeframe. However, the former group exhibited a greater incidence of PD discontinuation and had reduced access to a new transplantation. Two-years PD survival was 59% in the transplantation group and 77.7% in the control group. Prior KTx failure and episodes of peritonitis during PD treatment were significantly predictive of PD discontinuation. A meta-analysis of 12 retrospective observational studies, including these studies, indicated that patients who began PD following KTx failure did not exhibit an elevated risk of mortality, PD discontinuation, or peritonitis in comparison to transplant-naive individuals.[18]

This study reported that while PD discontinuation rates were elevated in patients with a KTx history compared to PD patients with no transplantation history, time on PD therapy were superior to those reported in prior studies.[9,15] This variation may arise from the evolution of practice approaches over different time periods and also highlights the importance of center activity in technical success, as demonstrated by Mujias et al.[17] Furthermore, although the adverse impacts of diabetes are well-documented on time on PD therapy, our control group with higher diabetes prevelance exhibited enhanced time on PD therapy compared to PD-postTx group. It should also be noted that the dialysis vintage before KTx may also affect the outcomes. The evidence suggests that instead of establishing a causal relationship between transplantation history and time on PD therapy, a comprehensive evaluation of the factors affecting time on PD therapy in this patient population, which is likely to include fast peritoneal solute transfer rate, is necessary.[19]

The predominant cause of technical failure identified in the previous studies was peritonitis.[17] In this study, the primary reason for transitioning to HD was dialysis inadequacy and/or ultrafiltration failure. The decline of RKF may correlate with PD discontinuation in both individuals with or without a transplantation history.[20] The rate of decline in RKF was observed to be more rapid in patients with failed KTx who initiated PD compared to those who had never undergone transplantation.[21,22] Even though some studies claimed that immunosuppression might prevent residual diuresis without elevating the risk of peritonitis and mortality,[23,24] our research indicates a reduction

in diuresis among patients with a transplantation history, irrespective of immunosuppression status. Furthermore, the increased risk of infectious complications, including peritonitis, attributed to immunosuppression requires careful consideration regarding the continuation or cessation of immunosuppression after transplant failure.[25,26] The fact that all patients in the PD-postTx group without immunosuppression experienced at least one peritonitis episode in this study, indicating the importance of evaluating risk factors of peritonitis other than immunosuppression. Residuel kidney function, which was identified as a protective factor against peritonitis and observed to decline more rapidly in patients with a transplantation history in the cohort, may play a crucial role in mitigating peritonitis and enhancing time on PD therapy.[27] It is essential to assess the effectiveness of multiple strategies proposed for patients undergoing PD to preserve RKF, including the blockade of the renin-angiotensin-aldosterone system, prevention of hypotensive episodes and hypertension, minimization of high ultrafiltration, reduction of dialysate glucose exposure, utilization of icodextrin solutions, implementation of incremental PD, and avoidance of contrast agents and nonsteroidal anti-inflammatory drugs, specifically in the context of kidney allograft failure cohort.[28]

The assessment of urine output, management of immunosuppressive therapy, and extended follow-up after the initiation of PD in patients represent notable strengths of this study. This research has several limitations. The study's limited sample size and retrospective design might permit for residual confounding. The assessment of the data are limited by the small patient sample and should not be generalized to the broader population. The differences in diabetes prevalence, and age between the groups necessitate cautious interpretation of the results.

In conclusion, this study indicates that patients experiencing kidney allograft loss are at an elevated risk of PD discontinuation, particularly those who have lost RKF. Dialysis modality selection after kidney allograft failure requires consideration of individualized patient factors, which can also enhance medical care. Patients with kidney allograft failure can achieve favorable outcomes with PD through careful management of complications and comorbidities.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Ankara University (Approval No: İ08-539-22, Date: 05.10.2022).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – G.K., K.K.; Design – G.K., K.A., K.K.; Supervision – K.A., S.S., K.K.; Materials – G.K. S.A.E.; Data Collection and/or Processing – G.K. S.A.E.; Analysis and/or Interpretation – G.K., K.A., K.K.; Literature Search – G.K.; Writing – G.K.; Critical Review – K.A., S.S., K.K.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. Poggio ED, Augustine JJ, Arrigain S, Brennan DC, Schold JD. Long-term kidney transplant graft survival—making progress when most needed. *Am J Transplant*. 2021;21(8):2824-2832. [CrossRef]
2. Lentine KL, Smith JM, Lyden GR, et al. OPTN/SRTR 2023 annual data report: kidney. *Am J Transplant*. 2025;25(2S1):S22-S137. [CrossRef]
3. Davis S, Mohan S. Managing patients with failing kidney allograft many questions remain. *Clin J Am Soc Nephrol*. 2022;17(3):444-451. [CrossRef]
4. Turkish Society of Nephrology Registry Board. *National Nephrology, Dialysis and Transplantation Registry Report of Turkey 2023*. 2024. Available at: https://nefroloji.org.tr/uploads/pdf/REGISTRY2023_web.pdf. Accessed April 1, 2025.
5. Knoll G, Muirhead N, Trpeski L, Zhu N, Badovinac K. Patient survival following renal transplant failure in Canada. *Am J Transplant*. 2005;5(7):1719-1724. [CrossRef]
6. Perl J, Dong J, Rose C, Jassal SV, Gill JS. Is dialysis modality a factor in the survival of patients initiating dialysis after kidney transplant failure? *Perit Dial Int*. 2013;33(6):618-628. [CrossRef]
7. Perl J, Hasan O, Bargman JM, et al. Impact of dialysis modality on survival after kidney transplant failure. *Clin J Am Soc Nephrol*. 2011;6(3):582-590. [CrossRef]
8. de Jonge H, Bammens B, Lemahieu W, Maes BD, Vanrenterghem Y. Comparison of peritoneal dialysis and haemodialysis after renal transplant failure. *Nephrol Dial Transplant*. 2006;21(6):1669-1674. [CrossRef]
9. Benomar M, Vachey C, Lobbedez T, et al. Peritoneal dialysis after kidney transplant failure: a nationwide matched cohort study from the French Language peritoneal dialysis Registry (RDPLF). *Nephrol Dial Transplant*. 2019;34(5):858-863. [CrossRef]
10. Chung BH, Lee JY, Kang SH, et al. Comparison of patient outcome according to renal replacement modality after renal allograft failure. *Ren Fail*. 2011;33(3):261-268. [CrossRef]
11. Badve SV, Hawley CM, McDonald SP, et al. Effect of previously failed kidney transplantation on peritoneal dialysis outcomes in the Australian and New Zealand patient populations. *Nephrol Dial Transplant*. 2006;21(3):776-783. [CrossRef]
12. Sasal J, Naimark D, Klassen J, Shea J, Bargman JM. Late renal transplant failure: an adverse prognostic factor at initiation of peritoneal dialysis. *Perit Dial Int*. 2001;21(4):405-410. [CrossRef]
13. Da Costa LA, Andreoli MCC, Carvalho AB, Draibe SA, Pestana JOM, Canziani MEF. Clinical outcomes of incident peritoneal dialysis patients coming from kidney transplantation program: a case-control study. *PLoS One*. 2020;15(1):e0227870. [CrossRef]
14. Li PKT, Chow KM, Cho Y, et al. ISPD peritonitis guideline recommendations: 2022 update on prevention and treatment. *Perit Dial Int*. 2022;42(2):110-153. [CrossRef]

15. Duman S, Aşçi G, Töz H, et al. Patients with failed renal transplant may be suitable for peritoneal dialysis. *Int Urol Nephrol*. 2004;36(2):249-252. [CrossRef]
16. Chaudhri S, Thomas AA, Samad N, Fan SL. Peritoneal dialysis in patients with failed kidney transplant: single centre experience. *Nephrology (Carlton)*. 2018;23(2):162-168. [CrossRef]
17. Mujais S, Story K. Patient and technique survival on peritoneal dialysis in patients with failed renal allograft: a case-control study. *Kidney Int Suppl*. 2006;70(103):S133-S137. [CrossRef]
18. Meng X, Wu W, Xu S, Cheng Z. Comparison of outcomes of peritoneal dialysis between patients after failed kidney transplant and transplant-naïve patients: a meta-analysis of observational studies. *Ren Fail*. 2021;43(1):698-708. [CrossRef]
19. Wilmer WA, Pesavento TE, Bay WH, et al. Peritoneal dialysis following failed kidney transplantation is associated with high peritoneal transport rates. *Perit Dial Int*. 2001;21(4):411-413. [CrossRef]
20. Liao CT, Chen YM, Shiao CC, et al. Rate of decline of residual renal function is associated with all-cause mortality and technique failure in patients on long-term peritoneal dialysis. *Nephrol Dial Transplant*. 2009;24(9):2909-2914. [CrossRef]
21. Bernardo A, Fonseca I, Rodrigues A, Carvalho MJ, Cabrita A. Predictors of residual renal function loss in peritoneal dialysis: is previous renal transplantation a risk factor? *Adv Perit Dial*. 2009;25:110-114.
22. Madar H, Korzets A, Ori Y, et al. Residual renal function in peritoneal dialysis after renal transplant failure. *Perit Dial Int*. 2010;30(4):470-474. [CrossRef]
23. Melo AGJT, Barbosa GSB, V R Cortes DDP, et al. Returning to PD after kidney transplant failure is a valuable option. *Int Urol Nephrol*. 2022;54(5):1123-1126. [CrossRef]
24. Jassal SV, Lok CE, Walele A, Bargman JM. Continued transplant immunosuppression may prolong survival after return to peritoneal dialysis: results of a decision analysis. *Am J Kidney Dis*. 2002;40(1):178-183. [CrossRef]
25. Han SS, Kim DK, Oh KH, Kim YS. Steroid use and infectious complication in peritoneal dialysis after kidney transplant failure. *Transplantation*. 2015;99(7):1514-1520. [CrossRef]
26. Smak Gregoor PJ, Zietse R, van Saase JL, et al. Immunosuppression should be stopped in patients with renal allograft failure. *Clin Transplant*. 2001;15(6):397-401. [CrossRef]
27. Han SH, Lee SC, Ahn SV, et al. Reduced residual renal function is a risk of peritonitis in continuous ambulatory peritoneal dialysis patients. *Nephrol Dial Transplant*. 2007;22(9):2653-2658. [CrossRef]
28. Tanriover C, Ucku D, Basile C, Tuttle KR, Kanbay M. On the importance of the interplay of residual renal function with clinical outcomes in end-stage kidney disease. *J Nephrol*. 2022;35(9):2191-2204. [CrossRef]

