

# Effectiveness of kidney transplantation in lorus nephritis: Literature review

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## ABSTRACT

**Aim:** Conducting a scientific analysis of domestic and foreign sources of information regarding modern conceptual views diagnostic and effectiveness of kidney transplantation in Lupus Nephritis.

**Materials and Methods:** Used methods of historical-bibliographic and systematic approach. The search for literary sources was carried out in four main scientific databases: Google Scholar, PubMed, The review included original articles, research, and official recommendations from medical associations. The search query used in both platforms was: («lupus nephritis» AND «kidney transplantation»). In Google Scholar, the results were limited to publications from 2017 to 2024. As a result of the search, Google Scholar provided 25 relevant articles, while PubMed yielded 57.

**Conclusions:** Scientific analysis confirmed better survival rates and a lower complication rate compared to hemodialysis and peritoneal dialysis. Survival rates for kidney transplantation over 5 to 10 years are comparable to those for patients with other diseases. Identifying new serological and immunological markers is crucial for the early diagnosis and prevention of acute kidney damage and subsequent graft loss.

**KEY WORDS:** effectiveness, lupus-nephritis, kidney transplantation, modern biomarkers

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## INTRODUCTION

Systemic lupus erythematosus (SLE) is a connective tissue disease with a high presence of autoantibodies, autoreactive T-lymphocytes or B-lymphocytes, and elevated levels of pro-inflammatory cytokine in the blood, leading to damage in multiple internal systems. The incidence of SLE in the USA averages 5.14 cases per 100,000 population per year, though this rate varies significantly by region [1].

In the last two decade, big progreses has been made in understanding the etiopathogenesis of systemic lupus erythematosus (SLE), particularly through the study of various forms of apoptosis.

However, SLE remains incompletely understood and manifests through systemic symptoms due to the involvement of multiple organs and tissues [2]. Lupus nephritis (LN) is considered a poor prognostic factor in SLE.

## AIM

Conducting a scientific analysis of domestic and foreign sources of information regarding modern conceptual views effectiveness of kidney transplantation in Lupus Nephritis.

## MATERIALS AND METHODS

The search for scientific sources related to the research topic was conducted using Google Scholar (Google Academy) and PubMed. This choice is justified because Google Scholar allows access to a wide range of full-text versions of scientific publications across all disciplines, while the specialized PubMed database focuses specifically on medical and biological sciences. The combined use of both platforms significantly expands the search results, capturing publications that may not be indexed in one of these services. This approach greatly enhances the quality of the subsequent review and critical analysis.

The search query used in both platforms was: («lupus nephritis» AND «kidney transplantation»). In Google Scholar, the results were limited to publications from 2017 to 2024. This timeframe was chosen to focus on recent research in the field. The following filters were applied for searching in PubMed: publication date within the last five years, and full-text availability.

As a result of the search, Google Scholar provided 25 relevant articles, while PubMed yielded 57. The subsequent processing of these publications followed

the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. This approach was chosen because the PRISMA framework ensures a structured, transparent, and reproducible process for systematic reviews and meta-analyses. It helps minimize bias, promotes comprehensive searching by including various sources, and enhances the quality of research by ensuring clear and standardized reporting. Adhering to PRISMA improves the scientific credibility of the results, reduces the risk of omitting important information, and ensures that the publications maintain a high reputation, which in turn increases their citation potential and future use in research and practice.

Thus, in this study, during the identification stage of scientific sources, which is the first and most critical step according to the PRISMA guidelines, the retrieved articles were compiled into a single document, and duplicates from overlapping indexing in both platforms were removed. Following this step, 55 articles were included in the review. During the screening and eligibility stages, several articles were excluded for being only tangentially related to the research topic or lacking full-text access. Consequently, at the inclusion stage, 21 articles that fully met the search criteria were selected for further review and analysis.

## ETHICS

All sources used in this literature review are publicly available.

## REVIEW AND DISCUSSION

The histological classification of LN includes six classes of glomerulonephritis, which were last revised by the International Society of Nephrology (ISN) and the Renal Pathology Society (RPS) in 2016, in Leiden, the Netherlands. During this revision, definitions were clarified, and indices of chronic activity of lupus nephritis were modified. This classification system is critical for guiding treatment and predicting outcomes in sick man with LN [3]. In the pathogenesis of LN, activation of B-lymphocytes and interferon production is observed in kidney tissues. B-lymphocytes contribute to the formation of autoantibodies, while interferons, particularly type I interferon, have a important role in driving the inflammatory and tissue damage. Knowledge these mechanisms is essential for progress targeted therapies to manage treat lupus nephritis effectively [4].

