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Kidney Outcomes with Corticosteroid Treatment in IgA Nephropathy According to the Oxford-MEST-C Classification

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Keywords
IgA nephropathy · Corticosteroids · Renal pathology · Oxford-MEST-C classification · Treatment

Abstract
Introduction: Despite optimization of renin-angiotensin-aldosterone system (RAAS) inhibition, patients with IgA nephropathy remain at risk for kidney failure. The effect of steroids on kidney outcomes in IgA nephropathy with different renal pathologic lesions has been uncertain. ***Objective:*** This study aimed to evaluate the efficacy of steroid treatment in IgA nephropathy patients classified according to the Oxford-MEST-C classification. ***Methods:*** We retrospectively studied 67 patients with biopsy-proven IgA nephropathy who were receiving optimized RAAS inhibitor therapy and had persistent proteinuria >1 g/day between January 2016 and December 2020. Clinical parameters, including estimated glomerular filtration rate (GFR) decline, were compared between the corticosteroid and supportive treatment groups. ***Results:*** Overall, 68.7% of patients received treatment with corticosteroids. The median estimated GFR decline was significantly lower in the steroid group compared to the controls {−0.65 (interquartile range [IQR] −3.45 to 7) vs. −5.75 (IQR −10.65 to −0.7) mL/min/1.73 m^2/year, p = 0.025}. The slope of estimated GFR was also significantly different between the steroid and control groups in patients with a baseline GFR >50 mL/min/1.73 m^2 (3.90 ± 11.42 vs. −9.31 ± 5.08 mL/min/1.73 m^2/year, p = 0.011), mesangial hypercellularity M0 score (4.69 ± 11.37 vs. −2.63 ± 6.42 mL/min/1.73 m^2/year, p = 0.049), and C0 score (2.48 ± 12.63 vs. −5.58 ± 8.4 mL/min/1.73 m^2/year, p = 0.026). Additionally, rapid GFR decline (>5 mL/min/1.73 m^2/year) occurred in 9 patients (19.6%) in the steroid group compared with 11 participants (52.4%) in the control group (p = 0.006). ***Conclusion:*** Corticosteroid therapy, in addition to optimized RAAS inhibition, lowers the risk of kidney disease progression in patients with IgA nephropathy, particularly those with a baseline GFR >50 mL/min/1.73 m^2 and those classified with Oxford scores M0 and C0.

Introduction

IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide in patients undergoing renal biopsy [1], with a highly variable clinical course ranging from benign to rapidly progressive kidney failure. Some patients may achieve remission or stable kidney function, while others progress to end-stage kidney disease (ESKD) [2, 3].

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The initial treatment for IgAN involves supportive care and renin-angiotensin-aldosterone system (RAAS) inhibitors for patients with proteinuria >0.5 g/day. According to KDIGO guidelines, immunosuppressive medications, especially corticosteroids, are recommended for high-risk patients, including those with proteinuria >1 g/day who have been on RAAS inhibitors for at least 90 days [4]. However, patients with an estimated glomerular filtration rate (GFR) <50 mL/min/1.73 m^2 may be at higher risk of adverse events with immunosuppressive therapy [5]. Notably, 2 patients in our cohort died from infections, highlighting the risks of such treatments. The VALIGA study supports the use of corticosteroids in addition to RAAS inhibitors for patients with proteinuria >1 g/day, even with an initial eGFR ≤50 mL/min/1.73 m^2 [6].

Recent advancements, such as the International Risk-Prediction Tool for IgAN, have provided new ways to predict kidney outcomes based on histological, clinical, and biomarker data [7]. Tubulointerstitial inflammation and fibrosis are strongly associated with renal decline [8], and the Oxford-MEST-C criteria have been validated as key indicators of poor prognosis [9–11]. However, data on the use of these pathological findings to guide immunosuppressive therapy remain limited. This study aims to analyze data from Thai patients diagnosed with IgAN at Phramongkutklao Hospital between 2016 and 2020, focusing on the correlation between renal characteristics and clinical outcomes of corticosteroid and RAAS inhibitor treatment compared to RAAS inhibitor treatment alone.

