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INFLUENCE OF SLEEP APNEA ON ONE YEAR OUTCOME OF ACUTE STROKE

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The aim was to determine whether sleep apnea affects the outcome of stroke patients.

Patients and Methods: The study analyzed 110 patients with acute stroke with sleep apnea and 110 patients without sleep apnea. Acute stroke has been verified either by computerized tomography or magnetic resonance imaging of the brain. There was no significant difference in patient's age with or without sleep apnea neither in men nor women. Neurological, neuropsychiatric, pulmonary tests were performed in all patients at five different periods. In these periods, all patients were evaluated: 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 survival rate of patients with sleep apnea is significantly lower than without sleep apnea. In men with apnea, the survival rate was significantly lower in patients without apnea. Survival of both gender in patients with apnea (22. 64.7%) was the lowest in groups older than 70 years of age. The average age of patients who died with apnea was significantly higher than patients without apnea. Survival of patients with ischemic stroke and without apnea is significantly better than in patients with ischemic and apnea. Survival of patients with hemorrhagic stroke with/without apnea is not significantly different.

Conclusion: Patients with sleep apnea and ischemic stroke have a significantly lower one-year survival rate compared with patients without sleep apnea.

Key words: Stroke, Sleep apnea

INTRODUCTION

Sleep apnea (SA) is associated with an increased risk of stroke in middle-aged and older adults, especially men. Men with moderate to severe sleep apnea were nearly three times more likely to have a stroke than men without sleep apnea or with mild sleep apnea. The risk from SA is independent of other risk factors such as weight, high blood pressure, race, smoking, and diabetes. They also report for the first time a link between sleep apnea and increased risk of stroke in women [1]. Sleep-disordered breathing (SDB) encompasses a broad spectrum of sleep-related breathing disorders, including obstructive sleep apnea (OSA), central sleep apnea, as well as sleep-related hypoventilation and hypoxemia. Diagnostic criteria have been updated in the International Classification of Sleep Disorders, Third Edition, and the American Academy of Sleep Medicine Manual for Scoring Sleep and Associated Events. OSA is the most common form of SDB and is highly prevalent and grossly under diagnosed. Recent studies suggest that prevalence rates in patients with neurologic disorders including epilepsy and stroke exceed general population estimates. The physiologic changes that occur in OSA are vast and involve complex mechanisms that play a role in the pathogenesis of cardiovascular and metabolic disorders and, although largely unproven, likely impact brain health and disease progression in neurologic patients. A tailored sleep history and examination, as well as validated screening instruments, are effective in identifying patients with SDB, although sleep testing is necessary for diagnostic confirmation. While continuous positive airway pressure therapy and other forms of noninvasive positive pressure ventilation remain gold standard treatments, newer therapies, including mandibular advancement, oral appliance devices, and hypoglossal nerve stimulation, have become available. Emerging evidence of the beneficial effects of treatment of SDB on neurologic outcomes underscores the importance of sleep education and awareness for neurologic providers [2]. Stroke disease is the third leading cause of death, after heart disease and cancer; an estimated 12% of all deaths are due to stroke. It accounts for an estimated 6% of total hospital costs in the United Kingdom (UK), but the long-term costs represent a huge financial burden on society [3]. Interest has recently grown in the occurrence of SDB and, in particular, OSA following stroke. Two studies have estimated that 62% of stroke patients exhibit SDB, predominantly upper

airway obstruction (UAO), in the first 24 hours after the onset of neurological symptoms [4, 5].SA syndrome is described as an isolated risk factor for stroke or recurrent stroke which (can cause deth)could because of death. They are independent of other cardiovascular and cerebrovascular risk factors. Hemodynamic, metabolic, and hematological changes associated with SDB during sleep lead to decreased cerebral perfusion and increased coagulability which might be in path physiological background of the stroke and death [6].The basic division of stroke, according to the type of pathological process, is into ischemic stroke (IS) which covers 70-85%, and hemorrhagic stroke (HS). As a consequence of stroke, different degrees of physical, cognitive, and psychosocial functioning have been reported in patients [7]. An important role in reducing the incidence and mortality of stroke is the identification and treatment of potential risk factors [8].

