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**Original Scientific Article**

# EVALUATION OF SERUM PERIOSTIN AND PIIINP AS BIOMARKERS OF RENAL FIBROSIS AND FUNCTION DECLINE IN RENAL TRANSPLANT PATIENTS

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**Abstract.** This study aimed to evaluate the potential of serum periostin and N-terminal propeptide of type III procollagen (PIIINP) as biomarkers for predicting renal fibrosis and functional decline in renal transplant patients. We conducted a two-visit observational study among 86 renal allograft patients, reduced to 35 at the two-year follow-up due to the COVID-19 pandemic. Blood samples were collected at baseline and follow-up, while urine samples were collected only at follow-up. Serum levels of PIIINP and periostin were measured using ELISA kits, and various renal function parameters were assessed. Serum PIIINP levels showed a significant decrease over two years ($p<0.001$, Wilcoxon test), while periostin levels significantly increased ($p<0.001$, Wilcoxon test). These changes correlated with declines in renal function, as indicated by decreased serum albumin and creatinine clearance levels, and increased serum creatinine levels. Significant correlations were found between changes in PIIINP and creatinine clearance (Spearman coefficient = 0.352, $p<0.05$), as well as between changes in periostin and creatinine clearance (Spearman coefficient = 0.626, $p<0.001$). Our findings suggest that serum periostin and PIIINP levels are valuable biomarkers for assessing renal fibrosis and functional decline in renal transplant patients. These biomarkers may provide insights into disease progression and guide therapeutic interventions.

**Key words**: renal fibrosis, kidney transplant, chronic allograft nephropathy (CAN), biomarkers, periostin, N-terminal propeptide of type III procollagen (PIIINP), renal function decline

## Introduction

Renal fibrosis, a critical pathological process involving various components of the kidney such as tubules, interstitial tissue, glomeruli, and blood vessels, can lead to a progressive decline in kidney function. Normally, fibrosis is a reparative response to injury; however, prolonged chronic injurious stimuli can result in excessive production and deposition of extracellular matrix (ECM), leading to pathological fibrosis [1,2].

In most cases, tubulointerstitial fibrosis is driven by chronic inflammatory processes. In these instances, renal injury is mediated by an inflammatory cascade that involves the activation of macrophages and the recruitment of immune cells. Under the influence of inflammatory cytokines, macrophages, tubular epithelial cells, and immune cells (mainly T-cells) produce profibrotic mediators such as Transforming Growth Factor-β (TGF-β), Connective Tissue Growth Factor (CTGF), and Platelet-Derived Growth Factor (PDGF), along with other proinflammatory mediators. These factors induce changes in epithelial cells and recruit fibroblasts, which then transform into contractile myofibroblasts responsible for ECM production. The contractile properties of myofibroblasts are crucial for wound contraction during the healing process [3,4].

When the injury is severe or persistent, fibrosis can progress to a point of no return, despite the resolution of the initial injury. Persistent inflammation results in further fibrosis progression and collagen deposition, creating a microenvironment that leads to cell damage and oxidative stress. Progressive kidney diseases are characterized by ECM deposition, primarily involving collagen types I, III, and IV. While all three collagen types are present in the tubulointerstitium, glomeruli contain only types III and IV [5,6].

Chronic allograft nephropathy (CAN) is one of the leading causes of graft loss in kidney transplant recipients, occurring in approximately 25% of patients within the first year post-transplant and up to 90% by ten years [7]. CAN is characterized by interstitial fibrosis and tubular atrophy (IF/TA), resulting from immune-mediated

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and non-immune mediated injuries. Immune-mediated injuries include cellular and antibody-mediated rejection, while non-immune mediated causes encompass calcineurin inhibitor nephrotoxicity, hypertension, and diabetic nephropathy [8]. Persistent inflammation and maladaptive repair mechanisms lead to progressive fibrosis, declining graft function, and eventual graft failure. Despite improvements in short-term patient and graft outcomes, long-term clinical outcomes of recipients of kidney transplants remain suboptimal [5].