Methods

This study is a retrospective cohort analysis approved by the Institutional Review Board of the Royal Thai Army Medical Department (Approval number R171h/64). The sample size was determined based on the study, "Corticosteroids in IgA Nephropathy: A Retrospective Analysis from the VALIGA Study." With a power of 80%, the sample size for each group was set at 198 patients, aiming for a p value of <0.05 to detect statistical significance.

Data were collected from patients diagnosed with IgAN through biopsy at Phramongkutklao Hospital between January 2016 and December 2020. The inclusion criteria were as follows: patients aged 20 years or older at the time of diagnosis, who received treatment and follow-up at Phramongkutklao Hospital for at least 1 year (or less if diagnosed with end-stage kidney disease), had proteinuria of at least 1 g per day, and did not receive other immunosuppressive drugs (except corticosteroids) or sodium-glucose cotransporter 2 inhibitors during the study period. Patients with Henoch-Schönlein purpura, diabetes, cancer, active infections, severe cardiovascular disease, chronic liver disease, pregnancy, other autoimmune disorders, or those who had recently received immunosuppressive therapy were excluded from the study.

The study collected basic demographic data from the patients, including gender, age, estimated GFR, prior use of RAAS inhibitors, prior use of immunosuppressive drugs, prior use of antihypertensive medications, biopsy findings classified according to the MEST-C criteria, follow-up duration, mean arterial pressure, and initial proteinuria levels. The decision to initiate corticosteroid therapy was made based on clinical discretion and local treatment guidelines, which considered factors such as persistent proteinuria despite optimized RAAS inhibition and baseline kidney function. However, as treatment decisions were not standardized and were influenced by individual clinician judgment, this could introduce selection bias and limit the ability to draw definitive conclusions regarding the efficacy of corticosteroids in all patients with IgAN. Corticosteroid therapy was generally initiated for patients with persistent proteinuria (>1 g/day) despite optimized RAAS inhibition and stable or mildly reduced eGFR. The standard regimen typically involved an induction phase with oral prednisolone at a dose of 0.5–1 mg/kg/day for 4–6 weeks, followed by a gradual tapering phase over 6 months. Adjustments to the dosing schedule were made based on clinical response and tolerability, with the specific regimen and duration individualized by the treating nephrologist.

The main objective of this study was to investigate the response to corticosteroids in combination with RAAS inhibitors compared to RAAS inhibitors alone in patients with IgAN, categorized by the Oxford classification based on the rate of decline in estimated GFR. The secondary objective was to compare the response to corticosteroids combined with RAAS inhibitors against RAAS inhibitors alone, focusing on a decline in estimated GFR of more than 50%, the rate of proteinuria decline (g/day/year), proteinuria levels of <1 g/day, and the development of ESKD.

Statistical Analysis

This research utilized IBM SPSS for Windows version 23.0 to calculate and analyze the data. The chi-square test or Fisher's exact test was employed to examine the relationships between categorical variables. For assessing differences in means between two independent groups, either the independent t-test or the Mann-Whitney U test was applied. Missing data were addressed using multiple

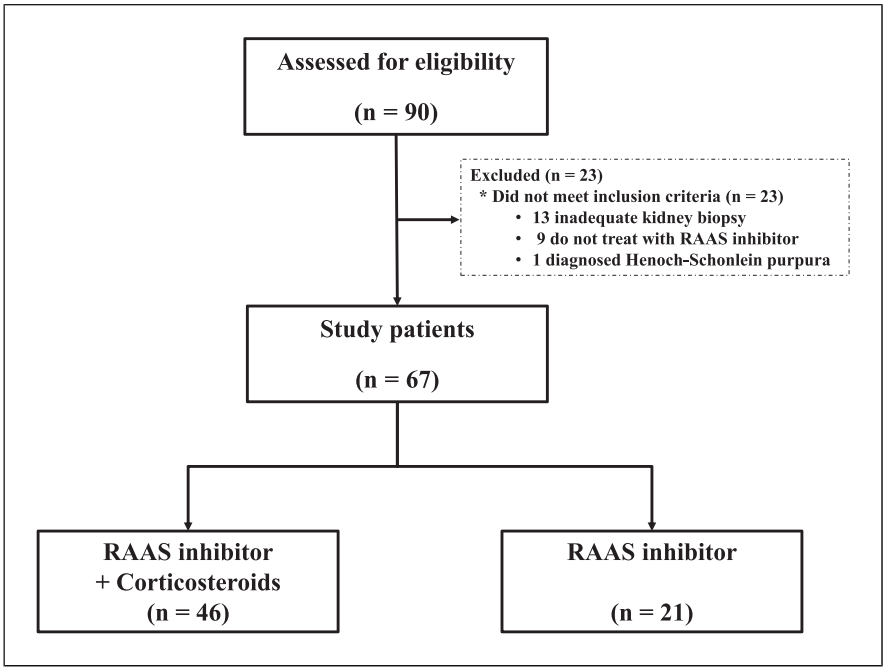

Fig. 1. Flowchart of the study.