PATIENTS AND METHODS

This prospective study was conducted at the Clinic of Neurology of the University Clinical Center in Tuzla. The examined group of 110 patients in the acute phase of stroke sleep apnea was evaluated. The average age was 65.13 ± 9.27 years. Among them, it was 65 (59%) men. The number of patients with no apnea in the control group was the same as well as the gender ratio, with an average age of 64±8.69 years. The study group included patients who meet the following criteria: confirmation of a diagnosis of ischemic stroke or a hemorrhagic stroke by computed tomography (CT) and/or magnetic resonance imaging (MR) of the brain, pulmonological and neuropsychiatric assessment of sleep apnea performed within seven days after stroke, Mini Mental test (MMT) > 23, Glasgow coma scale (GCS) > 8, written consent for participation in the research by the patients or a member of the patients immediate family. 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 patients relatives, data from previous medical findings) and based on the Neurological, neuropsychiatric, internist and pneumological tests were performed in all patients at five different periods: the first test - in the acute phase of stroke (first week of stroke), second test - one month after the stroke, third test- three months after stroke, fourth test - six months after stroke and fifth test - twelve months after stroke. In these periods, all patients were evaluated: The National Institute of Health Stroke Scale [9], Mini Mental Test [10], The Sleep and snoring Questionnaire Test [11]. The Berlin Questionnaire Test [12], The Epworth Sleepiness Scale[13], The Stanford Sleepiness Scale [14], and The general sleep questionnaire [15]. The findings of CT of the brain and MR of the brain were interpreted by a radiologist who was not familiar with the goals and hypotheses of the research and based on whose results were established: type of stroke, localization of the lesion, and lesion size. The research included the registration of the following socio-demographic characteristics: gender and age.

Statistical Analyses

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 as well as the Long rank test with $p < 0.05$ considered significant. The research was approved by the Committee of the University - Clinical Center Tuzla.

RESULTS

One year after stroke onset survived 91 (82.7%) out of 110 patients with apnea. The average age of survived patients was 63.66±8.78 years. The survival rate of patients with sleep apnea is significantly less than without sleep apnea ($X2 = 7.49$; $p = 0.01$). Among them 52 (80%) were men. In the control group, without apnea survived 104 (94.5%) patients with an average age of 65.00 ± 8.62 years. Among them 62 (95.4%) were men. In men with apnea, there is a significantly lower survival range to patients without apnea ($X2 = 8.22$, $p = 0.004$). In women, there is no difference (Table 1).

Table 1. One - year survival rate of stroke patients with and without sleep apnea by sex

Survival rate (months)	Men with apnea N (65)%		Men without apnea N (65)%		Women with apnea N (45)%		Women without apnea N (45)%		Total with apnea N (110) %	
1	64	98.5	65	100.0	45	100.0	45	100.0	109	99.1
2	62	95.4	64	98.5	43	95.5	44	97.8	105	95.5
3	62	95.4	64	98.5	42	93.3	43	95.6	104	94.5
4	61	93.8	63	96.9	42	93.3	43	95.6	103	93.6
5	61	93.8	63	96.9	42	93.3	43	95.6	103	93.6
6	59	90.8	63	96.9	41	91.1	43	95.6	100	91.0
7	58	89.2	63	96.9	41	91.1	43	95.6	99	90.0
8	56	86.2	63	96.9	41	91.1	43	95.6	97	88.2
9	56	86.2	63	96.9	41	91.1	43	95.6	97	88.2

10	56	86.2	63	96.9	41	91.1	42	93.3	97	88.2
11	54	83.1	62	95.4	40	88.9	42	93.3	94	85.5
12	52	80.0	62	95.4	39	86.7	42	93.3	91	82.7