10.5152/turkjnephrol.2025.24752

Original Article

Turkish Journal of Nephrology

The Impact of Citrate-Based Dialysis Solution on the Efficacy of Hemodialysis

Kerim Erer[1], Cihan Uysal[2], Oktay Oymak[2]

[1]Department of Internal Medicine, Erciyes University Faculty of Medicine, Kayseri, Türkiye
[2]Division of Nephrology, Erciyes University Faculty of Medicine, Kayseri, Türkiye

ABSTRACT

Objective: The current study focused on the possible effects of citrate-containing acidic dialysis solutions on laboratory parameters and dialysis adequacy.
Methods: Only patients who were undergoing chronic hemodialysis (HD) were enrolled and analyzed. The HD treatment was defined as 3 times per week, with each dialysis session lasting 4 hours. Only the arteriovenous fistula was preferred for vascular access. Dialysis sessions were performed with citrate-containing acidic dialysis solutions for 3 months. Afterward, the outcomes of this period were compared with the prior 3-month period using a standard acetate-containing acidic dialysis solution.
Results: In this study, 80 patients were analyzed. The average Kt/V urea value was 1.47 (1.35-1.80) during the HD with acetate-containing acidic dialysis solution, whereas it was 1.57 (1.38-1.80) during HD with citrate-containing acidic dialysis solution (P = .003). The average urea reduction ratio was 72.1 ± 5.7 during the HD with acetate-containing acidic dialysis solution, while it was 73.5 ± 5.6 during the HD with citrate-containing acidic dialysis solution (P = .015). Lower total serum calcium levels were determined during the citrate-containing acidic dialysis solution period (P < .001). A significant decrease was observed in clotting events during the citrate-containing acidic dialysis solution period (P = .026).
Conclusion: Outcomes underscore that dialysis efficiency could be augmented by using citrate-containing acidic dialysis solution.
Keywords: Anticoagulation, citrate, dialysis solution, hemodialysis

Corresponding author: Kerim Erer ✉ kerimerer@gmail.com **Received:** April 29, 2024 **Revision Requested:** May 30, 2024 **Last Revision Received:** May 30, 2025 **Accepted:** June 16, 2025 **Publication Date:** October 1, 2025

Cite this article as: Erer K, Uysal C, Oymak O. The impact of citrate-based dialysis solution on the efficacy of hemodialysis. *Turk J Nephrol.* 2025;34(4):304-310.

INTRODUCTION

Hemodialysis (HD) is still the most commonly administered kidney replacement therapy worldwide. The survival of dialysis patients is made possible by the removal of uremic solutes by dialysis. Also, dialysis duration can impact survival.[1]

The primary mechanism for the removal of solutes from the blood is diffusion in HD. Substance transport occurs between blood and dialysate through the dialysis membrane. The dialysate is a non-sterile aqueous electrolyte solution that resembles normal electrolyte levels found in extracellular fluid, excluding bicarbonate buffer and potassium.[2]

The dialysate is composed of pure water and a mixture of dialysis solutions. The HD solutions are formed by mixing specific ratios of acidic and alkaline concentrates. Bicarbonate is used as a standard alkaline substance, however, cations such as calcium and magnesium are incompatible with bicarbonate and can lead to precipitation. Therefore, these cations are added to the acidic concentrate solutions, and acetate is mostly used as an acidifier.[3]

Occasionally, citric acid is used as an alternative acidifying agent instead of standard acetic acid. Additionally, citric acid may reduce anticoagulation counts and the risk of clotting in the dialysis set-dialyzer system.[4]

Dialysis adequacy is a concept that encompasses both clinical findings and laboratory parameters. Mathematical formulas have been successfully used to evaluate dialysis dosage and adequacy. The urea kinetic model was first described in 1972, and a simple logarithmic equation was developed using pre- and post-dialysis blood urea nitrogen (BUN) values, ultrafiltration (UF) volume, and body weight.[5] Kt/V is more sensitive than the urea reduction ratio (URR) for dialysis effectiveness.[6] According to the Kidney Disease Outcomes Quality Initiative guidelines, dialysis dose adequacy should be assessed at least once a month in long-term HD patients, and for a patient undergoing HD 3 times a week, the recommended target single-pool Kt/V is 1.2 as a minimum value.[7]

Anticoagulation protocols enhance the effectiveness of dialysis by preventing clotting in the circuit and improving membrane pore patency during HD. Several studies have indicated that the use of citrate-containing acidic dialysis solution may improve the Kt/V values due to their anticoagulant effects.[8] The current study aimed to evaluate the utility of citrate-containing acidic dialysis solution on HD efficiency.

METHODS

Study Design

The study protocol was approved by the Local Ethics Committee of Erciyes University with the decision numbered 2021/699 on November 03, 2021. This clinical investigation was carried out in accordance with the Helsinki declaration.Informed consent was obtained from all participants included in the study.

This study was conducted in a single HD center. Adult chronic HD patients were enrolled and analyzed. Only patients who had an arteriovenous fistula were enrolled to minimize vascular access problems. Patients with acute illnesses, vascular access problems, unstable hemodynamics, or who received chronic anticoagulation therapy for other indications were excluded.

MAIN POINTS

- Citrate-containing acidic dialysis solution improved dialysis efficacy.
- Citrate-containing acidic dialysis solution utilization decreased serum calcium levels; however, symptomatic hypocalcemia was not observed.
- Citrate-containing acidic dialysis solution utilization altered clotting events.

In the dialysis center, all patients underwent HD session with citrate-containing acidic dialysis solution for only 3 months due to technical reasons. All patients then returned to HD with a standard acetate-containing acidic dialysis solution. The laboratory and clinical parameters while using citrate-containing acidic dialysis solution were compared with the prior 3-month period (standard acetate-containing acidic dialysis solution).

Glucose, BUN, creatinine, electrolytes, hemogram, albumin, liver function tests, venous blood gases, Kt/V, URR, heparin dosage, clotting events, and bleeding events were assessed once a month. Parathyroid hormone (PTH) level was measured only 1 time in these 3 months. The average values were used in the analysis for each parameter in 2 periods. Heparin dosage, bleeding, and clotting events were recorded in every HD session as clinical parameters. Also, Kt/V urea <1.2 was defined as dialysis inadequacy (DI) in this study.

Hemodialysis Procedure

Chronic HD treatment was defined as 3 times per week, with each dialysis session lasting 4 hours. The dialysis sessions were performed using a Braun Dialog+© dialysis machine and a high-flux single-use polyethersulfone membrane (Purifier©; H160 or 180 with an effective surface area of 1.6 and 1.8 m^2 and an UF coefficient of 67 and 75 ml/h mmHg, respectively). The blood flow rate was maintained between 300 and 400 mL/min. The dialysate flow rate was maintained stable at 500 mL/min. The initial unfractionated heparin dose was 4.000 IU per HD session, and the dosage was adjusted individually when necessary in follow-up. Acetate concentration was 3.0 mmo/L in a standard acidic dialysis solution. Citrate concentration was 1.0 mmo/L in an acidic dialysis solution. Dialysis solutions were produced by Farmasol© (Türkiye) and the fluid composition was as following; sodium 140 mmol/L, potassium 2.0 mmol/L, calcium 1.25 mmol/L, magnesium 0.5 mmol/L, chloride 111.5 mmol/L, bicarbonate 33 mmol/L, glucose 1.0 g/L, and osmolarity 294.8 mOsm/L. Acidic and basic solutions dilution rate was 1/34.

There were no special changes in dialysis-related nursing behaviors to the patients. The nurse performing dialysis did not implement any different practices regarding the solution used for the patient.

Blood Sampling

Pre-dialysis blood sampling was performed just before the dialysis session. Post-dialysis sampling was performed after the blood pump rate was decreased to 100 mL/min for 15 seconds and stopped. Kt/V was calculated using a second-generation single-pool Daugirdas formula ($Kt/V = -\ln(R - 0.03) + [(4 - 3.5 \times R) \times (UF/W)]$ where R = post-dialysis BUN/pre-dialysis BUN, UF = net UF and W = weight).[5] The URR was calculated using the following formula ($URR = (1 - \text{post-dialysis BUN/pre-dialysis BUN}) \times 100\%$).

