

## Combined Therapy Superior to Monotherapy in Overactive Bladder Patients with Pelvic Organ Prolapse: A Retrospective Comparative Study

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**Objective:** To compare short-term outcomes of behavioral, anticholinergic, and combined therapies in overactive bladder (OAB) patients with pelvic organ prolapse (POP).

**Methods:** This single-center retrospective study included 90 women with OAB and POP (POP-Q stage  $\leq 2$ ) categorized as: Group 1 (behavioral therapy; n=30), Group 2 (anticholinergic therapy; n=30), and Group 3 (combined therapy; n=30). Validated questionnaires (IIQ-7, UDI-6, OAB-V8, ICIQ-SF) were used to assess symptom severity and quality of life (QoL) pre- and post-treatment. Statistical analyses employed ANOVA and paired t-tests, with  $p < 0.05$  considered significant.

**Results:** All groups showed significant improvement in all questionnaires post-treatment ( $p < 0.05$ ), except UDI-6 in Groups 1 and 2. Combined therapy (Group 3) achieved the greatest reductions in scores: ICIQ-SF: ( $\Delta 10.74$ ), IIQ-7: ( $\Delta 4.57$ ), OAB-V8: ( $\Delta 4.31$ ). Behavioral therapy (Group 1) outperformed anticholinergic therapy alone (Group 2) in symptom reduction (IIQ-7:  $\Delta 4.69$  vs.  $\Delta 2.55$ ; OAB-V8:  $\Delta 2.83$  vs.  $\Delta 3.62$ ; both  $p < 0.05$ ). Daily pad usage differed significantly among groups (Group 1:  $2.2 \pm 1.4$ ; Group 2:  $3.1 \pm 0.8$ ; Group 3:  $4.3 \pm 1.3$ ;  $p < 0.001$ ).

**Conclusion:** While all therapies improved OAB symptoms, combined behavioral-pharmacological therapy demonstrated superior efficacy in reducing symptom severity and enhancing QoL in patients with concomitant POP. Behavioral monotherapy may be more effective than anticholinergic alone, supporting multimodal approaches as first-line management.

**Keywords:** Anticholinergic, Combined treatment, Conservative treatment, Overactive bladder, Pelvic organ prolapse

### 1. INTRODUCTION

Overactive bladder (OAB) is a common and distressing condition that affects patients' quality of life (QoL). According to the International Continence Society (ICS) standardization committee, OAB is characterized by urinary urgency, with or without urge urinary incontinence, usually accompanied by frequency and nocturia, in the absence of infection or other pathology.<sup>1</sup> The global prevalence of OAB is estimated at 11.8%, while at least one lower urinary tract symptom (LUTS) is reported by 64.3% of adults.<sup>2</sup> Pelvic organ prolapse (POP), defined as the descent of pelvic structures such as the bladder, uterus or rectum into the vaginal canal, can further impair bladder function due to disruption of pelvic floor dynamics. Studies indicate detrusor overactivity occurs in up to 20% of moderate and 52% of severe prolapse.<sup>3</sup> Significant POP is also seen in more than 40% of

women with urethral sphincter insufficiency/incompetence.<sup>4</sup> First-line management for OAB includes behavioral interventions, pharmacotherapy, and combination approaches. Despite their widespread use, comparative data on these strategies in patients with concurrent POP remain limited. Therefore, this study aimed to evaluate and compare the short-term outcomes of behavioral, pharmacologic, and combined therapies in OAB patients with coexistent POP.

### 2. MATERIAL-METHODS

This single-center retrospective study was approved by the Ethics Committee of Sakarya University (institutional review board number: 71522473/050.01.04/222). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national

research committee, as well as with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

We included female patients diagnosed with OAB and POP who presented to the outpatient clinic of Sakarya University Urology Department between December 2017 and June 2018.