Recent advances in understanding the pathogenesis of CAN have highlighted the importance of identifying reliable and non-invasive biomarkers for early detection and monitoring of disease progression. Non-invasive biomarkers are particularly valuable as they offer a safer and more practical alternative to repeated biopsies, often not feasible in routine clinical practice. Emerging evidence suggests that certain urine biomarkers, such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and interleukin-18 (IL-18), may be indicative of ongoing renal injury and associated with adverse outcomes in kidney transplant recipients [7,9]. Building on these findings, this study aims to evaluate the potential of both serum and urine biomarkers, including periostin (POSTN) and the N-terminal propeptide of type III procollagen (PIIINP), in predicting CAN progression and to explore their utility in early detection and therapeutic monitoring. By investigating these biomarkers, we hope to contribute to the development of more precise and proactive strategies for managing chronic allograft injury and improving long-term graft survival.

## Material and Methods

### Study Design and Participant Selection

This study was conducted among renal transplant patients who visited the Nephrology Clinic at the University Clinical Center of Nis, Serbia, between 2020 and 2022. Ethical approval was granted by the Board of Ethics of the University Clinical Center of Nis (No 31445/5). Inclusion criteria included adults of both sexes, aged over 18 years, with a functional transplant for at least 6 months post-operation. Exclusion criteria were acute transplant rejection, active infections, or malignancies.

*Data Collection*

Upon enrollment, comprehensive demographic, clinical, and laboratory data were prospectively collected through medical records and the hospital's health information system (Heliant, v7.3, r48602). Collected information included demographic details (such as age, gender, and BMI), medical history, and various laboratory measurements. Blood and urine samples were collected from all participants during routine clinic visits. Samples were processed within 2 hours of collection, with plasma and urine separated by centrifugation at 3000 rpm for 10 minutes and stored at -80°C until further analysis.

*Biomarker Measurement*

Levels of N-terminal propeptide of type III procollagen (FineTest Corp.; Cat.No: EH0960) and periostin (FineTest Corp.; Cat.No: EH0255) were measured using ELISA kits from FineTest, adhering to the provided guidelines. The N-terminal propeptide of type III procollagen ELISA kit has a sensitivity of 18.75 pg/ml, while the periostin kit has a sensitivity of 0.094 ng/ml. Assays were performed according to the manufacturer's instructions, and the sensitivity and potential interference from other substances were evaluated to ensure the accuracy and validity of the results.

*Outcome*

We compared serum levels of PIIINP and periostin between the initial measurement and the two-year follow-up. The primary outcome was the progression of chronic kidney disease (CKD), defined by changes in serum albumin levels, serum creatinine levels, and creatinine clearance. The goal of this study was to determine whether these biomarkers could serve as predictive factors for the decline in kidney function in allograft patients.

*Statistical Analysis*

The data were statistically processed using IBM SPSS v27.0, with measures of central tendency and variability determined. The Kolmogorov-Smirnov test was used to assess the normality of the data distribution. Depending on the data characteristics, various statistical tests were applied: Student's t-test for paired samples and independent samples, Mann-Whitney U test, Wilcoxon signed-rank test, and Spearman and Pearson correlation analysis. Statistical significance was set at a p-value of $<0.05$.

## Results

### Patient Demographics and Clinical Characteristics

Initially, 86 renal allograft patients were enrolled in this study. However, at the two-year follow-up, the number of participants was reduced to 35 (71.4% men, 28.6% women). The mean age of the patients was 44.37±11.58 years, the mean time since transplantation was 6.73±4.33 years, and the mean BMI was 25.37±4.33. This study involved a two-visit observational design, with blood samples collected at the initial visit and both blood and urine samples collected at the follow-up visit. Descriptive statistics of the examined laboratory parameters in renal allograft patients are shown in Table 1, and the levels of examined biomarkers are presented in Table 2. Table 1 shows the significant decrease in PIIINP levels from 18.015±4.18 ng/ml at baseline to 13.22±2.85 ng/ml at follow-up. Continuous variables with normal and skewed distributions were expressed as means with standard deviations or medians with interquartile ranges.

The primary objective was to determine whether PIIINP and periostin levels could reflect a decrease in renal function in these patients. Serum levels of PIIINP and periostin were measured at baseline and the two-year follow-up. Additionally, we assessed creatinine clearance and serum albumin levels.