Recent studies have determined that several types of non-hematopoietic kidney cells express various immune molecules, contributing to the progression of the

inflammatory in the kidneys. These connections suggest that not only immune cells but also proper kidney cells, such as tubular epithelial and mesangial cells, play active roles in the pathogenesis of LN by promoting local inflammation and immune responses [5].

In recent years, the insights of the geneticopathogenic base of LN has significantly improved, thanks to extensive studies on various aspects of its pathogenesis. Apoptosis and secondary necrosis of leukocytes play a leading role in this process. Despite these advancements, kidney damage stay alone of the primary occasion of lethality in sick man with SLE, highlighting the need for on-going research and improved therapeutic strategies [6].

In 2019, a group of scientists applied single-cell RNA sequencing to kidney biopsies of sick man with lupus nephritis and analyzed keratinocyte sequencing in skin biopsies of case with proliferative LN, comparing these results to a control group. Their findings revealed that high levels of interferon and fibrosis in kidney glomeruli were associated with treatment ineffectiveness [7]. Additionally, B-lymphocyte IFN- $\beta$  correlated with the severe course of LN and depositions of small immune complexes (IK) in basal membrane of kidney glomeruli. In recent years, the frequency of kidney transplantation has increased as a strategy to improve the treatment of relapses and to alleviate complications associated with chronic kidney disease. This approach aims to provide better long-term outcomes and character of life for case suffering from refractory LN.

The results of our latest studies (2021) align with those of Taiwanese scientists from 2019. However, while we compared to effectiveness of kidney transplantation (KT) one month after surgery in a group of patients with terminal stage kidney disease, the Taiwanese researchers specifically examined the consequence and survival rate of case with end-stage renal failure caused by LN. Their study evaluated three distinctive renal subsitution therapies: peritoneal dialysis, hemodialysis and kidney transplantation. Scientists from Taiwan retrospective analyzed 94 patients with stage V chronic kidney disease caused by disease kidney. Among them, 42 (44.6%) get hemodialysis, 12 (12.7%) accepted peritoneal dialysis, 40 (42.5%) have KT. The study recorded potential bad events, survival rate, and accident of death. The general survival were higher in the KT compared to the peritoneal dialysis or hemodialysis groups. This indicates that KT is the most efficacious treatment therapy for sick man with V stage kidney failure caused by lupus nephritis [8].

Patients with SLE who require kidney transplantation need additional screening tests before surgery. These include tests for autoantibodies to dsDNA, ANA, and antiphospholipid antibodies (aCL, AFA), as well as a com-

prehensive thrombophilia screening. Special evaluation tests for immunological compatibility and radiological assessments for avascular necrosis of the femoral neck and coronary artery diseases are also necessary.

Screening for thrombophilia in SLE candidates for kidney transplantation includes testing for antiphospholipid antibodies (lupus anticoagulant, antiphospholipid antibodies), and other hemostatic markers of coagulation (protein C and S, antithrombin III, Leiden factor V). Additionally, a detailed history of vascular thrombosis, spontaneous abortions, and premature births should be obtained to ensure thorough assessment and optimal management of these patients [9].

Before kidney transplantation, patients must undergo tests for immunological compatibility. In patients with lupus nephritis, these tests have unique considerations. For example, complement-dependent cytotoxicity (CDC) cross-match test can yield pseudo-positive results due to the presence of autoantibodies or other autoimmune conditions, as SLE can cause cell lysis. To ensure reliable results, an autocross-match is performed using the recipient's serum and lymphocytes. Additionally, the solid-phase cross-match on a flow cytometer (FCXM) is used for greater accuracy and reliability in assessing immunological compatibility [10].

Clinical features of transplantation in lupus nephritis indicate the following: most patients with SLE who undergo hemodialysis do not exhibit active SLE. However, in some cases, SLE activity may persist despite hemodialysis. Many transplant centers recommend pre-transplant hemodialysis to reduce disease activity. While this approach can be beneficial in managing SLE, it may moderately worsen the long-term prognosis of kidney graft survival. With peritoneal dialysis, graft survival tends to fluctuate in tandem with the activity of SLE. This suggests that the effectiveness of peritoneal dialysis is closely linked to the disease's activity levels. Extended waiting periods for transplantation may be associated with outcomes that are equivalent to or worse than those of patients who receive a transplant sooner. This highlights the need for careful management and timely transplantation to optimize outcomes for patients with lupus nephritis [11].