### 2.1. Inclusion criteria

Patients were enrolled based on:

1. Complete documentation of: presenting complaints, Pelvic Organ Prolapse Quantification (POP-Q) examination findings, medical history, voiding diary data
2. Normal post-void residual volume (<50 mL) and absence of obstruction on uroflowmetry
3. Normal urinalysis results
4. POP-Q findings showing: prolapse not extending beyond the hymen, no prolapse-related symptoms, no request for prolapse treatment

### 2.2. Exclusion criteria

Patients were excluded if they had any of the following:

1. Neurogenic disorders (e.g., multiple sclerosis, spinal cord injury)
2. Documented psychological/psychiatric conditions
3. History of urinary or pelvic surgery
4. Evidence of bladder outlet obstruction
5. Diagnosed Diabetes Mellitus or metabolic syndrome

### 2.3. Intervention groups

Per EAU (European Association of Urology) 2018 guidelines for OAB management:

- Group 1 (Behavioral therapy): Received Grade A recommendations including: weight management, smoking cessation, dietary modifications, fluid intake regulation, bladder training, and pelvic floor muscle training (for patients with adequate pelvic muscle strength)
- Group 2 (Pharmacological therapy): Received anticholinergic treatment

- Group 3 (Combined therapy): Received both behavioral and anticholinergic treatments

### 2.4. Questionnaire forms

#### 2.4.1. International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF)

The ICIQ-SF is a validated, reliable, and easily administrable questionnaire assessing urinary incontinence and its impact on QoL.<sup>5</sup> This 6-item instrument evaluates: frequency of urinary incontinence, volume of leakage and degree of impact on daily life. The Turkish version has undergone formal validation and is widely used in clinical practice to quantify incontinence severity and its QoL consequences in affected patients.<sup>6</sup>

#### 2.4.2. Incontinence Impact Questionnaire (IIQ-7) and Urogenital Distress Inventory (UDI-6)

The UDI-6 and IIQ-7 are multidimensional, self-administered questionnaires utilizing a Likert-type scale with response options: 0=Not at all, 1=Mildly, 2=Moderately, 3=Greatly. UDI-6 Structure is total score range: 0-18 and three subscales assess: irritative symptoms (items 1-2), stress symptoms (items 3-4), obstructive/discomfort symptoms (items 5-6). IIQ-7 Structure is total score range: 0-21 and four subscales evaluate: physical activity (items 1-3), travel (item 4), social relationships (item 5), emotional health (items 6-7). Scores are converted to percentages, with higher scores indicating greater QoL impairment. The Turkish versions were validated in 2007, demonstrating excellent reliability: IIQ-7: Cronbach's  $\alpha = 0.87$  and UDI-6: Cronbach's  $\alpha = 0.74$ .<sup>7</sup>

#### 2.4.3. Overactive Bladder Questionnaire (OAB-V8)

The Overactive Bladder Questionnaire (OAB-q) was first developed in English by Coyne et al. in 2002 as the initial condition-specific instrument to evaluate OAB symptoms and QoL.<sup>8</sup> This comprehensive 33-item questionnaire consists of an 8-item symptom scale and a 25-item QoL, designed for use with both wet and dry OAB patients. Subsequent research led to the development of shorter versions including the OAB-q short form and the 8-item OAB-V8, which

comprises the first eight questions of the original OAB-q and serves as a recommended screening and awareness tool.<sup>9</sup> The Turkish version of OAB-V8 has been validated as a reliable, easy-to-understand, and practical instrument specifically adapted for assessing OAB in Turkish-speaking populations. Its brevity and clarity make it particularly suitable for clinical implementation while maintaining the psychometric robustness of the original questionnaire.<sup>10</sup>

## 2.5. Statistical analysis

Descriptive statistics were presented as mean  $\pm$  standard deviation or median (minimum-maximum) for continuous variables, and as frequency (%) for categorical variables. The normality of variable distributions was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. For normally distributed numerical variables with two subgroups, comparisons were made using the independent samples t-test. For normally distributed numerical variables with more than two subgroups, one-way ANOVA was used. For non-normally distributed variables with multiple subgroups, the Kruskal-Wallis test was employed. Categorical variables were compared using Pearson's chi-square test. Statistical analyses were conducted using IBM SPSS Statistics for Windows (version 26.0, IBM Corp., Armonk,

NY, USA). A p-value of less than 0.05 was considered statistically significant.

## 3. RESULTS

### 3.1. Patient characteristics

The study included 90 patients diagnosed with both OAB and POP, who were divided into three treatment groups. Table 1 summarizes the demographic characteristics of all participants. Upon initial evaluation, patients presented with various urinary symptoms. Urgency accompanied by urgency urinary incontinence (UUI) was observed in 21 (30.8%), 25 (36.7%), and 22 (32.5%) patients in groups 1, 2, and 3 respectively. Stress urinary incontinence (SUI) was reported by 9 (19.6%), 18 (39.1%), and 19 (41.3%) patients across the three groups. Additionally, coital incontinence was present in 4 (19.0%), 9 (42.9%), and 8 (38.1%) patients in each respective group.