**Table 1** Level of biomarkers in first and second measurement

| Biomarker | | Mean±SD, Median (IQR) | Statistical significance (p) |
|---|---|---|---|
| PIIINP (ng/ml) | Baseline | 18.015± 4.18 18.79 (7.23) | Wilcoxon=-3.748, p<0.001 |
| | Follow-up | 13.22 ± 2.85 12.35 (1.83) | |
| POSTN (ng/ml) | Baseline | 7.45 ± 7.30 5.85 (4.72) | Wilcoxon=4.021, p<0.001 |
| | Follow-up | 15.67 ± 3.71 15.67 (4) | |

PIIINP- N-terminal propeptide of type III procollagen, POSTN-periostin

**Table 2** Descriptive statistics of laboratory parameters with Student t-test and Wilcoxon test

| Laboratory Parameters | | Mean±SD | Statistical significans (p) |
|---|---|---|---|
| Albumine (g/l) | Baseline | 40.70± 3.44 | t=5.906, p<0.001 |
| | Follow-up | 37.63± 2.93 | |
| Creatinine (μmol/l) | Baseline | 127.83±37.73 | t= -2.490, p<0.05 |
| | Follow-up | 139.24±43.63 | |
| Creatinine Clearance (ml/min) | Baseline | 70.76± 24.13 | t=3.638, p<0.001 |
| | Follow-up | 63.86± 22.78 | |
| Creatine kinase (U/l) | Baseline | 98.90± 97.97 | Wilcoxon=223.5 0, p=0.897 |
| | Follow-up | 87.97± 63.05 | |
| Glucose (mmol/l) | Baseline | 5.43± 1.43 | Wilcoxon=235.5 0, p<0.05 |
| | Follow-up | 5.56± 1.57 | |
| Potassium (mmol/l) | Baseline | 4.36± 0.51 | Wilcoxon=92.50, p<0.05 |
| | Follow-up | 4.26± 0.48 | |
| Sodium (mEQ/l) | Baseline | 138.70± 2.73 | Wilcoxon=88.50, p<0.05 |
| | Follow-up | 136.88± 3.07 | |
| Calcium (mg/dl) | Baseline | 2.43± 0.16 | Wilcoxon=68.00, p<0.01 |
| | Follow-up | 2.35± 0.20 | |
| Phosphorus (mmol/l) | Baseline | 1.04± 0.18 | t=0.317, p=0.753 |
| | Follow-up | 1.02± 0.14 | |
| Urea (mg/dl) | Baseline | 8.07± 2.92 | t=1.878, p=0.071 |
| | Follow-up | 7.22± 2.63 | |
| Uric acid (nmol/l) | Baseline | 397.33± 86.82 | Wilcoxon=154.0 0, p=0.170 |
| | Follow-up | 373.62± 73.51 | |
| Cholesterol (mmol/l) | Baseline | 4.91± 1.09 | t= -5.725, p<0.001 |
| | Follow-up | 5.59± 1.24 | |
| Triglicerides (mmol/l) | Baseline | 4.93± 16.47 | Wilcoxon=157.5 0, p=0.194 |
| | Follow-up | 1.68± 0.63 | |
| ALT (U/l) | Baseline | 33.00± 18.58 | Wilcoxon=96.00, p<0.05 |
| | Follow-up | 30.42± 16.35 | |
| AST (U/l) | Baseline | 19.93± 7.07 | Wilcoxon=85.00, p=0.106 |
| | Follow-up | 18.70± 7.52 | |
| GGT (U/l) | Baseline | 29.07± 14.20 | Wilcoxon=105.0 0, p<0.05 |
| | Follow-up | 28.91± 16.62 | |
| LDH (U/l) | Baseline | 389.07±119.28 | Wilcoxon=77.00, p<0.01 |
| | Follow-up | 365.74±110.70 | |

Using Student's t-test, we found that, after two years, the levels of serum albumin (t=5.906, p<0.001) and creatinine clearance (t=3.638, p<0.001) were significantly lower at the second visit compared to the first. During the follow-up period, serum creatinine levels increased (t= -2.490, p<0.05), indicating impaired renal function. The Wilcoxon test was used to compare PIIINP and periostin concentrations between the two measurement time points.