Men with and without apnea (X2=8.22, p=0.004); Women with and without (X2=0.49, p=0.48);Total with and without apnea (*X2= 7.49, p = 0.01).*

Survival (one-year) of both gender in patients with apnea 22 (64.7%) was lowest in the group older than 70 years (p = 0.03), followed by the age group 61-70 years 39 (88.6%). The mean age of deaths of patients with apnea was statistically significantly higher (69.84 ± 9.43) than that of survivors (63.66 ± 8.78) (t = -3.86, p < 0.001). According to the age groups, the least surviving patients of both sexes with apnea were in the age group over 70 years 22 (64.7%). The mean age of deaths of men with apnea was 70.54 ± 9.61 (range 41 to 85) years, and women 75.67 ± 3.93. The student's t-test did not determine a statistically significant difference in the age of deceased men and women with apnea (t = -1.65, p = 0.12) (Table 2).

Table 2. One-year outcome in patients with sleep apnea according to the age

Survival rate (months)	Age 41-50 N (4)%		Age 51-60 N (28)%		Age 61-70 N (44)%		Age > 70 N (34)%		Total N (110)%
1	4	100.0	27	96.4	44	100.0	34	100.0	109
2	4	100.0	27	96.4	44	100.0	33	97.0	105
3	4	100.0	27	96.4	44	100.0	30	88.2	104
4	4	100.0	27	96.4	44	100.0	30	88.2	103
5	4	100.0	27	96.4	44	100.0	29	85.3	103
6	4	100.0	26	92.6	42	95.5	26	76.5	100
7	4	100.0	26	92.6	42	95.5	26	76.5	99
8	4	100.0	26	92.6	41	93.2	25	73.5	97
9	4	100.0	26	92.6	41	93.2	25	73.5	97
10	4	100.0	26	92.6	41	93.2	22	64.7	97
11	4	100.0	26	92.6	39	88.6	22	64.7	94
12	4	100.0	26	92.6	39	88.6	22	64.7	91

With apnea >70year (*t=-3.86, p<0.001)

The lowest number of surviving patients of both sexes without apnea was in the age group over 70 out of 33 survivors 27 (81.2%) (men 18;85.7%, women 9;75.5%), while in other age groups there were no deaths. The mean age of deaths of men without apnea was 57.67 ± 9.81 (range 41 to 85) years, and that of women 70.00 ± 9.16 (range 41 to 85). No statistically significant difference was found in the age of deceased and surviving patients without apnea (t = 0.318, p = 0.751). Analyzing the age of deaths with and without apnea, it was found that the mean age of deaths with apnea was statistically significantly higher than the age of patients without apnea (t = 1.97, p = 0.03 - unilateral testing). Statistical Log Rank test found that there was no statistically significant difference in the survival curves of patients without apnea of both sexes concerning the age (X2 = 2.1, p = 0.56). Furthermore, the same test did not find a statistically significant difference in the survival curve of patients with and without apnea for the age groups 51 - 60 years (X2= 0.13, p = 0.72). However, this test found a statistically significant difference in survival for age groups of 61-70 years (X2= 3.86, p = 0.05) and age groups over 70 years (X2= 7.1, p = 0.01) and without apnea (Table 3).