A significant difference was noted in daily pad usage among the groups ( $p < 0.05$ ). Group 1 patients used an average of  $2.2 \pm 1.4$  pads per day, while Groups 2 and 3 reported averages of  $3.1 \pm 0.8$  and  $4.3 \pm 1.3$  pads daily, respectively. The mean POP stage was  $1.6 \pm 0.7$  in Group 1,  $1.4 \pm 0.4$  in Group 2, and  $1.6 \pm 0.5$  in Group 3. Cough stress test results showed positive findings in 6 patients (17.6%), 13 patients (38.2%), and 15 patients (44.1%) across Groups 1, 2, and 3 respectively.

**Table 1.**

*Demographic and clinical characteristics of patients*

Characteristic	Group 1 (n=30)	Group 2 (n=30)	Group 3 (n=30)	p-value
Age*	54.71 $\pm$ 9.50	55.12 $\pm$ 10.56	51.56 $\pm$ 13.61	0.411
BMI (kg/m <sup>2</sup> )*	29.91 $\pm$ 4.54	29.67 $\pm$ 4.32	30.43 $\pm$ 4.32	0.795
UUI (Urge Urinary Incontinence)#				<0.001
- Present	21 (30.8%)	25 (36.7%)	22 (32.5%)	
- Absent	9 (40.9%)	5 (22.7%)	8 (36.4%)	
SUI (Stress Urinary Incontinence) #				0.017
- Present	9 (19.6%)	18 (39.1%)	19 (41.3%)	
- Absent	21 (47.7%)	12 (27.3%)	11 (25.0%)	
Smoking#				0.172
- Yes	11 (32.4%)	8 (23.5%)	15 (44.1%)	
- No	19 (33.9%)	22 (39.2%)	15 (26.9%)	

**Table 1.** (Continued)

Constipation <sup>#</sup>				0.031
- Yes	13 (46.0%)	11 (39.3%)	4 (14.3%)	
- No	17 (27.4%)	19 (30.6%)	26 (42.0%)	
Number of Vaginal Deliveries*	2.40 ± 0.81	2.21 ± 1.11	2.95 ± 1.45	0.493
Daily Pad Use *	2.28 ± 1.46	3.12 ± 0.83	4.30 ± 1.33	<0.001
POP-Q Localization <sup>#</sup>				0.995
- Anterior	8 (33.3%)	8 (33.3%)	8 (33.3%)	
- Apical	8 (38.1%)	7 (33.3%)	6 (28.6%)	
- Posterior	7 (30.4%)	8 (34.8%)	8 (34.8%)	
- Anterior + Apical	7 (31.8%)	7 (31.8%)	8 (36.4%)	

### 3.2. Questionnaire outcomes across treatment groups

Comparative analysis of the IIQ-7 scores revealed pre-treatment means of  $12.03 \pm 2.99$ ,  $13.43 \pm 3.20$ , and  $13.86 \pm 4.38$  for Groups 1, 2, and 3, respectively. Post-treatment scores decreased to  $10.46 \pm 2.76$ ,  $12.70 \pm 2.87$ , and  $11.43 \pm 3.79$ . While Groups 1 and 3 demonstrated more pronounced reductions, all groups showed statistically significant improvements ( $p < 0.05$ ). For the UDI-6 questionnaire, pre-treatment means were  $10.30 \pm 2.15$  (Group 1),  $11.53 \pm 2.38$  (Group 2), and  $12.06 \pm 3.08$  (Group 3), with post-treatment values declining to  $9.26 \pm 2.34$ ,  $10.96 \pm 2.52$ , and  $9.4 \pm 3.1$ , respectively. These reductions reached

statistical significance across all groups ( $p < 0.05$ ). Analysis of the OAB-V8 scores demonstrated pre-treatment baseline values of  $21.80 \pm 7.18$  (Group 1),  $24.73 \pm 6.13$  (Group 2), and  $27.23 \pm 7.8$  (Group 3). Post-treatment scores improved to  $18.86 \pm 6.35$ ,  $23.06 \pm 6.10$ , and  $22.26 \pm 6.72$ , with all groups achieving statistically significant reductions ( $p < 0.05$ ). The ICIQ-SF questionnaire results showed pre-treatment means of  $11.1 \pm 2.9$  (Group 1),  $12.53 \pm 2.43$  (Group 2), and  $14.93 \pm 3.45$  (Group 3). Post-treatment scores decreased to  $9.9 \pm 3.18$ ,  $11.7 \pm 2.59$ , and  $12.33 \pm 3$ , respectively. All groups exhibited statistically significant improvements in ICIQ-SF scores ( $p < 0.05$ ) (Table 2).