### Relationship between serum PIIINP and renal function

Serum PIIINP levels in plasma samples were significantly different, showing a decrease after two years (p<0.001, Wilcoxon test z=-3.748) (Figure 1). This decrease paralleled the decline in renal function, as indicated by lower serum albumin and creatinine clearance levels, and increased serum creatinine levels. Table 1 shows the significant decrease in PIIINP levels from 18.015±4.18 ng/ml at baseline to 13.22±2.85 ng/ml at follow-up.

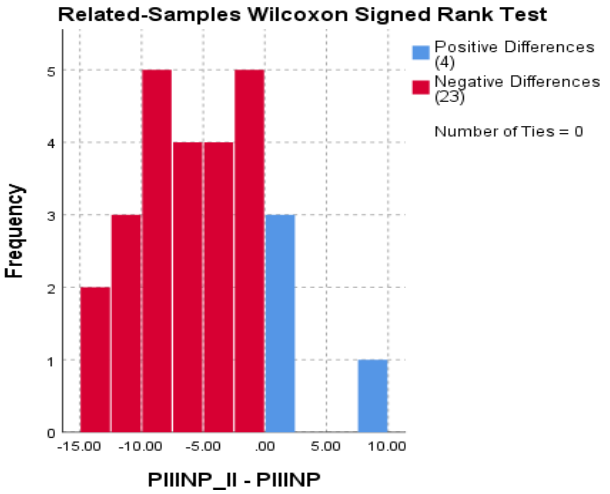


**Fig. 1** Frequency of positive differences between second and first measurement of PIIINP versus negative differences

### Relationship between serum periostin and renal function

Mean periostin serum levels were significantly higher in the second measurement compared to the first (p<0.001, Wilcoxon test z=4.021) (Figure 2). This increase paralleled

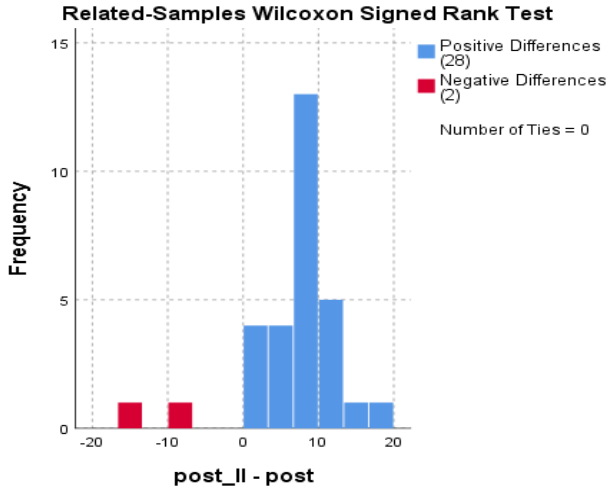


**Fig. 2** Frequency of positive differences between second and first measurement of periostin versus negative differences

the decline in renal function, as indicated by lower serum albumin and creatinine clearance levels, and increased serum creatinine levels. Table 1 demonstrates the significant increase in periostin levels from 7.45±7.30 ng/ml at baseline to 15.67±3.71 ng/ml at follow-up.

### Correlation of Biomarkers with Kidney Function

In addition to examining the levels of procollagen III and periostin and establishing a statistically significant decrease in serum procollagen III and an increase in serum periostin, we aimed to define the significance of these biomarkers in assessing kidney function. We analyzed the correlation between the changes in PIIINP (the difference between the first and second measurements) and changes in creatinine clearance, albumin, and blood creatinine levels. Similarly, we assessed the correlation for the difference in periostin levels. The differences were calculated by subtracting the initial measurement values from the follow-up values for all parameters (Table 3),

**Table 3** Descriptive statistics of differences between second and first measurement

| Biomarker | Mean ± SD |
|---|---|
| ΔPIIINP | -2.71 ± 9.15 |
| ΔPeriostin | 8.22 ± 6.49 |
| ΔCLCr | 0.86 ± 26.83 |
| ΔCr | 28.66 ± 69.15 |
| ΔAlbumine | -0.48 ± 19.43 |
| ΔUrea | 0.46 ± 4.79 |
| ΔUric acid | 22.37 ± 162.94 |

Δ-difference between second and first measurement, PIIINP-N-terminal propeptide of type III procollagen, CLCr-cretinine clearance, Cr- creatinine

### Correlation between Difference in PIIINP and Differences in Creatinine Clearance and Albumin

A statistically significant correlation was found between the difference in PIIINP and the difference in creatinine clearance (Spearman coefficient = 0.352, p<0.05) (Figure 3). Additionally, a decrease in albumin levels was associated with an increase in PIIINP levels (Spearman coefficient = 0.38, p<0.05) (Figure 4).