Statistical Analysis

SPSS version 22 software (IBM SPSS Corp.; Armonk, NY, USA) was used for data analysis. The Shapiro–Wilk test was employed to assess whether numerical data followed a normal distribution. Numerical data showing a normal distribution were presented as mean ± standard deviation, while non-normally distributed numerical data were presented as median (first quartile-third quartile). Non-numerical (categorical) data were expressed as percentages. The paired *t*-test was used to analyzing normally distributed parameters. The Wilcoxon test was used used to analyzing non-normally distributed parameters. The chi-square test was employed to assess non-numerical data. Results were evaluated at a 95% CI, with significance set at $P < .05$.

RESULTS

The total number of included patients in this study was 80. All patients have fulfilled the study protocol. Among these patients, 54 were males (67.5%) and 26 were females (32.5%). The mean age of the patients was 57.1 ± 11.6 years. The average HD duration for patients was 95.4 ± 61.3 months. The baseline characteristic features of the patients are summarized in Table 1.

Table 1. Baseline Characteristic Features of the Patients

Parameters	Results
Gender	
Male	54 (67.5%)
Female	26 (32.5%)
Age (years)	57.1 ± 11.6
BMI (kg/m^2)	24.8 (22.8-27.6)
Hemodialysis vintage (months)	95.46 ± 61.28
Comorbidities	
Hypertension	35 (43.7%)
Diabetes mellitus	23 (28.7%)
Coronary artery disease	15 (18.7%)
Heart failure	8 (10.0%)
Stroke	3 (3.7%)
Kt/V	1.42 (1.32-1.67)
URR (%)	72.2 ± 6.4
Urea predialysis (mg/dL)	143.2 ± 22.7
Creatinine predialysis (mg/dL)	8.8 ± 2.3
Sodium (mEq/L)	137.2 ± 2.8
Potassium (mEq/L)	5.1 ± 0.7
Calcium (mg/dL)	9.0 (8.5-9.3)
Phosphate (mg/dL)	4.7 ± 0.9
CaXP (mg^2/dL^2)	46.4 ± 11.0
PTH (pg/mL)	351 (226-602)
Albumin (g/dL)	3.8 ± 0.3
Bicarbonate (mEq/L)	22.7 (22.0-24.8)
Hemoglobin (g/dL)	10.9 ± 1.7
Ferritin (ng/mL)	539.0 ± 112.7

Values are expressed as n (%), mean ± standard deviation, median (first-third quartiles).
BMI, body mass index; CaXP, calcium-phosphate products; PTH, parathyroid hormone; URR, urea reduction rate.

The 2 different dialysis solution periods were compared to each other. The results of comparison according to laboratory parameters are summarized in Table 2. Firstly, DI (average Kt/V urea < 1.2) was evaluated. The frequency of DI was 5.4% in the acetate-containing acidic dialysis solution period, and it was 5.0 % in the citrate-containing acidic dialysis solution period.

Solute clearance and dialysis efficiency were analyzed according to acetate and citrate-containing acidic dialysis solution periods. The average Kt/V urea was 1.47 (1.35-1.80) during acetate-containing acidic dialysis solution period, whereas was 1.57 (1.38-1.80) during citrate-containing acidic dialysis solution period. The average Kt/V value was significantly higher during the period using the citrate-containing acidic dialysis solution compared to the period using the acetate-containing acidic dialysis solution ($P = .003$).

The average URR value was 72.1 ± 5.7% during acetate-containing acidic dialysis solution period, while the average for citrate-containing acidic dialysis solution was 73.5 ± 5.6%. The average URR value was statistically significantly increased in the citrate-containing acidic dialysis solution period ($P = .015$). The results are summarized in Table 3. The comparison of Kt/V and URR values according to treatment months was demonstrated in Figure 1.

The median total serum calcium level was 8.9 (8.6-9.3) mg/dL in the acetate-containing acidic dialysis solution period and decreased to 8.6 (8.2-8.8) mg/dL in the citrate-containing dialysate period. The average total serum calcium level was statistically significantly decreased in the citrate-containing acidic dialysis solution period ($P < .001$).

The average phosphate level was 4.7 ± 0.9 mg/dL in the acetate-containing acidic dialysis solution period and increased to 4.8 ± 1.1 mg/dL in the citrate-containing acidic dialysis solution period. The average phosphate level was no statistically significantly increased in the citrate-containing acidic dialysis solution period ($P = .053$).

The median PTH level was 351 (226-602) pg/mL in the acetate-containing acidic dialysis solution period, and it increased to 402.0 (274-718) pg/mL in the citrate-containing acidic dialysis solution period. The average PTH level was statistically significantly increased in the citrate-containing acidic dialysis solution period ($P = .044$).

Table 2. Comparison of the Average Laboratory Results of the Both Dialysis Solution Periods

Parameters	Acetate-Containing Acidic Dialysis Solution Period	Citrate-Containing Acidic Dialysis Solution Period	*P*
Sodium (mEq/L)	137.9 ± 2.1	136.5 ± 2.1	.126
Potassium (mEq/L)	5.2 ± 0.6	5.1 ± 0.5	**.007**
Calcium (mg/dL)	8.9 (8.6-9.3)	8.6 (8.2-8.8)	**<.001**
Phosphate (mg/dL)	4.7 ± 0.9	4.8 ± 1.0	.053
CaxP (mg^2/dL^2)	42.6 ± 8.4	42.9 ± 9.4	.775
PTH (pg/mL)	351 (226-602)	402.0 (274-718)	**.044**
Albumin (g/dL)	3.7 ± 0.2	3.6 ± 0.3	.236
Hemoglobin (g/dL)	10.9 ± 1.5	11.1 ± 1.6	.168
Bicarbonate (mEq/L)	24.0 (22.0-26.0)	21.0 (20.0-23.0)	**<.001**

Values are expressed as mean ± standard deviation, median (first[t]-third quartiles).
CaxP, calcium-phosphate product; PTH, parathyroid hormone. P values in bold indicate statistical significance.

The average bicarbonate level was 24.0 (22.0-26.0) mEq/L in the acetate-containing acidic dialysis solution period, and it decreased to 21.0 (20.0-23.0) mEq/L in the citrate-containing acidic dialysis solution period. The average bicarbonate level was statistically significantly decreased in the citrate-containing acidic dialysis solution period (*P* < .001).

Finally, the patients were analyzed concerning clotting events and anticoagulant therapy. The average heparin dose was 3879 ± 455 IU in acetate-containing acidic dialysis solution period, and 3835 ± 437 IU in citrate-containing acidic dialysis solution period (Figure 2). There was no significant change in heparin dosage between the 2 dialysis solution periods (*P* = .088). Furthermore, no major bleeding events were observed in the patients during both acetate and citrate-containing acidic dialysis solution periods.

The frequency of clotting events during HD sessions was assessed according to the types of dialysis solutions. There was a reduction in the number of clotting events during the citrate-containing acidic dialysis solution period (3.8%) when compared to the acetate-containing acidic dialysis solution period (5.3%), and this was a statistically significant decrease (*P* = .026). The results are summarized in Table 3.

DISCUSSION

The amount of uremic toxins clearance affects mortality and morbidity in dialysis treatment. Kt/V urea is calculated by dividing the plasma volume removed of urea by the urea distribution volume and is an established parameter assess dialysis effectiveness. The current study represents data from a 3-month prescription of citrate-containing acidic dialysis solution with high-flux dialyzers in an outpatient-based dialysis center.

Using citrate-containing dialysate has some effects on dialysis practice. Citric acid has been proposed as an alternative dialysis buffer due to its anticoagulant, anti-inflammatory, and antioxidant properties. In vitro, low concentrations of citrate can reduce complement and granulocyte activation. Also, citrate reduces endothelial cell dysfunction and vascular smooth muscle cell osteoblastic differentiation. Clinically, using citrate-containing dialysate significantly reduces chronic inflammation parameters. Additionally, citrate-containing dialysate may offer greater hemodynamic stability with significantly fewer episodes of arterial hypotension. By chelating ionized calcium in plasma, the use of citrate-containing dialysate decreases thrombogenicity. Citrate has a local anticoagulant effect inside the dialyzer, allowing reduced heparin dosing while maintaining extracorporeal patency and optimizing dialyzer clearances. Lastly, citrate-containing dialysate helps to control acid-base balance by correcting acidosis between sessions and avoiding/reducing post dialysis alkalosis.[9-11] Also, citrate-containing acidic dialysis solution can be used for every patient.

The main outcome of this study was that using citrate in the dialysate as an acidifying agent could augment dialysis efficiency. Also, this improvement was observed in both Kt/V urea and URR. The increment was determined to be 6.8% in Kt/V urea and 1.9% in URR during the citrate-containing acidic dialysis

Table 3. Monthly Results of Dialysis Efficacy and Circuit Clotting for Both Dialysis Solution Periods

Parameters	Acetate-Containing Acidic Dialysis Solution Period			Citrate-Containing Acidic Dialysis Solution Period			*P**
	First	Second	Third	First	Second	Third	
Kt/V urea	1.46 (1.32-1.67)	1.46 (1.31-1.70)	1.49 (1.36-1.80)	1.57 (1.38-1.81)	1.64 (1.45-1.77)	1.49 (1.32-1.80)	**.003**
URR	72.7 ± 6.4	71.9 ± 6.7	73.2 ± 7.0	73.7 ± 6.3	74.0 ± 6.1	72.8 ± 6.6	**.015**
Clotting events (%)	5.2	5.6	5.3	3.8	4.2	3.5	**.026**

Values are expressed as n (%), mean ± standard deviation, median (first-third quartiles). URR: urea reduction rate. * result of overall period comparisons.
URR, urea reduction rate.
*Result of overall period comparisons.