**Table 2.**

*Mean changes in questionnaire scores before and after treatment by group*

Questionnaire	Timepoint	Group 1	Group 2	Group 3	p-value
IIQ-7*	Pre-treatment	$12.03 \pm 2.99$	$13.43 \pm 3.20$	$13.86 \pm 4.38$	<0.001
	Post-treatment	$10.46 \pm 2.76$	$12.70 \pm 2.87$	$11.43 \pm 3.79$	
UDI-6*	Pre-treatment	$10.30 \pm 2.15$	$11.53 \pm 2.38$	$12.06 \pm 3.08$	<0.001
	Post-treatment	$9.26 \pm 2.34$	$10.96 \pm 2.52$	$9.41 \pm 3.12$	
OAB-V8*	Pre-treatment	$21.80 \pm 7.18$	$24.73 \pm 6.13$	$27.23 \pm 7.80$	<0.001
	Post-treatment	$18.86 \pm 6.35$	$23.06 \pm 6.10$	$22.26 \pm 6.72$	
ICIQ-SF*	Pre-treatment	$11.10 \pm 2.90$	$12.53 \pm 2.43$	$14.93 \pm 3.45$	<0.001
	Post-treatment	$9.91 \pm 3.18$	$11.74 \pm 2.59$	$12.33 \pm 3.33$	

\* Mean ± SD, one-way ANOVA, ICIQ-SF: International Consultation on Incontinence Questionnaire Short Form, IIQ-7: Incontinence Impact Questionnaire, OAB-V8: Overactive Bladder Questionnaire, UDI-6: Urogenital Distress Inventory

### 3.3. Comparative analysis of questionnaire score changes across prolapse compartments

Intergroup analysis revealed significant variations in questionnaire score improvements (Table 3). In

Group 1, the mean differences between pre- and post-treatment scores were 4.69 ( $p < 0.05$ ) for IIQ-7, 3.66 ( $p > 0.05$ ) for UDI-6, 2.83 ( $p < 0.05$ ) for OAB-V8, and 8.16 ( $p < 0.05$ ) for ICIQ-SF. Group 2 exhibited mean differences of 2.55 ( $p > 0.05$ ) for

IIQ-7, 2.16 ( $p > 0.05$ ) for UDI-6, 3.62 ( $p > 0.05$ ) for OAB-V8, and 8.71 ( $p < 0.05$ ) for ICIQ-SF. Group 3 demonstrated the most consistent statistically significant improvements, with mean differences of 4.57 for IIQ-7, 3.23 for UDI-6, 4.31 for OAB-V8,

and 10.74 for ICIQ-SF (Table 4). These findings highlight differential treatment efficacy across prolapse compartments, with Group 3 achieving the most robust and statistically significant outcomes in all measured domains.

**Table 3.**

*Distribution of treatment groups according to prolapse compartments*

	Anterior	Posterior	Apical	Anterior and Posterior
Group 1 (n) (%)	8 (26.7%)	7 (23.3%)	8 (26.7%)	7 (23.3%)
Group 2 (n) (%)	8 (26.7%)	8 (26.7%)	7 (23.3%)	7 (23.3%)
Group 3 (n) (%)	8 (26.7%)	8 (26.7%)	6 (20.0%)	8 (26.7%)