Table 3. One - year outcome in patients without sleep apnea according to the age

Survival rate (months)	Age 41-50 N (5)%		Age 51-60 N (27)%		Age 61-70 N (45)%		Age > 70 N (33)%		Total N (110)%
1	4	100.0	27	100.0	45	100.0	33	100.0	110
2	4	100.0	27	100.0	45	100.0	31	93.9	108
3	4	100.0	27	100.0	45	100.0	30	91.0	107
4	4	100.0	27	100.0	45	100.0	29	87.9	106
5	4	100.0	27	100.0	45	100.0	29	87.9	106
6	4	100.0	27	100.0	45	100.0	29	87.9	106
7	4	100.0	27	100.0	45	100.0	29	87.9	106
8	4	100.0	27	100.0	45	100.0	29	87.9	106

9	4	100.0	27	100.0	45	100.0	29	87.9	106
10	4	100.0	27	100.0	45	100.0	28	84.8	105
11	4	100.0	27	100.0	45	100.0	27	81.2	104
12	4	100.0	27	100.0	45	100.0	27	81.2	104

With/without apnea 61-70 year (*X2=3.86, p=0.05) >70 year (*X2=7.1, p=0.01)

During one year the majority of apnea survivors had ischemic stroke (78/84.9% of 92) and hemorrhagic stroke (13/72.2% of 18).(Table 4).

Table 4. One - year survival rate with sleep apnea according to the type stroke

Survival rate with apnea (months)	Ischemic stroke N=92	100.0 %	Hemorrhagic stroke N= 18	100.0%	Total N =110	100%
1	91	98.9	18	100.0	109	99.1
2	89	96.7	17	94.4	106	96.4
3	88	95.7	16	88.9	104	94.5
4	87	94.6	16	88.9	103	93.6
5	87	94.6	16	88.9	103	93.6
6	86	93.5	14	77.8	100	90.9
7	85	92.4	14	77.8	99.0	90.0
8	84	91.3	13	72.2	97.0	88.2
9	84	91.3	13	72.0	97.0	88.2
10	84	91.3	13	72.0	97.0	88.2
11	81	88.0	13	72.2	91.0	82.7
12	78	84.9	13	72.2	91.0	82.7

*X2 = 5.46, p=0.02 (Ischemic stroke with/without apnea), X2 = 2.1, p=0.15 (Hemorrhagic stroke with/ without apnea) During one year, the number of survivors without apnea who suffered from ischemic stroke were (88/95.7%) and (16/88.9%) with hemorrhagic stroke.The majority of survivors of ischemic stroke were women (34/94.4%), and hemorrhagic stroke the number of survivors of both sexes was equal (8/88.9%). Survival curves for ischemic stroke with and without apnea were statistically significantly different (X2 = 5.46, p = 0.02) while for hemorrhagic ally statistically significant difference was not found (X2 = 2.1, p = 0.15) (Table 5).

Table 5. One-year survival rate without sleep apnea according to the type stroke

Survival rate without apnea (months)	Ischemic stroke N=92	100.0 %	Hemorrhagic stroke N= 18	100.0%	Total N =110	100%
1	92	100.0	18	100.0	110	100.0
2	92	100.0	16	88.9	108	98.2
3	91	98.9	16	88.9	107	97.3
4	90	97.8	16	88.9	106	96.4
5	90	97.8	16	88.9	106	96.4
6	90	97.8	16	88.9	106	96.4
7	90	97.8	16	88.9	106	96.4
8	90	97.8	16	88.9	106	96.4
9	90	97.8	16	88.9	106	96.4
10	89	96.7	16	88.9	105	95.5
11	88	95.7	16	88.9	104	94.5
12	88	95.7	16	88.9	104	94.5

*X2=5.46, p=0.02 (Ischemic stroke with/without apnea), X2=2.1, p=0.15 (Hemorrhagic stroke with/without apnea)

According to the side of AS the largest number of patients with and without sleep apnea had a lesion in the left and or right hemisphere 50 (45.4%). There was no statistically significant correlation between patients with sleep apnea and localization of stroke in the left hemisphere (X2 = 0.59, p =0.44) or localization in both sides (X2= 0.0, p = 1). There was a statistically significant correlation between the localization of stroke in the right hemisphere in patients with apnea (X2 =4.65, p = 0.03). The chance of stroke on the right side is 1.95 times (95% CI: 1.06-3.62) higher in patients with apnea than in patients without apnea (Table 6).