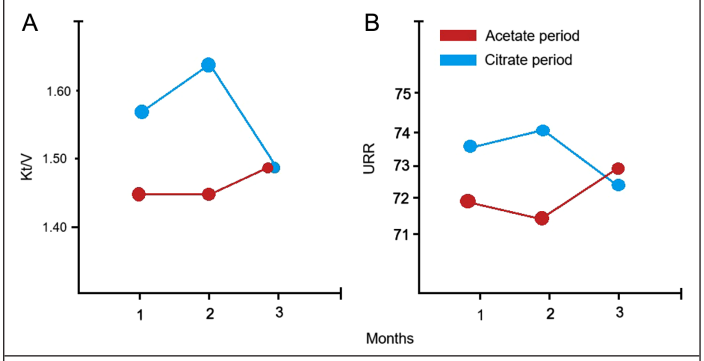


Figure 1. The course of Kt/V and URR values according to treatment months.

solution period. Although there was a decrease in the third month, there was an increase when looking at overall period. The short period of citrate use in the study, three months, prevents an elaborate explanation of this decrease. These results could be explained by the anticoagulant effect of citrate molecules and the prevention of the closing of the membrane pores, which increases dialyzer efficiency. In fact, the results were compatible with previous studies. Kossmann et al[8] used citrate as an acidifying agent in dialysis solution for 147 HD patients over six months. An increase in the Kt/V urea value (from 1.51 to 1.57) of the patients was observed. Also, when the standard acetate-containing acidic dialysis solution was reused, the Kt/V urea value decreased. This impact of citrate was attributed to improving solute clearance.[12] The results of a different study reported that citrate-containing acidic dialysis solution is associated with an increase in dialyzer reuse, reduced clotting, and increased Kt/V urea (1.23 to 1.47).[13]

In addition, fluctuating Kt/V values were observed in the third month of the citrate-containing acidic dialysis solution period, in contrast to stable values in the acetate-containing acidic dialysis solution period. This fluctuation of Kt/V was not easily explained with simple because it was shown that significant variation occurs within individuals. Vascular access efficacy, blood pump rate, time on dialysis, and fluid removal were associated with Kt/V calculation. Also, anticoagulation and circuit

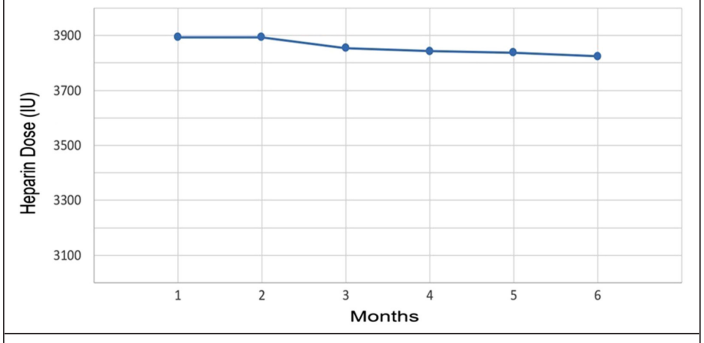


Figure 2. The average administered heparin dose per hemodialysis session according to monthly.

clotting affect the mentioned parameters. Lambie et al[14] investigated intra-individual variation of Kt/V. They also stated that 55% of patients had Kt/V variation that could change their status from adequate to inadequate dialysis within one month. When the medical records of the cohort were examined, hypotension attacks were detected in a few patients whose Kt/V values decreased in the third month. This may have been a factor that reduced dialysis efficacy.

This contribution of citrate to dialysis efficiency was mainly attributed to its anticoagulant features. Blood clotting inhibition in dialysis equipment is an important factor for effective dialysis. Blood comes into contact with intravenous cannulas, dialysis circuits, drip chambers, internal parts of the dialyzer, and the dialysis membrane during HD. Clotting could be initiated by these thrombogenic surfaces and exposure to air in the drip chambers.

Heparin is the most commonly preferred pharmacological agent for anticoagulation. The efficiency of the dialyzer is decreased by clogging of fibers and pores due to blood clots. Microcoagulation of dialyzer fibers and membrane pores frequently occurs during the use of heparin, although it is usually not noticed.[13] This ignored coagulation on pores does not hinder the completion of HD, however, reduces the solute movements and dialysis efficiency. Clotting may also decrease even Kt/V values, which is the indicator of dialysis adequacy. Additionally, heparin had some undesired side effects; such as bleeding risk, thrombocytopenia, hyperkalemia, hypertriglyceridemia, and metabolic bone disease.[15]

Systemic citrate anticoagulation was successfully applied during HD. Also, Mehta et al[16] administered regional citrate for anticoagulation of continuous hemodiafiltration. Citrate administration provided extended filter life and decreased filter clogging during dialysis in critical care patients.[17]

In this study citrate was not used an alternative anticoagulant to heparin. Occasionally, there are dialysate varieties that contain citric acid as an alternative acidifying agent instead of standard acetic acid. Furthermore, it is claimed that the use of citric acid reduces the anticoagulant requirement and the risk of clotting in the dialysis circuit and dialyzer. However, in a study conducted by Leung et al,[18] a statistically significant decrease was not observed in heparin dose with citrate-containing acidic dialysis solution compared to acetate-containing acidic dialysis solution in 20 HD patients. In the observed results, the required heparin dose did not decrease. Also, previous studies revealed that citrate can increase the efficiency of HD by reducing platelet accumulation on the dialyzer membrane.[4]

The outcomes are not surprising because citrate molecules have a limited impact on blood coagulation due to being situated on the dialysate side. Although a small amount of citrate does enter the patient's bloodstream, the concentration in the

patient's blood is only one-sixth of the citrate concentration used for dialysis anticoagulation. Consequently, this does not augment a systemic anticoagulation effect. Calcium-citrate complexes are adequately removed via dialysis procedure. In fact, approximately 75% of the citrate load is removed through both diffusion and convection, enhancing the viability of citrate-based anticoagulation protocols.[19] This increases the applicability of citrate-based anticoagulation protocols.[20] The results from Bakker et al indicated plasma citrate levels lower than 0.29 mmol/L, a value well below the upper safety limit of 0.85 mmol/L.[21]

The potential impact of citrate-containing acidic dialysis solution on metabolic parameters, particularly plasma calcium levels, is a critical clinical concern. Grundström et al[22] conducted a study examining the effects of citrate and acetate containing acidic dialysis solutions on metabolic parameters in HD. In this short-term study, both groups underwent HD using solutions with the same calcium concentration (1.5 mmol/L). The researchers observed a decrease in plasma ionized calcium levels and an increase in PTH levels in the citrate dialysis group. Moreover, there were no discernible differences in plasma levels of inflammation and oxidative stress markers between the 2 groups. Similar findings were reported in another study where additional calcium was introduced into citrate-containing acidic dialysis solution and compared with acetate-containing dialysate. This comparison revealed low calcium levels and elevated PTH levels in the citrate-containing acidic dialysis solution group.[10]

A reduction in serum calcium levels was determined in the patients, aligning with findings in existing literature. Also, there was an increase in PTH levels. However, no significant differences were identified in serum phosphate levels and calcium-phosphate product (CaxP) values between the 2 periods. Despite this statistically significant variance, no clinical signs of hypocalcemia or heightened incidence of dialysis-related cramps were noted. In a separate multicenter randomized study involving 120 patients undergoing HD with a high concentration of (3 mmol/L) citrate-containing acidic dialysis solution, severe hypocalcemia or acid-base disturbances were not reported. These datas conform with the findings. Furthermore, a statistically significant decrease in predialysis venous bicarbonate levels was observed in this study, consistent with the majority of studies in the existing literature.[23,24]

A significant decrease in the frequency of clotting events was observed during the citrate-containing acidic dialysis solution period. Furthermore, there were no serious bleeding events reported during the follow-up period with both citrate and acetate. There was no statistically significant change in the heparin dose for both dialysate periods. It's important to note that no specific reduction in heparin dose was implemented during the citrate-containing acidic dialysis solution period. The primary reason for reducing heparin dose was prolonged post-dialysis vascular access hold time, while increased clotting in the dialysis circuits was the main factor for dose escalation.

Some limitations of the current study, such as the lack of a control group and nursing behavior records, can be mentioned. The main reason for creating a control group was the inability to reach the same number of patients (n = 80) who met the inclusion criteria in the center where the study was conducted. Because the anticoagulant treatments and the presence of dialysis catheters as vascular access were obstacles to the inclusion of the patients in the study. There were no records about nursing behaviors to the patients. However, the nurse performing dialysis did not implement any different practices regarding the solution used by the patient.

Also, the duration of citrate-containing acidic dialysis solution application was as short as 3 months. Extending this period would allow for comprehensive analyzes of clinical parameters. Moreover, this study focused on assessing solute clearance via a small-sized molecule like urea.