Results from other studies indicate that kidney transplantation reduces the incidence of cardiological and vascular complications in sick man with LN. To further enhance the benefits of preventive kidney transplantation in SLE, it is essential to address socio-demographic difference and the extraordinary challenges angular by these case. Improving access to transplantation and tailoring care to the specific needs of SLE patients can help optimize outcomes and mitigate complications associated with the disease [12].

After kidney transplantation, 2-9% sick man with SLE may experience recurrent LN. Risk factors for recurrence include female sex, young age (under 33 years), African-American race, and the attendance of anticardiolipin antibodies in the recipient. Diagnosis of recurrent LN is confirmed by several indicators: a rapid increase in previously existing proteinuria, the new appearance of protein and erythrocytes in the urine, and a transplant biopsy. Management of recurrent lupus nephritis typically involves modifying the immunosuppressive regimen, increasing the dose of glucocorticosteroids, and administering cytotoxic agents to control the disease and protect the transplanted kidney.

The literature on the prognosis and effectiveness of KT in LN over a 15-years period reveals encouraging results. In studies conducted during this time frame, recipients did not experience arterial or venous thrombosis. Standard immunosuppressive protocols were employed in the treatment, and incidents of acute rejection transplanted were reported to be low, ranging from 1% to 2%. Furthermore, kidney transplant function was deemed satisfactory in 90% of recipients, highlighting the long-term success and stability of transplantation for lupus nephritis patients. Further studies assessed the survival rates of 185 kidney transplant recipients with lupus nephritis, revealing the following outcomes: 88% survival at one year, 82% at three years, 78% at five years, and 67% at ten years. Graft survival rates, excluding deaths, were 93% at one year, 89% at three years, 87% at five years, and 80% at ten years. Recurrent lupus nephritis was diagnosed in 2 patients (1.08%), but no grafts were lost due to this condition. During the follow-up period, 39 patients (21.1%) died, and 65 patients (35.1%) experienced graft loss. Multivariable Cox analysis identified that older recipients age and a glomerular filtration rate (GFR) of less than 45 mL/min/1.73 m<sup>2</sup> one month post-transplant were associated with poorer patients survival and an increased risk of graft loss. Conversely, induction immunosuppressive therapy was found to have a protective effect on patient survival [13].

Our studies on predicting kidney transplant loss in a cohort of 152 recipients, including five with SLE, confirmed these findings. Exploitation Kaplan-Meier method, Cox multivariate analysis, and advanced mathematical prediction techniques, we found that biochemical and immunological indicators—such as leukocyte counts, creatinine levels, proteinuria, and HLA antigen compatibility—played a crucial role. Additionally, the impact of different immunosuppression protocols was also significant in determining transplant outcomes one month after transplantation [14-16].

Elevated levels of both biomarkers were observed in two of the three recipients, who subsequently

experienced acute rejection crises and loss of graft function. NGAL is a promising biomarker for detecting proximal tubular damage and predicting retarded graft function in KT recipients, yet, its prognostic value varies between studies. One meta-analysis comparing the presageful values of urine NGAL and blood NGAL found that urine NGAL had superior predictive value for delayed graft function [17]. Another important biomarker of acute tubular dysfunction is uCystatin C, a 13 kDa protein from the cystatin family that inhibits cysteine proteases. Synthesized by fully nucleated cells at a persevering rate, Cystatin C is fully reabsorbed and metabolized in the renal tubules, resulting in complete clearance from the body. Cystatin C levels in urine and plasma are largely independent of body weight, age, and sex [18].