imputation with fully conditional specification, and sensitivity analyses were performed to assess the impact of missing data on the results. Potential confounders, including baseline GFR, proteinuria, and comorbidities, were adjusted for in multivariate regression models to minimize confounding. Additionally, stratified analyses were conducted based on baseline GFR and Oxford-MEST-C classification scores to account for heterogeneity in patient characteristics.

Results

We collected patient data from January 2016 to December 2020. From the initial cohort, 90 patients met the inclusion criteria. However, 9 patients were excluded for not using RAAS inhibitors, 13 due to inadequate biopsy results, and 1 for a diagnosis of Henoch-Schönlein purpura. Ultimately, a total of 67 patients were included in the study, as illustrated in Figure 1.

Baseline Characteristics

Among the included patients, 68.7% received corticosteroid treatment. The baseline characteristics were similar between the corticosteroid and control groups, except for the estimated GFR, which was significantly higher in the corticosteroid group (59.64 ± 32.48 vs. 40.75 ± 18.57; $p = 0.004$). Regarding baseline use of RAAS inhibitors, only 26% of patients in the control group and 43% in the steroid group were taking RAAS inhibitors at the time of kidney biopsy. However, during the follow-up period, all patients in both groups received RAAS inhibitors. Additionally, the percentage of patients with segmental glomerulosclerosis was lower in the corticosteroid group (33 [71.74%] vs. 21 [100%]; $p = 0.006$) (Table 1).

Clinical Outcomes

The follow-up period for all patients was at least 6 months, with a median follow-up time of 14 months (interquartile range: 7–23 months). The median decline in eGFR was significantly lower in the corticosteroid group compared to the control group (−0.65 [IQR −3.45 to 7] vs. −5.75 [IQR −10.65 to −0.7] mL/min/1.73 m^2/year; $p = 0.025$). Rapid eGFR decline (>5 mL/min/1.73 m^2/year) occurred in 9 patients (19.6%) in the corticosteroid group, compared to 11 patients (52.4%) in the control group ($p = 0.006$). However, there were no significant differences between the groups regarding the incidence of ESKD, eGFR decline >50%, or proteinuria remission (Table 2).

We report both the mean and median changes in proteinuria (g/day/year) as quantitative measures of response to treatment. Although the overall reduction in proteinuria did not achieve statistical significance between the groups ($p = 0.101$), the corticosteroid group showed a greater reduction in proteinuria and a higher proportion of patients achieving proteinuria levels <1.0 g/day compared to the control group.

Table 1. Baseline characteristics

Baseline characteristics	Without corticosteroid (n = 21)	With corticosteroid (n = 46)	p value
Male, n (%)	7 (33.33)	14 (30.43)	0.812
Age, years	44.38±13.83	38.04±12.09	0.062
Estimated GFR, mL/min/1.73 m^2	40.75±18.57	59.64±32.48	0.004
Prior RAAS inhibitors at the time of kidney biopsy, n (%)	9 (42.86)	12 (26.09)	0.170
Prior immunosuppressive agents, n (%)	–	2 (4.35)	0.999
Prior antihypertensive agent, n (%)	10 (47.62)	11 (23.91)	0.052
Duration of disease, years	1.71±1.01	1.57±1.07	0.360
Mean arterial blood pressure at the time of kidney biopsy, mm Hg	99.52±11.24	100.35±12.65	0.799
Average mean arterial blood pressure during the follow-up period, mm Hg	90.27±8.15	88.35±7.12	0.490
Urine protein, g/day	3.05±1.79	3.68±2.38	0.284
Mean urine protein with IQR, g/day	3.0 (1.6–3.5)	3.1 (1.9–4.47)	
The Oxford-C classification			
Mesangial hypercellularity, n (%)			0.479
M0	12 (57.14)	22 (47.83)	
M1	9 (42.86)	24 (52.17)	
Endocapillary proliferation, n (%)			0.173
E0	10 (47.62)	30 (65.22)	
E1	11 (52.38)	16 (34.78)	
Segmental glomerulosclerosis, n (%)			0.006
S0	–	13 (28.26)	
S1	21 (100.00)	33 (71.74)	
Tubular atrophy/interstitial fibrosis, n (%)			0.122
T0	9 (42.86)	29 (63.04)	
T1-2	12 (57.14)	17 (36.96)	
Crescents, n (%)			0.465
C0	16 (76.19)	31 (67.39)	
C1-2	5 (23.81)	15 (32.61)	