**Table 4.**

*Mean changes in questionnaire scores by prolapse compartment in group 3*

Questionnaire	Timepoint	Anterior	Apical	Posterior	Anterior + Posterior	p-value
IIQ-7*	Pre-treatment	12.37 ± 6.04	13.5 ± 4.32	13.51 ± 3.96	16.09 ± 2.44	0.007
	Post-treatment	10.04 ± 5.04	11.33 ± 3.28	10.75 ± 3.37	13.62 ± 2.66	
UDI-6*	Pre-treatment	11.12 ± 3.04	11.83 ± 2.78	11.25 ± 3.77	14.02 ± 2.07	0.009
	Post-treatment	8.12 ± 3.48	9.66 ± 2.33	8.51 ± 3.24	11.55 ± 2.50	
OAB-V8*	Pre-treatment	23.25 ± 10.75	29.33 ± 6.02	26.52 ± 7.78	30.37 ± 4.27	0.009
	Post-treatment	18.12 ± 8.62	24.16 ± 4.44	21.12 ± 5.93	26.12 ± 4.73	
ICIQ-SF*	Pre-treatment	15.12 ± 3.22	14.51 ± 3.01	14.62 ± 4.53	15.37 ± 3.42	0.007
	Post-treatment	12.25 ± 3.37	12.33 ± 3.01	11.87 ± 2.85	12.87 ± 3.31	

\* Mean ± SD, one-way ANOVA, ICIQ-SF: International Consultation on Incontinence Questionnaire Short Form, IIQ-7: Incontinence Impact Questionnaire, OAB-V8: Overactive Bladder Questionnaire, UDI-6: Urogenital Distress Inventory

#### 4. DISCUSSION

POP refers to the descent of pelvic structures—such as the uterus, bladder, colon, or rectum—into the vaginal canal due to weakening of the supporting tissues. Although not life-threatening, POP can substantially impair QoL because of its associated morbidity. Advanced apical prolapse may cause ureteral traction, potentially leading to hydroureteronephrosis. Established risk factors for POP development include advanced age, multiparity (particularly vaginal deliveries), genetic predisposition, estrogen deficiency, diminished pelvic floor muscle strength, and smoking.

In a population-based study of 641 women aged 20-59, Samuelsson et al. reported a 30.8%

prevalence of POP. Multivariate analyses identified advancing age, parity, and high birth weight as significant contributors.<sup>11</sup> These findings are consistent with Nygaard et al. who evaluated 1,961 women and demonstrated that at least one pelvic floor disorder was present 23.7% of participants, including urinary incontinence (15.7%) and POP (2.9%). Together, these studies emphasize that the likelihood of prolapse increases with both age and parity.<sup>12</sup>

Cigarette smoking exacerbates OAB symptoms through two primary mechanisms: repeated coughing episodes in patients with SUI and bladder irritation caused by urinary excretion of nicotine and other toxins. Therefore, smoking cessation is strongly recommended -not only to

improve overall health and lower bladder cancer risk but also to reduce coughing frequency, thereby indirectly mitigating SUI.

Dallosso et al. investigated this relationship in a cohort of 6,424 patients aged over 40 years, comparing smokers and non-smokers over a 1-year follow-up period. Their findings revealed no significant association between smoking and SUI but demonstrated a statistically significant link to OAB symptom exacerbation.<sup>13</sup> In a complementary study, Hannestad et al. identified heavy smoking (defined as >20 cigarettes/day or >15 pack-years) as a key risk factor for increased urinary incontinence frequency.<sup>14</sup>

Conservative management remains a cornerstone in the treatment of OAB and SUI, as highlighted in the International Consultation on Incontinence (ICI) first-line therapy.<sup>15</sup> In a retrospective study by Cammu et al. 49% of 449 women with SUI or UI achieved complete symptom resolution following conservative interventions. Higher success rates were observed in moderate UI cases, with 67% achieving pad-free status, 63% reporting no daily UI episodes, and 60% demonstrating no leakage during initial coughing. Independent predictors of treatment failure included  $\geq 2$  daily incontinence episodes, leakage upon first cough, and antidepressant use.<sup>16</sup>

In the present study, increasing parity correlated with greater urgency frequency, pad usage, and nocturia; however, these trends did not reach statistical significance. Importantly, patients in the behavioral therapy group—who received dietary modifications, weight management, and pelvic floor muscle training (PFMT)—experienced significant improvements in symptom severity, reinforcing the clinical value of multimodal behavioral interventions even in the absence of direct parity-symptom link. Our findings are consistent with prior evidence demonstrating the effectiveness of conservative approaches. For instance, Burgio et al. reported an 80.7% reduction in incontinence among 197 women aged 55–92 after an eight-week conservative program.<sup>17</sup> While Hagen et al. found similar benefits of PFMT, patients with Stage 1-2 POP.<sup>18</sup>

In our cohort, behavioral therapy alone led to notable symptom relief across multiple validated questionnaires (IIQ-7:  $\Delta 4.69$ , OAB-V8:  $\Delta 2.83$ , ICIQ-SF:  $\Delta 8.16$ ; all  $p < 0.05$ ). Although UDI-6 improvements ( $\Delta 3.66$ ) were not statistically significant, the collective findings align with existing evidence supporting conservative strategies for enhancing symptom severity and QoL in incontinence patients. These outcomes underscore the clinical relevance of first-line behavioral interventions, particularly given their low-risk profile and patient-centered focus.