Several serological tests are effective in predicting acute kidney injury and transplant rejection: interleukin-18 (IL-18): this pro-inflammatory cytokine, excreted by macrophages, epithelial cells, and activated T lymphocytes, plays a basic role in inflammation and immune responses. KIM-1 (Kidney Injury Molecule-1): biomarker indicating kidney damage. L-FABP (Liver Fatty Acid-Binding Protein): a liver protein that binds adipose acids and is used to assess renal injury. Additionally, two genes are known to predict acute rejection: GOT2 (Glutamic-Oxaloacetic Transaminase 2): An enzyme involved in amino acid metabolism. STXB3 (Syntaxin Binding Protein 3): A protein that interacts with syntaxin 3, influencing cellular processes. Interleukin-21 (IL-21): This cytokine promotes type 1 activation and cytotoxicity of CD56+ dim CD16+ bright natural killer (NK) cells during antibody-mediated rejection of renal allografts, highlighting a novel connection between adaptive allo-immunity and innate humoral allo-immunity. Importantly, interleukin-6 (IL-6) and its receptor can be effectively inhibited by administering anti-IL-6/IL-6R monoclonal antibodies. This inhibition induces T regulatory (Treg) and B regulatory (Breg) lymphocytes in vivo, which may be crucial for preventing the cultivated of donor-specific antibodies (DSA) and mitigating allograft rejection. Preformed donor-specific DSA are a significant risk factor for acute rejection crises and graft loss. Even recipients who undergo desensitization regimens to address these antibodies face a statistically significant increased danger of acute rejection and graft loss after KT. Consequently, many kidney transplants ultimately fail after several years, typically due to chronic graft rejection and other undetected injuries [19, 20].

To address the need for early discovery of circulating pathology in transplantation, specific biomarker known as donor-derived cell-free DNA (ddcfDNA) was developed in the USA. This biomarker offers a proactive

beginning to monitoring by enabling first eduction of transplant-related issues. CcfDNA is present in plasma and can be measured using various methods. Advances now allow for the differentiation of ddcfDNA from recipient cfDNA in the plasma or urine of solid organ transplant recipients, even without prior genotyping case of donor and recipient.

The ddcfDNA assay is gaining attention as a non-invasive tool for determine acute AR in solid organ transplantation, including subclinical rejection crises, infections, or acute tubular damage. However, it can too be detected in clinically stable sick-man with normal histology. The assay shows higher sensitivity for detecting AMR compared to CMR. Unfortunately, normal ddcfDNA levels do not rule out significant cellular rejection. Therefore, while ddcfDNA measurement provides valuable information, it cannot replace biopsy, which last the basic standard for diagnosing AR [21].

Regulatory B-lymphocytes (Bregs) acting a crucial role in modulating the immune response across various diseases, including transplantation. Interleukin-10 (IL-10) expression is the most commonly used to marker for identifying Bregs. Although this review primarily focuses on transplantation efficacy in lupus nephritis, the role of Bregs in clinical transplantation is also significant. The overall impact B-lymphocytes on the immune responses and clinical exist results from a balance between Bregs and effector B-lymphocytes. Evidence suggests that the IL-10 in B-lymphocytes can predict immunological reactivity or clinical outcomes in kidney transplantation, offering valuable mechanistic insights into potential therapeutic strategies. Establishing immune tolerance and monitoring recipient immune status to improve allograft survival remain primary objectives in kidney transplantation [22].

Additionally, recent studies highlight that inhibiting activin can reduce the innate immune response in the early stages of KT in animals models. This inhibition also limits fibroblast accumulation in the graft, propose that activins may play a role in early fibrogenic signaling post-transplant. Serum activin A has been implicated in promoting vascular calcification and renal fibrosis in chronic kidney failure, with post-transplant activin levels independently associated with both allograft function and coronary artery calcification in renal transplant patients [23].

## CONCLUSIONS

Based on the above findings, we can conclude that KT is a favorable choice for patients with LN and V stage chronic kidney disease. It offers better survival rates and a lower complication rate compared to hemodialysis

and peritoneal dialysis. Survival rates for kidney transplantation over 5 to 10 years are comparable to those for patients with other diseases. The risk of recurrent lupus nephritis (2-9%) is lower compared to other glomerular diseases. While recurrent lupus nephritis can occur, particularly when assessed by treatment protocols and biopsy results, it rarely progresses to graft failure in most patients. However, serological markers such

as dsDNA titers and complement levels are not always reliable for predicting disease recurrence. Therefore, thrombophilia screening is recommended for transplant candidates with SLE, and anticoagulants should be prescribed for patients with antiphospholipid antibodies. Identifying new immunological markers is crucial for the early diagnosis and prevention of acute kidney damage and subsequent graft loss.

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### CONFLICT OF INTEREST

The Author declare no conflict of interest

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