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Acute Stroke Patients with Sleep Apnea Acording to the Disability and Incidence of Relapse

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ABSTRACT

Background: Sleep is a complex process involving the interactions of several brain regions, which play a key role in regulating the sleep process, particularly the brainstem, thalamus, and anterior basal brain regions. The process of sleep is accompanied by a change in body functions, as well as a change in cerebral electrical activity, which is under the control of the autonomic nervous system. **Objective:** The aim of the study was to analyze the frequency of stroke recurrence and disability of patients with stroke and apnea. **Methods:** It was analyzed 110 acute stroke patients with sleep apnea. All patients were evaluated with: Glasgow scale, The American National Institutes of Health Scale Assessment, Mini Mental Test, The Sleep and snoring Questionnaire Test, The Berlin Questionnaire Test, The Epworth Sleepiness Scale, The Stanford Sleepiness Scale, and The general sleep questionnaire. **Results:** The largest number of patients with apnea on admission had a degree of disability of 4, and on discharge of 1. There was a statistically significant difference between the mean values of incapacity for admission and discharge. The student's t - test did not determine a statistically significant difference in disability according to the Rankin scale between patients with and without apnea at admission ($t = 0.059$, $p = 0.95$) and discharge ($t = 0.71$, $p = 0.48$). According to the NIHS scale, patients of both sexes with apnea had a neurological deficit of 7.55 ± 5.22 on admission and 7.1 ± 4.3 without apnea. Statistically significant difference was not found on the neurological deficit of both sexes, with and without apnea, at admission and discharge. With apnea, there were 13 relapses of stroke during one year, and without apnea in only 3 patients. **Conclusion:** Patients with acute stroke have a significantly higher correlation rate according to sleep apnea. There is no significant correlation in the degree of disability between patients with and without apnea.

Keywords: Acute stroke, Sleep Apnea, Disability, Relapse.

1. BACKGROUND

Sleep is a complex process involving the interactions of several brain regions, which play a key role in regulating the sleep process, particularly the brainstem, thalamus, and anterior basal brain regions (1, 2). The process of sleep is accompanied by a change in body functions, as well as a change in cerebral electrical activity, which is under the control of the autonomic nervous system. Structural lesions in the brain, such as stroke (hemorrhagic or ischemic), trauma, and others can result in refractory sleep and breathing disorders (3). There is a clear link between sleep-disordered breathing (SDB), such as sleep apnea (SA) and stroke, although it remains unclear whether apnea is a consequence or cause of stroke. Complex processes involving neural, hemodynamic, metabolic, and inflammatory mechanisms can be caused by abnormal respiratory events and lead to stroke. Likewise, stroke may exacerbate SDB (4, 5). Sleep-disordered breathing and wakefulness disorders are common in patients with stroke. These disorders must be taken into account because they can significantly affect the rehabilitation process and the quality of life of patients, and increase the risk of recurrence of stroke. In practice, al-

most 40% of patients have symptoms of sleep-disordered breathing, but they often go unrecognized (6). SDB occurs in about 1% of the total population, in 4% of men and 3% of women. Their prevalence increases with age and they are three times more common in adults over 40 years of age. (7).

Apnea is defined as a condition in which sleep is interrupted repeatedly due to instantaneous interruptions in breathing. It represents the cessation of airflow in the respiratory system for more than 10 seconds. Reduction of airflow by more than 50% with desaturation of oxygen on the periphery to 4% and lasting more than 10 seconds is referred to as hypopnea. Pathological apneas are when more than five apneas occur in one hour, or if the sum of apneas and hypopneas in one hour is greater than ten. There are considered to be three types of sleep apnea disorders: obstructive, central, and mixed sleep apnea (8). According to the tenth revision of the International Classification of Diseases (ICD–10), sleep apnea is divided into central and obstructive (9).

2. OBJECTIVE

The aim of the study was to analyze the frequency of stroke recurrence and disability of patients with stroke and apnea, estimated on the Rankin and NIHSS scale.