CONCLUSION

In conclusion, while acetate-containing acidic dialysis solution is commonly used in HD globally, this study observed enhanced dialyzer function with effective anticoagulation of the extracorporeal system using citrate-containing acidic dialysis solution. Furthermore, the adoption of citrate-containing acidic dialysis solution could yield economic benefits, especially in countries where reused dialyzers are prevalent in HD practice. It would be beneficial to explore the impact of this increased Kt/V urea value on clinical manifestations and overall survival through long-term studies.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Erciyes University (Date: 03.11.2021; Number: 2021/699).

Informed Consent: Verbal and written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – K.E., O.O.; Design – K.E., O.O.; Supervision – O.O.; Resources – O.O.; Materials – K.E.; Data Collection and/or Processing – C.U.; Analysis and/or Interpretation – C.U., K.E.; Literature Search – C.U.; Writing Manuscript – K.E., C.U.; Critical Review – O.O.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. Lowrie EG, Laird NM, Parker TF, Sargent JA. Effect of the hemodialysis prescription of patient morbidity: report from the National Cooperative Dialysis Study. *N Engl J Med*. 1981;305(20):1176-1181. [CrossRef]
2. Cheung AK, Leypoldt JK. The hemodialysis membranes: a historical perspective, current state and future prospect. *Semin Nephrol*. 1997;17(3):196-213.
3. Novello A, Kelsch RC, Easterling RE. Acetate intolerance during hemodialysis. *Clin Nephrol*. 1976;5(1):29-32.
4. Hofbauer R, Moser D, Frass M, et al. Effect of anticoagulation on blood membrane interactions during hemodialysis. *Kidney Int*. 1999;56(4):1578-1583. [CrossRef]
5. Daugirdas JT. Second generation logarithmic estimates of single-pool variable volume Kt/V: an analysis of error. *J Am Soc Nephrol*. 1993;4(5):1205-1213. [CrossRef]
6. Eknoyan G, Beck GJ, Cheung AK, et al. Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med*. 2002;347(25):2010-2019. [CrossRef]
7. Daugirdas JT, Depner TA, Inrig J. KDOQI clinical practice guideline for hemodialysis adequacy: 2015 update. *Am J Kidney Dis*. 2015;66(5):884-930. [CrossRef]
8. Kossmann RJ, Gonzales A, Callan R, Ahmad S. Increased efficiency of hemodialysis with citrate dialysate: a prospective controlled study. *Clin J Am Soc Nephrol*. 2009;4(9):1459-1464. [CrossRef]
9. Huang S, Sandholm K, Jonsson N, et al. Low concentrations of citrate reduce complement and granulocyte activation in vitro in human blood. *Clin Kidney J*. 2015;8(1):31-37. [CrossRef]
10. Sequera P, Pérez García R, Molina Nuñez M, et al. Prospective randomized multicenter study to demonstrate the benefits of haemodialysis without acetate (with citrate): ABC-treat Study. Acute effect of citrate. *Nefrol (Engl Ed)*. 2019;39(4):424-433. [CrossRef]
11. Dellepiane S, Medica D, Guarena C, et al. Citrate anion improves chronic dialysis efficacy, reduces systemic inflammation and prevents chemerin-mediated microvascular injury. *Sci Rep*. 2019;9(1):10622. [CrossRef]
12. Panichi V, Fiaccadori E, Rosati A, et al. Post-dilution on line haemodiafiltration with citrate dialysate: first clinical experience in chronic dialysis patients. *ScientificWorldJournal*. 2013;2013:703612. [CrossRef]
13. Ahmad S, Callan R, Cole J, Blagg C. Increased dialyzer reuse with citrate dialysate. *Hemodial Int*. 2005;9(3):264-267. [CrossRef]
14. Lambie SH, Taal MW, Fluck RJ, McIntyre CW. Analysis of factors associated with variability in haemodialysis adequacy. *Nephrol Dial Transplant*. 2004;19(2):406-412. [CrossRef]
15. Lai KN, Ho K, Cheung RC, et al. Effect of low molecular weight heparin on bone metabolism and hyperlipidemia in patients on maintenance hemodialysis. *Int J Artif Organs*. 2001;24(7):447-455. [CrossRef]
16. Mehta RL, Mcdonald BR, Aguilar MM, Ward DM. Regional citrate anticoagulation for continuous arteriovenous hemodialysis in critically ill patients. *Kidney Int*. 1990;38(5):976-981. [CrossRef]
17. Bihorac A, Ross EA. Continuous venovenous hemofiltration with citrate-based replacement fluid: efficacy, safety, and impact on nutrition. *Am J Kidney Dis*. 2005;46(5):908-918. [CrossRef]
18. Leung KC, Tai DJ, Ravani P, Quinn RR, Scott-Douglas N, MacRae JM. Citrate vs. acetate dialysate on intradialytic heparin dose: a double blind randomized crossover study. *Hemodial Int*. 2016;20(4):537-547. [CrossRef]
19. Ortiz-Melo DI, Kovalik EC. *Methods of Hemodialysis Anticoagulation. Handbook of Dialysis Therapy*. Elsevier; Amsterdam; 2023:118-125.
20. Kozik-Jaromin J, Nier V, Heemann U, Kreymann B, Böhler J. Citrate pharmacokinetics and calcium levels during high-flux dialysis with regional citrate anticoagulation. *Nephrol Dial Transplant*. 2009;24(7):2244-2251. [CrossRef]
21. Bakker AJ, Boerma EC, Keidel H, Kingma P, van der Voort PH. Detection of citrate overdose in critically ill patients on citrate-anticoagulated venovenous haemofiltration: use of ionised and total/ionised calcium. *Clin Chem Lab Med*. 2006;44(8):962-966. [CrossRef]
22. Grundström G, Christensson A, Alquist M, Nilsson L-G, Segelmark M. Replacement of acetate with citrate in dialysis fluid: a randomized clinical trial of short term safety and fluid biocompatibility. *BMC Nephrol*. 2013;14(1):216. [CrossRef]
23. Gabutti L, Lucchini B, Marone C, Alberio L, Burnier M. Citrate-vs. acetate-based dialysate in bicarbonate haemodialysis: consequences on haemodynamics, coagulation, acid-base status, and electrolytes. *BMC Nephrol*. 2009;10:7. [CrossRef]
24. Molina Nuñez M, de Alarcón R, Roca S, et al. Citrate versus acetate-based dialysate in on-line haemodiafiltration. A prospective crossover study. *Blood Purif*. 2015;39(1-3):181-187. [CrossRef]

10.5152/turkjnephrol.2025.251049

Turkish Journal of Nephrology

Linagliptin-Induced Bullous Pemphigoid in Chronic Kidney Disease

Gerry George Mathew[1], Priya Cinna T Durai[2]

[1]Department of Nephrology, SRM Medical College Hospital and Research Centre, Chennai, India
[2]Department of Dermatology, SRM Medical College Hospital and Research Centre, Chennai, India

Corresponding author: Gerry George Mathew ✉ gerrygeorge007@gmail.com **Received:** April 22, 2025 **Revision Requested:** May 19, 2025
Last Revision Received: June 28, 2025 **Accepted:** July 1, 2025 **Publication Date:** October 1, 2025

Cite this article as: Mathew GG, Durai PCT. Linagliptin-induced bullous pemphigoid in chronic kidney disease. *Turk J Nephrol.* 2025;34(4): 311-313.

Linagliptin-induced bullous pemphigoid (BP) is a rare autoimmune blistering dermatological condition that can be triggered by various drug-related interactions, involving complement activation and exacerbation of inflammatory processes.[1] Here, we present a rare case of early onset BP caused by linagliptin in a patient with chronic kidney disease.

A 70-year-old female patient with a history of diabetes mellitus for 15 years and chronic kidney disease for 2 years presented with pruritus for 2 weeks, excoriations with superficial erosions (Figure 1A), and tense bullae for 1 week. Written informed consent was obtained from the patient. The medication history included the addition of linagliptin 20 days ago to existing oral hypoglycaemic agents (metformin and gliclazide). Laboratory evaluation revealed hemoglobin—9.4 gr/dL, white blood cell count—15 170/mm^3, platelet count—359 000/mm^3, creatinine—3 mg/dL, urea—66 mg/dL, normal serum electrolytes, serum calcium—8.2 mg/dL, serum phosphorous—9.8 mg/dL, parathyroid hormone—448 pg/mL, and liver function tests. The blood, urine, and skin cultures were sterile. Skin biopsy showed dermis with perivascular eosinophilic infiltrate (Figure 1B), blister roof with necrotic keratinocytes (Figure 1C), and spongiosis with a subepidermal blister cavity containing fibrin, inflammatory cells, and red blood cells (Figure 1D), suggestive of BP. Antibodies against BP 180 and BP 230 were negative. Immunofluorescence revealed linear fluorescence of IgG (2+) (Figure 1E) and C3 (1+) (Figure 1F) at the dermal–epidermal junction. Linagliptin discontinuation and treatment with steroids (0.5 mg/kg/day) and topical clobetasol propionate for 3 weeks resulted in complete clinical remission of the bullous lesions after 3 weeks. Steroids were discontinued after 6 weeks and there was no clinical relapse of BP on follow-up after 6 months