Data are presented as mean and standard deviation. GFR, glomerular filtration rate; IQR, interquartile range; MAP, mean arterial pressure; RAAS, renin-angiotensin-aldosterone system.

Subgroup Analysis

Subgroup analyses indicated that corticosteroid treatment was associated with a significantly slower rate of eGFR decline per year in patients with a baseline eGFR >50 mL/min/1.73 m^2 (3.9 ± 11.42 vs. −9.31 ± 5.08 mL/min/1.73 m^2/year; p = 0.001), those with mesangial hypercellularity (M0) (4.69 ± 11.37 vs. −2.63 ± 6.42 mL/min/1.73 m^2/year; p = 0.049), and patients with crescentic glomerulonephritis (C0) (2.48 ± 12.63 vs. −5.58 ± 8.4 mL/min/1.73 m^2/year; p = 0.026) (Table 3). However, there were no significant differences in proteinuria remission outcomes between the groups (Table 4).

Adverse Events

The incidence of adverse events, including hospitalization, was similar across both treatment groups. The most common adverse events were pneumonia and urinary tract infections, occurring in 3 (14.28%) patients in the control group and 7 (15.2%) in the corticosteroid

Table 2. Clinical outcomes in patients with and without corticosteroid treatment

Outcomes	Without corticosteroid (n = 21)	With corticosteroid (n = 46)	p value
GFR decline (mL/min/1.73 m^2/year)			
Mean±SD	−5.68±7.89	2.81±16.00	0.025
Median (IQR)	−5.75 (−0.7 to −10.65)	−0.65 (7 to− 3.45)	
GFR decline >5 mL/min/1.73 m^2/year, n (%)	11 (52.38)	9 (19.57)	0.006
GFR decline >50% from baseline, n (%)	2 (9.52)	4 (8.70)	0.999
ESKD, n (%)	5 (23.81)	6 (13.04)	0.301
Proteinuria reduction (g/day/year)			
Mean±SD	0.37±5.59	−1.34±2.84	0.101
Median (IQR)	0.47 (0.2 to 0.98)	1.28 (0.33 to 2.35)	
Proteinuria <0.5 g/day, n (%)	–	7 (15.22)	0.089
Proteinuria <1.0 g/day, n (%)	6 (28.57)	19 (41.30)	0.317

Data are presented as mean and standard deviation. GFR, glomerular filtration rate; IQR, interquartile range; MAP, mean arterial pressure; ESKD, end-stage kidney disease.

Table 3. GFR decline per year categorized by baseline estimated GFR, proteinuria, and pathological findings

	Without corticosteroid (n = 21)	With corticosteroid (n = 46)	p value
Baseline estimated GFR			
≤50 mL/min per 1.73 m^2	−4.23±8.47	1.61±20.07	0.269
>50 mL/min per 1.73 m^2	−9.31±5.08	3.9±11.42	0.011
Baseline proteinuria			
1 to <3 g/day	−4.09±6.46	1.81±12.03	0.159
≥3 g/day	−7.13±9.05	3.64±18.91	0.082
Mesangial hypercellularity			
M0	−2.63±6.42	4.69±11.37	0.049
M1	−9.76±8.13	1.08±19.39	0.117
Endocapillary proliferation			
E0	−4.65±6.77	4.61±17.56	0.178
E1	−6.62±9.01	−0.57±12.36	
Segmental glomerulosclerosis			
S0	–	5.24±11.91	–
S1	−5.68±7.89	1.85±17.42	0.069
Tubular atrophy/interstitial fibrosis			
T0	−4.07±6.13	4.22±13.22	0.079
T1-2	−6.9±9.05	0.4±20.1	0.252
Crescents			
C0	−5.58±8.4	2.48±12.63	0.026
C1-2	−6.03±6.79	3.48±21.91	0.360

Data are presented as mean and standard deviation. GFR, glomerular filtration rate; IQR, interquartile range; MAP, mean arterial pressure; ESKD, end-stage kidney disease.