3. PATIENTS AND METHODS

The research was conducted prospectively at the Clinic for Neurology of the University Clinical Center Tuzla. Out of 110 patients with stroke and apnea syndrome, of all ages and both sexes, were analyzed, and the control group consisted of the same number of patients with MU, but without apnea syndrome. The study group included patients who met the following criteria: confirmation of the diagnosis of cerebral infarction or intracerebral hemorrhage by computed tomography (CT) and/or magnetic resonance imaging (MR) of the brain. The study included patients without severe speech impairment, cognitive impairment, or mild cognitive impairment (Mini Mental Test–MMT> 23) (10). The selection of patients was performed consecutively over for one year. All selected patients were from the Tuzla Canton, and the testing was conducted at the Clinic of Neurology, University Medical Center Tuzla, in hospital or outpatient settings. The diagnosis of apnea syndrome was made based on the Snoring and Apnea Syndrome Questionnaire (the patient had to answer yes to questions 1, 3, 4, 8, and 9) (11), the Epworth sleep scale (total score had to be greater than 12) (12), the Berlin Questionnaire (13), the Stanford Sleepiness Scale (14) and the General Sleep Questionnaire (15). The severity of stroke was assessed by the Rankin scale (16) and the scale of the American National Institutes of Health Stroke Scale (NIHSS) (17).

Patients with a Glasgow score < 8 on the day of neuropsychiatric examination were excluded from the study, as well as patients with epileptic seizures at the onset of stroke, with aphasia, with MMT< 23, with verified previous dementia /cognitive impairment (based on hetero anamnesis data from patient relatives, data from previous medical findings and based on the, MMT of patients with verified alcohol abuse (defined by at least 5 drinks per day).

Neurological, neuropsychological, internal medicine, and pulmonologist tests were performed on all patients for the first time at the Clinic of Neurology after admission in the acute phase of stroke (first week since the onset of stroke), and subsequent tests were performed on an outpatient basis, after the third, sixth, and twelfth months. They were then contacted by telephone to verify the survival of both groups of patients. Written consent of each patient or close family member was obtained to participate in the research.

Statistical analysis

Numerical test results were statistically processed, analyzed and compared, to obtain answers to questions formulated within the research objectives. From the basic descriptive statistical parameters, standard statistical methods were used for qualitative and quantitative evaluation of the obtained results: absolute numbers, relative numbers, arithmetic mean (X), standard deviation (SD) and range of values. When testing the statistical significance of main differences, the standard Student T-test was used. Descriptive statistics were processed using the X2 (Hi–square test) and the proportional test. When testing statistical hypotheses, a significance level of $p < 0.05$ was taken. All calculations were performed using the Arcus Quickstat Biomedical statistical data processing program. The research was approved by the Committee of the University-Clinical Center Tuzla.

4. RESULTS

The study included 110 patients in whom sleep apnea-type breathing disorder (hereinafter apnea) was verified, with mean age of 65.13 ± 9.27 years, most of whom were men (65 or 59%). The control group consisted of the same number of patients without apnea (n = 110), mean age of 64.94 ± 8.69 years, with the same sex distribution (men = 65; women = 45). There is no statistically significant difference in the age of patients with and without apnea, neither in men (t = -0.46, p = 0.65) nor in women (t = 0.32, p = 0.75), nor in total men and women (t = -0.16, p = 0.88) (Table 1).

The largest number of both sexes with apnea were in the age group of 61–70 years 44 (40%), followed by the age group over 70 years 34 (31%). The mean age of men was 65.68 ± 9.12 (range 41 to 85) years, and women 64.33 ± 9.54 (range 41 to 85). Most patients without apnea were in the age group of 61–70 years (45 or 41%), followed by the age group over 70 years of age 33 or 30%. The mean age of men without apnea was 64.94 ± 9.22 (range 41 to 85) years, and women 65.13 ± 9.12 (range 41 to 85) years. There is no statistically significant difference in the age of men and

Sex	With apnea (age in years)		Without apnea (age in years)		t	p
	X	SD	X	SD		
Men	65.68	9.12	64.94	9.22	-0.46	0.65
Women	64.33	9.54	65.13	9.12	0.32	0.75
Total	65.13	9.27	64.94	8.69	-0.16	0.88

Table 1. Distribution of patients with and without apnea according to age and sex. X = arithmetic mean; SD = standard deviation p = degree of significance