Bullous pemphigoid is a common subepidermal blistering condition and its pathogenesis involves immune antibody generation against hemidesmosome proteins (BP 180 and BP 230) and improper T cell response, leading to complement activation, neutrophil chemotaxis, and basement membrane degradation.[1,2] Bullous pemphigoid presents in the elderly as intense pruritus, tense blisters, and erosions over the trunk and extremities. Predisposing conditions include multiple sclerosis, dementia, underlying haematological malignancies, diabetes, chronic kidney disease, lichen planus, and thrombotic disorders.[2-4] Diabetes, chronic kidney disease, elevated serum phosphorous, and parathyroid hormone levels may have aggravated pruritus in our patient with an onset of less than 1 month.[5] In linagliptin-induced BP, similar to all dipeptidyl peptidase IV (DPP4) inhibitors, target antigens include the mid-portion of BP180's extracellular domain, including LAD-1, and the C-terminal domain.[2] Our patient was negative for these antibodies probably due to epitope spreading,

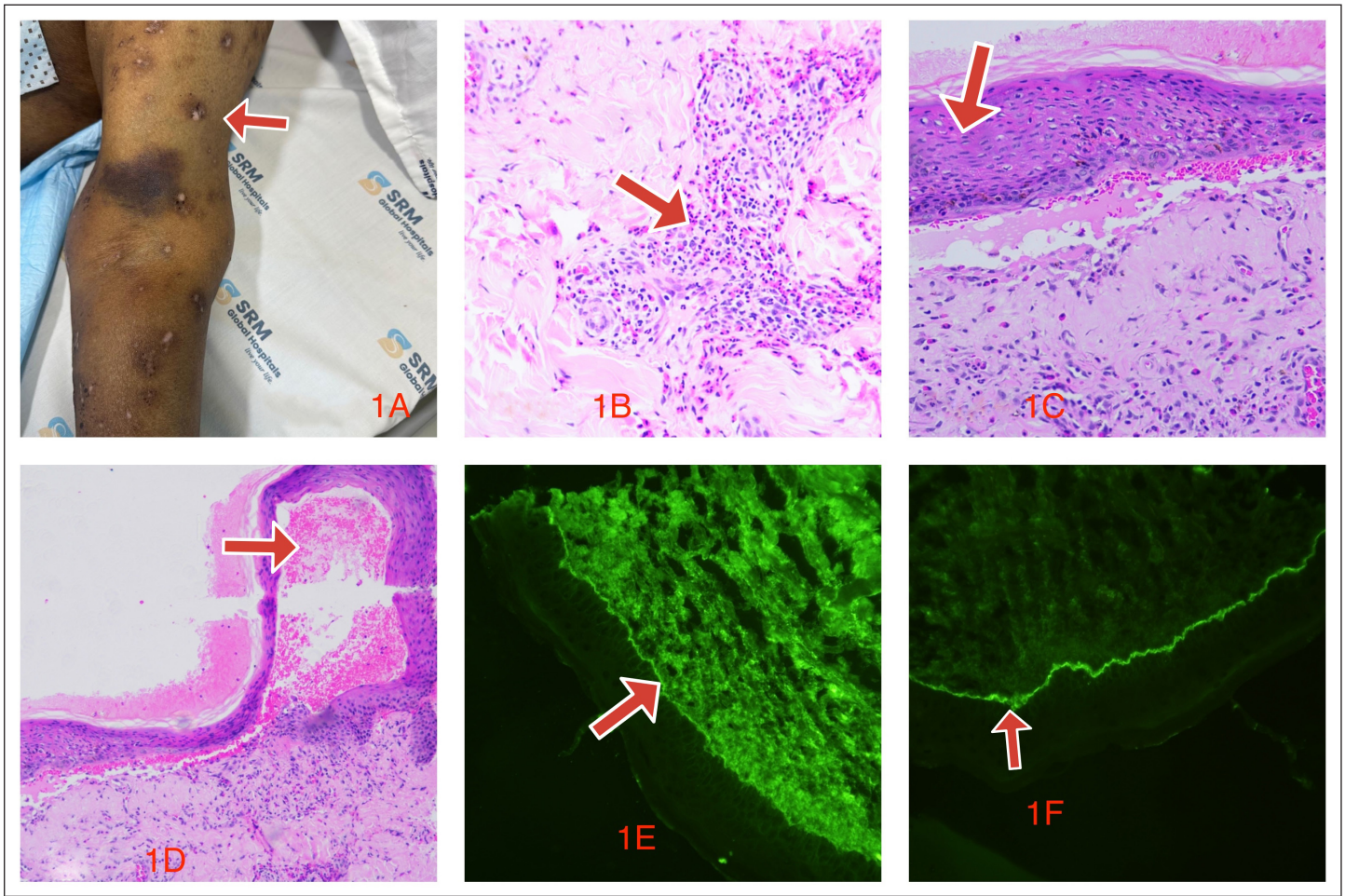


Figure 1. (A) Clinical photograph of legs showing post-lesional hyperpigmented skin (red arrow) of bullous pemphigoid (magnification: 600 DPI). (B) Histopathology revealing dermis with perivascular eosinophilic infiltrate (red arrow) (H&E stain, Magnification: 200×; 600 DPI). (C) Histopathology revealing roof of blister (red arrow) with necrotic keratinocytes and spongiosis (H&E stain, Magnification: 200×; 600 DPI). (D) Histopathology revealing subepidermal blister cavity containing fibrin, red blood cells and inflammatory cells (red arrow) (H&E stain, Magnification: 100×; 600 DPI). (E) Immunofluoroscence revealing linear fluorescence of IgG (2+) at the dermal–epidermal junction (red arrow) (magnification: 600 DPI). (F) Immunofluoroscence revealing linear fluorescence of C3 (1+) at the dermal–epidermal junction (red arrow) (magnification: 600 DPI).

resulting in secondary epitopes not detected by conventional test kits.[2,4] Other reasons for negative antibody test include, low antibody titers, false-negative results, or the presence of a different subepidermal blistering disease.[2,4] Inactivation of DPP4 leads to dysregulated immune tolerance and enhanced activity of proinflammatory chemokines, promoting eosinophil activation in the skin and blister formation.[1-3] Standard treatment for DPP4 inhibitor-induced BP includes withdrawal of the offending drug, topical clobetasol propionate, and minimal systemic steroids (0.5 mg/kg/day), resulting in clinical remission in most cases.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Informed Consent: Written informed consent was obtained from patient who agreed to take part in the presentation.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – G.G.M.; Design – G.G.M.; Supervision – G.G.M., P.C.T.D.; Resources – G.G.M., P.C.T.D.; Materials – G.G.M., P.C.T.D.; Data Collection and/or Processing – G.G.M.; Analysis and/or Interpretation – G.G.M., P.C.T.D.; Literature Search – G.G.M., P.C.T.D.; Writing Manuscript – G.G.M., P.C.T.D.; Critical Review – G.G.M., P.C.T.D.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. Ganeva M, Gancheva T, Manuelyan K, Hristakieva E. Gliptin-induced bullous pemphigoid. *Int J Clin Pharmacol Ther*. 2024;62(2):89-95. [CrossRef]
2. Chouchane K, Di Zenzo G, Pitocco D, Calabrese L, De Simone C. Bullous pemphigoid in diabetic patients treated by gliptins: the other side of the coin. *J Transl Med*. 2021;19(1):520. [CrossRef]

3. Haber R, Fayad AM, Stephan F, Obeid G, Tomb R. Bullous pemphigoid associated with linagliptin treatment. *JAMA Dermatol*. 2016;152(2):224-226. [CrossRef]
4. Charitaki E, Damianakis N, Garbidaki A, et al. DPP4 inhibitor-induced bullous pemphigoid in patients with diabetes and chronic kidney disease: clinical case series. *Nephron*. 2023;147(2):97-102. [CrossRef]
5. Mani H, Safo P, Onitilo AA. Linagliptin-associated bullous pemphigoid treated with rituximab. *BMJ Case Rep*. 2019;12(9):e229902. [CrossRef]

10.5152/turkjnephrol.2025.24912

Turkish Journal of Nephrology

Nivolumab-Associated Acute Tubulointerstitial Nephritis in a Gastric Cancer Patient

Engin Onan[1], Tuba Canpolat[2], Dilek Torun[1], Ruya Kozanoglu[1], Hasan Micozkadioglu[1], Fatih Kose[3]

[1]Divison of Nephrology, Adana Başkent University Dr. Turgut Noyan Traning and Research Hospital, Adana, Türkiye
[2]Department of Pathology, Adana Başkent University Dr. Turgut Noyan Traning and Research Hospital, Adana, Türkiye
[3]Divison of Oncology, Adana Başkent University Dr. Turgut Noyan Traning and Research Hospital, Adana, Türkiye

Corresponding author: Engin Onan ✉ onanmd@gmail.com
Received: November 21, 2024 **Revision Requested:** January 6, 2025
Last Revision Received: February 6, 2025 **Accepted:** May 2, 2025 **Publication Date:** October 1, 2025

Cite this article as: Onan E, Canpolat T, Torun D, Kozanoglu R, Micozkadioglu H, Kose F. Nivolumab-associated acute tubulointerstitial nephritis in a gastric cancer patient. *Turk J Nephrol.* 2025;34(4):314-315.