Anticholinergic therapy also demonstrated beneficial effects. Hill et al. conducted a randomized controlled trial of 400 women >65 years, showing darifenacin significantly reduced UI and improved OAB-specific QoL scores.<sup>19</sup> Both groups exhibited significant reductions in UI episodes, but the anticholinergic group demonstrated markedly greater improvements in OAB-specific QoL scores compared to placebo. These findings highlight the dual role of anticholinergics in alleviating both symptom burden and QoL impairment. Subsequent phase 3 trials by Chapple et al. further validated the efficacy of solifenacin (5/10 mg daily) in reducing urgency, incontinence, frequency, and nocturia across 2,800 patients, establishing its superiority over placebo.<sup>20</sup>

In our study, patients receiving anticholinergic monotherapy showed mixed outcomes: IIQ-7: mean reduction = 2.55, UDI-6: mean reduction = 2.16, OAB-V8: mean reduction = 3.62, and ICIQ-SF: mean reduction = 8.71.

While most questionnaire scores did not reach statistical significance, subjective symptom intensity assessments revealed meaningful clinical benefits, suggesting anticholinergics may improve patient-reported outcomes even in the absence of robust statistical significance. This aligns with Klutke et al.'s findings in 357 patients dissatisfied with prior antimuscarinic therapy, where combining anticholinergics with behavioral interventions enhanced treatment satisfaction and bladder diary parameters over 16 weeks.<sup>21</sup>

Most notably, the combined therapy group demonstrated consistent and statistically

significant improvements across all parameters (IIQ-7:  $\Delta 4.57$ ; UDI-6:  $\Delta 3.23$ ; OAB-V8:  $\Delta 4.31$ ; ICIQ-SF:  $\Delta 10.74$ ). These results underscore the synergistic efficacy of multimodal approaches, with combined therapy demonstrating superior outcomes compared to conservative or anticholinergic treatments alone. The significant reductions in symptom severity and QoL impairment across all questionnaires suggest that integrating behavioral strategies with pharmacotherapy addresses both physiological and lifestyle-related contributors to OAB.

#### 4.1. Study limitations

This study has several limitations. The retrospective design introduces potential biases, including selection bias and limited adherence assessment, which may affect the interpretation of results. The sample size was modest, and objective measures of adherence to behavioral recommendations (e.g., PFMT compliance, fluid intake regulation) were not systematically recorded. Additionally, POP-Q reevaluation was not conducted post-treatment, limiting insight into anatomical changes following intervention. Finally, the 3-month follow-up duration may be seen appropriate for short-term outcomes, but long-term persistence of symptom improvement remains unknown. Despite these limitations, this study provides meaningful comparative data highlighting the superiority of combined therapy in this patient population.

#### 5. CONCLUSION

This study underscores OAB as a significant public health concern that markedly impairs QoL, while demonstrating that POP may contribute to OAB symptom development. To our knowledge, this is the first study to evaluate OAB treatment efficacy in women while accounting for concurrent POP. As expected, combined therapy is more effective than both conservative therapy and medical therapy alone, even in patients with POP and OAB.

#### Article Information Form

##### Authors' Contribution

HCD: Research conception and design, Data collection, Data analysis/interpretation, Writing, Literature review AE: Data

analysis/interpretation, Drafting of the manuscript, Technical support HIC: Data analysis and interpretation, Critical revision of content, DG: Data collection, Critical revision of the manuscript, YTA: Data collection analysis and interpretation, Critical revision of content OK: Research conception and design, Literature review, Approval of the final manuscript.

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#### **The Declaration of Conflict of Interest/ Common Interest**

No conflict of interest or common interest has been declared by authors.

#### **Artificial Intelligence Statement**

No artificial intelligence tools were used while writing this article.

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