Age (years)	With apnea				Without apnea				Total			
	Men		Women		Men		Women		With		Without	
	N	%	N	%	N	%	N	%	N	%	N	%
41 - 50	1	1.5	3	6.6	2	3.1	3	6.6	4	3.6	5	4.5
51 - 60	16	24.6	12	26.7	15	23.1	12	26.7	28	25.5	27	24.5
61 -70	26	40.0	18	40.0	27	41.5	18	40.0	44	40.0	45	41.0
> 70	22	33.9	12	26.7	21	32.3	12	26.7	34	30.9	33	30.0
Total	65	100.0	45	100.0	65	100.0	45	100.0	110	100.0	110	100.0

Table 2. Distribution of patients with and without apnea according to age and sex With apnea (t=0.75, p=0.46) Without apnea (t=0.27, p=0.79)

Rankin scale	Admission				Discharge				Total			
	Men		Women		Men		Women		Admission		Discharge	
	N	%	N	%	N	%	N	%	N	%	N	%
0	1	1.5	0.0	0.0	9	13.8	4	8.9	1	1.5	13	11.9
1	6	9.2	3	6.7	14	21.5	12	26.7	9	8.2	26	23.6
2	7	10.7	1	2.2	10	15.4	8	17.8	8	7.3	18	16.4
3	11	16.9	10	22.2	15	23.1	9	20.0	21	19.0	24	21.8
4	28	43.1	20	44.4	15	23.1	10	22.2	48	43.6	25	22.7
5	12	18.5	11	24.4	2	3.1	2	4.4	23	21.0	4	3.6
Total	65	100.0	45	100.0	65	100.0	45	100.0	110	100.0	110	100.0

Table 3. Distribution of patients with apnea according to the Rankin scale of disability on admission and discharge men–women (t =-0.146, p = 0.88) admission–discharge (*t=12.11, p<0.0001)

Rankin scale	Admission				Discharge				Total			
	Men		Women		Men		Women		Admission		Discharge	
	N	%	N	%	N	%	N	%	N	%	N	%
0	0.0	0.0	0.0	0.0	11	16.9	2	4.4	0.0	0.0	13	11.8
1	6	9.2	2	4.4	14	21.5	15	33.3	8	7.3	29	26.7
2	5	7.7	5	11.1	9	4.0	12	27.7	10	9.1	21	19.1
3	9	13.8	12	26.7	14	21.5	6	13.3	21	19.0	20	18.2
4	33	50.8	19	42.2	16	24.6	5	11.1	52	47.2	21	19.1
5	12	18.5	7	15.6	1	1.5	5	11.1	19	17.3	6	5.5
Total	65	100.0	45	100.0	65	100.0	45	100.0	110	100.0	110	100.0

Table 4. Distribution of patients without apnea according to the Rankin scale of disability on admission and discharge men–women (t=64, p=0.52) admission–discharge (*t=13.4, p<0.0001)

women, both with apnea (t = 0.75, p = 0.46) and without apnea (t = 0.27, p = 0.79) (Table 2).

The largest number of men with apnea belonged to the age group of 61-70 years (26/40.0%), followed by the age group over 70 years (22/33.9%). The largest number of women belonged to the age group of 61-70 years (18/40%), followed by the age group over 70 years and 51-60 years (12/26.7%).

The largest number of men without apnea belonged to the age group of 61-70 years (27/41.5%), followed by the age group over 70 years (21/32.3%). The largest number of women belonged to the age group of 61-70 years (18/40%), followed by the age group over 70 years and 51-60 years (12/26.7%).

According to the Rankin scale of disability, the largest number of patients with apnea at admission had a degree of disability of 4 (48/43.63%), followed by patients with a degree of 5 (23/20.90%). At discharge, the largest number of patients with apnea had a degree of disability on the same scale of 1 (26/23.6%), followed by patients with a degree of 4 (25/22.72%). Patients of both sexes with apnea, on admission according to the Rankin scale, had an average disability of 3.59 ± 1.19, males 3.46 ± 1.26, and females 3.78 ± 1.06. The difference between men and women was not statistically significant (t =–1.38, p = 0.17). According to Rankin's disability scale, patients of both sexes had a disability of 2.31 ± 1.44, men 2.29 ± 1.47, and women 2.33 ± 1.43. The difference between men and women was not statistically significant (t = -0.146, p = 0.88). The paired t-test determined that there is a statistically significant difference in the mean values of disability according to the Rankin scale on admission and discharge (t = 12.11, p< 0.0001) (Table 3).