To the Editor,

This letter presents a case of nivolumab-induced acute tubulointerstitial nephritis (ATIN) in a patient with advanced gastric cancer. It highlights the nephrotoxicity of immune checkpoint inhibitors (ICIs) and the importance of vigilant monitoring and timely intervention.[1] Immune checkpoint inhibitors, including anti-PD-1, anti-PD-L1, and CTLA-4 inhibitors, have revolutionized cancer therapy by enhancing immune responses against tumors. However, these therapies are associated with immune-related adverse events (irAEs), including ATIN, which can lead to acute kidney injury (AKI).[2]

A 66-year-old male with a history of goiter surgery presented with progressive abdominal pain, nausea, and an unintended weight loss of 6 kg over 1 month. Written informed consent was obtained from the patient for publication of this case report. Imaging and endoscopic evaluation confirmed a gastric cardia tumor with liver metastases. Initial treatment with Fluorouracil, Folinic Acid, and Oxaliplatin was well tolerated. After the addition of nivolumab (240 mg biweekly), the patient developed fever, fatigue, and stage 3 AKI following the seventh dose. Laboratory results showed a serum creatinine increase from 0.7 mg/dL to 6.45 mg/dL, requiring urgent hemodialysis performed in 4 sessions. Laboratory findings at admission revealed significant proteinuria (981 mg/24 h), hematuria (11 red blood cells/high-power field), and leukocyturia (16 white blood cells/high-power field). A kidney biopsy was performed on day 6 of hospitalization. Histopathological evaluation demonstrated interstitial infiltration by CD4+ and CD8+ T cells, mononuclear cells, and mild tubulitis. Immunofluorescence did not reveal significant immune complex deposition, supporting the diagnosis of immune-mediated ATIN. Corticosteroid therapy was initiated at 1 mg/kg/day of prednisone, leading to rapid kidney recovery, with dialysis discontinuation within 3 weeks. A rapid tapering protocol was followed, and serum creatinine normalized (0.85 mg/dL) at the 6-week follow-up.

Apart from ICI-associated ATIN, other potential causes of AKI in this patient should be considered. Sepsis-related AKI is a possibility, given the presence of fever and systemic symptoms; however, no clinical or microbiological evidence of infection was found. Contrast-induced nephropathy could be another concern, but the patient's kidney function was stable before the AKI episode, and there was no recent exposure to iodinated contrast agents. Additionally, prerenal causes such as dehydration or tumor-related cachexia could contribute to kidney dysfunction, yet volume resuscitation did not lead to improvement, supporting an intrinsic kidney injury mechanism. Given these considerations, the clinical course and biopsy findings strongly pointed toward an immune-mediated etiology.

Though rare (1%-3% incidence), ICI-associated ATIN is increasingly recognized as a severe irAE.[3] Immune checkpoint inhibitors disrupt immune tolerance, triggering T-cell-mediated inflammation in various organs, including the kidneys.[4] Kidney biopsy typically reveals interstitial infiltration of CD4+ and CD8+ T-cells, along with cytokine release, driving kidney injury. The timing of kidney biopsy in ICI-associated ATIN remains debated. The American Society of Clinical Oncology guidelines recommend biopsy for stage 3 AKI, though earlier biopsy and steroid initiation might improve outcomes.[5] In this case, early intervention led to kidney recovery and prevented irreversible damage.

While ICIs are transformative in cancer treatment, their nephrotoxic potential cannot be overlooked. This case underscores the necessity of awareness, regular monitoring, and early management of nephrotoxic irAEs in patients undergoing ICI therapy.

Data Availability Statement: N/A.

Informed Consent: Written informed consent was obtained from the patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – E.O.; Design – E.O., D.T.; Supervision – F.K.; Resources – T.C.; Materials – T.C.; Data Collection and/or Processing – R.K.; Analysis and/or Interpretation – H.M.; Literature Search – H.M., R.K.; Writing Manuscript – E.O., D.K.; Critical Review – F.K.; Other – E.O.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. Cortazar FB, Marrone KA, Troxell ML, et al. Clinicopathological features of acute kidney injury associated with immune checkpoint inhibitors. *Kidney Int*. 2016;90(3):638-647. [CrossRef]
2. Wang PF, Chen Y, Song SY, et al. Immune-related adverse events associated with anti-PD-1/PD-L1 treatment for malignancies: a meta-analysis. *Front Pharmacol*. 2017;8:730. [CrossRef]
3. Esposito P, Bottini A, Lecini E, et al. Biopsy-proven acute tubulointerstitial nephritis in patients treated with immune checkpoint inhibitors: a pooled analysis of case reports. *Front Oncol*. 2023;13:1221135. [CrossRef]
4. Gumusay O, Callan J, Rugo HS. Immunotherapy toxicity: identification and management. *Breast Cancer Res Treat*. 2022;192(1):1-17. [CrossRef]
5. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of clinical oncology clinical practice guideline. *J Clin Oncol*. 2018;36(17):1714-1768. [CrossRef]

10.5152/turkjnephrol.2025.25965

Turkish Journal of Nephrology

F18-FDG PET/CT Findings in Kidney Graft Intolerance Syndrome

Yağmur Tahıllıoğlu[1], Rabia Hacer Hocaoğlu[1], Ayşe Serra Artan[1], Ahmet Burak Dirim[1], Duygu Has Şimşek[2], Özgür Oto Akın[1], Halil Yazıcı[1], Savaş Öztürk[1], Aydın Türkmen[1]

[1]Division of Nephrology, Department of Internal Medicine, Istanbul University Faculty of Medicine, Istanbul, Türkiye
[2]Department of Nuclear Medicine, Istanbul University Faculty of Medicine, Istanbul, Türkiye

Corresponding author: Yagmur Tahıllıoğlu ytahillioglu@gmail.com **Received:** January 30, 2025 **Revision Requested:** February 27, 2025
Last Revision Received: February 27, 2025 **Accepted:** February 28, 2025 **Publication Date:** October 1, 2025

Cite this article as: Tahıllıoğlu Y, Hocaoğlu RH, Artan AS, et al. F18-FDG PET/CT findings in kidney graft intolerance syndrome. *Turk J Nephrol.* 2025;34(4):316-317.

To the Editor,

The case of a 26-year-old male patient diagnosed with kidney failure secondary to vesicoureteral reflux, who underwent kidney transplantation and developed graft intolerance syndrome (GIS) following graft failure 10 years post-transplantation is presented here. The patient had lost his graft 3 months prior, was initiated on thrice-weekly hemodialysis, and his immunosuppressive therapy was gradually tapered, starting with mycophenolate mofetil and followed by tacrolimus. He presented with fever while being monitored for retransplantation and maintained on 5 mg of prednisolone. The patient initially responded to intravenous antibiotic therapy for catheter-associated infection, with acute-phase reactants declining and no growth observed in follow-up cultures. However, during follow-up, acute-phase reactants increased again, fever recurred, and he developed resistant hypertension, anemia resistant to erythropoiesis-stimulating agents, and tenderness over the graft site. Urinary tract infection was ruled out. Clinically, GIS was considered, and the patient's methylprednisolone therapy was adjusted to 40 mg, resulting in a decrease in C-reactive protein (CRP) levels from 42 mg/L to 5 mg/L. With an improvement in symptoms, the methylprednisolone dose was tapered to 16 mg.

In the patient undergoing preparation for retransplantation, protein electrophoresis revealed an M-spike, with a kappa/lambda ratio of 0.12 and IgG lambda detected on serum immunofixation. To investigate suspected post-transplant lymphoproliferative disorder, a bone marrow aspiration biopsy and Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (F18-FDG PET/CT) were performed. F18-FDG PET/CT showed diffuse moderate FDG uptake in the graft parenchyma, while urine in the bladder demonstrated no radioactivity. Lack of FDG uptake in the bladder urine suggested kidney failure, whereas the FDG uptake in the graft was attributed to inflammation (Figure 1). Despite this appearance, the steroid dose was not increased again as the patient had no accompanying clinical findings. The patient was discharged with a plan for close follow-up and gradual tapering of methylprednisolone therapy.

Currently, asymptomatic failed kidney grafts are left in situ, and immunosuppressive therapy is gradually tapered.[1] Following graft rejection, as immunosuppression is tapered, the remaining kidney may begin to show symptoms and develop a reaction known as GIS. Graft intolerance syndrome is a significant cause of morbidity and mortality in kidney transplant recipients with kidney graft failure. It is characterized by graft enlargement, pain, hematuria, fever, elevated acute phase reactants, and may additionally lead to graft perforation. Graft intolerance syndrome typically occurs within the first year after a reduction or cessation of

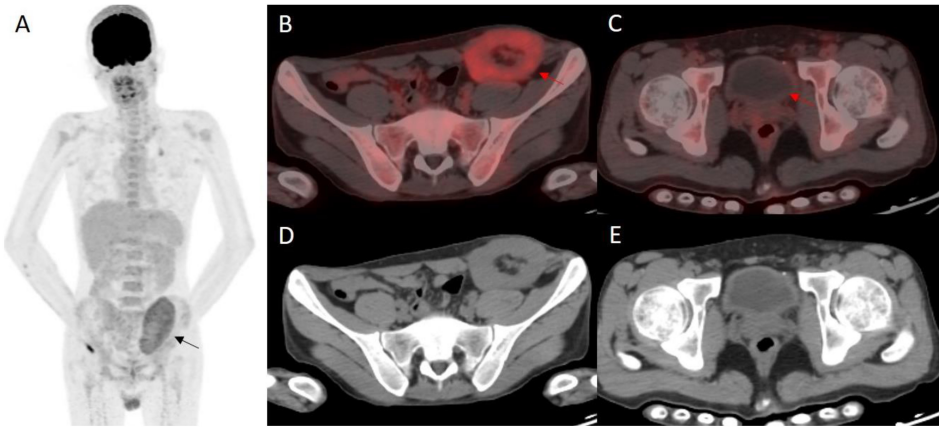


Figure 1. Moderate diffuse FDG uptake (SUVmax: 3.64) in the renal graft parenchyma was demonstrated in F18-FDG PET/CT maximum intensity projection (A: black arrow) and axial fused image (B: red arrow) with corresponding axial CT image (D). Lack of FDG uptake in the bladder was shown in the axial fused image (C: red arrow) with corresponding axial CT image (E).