Table 4. Proteinuric remission (<1 g/day) categorized by baseline estimated GFR, proteinuria, and pathological findings

	Without corticosteroid (n = 21)	With Corticosteroid (n = 46)	p value
Baseline estimated GFR			
≤50 mL/min per 1.73 m^2	4 (26.67)	7 (31.82)	0.736
>50 mL/min per 1.73 m^2	2 (33.33)	12 (50.00)	0.657
Baseline proteinuria			
1 to <3 g/day	3 (30.00)	11 (52.38)	0.242
≥3 g/day	3 (27.27)	8 (32.00)	0.999
Mesangial hypercellularity			
M0	4 (33.33)	11 (50.00)	0.350
M1	2 (22.22)	8 (33.33)	0.536
Endocapillary proliferation			
E0	3 (30.00)	15 (50.00)	0.271
E1	3 (27.27)	4 (25.00)	0.999
Segmental glomerulosclerosis			
S0	–	7 (53.85)	NA
S1	6 (28.57)	12 (36.36)	0.554
Tubular atrophy/interstitial fibrosis			
T0	4 (44.44)	16 (55.17)	0.573
T1-2	2 (16.67)	3 (17.65)	0.999
Crescents			
C0	4 (25.00)	14 (45.16)	0.178
C1-2	2 (40.00)	5 (33.33)	0.787

Data are presented as mean and standard deviation. GFR, glomerular filtration rate; IQR, interquartile range; MAP, mean arterial pressure; ESKD, end-stage kidney disease.

group. No significant differences were observed in the rates of uncontrolled hyperglycemia or psychosis between the two groups.

Discussion

IgAN remains a significant challenge in nephrology due to its heterogeneous clinical presentation and variable progression to ESKD. Our study provides insight into the efficacy of corticosteroids combined with RAAS inhibitors compared to RAAS inhibitors alone in a cohort of Thai patients diagnosed with IgAN. The results suggest that corticosteroid treatment may be beneficial in slowing the decline of renal function in specific patient subgroups.

The variability in disease progression observed in IgAN is well-documented. While some patients may experience stable kidney function or remission, others can rapidly progress to ESKD [12]. This heterogeneity complicates treatment decisions, particularly regarding the use of immunosuppressive therapies. A significant randomized controlled trial, the TESTING study, involving 503 participants, found that a 6- to 9-month course of oral methylprednisolone significantly reduced the risk of kidney function decline, kidney failure, or death due to kidney disease compared to placebo. However, this benefit was accompanied by an increased risk of serious adverse events, particularly with high-dose therapy [13]. Despite this, there was some evidence favoring methylprednisolone for kidney outcomes. Our findings indicate that corticosteroid treatment was associated with a significantly slower rate of eGFR decline, particularly in patients with a baseline eGFR >50 mL/min/1.73 m^2, no mesangial hypercellularity, and no crescentic changes. These results are consistent with findings from the TESTING and VALIGA studies, which demonstrated improved renal outcomes in patients with significant proteinuria receiving corticosteroids [14].

Moreover, our study reinforces the importance of patient stratification based on baseline renal function and histopathological features. The Oxford-MEST-C classification has emerged as a valuable tool in predicting

outcomes in IgAN [15]. The identification of tubular atrophy and interstitial fibrosis as poor prognostic indicators aligns with our subgroup analyses, where specific histological features correlated with treatment response. However, the current literature lacks consensus on the role of these histological findings in guiding immunosuppressive therapy, necessitating further investigation.

While our results are promising, the risks of corticosteroid therapy must be carefully considered. Corticosteroids have demonstrated efficacy in slowing IgAN progression, but their use is associated with short-term side effects such as increased infection risk, hyperglycemia, and fluid retention, as well as long-term complications like osteoporosis, cataracts, hypertension, and weight gain. Steroid therapy may also exacerbate comorbid conditions like diabetes and cardiovascular disease. Therefore, careful patient selection and ongoing monitoring are essential to balance the benefits of corticosteroids in preventing rapid eGFR decline with the potential risks. Future studies should focus on optimizing treatment regimens to minimize adverse effects while maximizing therapeutic outcomes.