The largest number of men with apnea had a degree of disability at admission, according to the Rankin scale 4 (28/43.1%), and at discharge, the largest number had a degree of 3 and 4 (15/23.1%). The largest number of women with apnea had a degree of disability at admission, according to the Rankin scale 4 (20/44.4), and at discharge degree 1 (12/26.7%). The largest number of patients without apnea on admission had a degree of disability, according to the Rankin scale 4 (52/47.2%), followed by patients with a degree of 5 (19/17.3%); on discharge, the largest number had grade 1 (29/26.7%) (Table 4).

In patients without apnea, the largest number of men, according to the Rankin scale of disability, had a grade of 4 (33/50.8%) and on discharge 4 (16/24.6%). The largest number of women without apnea had a degree of disability at admission 4 (19/42.2), and at discharge level 1 (15/33.3%).

Rankin scale	With apnea				Without apnea			
	Admission		Discharge		Admission		Discharge	
	N	%	N	%	N	%	N	%
0	1	1.5	13	11.9	0.0	0.0	13	11.8
1	9	8.2	26	23.6	8	7.3	29	26.7
2	8	7.3	18	16.4	10	9.1	21	19.1
3	21	19.0	24	21.8	21	19.0	20	18.2
4	48	43.6	25	22.7	52	47.2	21	19.1
5	23	21.0	4	3.6	19	17.3	6	5.5
Total	65	100.0	110	100.0	65	100.0	45	100.0

Table 5. Distribution of patients with and without apnea according to the Rankin scale disability, on admission and discharge with – without– apnea admission (t = 0.059, p = 0.95) discharge (t = 0.71, p = 0.48).

followed by a medium one (24/37%), while on discharge the most common was a mild deficit (60/92.3%), followed by medium (4/6.2%). According to the NIHSS scale, women with apnea on admission most often had a mild deficit (23/51.1%), followed by a moderate one (15/33.3%), while on discharge the most common was a mild deficit (38/84.4%), followed by a moderate one (6/13.3%) neurological deficit.

According to the NIHHS scale, patients of both sexes with apnea had a neurological deficit of 7.55 ± 5.22, men 7.17 ± 5.33, and women 8.09 ± 5.06. The student's t-test did not prove a statistically significant difference in neurological deficit according to the NIHSS scale between men and

NIHSS scale	Admission				Discharge				Total			
	Men		Women		Men		Women		Admission		Discharge	
	N	%	N	%	N	%	N	%	N	%	N	%
(0-7)	35	53.8	23	51.1	60	92.3	38	84.4	58	52.7	98	89.1
(8-14)	24	37.0	15	33.3	4	6.2	6	13.3	39	34.5	10	9.0
>14	6	9.2	7	15.6	1	1.5	1	2.3	13	11.8	2	1.9
Total	65	100.0	45	100.0	65	100.0	45	100.0	110	100.0	110	100.0

Table 6. Distribution of patients with apnea according to the neurological deficit according to the NIHSS Scale, on admission and discharge men–women (t = -0.41, *t = 9.74, p < 0.0001 (admission–discharge)

NIHSS scale	Admission				Discharge				Total			
	Men		Women		Men		Women		Admission		Discharge	
	N	%	N	%	N	%	N	%	N	%	N	%
(0-7)	40	61.6	25	55.6	57	87.7	40	88.9	65	59.1	97	88.2
(8-14)	19	29.2	18	40.0	8.0	12.3	4	8.9	37	33.6	12	10.9
>14	6	9.2	2	4.4	0.0	0.0	1	2.2	8.0	7.3	1	0.9
Total	65	100.0	45	100.0	65	100.0	45	100.0	110	100.0	110	100.0

Table 7. Distribution of patients without apnea according to the neurological deficit according to the NIHSS Scale, on admission and discharge men–women (t= 0.37, p = 0.71). * t = 13.85, p < 0.0001 (admission–discharge)

According to the Rankin scale, patients of both sexes without apnea had a disability of 3.58 ± 1.10, men 3.62 ± 1.15, and women 3.52 ± 1.05. The student's t-test did not prove a statistically significant difference in disability according to the Rankin scale between men and women at admission (t = 0.46, p = 0.65). According to the same scale, patients of both sexes had a disability of 2.17 ± 1.39 on discharge, men 2.24 ± 1.45, and women 2.07 ± 1.32. The student's t-test did not prove a statistically significant difference in disability according to the Rankin scale between men and women (t = 64, p = 0.52). The paired t-test determined that there is a statistically significant difference between the mean values of disability according to the Rankin scale on admission and discharge (t = 13.4, p <0.0001). The student's t-test did not determine a statistically significant difference in disability according to the Rankin scale between patients with and without apnea at admission (t = 0.059, p = 0.95) and discharge (t = 0.71, p = 0.48) (Table 5).