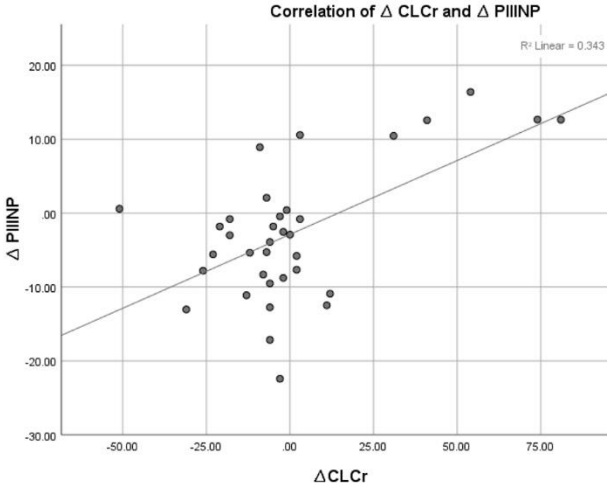


**Fig. 3** Correlation of ΔCLCr and ΔPIIINP

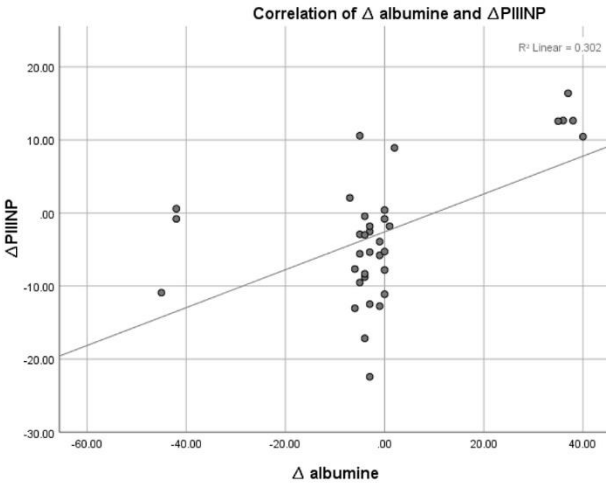


**Fig. 4** Correlation of Δ albumine and ΔPIIINP

### Correlation between Difference in Periostin and Difference in Creatinine Clearance

A significant positive correlation was established between the difference in periostin levels and the change in creatinine clearance (Spearman coefficient = 0.626, p<0.001). This suggests that increases in periostin levels are associated with declines in renal function, as indicated by decreased creatinine clearance (Figure 5).

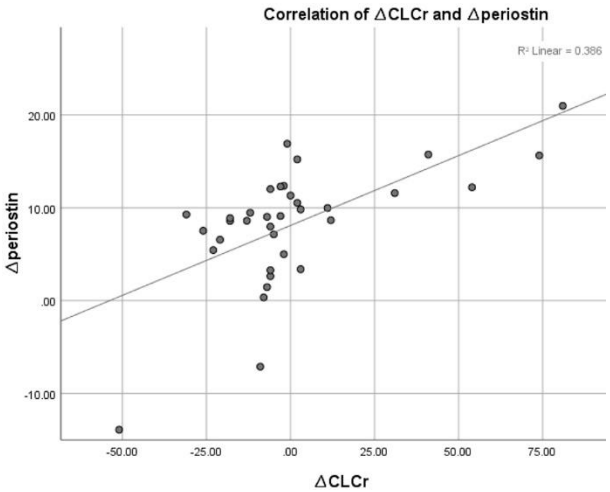


**Fig. 5** Correlation of ΔCLCr and Δ periostin

## Discussion

Our study highlights the significance of serum PIIINP and periostin levels as biomarkers in predicting renal fibrosis and functional decline in renal transplant patients. We found that serum PIIINP levels significantly decreased, while periostin levels significantly increased over two years, both correlating with a decline in renal

function. This suggests that serum periostin may serve as a potential biomarker for ongoing fibrotic processes, while serum PIIINP could reflect changes in extracellular matrix turnover.