Table 6. Distribution of patients with and without sleep apnea according to the sex and side of stroke

	With apnea				Without apnea				Total With Without		
	Men		Women		Men		Women				
Side of lesion	N	%	N	%	N	%	N	%	N%	%	N%
Left side	17	26.2	9	2.0	19	29.2	13	28.9	26	23.6	32
Right side	30	46.1	14	31.1	17	26.2	11	24.4	44	40.0*	28
Both sides	18	27.7	22	48.9	29	44.6	21	46.7	50	45.4	50
Total	65	100.0	45	100.0	65	100.0	45	100.0	110	100.0	110

Left side (X2=0.59, p=0.44), both sides (X2=0.0, p=1) *X2=4.65, p=0.03 (right side)

The majority of patients who survived with apnea (23; 88.5%) had a left hemisphere lesion but the difference was not statistically significant (X2 = 4.37, p = 0.11), while patients without apnea 48 (96%) had lesion(s) at both sides (X2 = 2.22, p = 0.33). The Log Rank test did not reveal a statistically significant difference in the survival curve concerning the stroke side in patients with apnea (X2= 4.37, p = 0.11) and without apnea (X2= 2.22, p = 0.33).

DISCUSSION

Young et al. [16] in his study states that apnea in the elderly ranges between 20% - 50%, and that the prevalence of apnea increases with age. The age group of 70 years and older has almost twice the percentage of SA than the age group of 40 years. Which corresponds to our results. The prevalence of SA increases with age and is three times more common in adults over 40 years of age. In women, incidence increases after menopause. In women who use hormonal therapy frequency of apnea is similar to the period before menopause. SA prevalence among men 30 to 60 years of age is 10 - 20% [17]. In the study of Shahar et al. [18] the rate of survival of patients with SA is primarily seen in men younger than 70 years. Women and men older than 70 years had increased mortality, which would match our results. Bixler et al. [19] in a study of 741 patients with AHI > 10, the presence of apnea was found in 3.3% in the 20 - 90 age group, with a maximum prevalence in the 45 - 64 age group. In conclusion, it is stated that the prevalence of apnea increases with age, but that the clinical significance and severity of apnea decrease. A higher incidence in older age groups has been found in several other studies that suggest 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, consistent with our study. SDB is an isolated risk factor that is correlated with poor outcomes and increased long-term mortality in patients with stroke [20, 21]. Munoz et al. [22] conducted a six-year prospective study on 394 patients with apnea aged 70 to 90 years and a mean age of 77.28 years. During follow-up, 20 IS were registered in patients with AHI> 30. The study concludes that severe apnea (AHI > 30) increases the risk of IMU ISand mortality in the elderly, independent of other known risk factors. According to a three-year study by Wyler et al. [23] conducted on 19 patients with stroke in whom apnea was verified in 68.5% and 21 (28.6%) patients with insomnia but without apnea. Higher mortality was found in patients with apnea 58.8% versus 33% of patients without apnea. The difference was not statistically significant (p = 0.14). Higher mortality was registered in the elderly after stroke, which would correspond to our study. According to Herman et al. [24] apnea is present in 50% to 59% of patients with stroke, and 77.6% according toRola et al. [25]which is more thanin their study patients with severe speech disorders were included, and polysomnography was used. In our study questionnaires for the diagnosis of apnea was used. According to Janssens et al. [26] study the prevalence of apnea increases with age and ranges from 11% to 62% which corresponds to our study. In the United States, at least 5% of the general population has OSA. It is a risk factor for the development of arterial hypertension and coronary heart disease and can lead to congestive heart failure and acute ischemic stroke [18, 27]. SA is found in 50 - 70% of patients with stroke 34 [24]. The majority of patients in our study were men (59%) which corresponds to the results of other studies because men are more susceptible to the occurrence of apnea due to the reduced threshold of carbon dioxide sensitivity compared to women [28]. The difference between the sexes may be related to a 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 also verified in 50% of men [29, 30]. Redline et al. [31] show a male-female ratio in the community with a range (2 to 3: 1 and 8: 1). It shows that the increased risk of stroke in men with SA is comparable to adding 10 years of age to a man. An increased risk of stroke in men occurs even with mild apnea. Redline et al. [1] in a study conducted on 5422 patients with apnea followed up during 8.7 years, 193patients with IS were found.A significant association between IS and apnea was observed in men (p = 0.016). Men with AHI> 19 have a risk ratio of 2.86 (95% confidence interval, 1.1 - 7.4). Each-unit increase in AHI in men increases the risk of stroke by 6% (95% confidence interval, 2 - 10%). In women, stroke is not significantly associated with AHI. Shahar et al. [18] in their study found that the survival rate of patients with apnea and stroke was significantly worse compared to patients without apnea. Apnea is, as the authors state, a risk factor for stroke independent of other cardiovascular and cerebrovascular risk factors for increased mortality. The increased risk for