In our study, we found no significant differences in ESKD incidence or proteinuria remission rates between treatment groups. This is in line with previous studies indicating that while corticosteroids may slow the decline of renal function, they do not necessarily improve all clinical outcomes [16–18]. The focus of future research should be to identify biomarkers or clinical features that could predict which patients would benefit most from corticosteroid therapy.

Recent advances in the treatment of IgAN, such as complement inhibitors and immunomodulatory agents, may offer new therapeutic options for patients, particularly those with refractory disease. The promising results from clinical trials with agents like iptacopan and ravulizumab suggest that targeting the underlying immunologic mechanisms of IgAN could complement, or even replace, traditional therapies like corticosteroids in certain patient populations [19–21]. However, given that our study primarily focuses on the use of corticosteroids in combination with RAAS inhibition, further research is needed to evaluate the effectiveness of these new therapies in comparison to or in combination with existing treatment regimens. Our findings provide valuable insight into the role of corticosteroids in managing IgAN, but future studies should consider these emerging treatments to refine the therapeutic approach and improve long-term outcomes.

While our study provides valuable insights into the treatment of IgAN, several limitations must be acknowledged that may influence the interpretation and generalizability of our findings. As a retrospective cohort study, and given the absence of a standardized treatment protocol, our analysis is subject to potential biases related to data collection and patient selection. The reliance on existing medical records may have introduced missing data or inconsistencies in the documentation of patient characteristics, treatment adherence, and outcomes.

Although our sample size of 67 patients was determined based on previous studies, it remains relatively small, limiting the statistical power to detect differences, particularly in subgroup analyses. Moreover, the inclusion and exclusion criteria in this study may have introduced selection bias. For instance, patients with significant comorbidities or those who did not receive corticosteroids may differ systematically from those who did.

The follow-up period, while sufficient for observing initial outcomes, may not capture the long-term effects of corticosteroid therapy on renal function and overall health. Chronic conditions like IgAN often require extended monitoring to fully understand the implications of treatment strategies. Finally, regarding the treatment choice for the control group, corticosteroids were not used because their potential benefits were considered limited due to the extent of kidney damage and chronicity in these patients. This is consistent with clinical practice, where, in advanced stages of IgAN – particularly with significant tubulointerstitial fibrosis – the response to corticosteroids is often suboptimal.

Although baseline estimated GFR was significantly higher in the corticosteroid group, other characteristics were similar between the groups. We adjusted for baseline GFR in our statistical models to mitigate its confounding effect. However, unmeasured factors may still influence the results, and future prospective studies with standardized treatment protocols may offer further clarity. While we focused on GFR decline and proteinuria remission, other important outcomes, such as quality of life and long-term cardiovascular health, were not assessed. Future studies should include a broader set of endpoints to better evaluate the overall impact of treatment strategies.

In conclusion, our study adds to the growing body of evidence suggesting that corticosteroid therapy may be beneficial for certain patients with IgAN, especially those with higher baseline estimated GFR and specific histological features. Future prospective studies are essential to validate these findings and refine treatment protocols, ensuring that the benefits of corticosteroids outweigh the risks associated with their use.

Acknowledgments

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Statement of Ethics

This study protocol was reviewed and approved by the Institutional Review Board of the Royal Thai Army Medical Department (IRB RTA), Approval No. R171h/64. This study was granted an exemption from requiring written informed consent by the Institutional Review Board of the Royal Thai Army Medical Department (IRB RTA) (Approval No. R171h/64).

Conflict of Interest Statement

The authors declare that there are no competing interests. Dr. Bancha Satirapoj served as a member of the Journal's Editorial Board at the time of submission.

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Author Contributions

B.S., T.C., N.N., and O.S. contributed to the concept and design of the study. B.S. and T.C. contributed to data acquisition, analysis, and interpretation of the data. B.S. wrote the first draft of the manuscript. All authors approved the final version submitted.

Data Availability Statement

The data that support the findings of this study are not publicly available due to the risk of participant identification and the need to protect the privacy of research participants but are available from the corresponding author upon reasonable request.

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