Type I and III collagens are key components of the extracellular matrix (ECM) that contribute to renal fibrosis. During the synthesis and deposition of type III collagen, an amino-terminal propeptide (PIIINP) with a molecular weight of 44 kDa is cleaved from the collagen and released into the extracellular matrix and bodily fluids, including blood and urine. Elevated circulating levels of PIIINP are indicative of ongoing fibrotic processes. Due to its molecular weight, PIIINP can be filtered in the glomeruli and reabsorbed in the proximal tubules. Thus, increased urinary excretion of PIIINP might indicate reduced tubular reabsorption [10].

Despite the expected increase in fibrosis typically observed in nephropathies post-transplantation and the use of certain immunosuppressants [11], our findings showed a significant decrease in serum PIIINP levels. Patients in our study were treated with cyclosporin, tacrolimus, or m-TOR inhibitors, all of which are known for their nephrotoxic potential. Additionally, corticosteroid therapy was also used. These therapies were administered both before the initial measurement and continued between the two measurements. Previous studies have shown that steroids and cyclophosphamide can decrease PIIINP synthesis [12,13], which could partially explain why serum PIIINP levels were not a representative biomarker for our transplant patients.

The discrepancy in our results may also be attributed to the impaired tubular reabsorption and increased urinary loss of PIIINP due to declining renal function. Considering the molecular weight and reabsorption characteristics of PIIINP, the decreased serum levels observed in our study might be more plausibly explained by impaired tubular reabsorption rather than decreased synthesis alone. This hypothesis aligns with our understanding of tubular function impairment leading to increased urinary excretion of PIIINP, rather than its local synthesis within the kidneys, opposing some previous findings that associate increased serum PIIINP with greater fibrosis [10,12].

Periostin is a protein involved in tissue repair, inflammation and fibrosis. It is part of the ECM and elevated levels can be observed in tissues undergoing fibrotic changes. Elevated levels of periostin are associated with carcinoma, diabetic retinopathy, cardiovascular diseases and polycystic kidney disease. It is induced during nephrogenesis but is not found in healthy adults [14].

Studies have shown that periostin is not filtered in the kidneys and its main source in urine is tubular. These findings support the proposition that periostin is a biomarker of tubular injury rather than glomerular injury [14]. The activation of the TGF-β pathway, a key event in the development of renal fibrosis, induces periostin expression [15]. In vitro studies have demonstrated that TGF-β1 stimulation of mesangial cells results in the induction of periostin [16]. Periostin interacts with integrins and promotes the deposition of collagen I, contributing to ECM remodelling and the progression of interstitial fibrosis [17,18].

In previous studies, renal expression of periostin was reported to contribute to cyst growth and fibrosis in polycystic kidney disease [19]. Additionally, periostin expression was highly induced during renal disease in wild-type mice, whereas mice lacking periostin expression exhibited less inflammatory changes, likely due to decreased TGF-β1 signalling [15].

The increased level of serum periostin in the second measurement in our study could indicate an ongoing fibrotic process. The correlation analysis showed that increases in periostin levels are associated with declines in renal function, as indicated by decreased creatinine clearance. This suggests that serum periostin could serve as a useful biomarker for monitoring renal fibrosis in renal transplant patients.

Based on the decrease in renal function shown through results (CLCr and albumin levels) and the previously mentioned statistical differences between periostin and PIIINP levels in the first and second measurements, we can conclude that the decline in kidney function is accompanied by an increase in serum periostin levels and a decrease in PIIINP levels in renal allograft patients. This indicates that these biomarkers may provide valuable insights into the progression of renal fibrosis and could potentially guide therapeutic interventions.

## Conclusion

Our findings indicate that serum periostin and PIIINP levels are valuable biomarkers for assessing renal fibrosis and functional decline in renal transplant patients. The increase in periostin and decrease in PIIINP levels over two years strongly correlate with impaired renal function, suggesting their potential utility in monitoring and guiding therapeutic interventions in this patient population.

STATEMENT OF ETHICS. *Study approval statement*: The study protocol was reviewed and approved by the Institutional Review Boards of the University Clinical Center Nis (approval number 31445/5). The study adhered to the guidelines outlined in the Helsinki Declaration, emphasizing ethical principles for medical research involving human subjects.

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