immunosuppressive therapy.[2,3] Written informed consent was obtained from the patient for publication of this case report and any accompanying images. It is common and often overlooked, and one study showed that nearly one-third of the subjects developed it within the first year of starting dialysis therapy.[4] The clinical symptoms are usually sufficient for diagnosis, but the clinical suspicion index has to be high. Investigational methods such as Doppler ultrasound and scintigraphy may be helpful in confirming the diagnosis. Even though its role is controversial, indium-111-labeled platelets have been reported as potentially useful.[5] A case series described diffuse FDG uptake in the graft kidney on PET/CT in 2 patients with GIS and recommended F18-FDG PET/CT as a diagnostic tool.[6] Similarly, the patient showed diffuse uptake in the graft parenchyma on F18-FDG PET/CT. Treatment options for GIS include increasing immunosuppressive therapy, nephrectomy, and embolization.[2,3] Graft nephrectomy is usually performed in cases refractory to immunosuppressive therapy. In this case, the dose of methylprednisolone was increased, which improved the symptoms. This clinical presentation suggested an association between the symptoms and GIS. In summary, GIS is a condition usually occurring within the first year after graft loss, relatively common but requiring clinical awareness for early diagnosis. Clinicians should remain vigilant for GIS, particularly in patients undergoing immunosuppressive tapering, and F18-FDG PET/CT may serve as a valuable adjunctive diagnostic tool.

Informed Consent: Written informed consent was obtained from the patient who is presented here.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – Y.T., A.B.D., D.H.Ş.; Design – Y.T., A.B.D., A.S.A., D.H.Ş.; Supervision – A.B.D., A.S.A., Ö.O.A., H.Y., S.Ö., A.T.; Resources – Y.T., D.H.Ş.; Materials – Y.T., D.H.Ş.; Data Collection and/or Processing – Y.T., D.H.Ş., R.H.H.; Analysis and/or Interpretation – Y.T., A.B.D., A.S.A., D.H.Ş.; Literature Search – Y.T., R.H.H.; Writing Manuscript – Y.T., Critical Review – A.B.D., A.S.A., Ö.O.A., H.Y., S.Ö., A.T. Other – A.B.D.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. Kiberd BA, Belitsky P. The fate of the failed renal transplant. *Transplantation*. 1995;59(4):645-647. [CrossRef]
2. Pérez-Flores I, Sánchez-Fructuoso A, Marcén R, Fernández A, Fernández Lucas M, Teruel JL. [Managing a failed kidney graft. Nephrectomy versus embolisation]. *Nefrologia*. 2009;29(suppl 1):54-61. [CrossRef]
3. Lea-Henry T, Chacko B. Management considerations in the failing renal allograft. *Nephrology (Carlton)*. 2018;23(1):12-19. [CrossRef]
4. Delgado P, Diaz F, Gonzalez A, et al. Intolerance syndrome in failed renal allografts: incidence and efficacy of percutaneous embolization. *Am J Kidney Dis*. 2005;46(2):339-344. [CrossRef]
5. Torregrosa JV, Bassa P, Lomeña FJ, et al. The usefulness of 111In-labeled platelet scintigraphy in the diagnosis of patients with febrile syndrome and a nonfunctioning renal graft. *Transplantation*. 1994;57(12):1732-1735. [CrossRef]
6. Luna B, Rubí S, Tugores C, Sampol C, Orta N, Peña C. 18F-FDG PET/CT and non-functioning renal graft intolerance syndrome. *Rev Esp Med Nucl Imagen Mol (Engl Ed)*. 2020;39(4):248-249. [CrossRef]

10.5152/turkjnephrol.2025.251102

Turkish Journal of Nephrology

Acute Tubular Necrosis Associated with Esflurbiprofen Patch Use

Hinpetch Daungsupawong[1], Viroj Wiwanitkit[2]

[1]Private Academic Consultant, Phonhong, Lao People's Democratic Republic
[2]Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences, Chennai, India

Corresponding author: Hinpetch Daungsupawong ✉ hinpetchdaung@gmail.com **Received:** June 10, 2025 **Revision Requested:** June 27, 2025
Last Revision Received: June 28, 2025 **Accepted:** June 30, 2025 **Publication Date:** October 1, 2025

Cite this article as: Daungsupawong H, Wiwanitkit V. Acute tubular necrosis associated with esflurbiprofen patch use. *Turk J Nephrol.* 2025;34(4):318-319.

To the Editor,

A 76-year-old woman was treated for spondylolisthesis caused by *E. coli* and Micrococcus, which included antibiotic therapy. On presentation, the patient exhibited mild dehydration. Blood pressure was normal range. Her urine output was 1200 mL/day. Her serum creatinine level was 1.8 mg/dL, which was high but asymptomatic. Additionally, blood urea nitogen (BUN) was 26 mg/dL, along with high neutrophil gelatinase-associated lipocalin (NGAL) levels in urine at 2000 ng/mL, indicating early kidney tubular damage. Regarding urinalysis, granular casts and kidney tubular epithelial cell casts were observed. Plasma and urine potassium were 6 and 10 mEq/L, respectively. Plasma and urine sodium were 140 and 60 mEq/L, respectively. Fractional excretion of sodium (FENa) was 2.14%. Despite normal kidney ultrasonography and urine production, these findings were consistent with non-oliguric ATN, most likely due to non steroidal anti inflammatory drug (NSAID)-induced kidney failure.

After withdrawing the esflurbiprofen patch, the patient was treated with oral fluids alone, with no additional medication intervention or intravenous infusion. Over the next 10 days, her kidney function improved, with creatinine and BUN levels returning to normal. Topical esflurbiprofen plaster is applied locally, its systemic absorption can still occur and is underreported for its possible adverse effect.[1,2] Similar to any NSAIDS, the use of the plaster requires monitoring for its side effects. In a recent report from Japan, 4% of patients receiving had kidney problems after use of the local NSAIDS.[3]

Notably, systemic absorption of topical NSAIDs like esflurbiprofen can occur, especially in elderly or dehydrated patients, potentially leading to significant plasma levels and kidney adverse effects.[4] NSAID-induced ATN results from inhibition of prostaglandin synthesis, causing kidney ischemia and direct tubular toxicity.[3] A pharmacological study confirmed measurable plasma concentration of esflurbiprofen after topical application, with systemic exposure increases in elderly and people with chronic kidney disease.[3] Similar case reports have described AKI induced by topical NSAIDs in older adults, underscoring the need for vigilance.[5]

In this case, the diagnosis was made based on a constellation of clinical features, including elevated creatinine and BUN, high urinary NGAL, preserved urine output, and the temporal relationship to NSAIDs exposures. As the patient was clinically stable and improved rapidly after withdrawal of the suspected offending agent and supportive care, kidney biopsy was not pursued.

This case highlights the potential for serious side effects, including AKI, from topical NSAID use in elderly, vulnerable patients.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Informed Consent: Written informed consent was obtained from the patient who agreed to take part in the study.

Author Contributions: Concept – H.P., V.W.; Supervision – V.W.; Analysis and/or Interpretation – H.P., V.W.; Literature Search – H.P., V.W.; Writing Manuscript – H.P., V.W.; Critical Review – H.P., V.W.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. Amemiya M, Nakagawa Y, Yoshimura H, et al. Comparison of tissue pharmacokinetics of esflurbiprofen plaster with flurbiprofen tablets in patients with knee osteoarthritis: a multicenter randomized controlled trial. *Biopharm Drug Dispos*. 2021;42(9):418-426. [CrossRef]
2. Otsuka N, Yataba I. Pharmacological action and clinical outcome of newly developed NSAIDs patch, "LOQOA® tape". *Nihon Yakurigaku Zasshi*. 2018;151(5):221-227. [CrossRef]
3. Miyake Y, Mitani S, Namba Y, Umehara N, Kawamoto T, Furuichi S. Efficacy of S-flurbiprofen plaster for analgesia following total hip arthroplasty. *Cureus*. 2024;16(8):e66805. [CrossRef]
4. Romejko K, Markowska M, Niemczyk S. The review of current knowledge on neutrophil gelatinase-associated lipocalin (NGAL). *Int J Mol Sci*. 2023;24(13):10470. [CrossRef]
5. Otsuka N, Yataba I, Matsushita I, Matsumoto H, Hoshino Y, Terada Y. A minimal impact of long-term S-flurbiprofen plaster application on kidney function in osteoarthritis patients. *Clin Exp Nephrol*. 2017;21(6):1060-1067. [CrossRef]