stroke is 60% higher in patients with apnea compared to those without apnea. Higher mortality was also found in cases of mild apnea (AHI <10/hour). Pasic [32] in the study among 200 patients with stroke, 40.5% of patients had OSA, and most of them, 76.8% had an IS. Sleep apnea is separated risk factor which correlates with the bad outcome and increases long-term mortality in patients with stroke. Rola et al. [26] in their study of 91 patients with stroke or TIA, who have been followed-up for two years,SA was noticed in 61 (67.7%) patients. The rate of recurrent stroke or TIA was significantly higher in the group with SA 12 (19.7%, p < 0.05) compared to the group without SA 3 (10%). Mortality rates were not significantly different in patients with and without SA (4/6.6% and 2/6.7%). Hu et al. [33] found that 63% of patients with IS have sleep apnea and 12.5% of patients without SA. Sleep-disordered breathing (SDB) accompanied by arterial ox hemoglobin desaturation is common in patients undergoing rehabilitation after stroke and is associated with higher mortality at 1 year and lower Barthel index scores at discharge and 3 and 12 months after stroke. SDB may be an independent predictor of worse functional outcomes. Obstructive sleep apnea appeared to be the most common form of SDB, and the frequent history of snoring suggests that SDB preceded the stroke in most patients [34]. Dyken et al. [35] found SA in 10 of 13 men with stroke (77%) and only 3 of 13 male subjects without stroke (23%) (p = 0169). Seven of 11 women with stroke (64%) had OSA, while only 2 of 14 female subjects without stroke (14%) had OSA (p =.0168). The 4 - year mortality for patients with stroke was 20.8%. All patients with stroke who died had OSA. In conclusion, he stated that the patients with stroke have an increased incidence of OSA compared with normal sex- and age-matched control subjects. Hypoxia and hemodynamic responses to OSA may have predisposed these patients to stroke. During the four years of monitoring patients with sleep apnea and stroke found mortality of 21% [8]. Arzt et al. [36] in a study that included 1475 patients with stroke and apnea patients and 1189 control group after 4 years of follow-find AHI > 20 increases the risk of stroke to 4:33 times (95% confidence interval, 1:32 to 14:24, p = 0.02) compared with patients with AHI < 5 where the hazard ratio 3.8 times higher (95% confidence interval, 0.74 - 12.81, p = 0.12). In conclusion, it is stated that the apnea is severe to moderate risk of stroke increases from 30% to 90%, independent of other risk factors. Wierzbick et al. [37] in their study analyzed 43 patients with stroke and SA are not verified a significant correlation between the apnea and the side of the stroke.

CONCLUSION

Patients with sleep apnea and ischemic stroke have significantly lower one year survival rate in comparison with sex- and age-matched controls. Survival rate in patients with/without apnea in hemorrhagic stroke has no statistical difference. The side of the stroke lesion does not influence survival rates.

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