According to the NIHSS, most patients with admission apnea had a mild deficit (score 0 to 7) (58/52.72%), followed by patients with a moderate deficit (score 8-14) (39/34.5%). At discharge, the largest number of patients with apnea had a mild deficit (98/89.1%), followed by patients with a moderate deficit (10/10.09%) (Table 6).

The largest number of men with apnea, according to the NIHSS scale, had a mild deficit on admission (35/53.8%),

NIHSS scale	With apnea				Without apnea			
	Admission		Discharge		Admission		Discharge	
	N	%	N	%	N	%	N	%
(0 - 7)	58	52.7	98	89.1	65	59.1	97	88.2
(8 - 14)	39	34.5	10	9.0	37	33.6	12	10.9
> 14	13	11.8	2	1.9	8	7.3	1	0.9
Total	65	100.0	45	100.0	65	100.0	45	100.0

Table 8. Distribution of patients with and without apnea according to the NIHSS Scale, on admission and discharge with–without- apnea admission (t = 0.77, p = 0.71) discharge (t = 0.44, p = 0.66)

women at admission (t = -0.91, p = 0.37). According to this scale, patients of both sexes had a neurological deficit of 3.75 ± 3.32 at discharge, men at 3.65 ± 3.05, and women at 3.91 ± 3.70. The student's t-test did not prove a statistically significant difference in the neurological deficit between men and women (t = -0.41, p = 0.68). A paired t-test showed that there was a statistically significant difference between the mean values of neurological deficit according to the NIHSS scale on admission and discharge (t = 9.74, p < 0.0001). According to the NIHSS scale, in the group of patients without apnea, the largest number had a mild deficit at admission (65/59.1%), followed by patients with a moderate deficit (37/33.63%), and the largest number of patients had a mild deficit at discharge (97/88.2%).) and the average deficit (12/10.90%) (Table 7). Men without apnea at admission most often had a mild deficit of 40 (61.6%), which was also the case at discharge (57 / 87.7%).

Women without apnea at admission most often had a mild deficit (25/55.6%), and at discharge also (40/88.9%).

According to the NIHSS Scale, patients of both sexes without apnea had a neurological deficit of 7.1 ± 4.3, men 7.25 ± 4.70, and women 6.76 ± 3.72. The student's t-test did not prove a statistically significant difference in neurological deficit according to the same scale between men and women (t = 0.58, p = 0.56). According to the NIHSS Scale, patients of both sexes had a neurological deficit of 3.55 ± 3.40 at discharge, men at 3.65 ± 3.37, and women at 3.40 ± 3.48, but the difference was not statistically significant (t = 0.37, p = 0.71). Paired t-test showed that there is a statistically significant difference between the mean values of the neurological deficit on the NIHSS Scale at admission and discharge (t = 13.85, p <0.0001). The student's t-test did not determine a statistically significant difference in neurological deficit according to NIHSS between patients of both sexes, with and without apnea, on admission (t = 0.77, p = 0.71) and discharge (t = 0.44, p = 0.66) (Table 8). In our study 13 relapses of stroke (8 ischemic and 5 hemorrhagic) were verified with apnea, and without apnea in 3 patients (2 ischemic and 1 hemorrhagic) stroke. There is a statistically significant difference in the number of relapses in patients with and without apnea (X2 = 5.46, p = 0.02).

5. DISCUSSION

The mean age of patients in both groups corresponded to the mean age of similar studies (18). Most studies have reported that the incidence of apnea and stroke increases with age. In a study by Ohayon et al. (19) the peak incidence was found in the age group with a range of 50 to 60 years and reduced incidence in the older age groups. According to the same author, snoring is also less common in the older age group.

According to age groups, most patients of both sexes with apnea were in the age group from 61 to 70 years 44 (40%), followed by the age group over 70 years 34 (31%). Endeshaw et al. (20) report that patients aged 57 years and older are 3.5 times more likely to have apnea, while Young et al. (21) state that patients in the age group of 70 to 80 years have almost twice the percentage of SDB compared to patients in the 40–year age group. A higher incidence in older age groups was also found in several other studies stating that aging alters the anatomy of the pharynx and the functioning of the pharyngeal dilator muscles and increases the risk of apnea and stroke in the elderly population (22, 23), consistent with our study.

The majority of patients in our study were men (59%) which corresponds to the results of other studies because men are more sensitive to the occurrence of apnea due to the reduced threshold of sensitivity to carbon dioxide compared to women (24). The difference between the sexes may be related to the greater distribution of body fat in the neck area in men than in women which is an important risk factor for narrowing and closing of the upper airways. Weight gain was verified in 50% of men (25, 26). Ronen et al. (27) state in their study that women have more stable upper airways than men. Redline et al. (28) show a male-female ratio in the community with a range (2 to 3: 1 and 8: 1). The Wisconsin cohort study found OSA in patients aged 30 to 60 years in 9% to 24% of men and in 4% to 9% of women. The estimated prevalence of OSA is 2% for women and 4% for men.

In this paper, the student's t-test did not determine a statistically significant difference in neurological deficit according to NIHSS between patients of both sexes, with and without apnea, on admission (t = 0.77, p = 0.71) and discharge (t = 0.44, p = 0.66), although research shows that recovery and functional outcome after stroke is worse when patients suffer from sleep-disordered breathing (29, 30, 31) and emphasize the importance of detecting and treating respiratory disorders in this population. Good et al. (32) in their study conducted on 19 patients after stroke in 18 (95%) verified apnea, of which 13 (68%) had AHI > 20 and 10 (53%) AHI> 30.

Physical functioning was assessed with the Barthel index of daily life activities. They state that stroke and apnea are associated with higher mortality in the first year and lower Barthel index at discharge, and after 3.6 months and one year after stroke (p <0.004 and p <0.02, respectively).

One of the possible explanations for the connection between apnea and a worse outcome is that patients with apnea develop a subtle deficit of attention and concentration and that this affects their ability to perform activities of daily living and acquire new skills. Iranzo et al. (33) in their study that apnea is common during the first night after stroke and is found in 62% of patients. Apnea is associated with early neurological deterioration, but not with poorer functional outcomes after 6 months.

According to the NIHSS scale, the survival curves for the mild discharge deficit for the groups with and without apnea differed statistically significantly (X2 = 5.10 p = 0.02) while for the medium deficit no statistically significant difference was found (X2 = 0.6, p = 0.44). There were no deaths for the severe deficit. Similar results were obtained by Culebras (34) in his study which found a causal link between apnea and stroke and a reduced chance of rehabilitation, and an additional increased risk of stroke recurrence and increased mortality. Tosun et al. (35) state that patients with stroke and apnea have a far higher risk of developing psychological changes and depression, delirium, poor response to verbal stimuli, and difficulty performing daily tasks, compared to patients with stroke, but without apnea.

One year after stroke with apnea, 13 patients had a recurrence of stroke (8 ischemic and 5 hemorrhagic), and without apnea, the recurrence was in 3 patients (2 ischemic and 1 hemorrhagic) stroke. The chi-square test (X2) determined a statistically significant difference in patients with and without apnea (X2 = 5.46, p = 0.02) concerning the frequency of stroke recurrence.

Dzivas et al. (36) in a study conducted on 34 women and 68 men with apnea and with a mean age of 64.5 +/- 13.7 years, reported recurrence of stroke in 19 patients. Patients with recurrence of stroke had higher AHI, compared to patients without recurrence (80% vs. 52%, p <0.05). It was stated that apnea is an independent risk factor for the recurrence of stroke.

6. CONCLUSION

Patients with apnea have a significantly higher number of stroke relapses, compared to patients without apnea (X2 = 5.46, p = 0.02). There is no significant association of patients with and without apnea concerning the degree of disability assessed by the Rankine and the scale of the American National Institutes of Health for the assessment of stroke.

- **Patients Consent Form:** Written informed consent was obtained from participants.
- **Author's contribution:** B.K.contributed to the idea. Z.D. O.Cl., Dz.S., A.I., A.S. and S.K.conributed to the critical revision of the paper. Final proofreading was made by the first author.
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