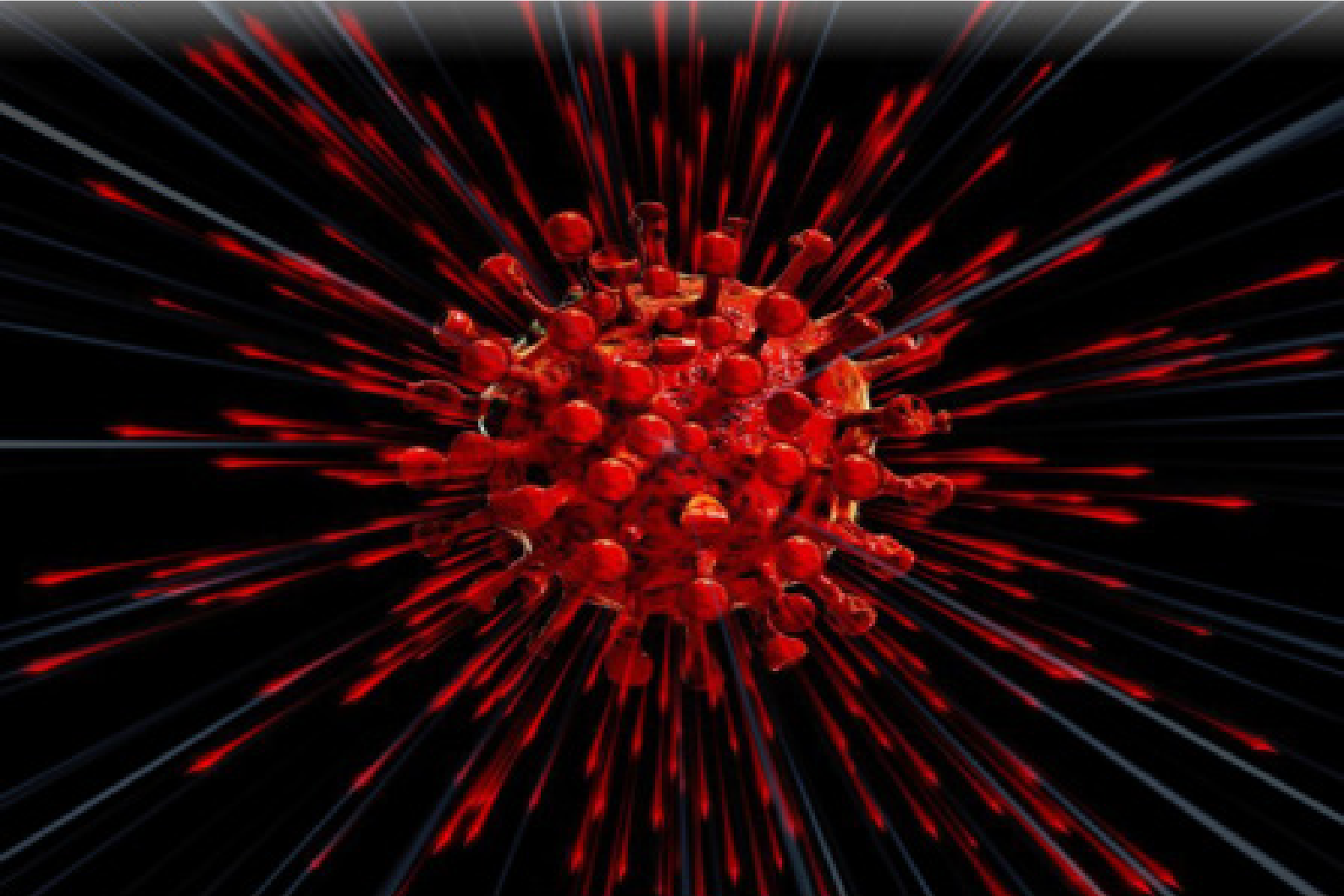


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# Lobectomy and pneumonectomy in patients over 70 years of age for the treatment of lung cancer: evaluation of surgical outcomes

✉ Mesut Buz<sup>1</sup>, ✉ Selime Kahraman<sup>2</sup>, ✉ Attila Özdemir<sup>1</sup>, ✉ Talha Doğruyol<sup>1</sup>, ✉ Berk Çimenoglu<sup>1</sup>,  
✉ Recep Demirhan<sup>1</sup>

<sup>1</sup>Department of Thoracic Surgery, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Türkiye

<sup>2</sup>Department of Thoracic Surgery, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, İstanbul, Türkiye

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## ABSTRACT

**Aims:** The primary aim of this study is to evaluate the surgical outcomes of lobectomy and pneumonectomy operations performed due to lung cancer in individuals aged 70 and above, and to analyze the factors influencing these outcomes.

**Methods:** This retrospective study covers lobectomy and pneumonectomy operations performed on 103 lung cancer patients over the age of 70, from January 2018 to December 2021. A dataset was created including patients' demographic information, smoking status, comorbidities, results of pulmonary function tests and echocardiography, preoperative complete blood count, and serum albumin levels, and these data were analyzed.

**Results:** The average age of the patients was 73.3; 83.5% were male, and 16.5% were female. The complication rate was 47.6%, and the 30-day surgical mortality rate was 8.7%. Patients with a high American Society of Anesthesiologists (ASA) score had higher rates of complications and mortality ( $p=0.015$ ). Low preoperative serum albumin ( $p=0.017$ ) and hemoglobin ( $p=0.026$ ) levels were associated with an increased risk of complications. Postoperative outcomes between Video Assisted Thoracoscopic Surgery (VATS) and thoracotomy were found to be similar.

**Conclusion:** The study demonstrates that in elderly lung cancer surgery, comorbidities and preoperative nutritional status are decisive factors affecting surgical outcomes. Preoperative albumin and hemoglobin levels emerge as significant indicators in assessing the risk of postoperative complications. VATS and thoracotomy are surgical techniques with similar safety and efficacy profiles.

**Keywords:** Lung cancer, elderly, lobectomy, pneumonectomy

## INTRODUCTION

In recent years, it is known that the increase in life expectancy worldwide, parallel to the increase in the frequency of cancer-related diseases, has led to a significant rise in lung cancer cases. This increase is particularly more pronounced among the elderly population. The latest reports from the World Health Organization predict that cancer cases could increase by 60% over the next decade, underscoring the importance of developing new strategies in the fight against cancer.<sup>1</sup>

Factors such as advancing age, increased comorbidities, and decreased functional reserve can significantly affect surgical success.<sup>2</sup> Particularly, chronic diseases and general health conditions observed in elderly patients can significantly alter the risks and outcomes

of surgical interventions, necessitating special attention and approach in planning and implementing surgical procedures.

Lung cancer remains the most common cause of death among men worldwide, and an increase in this rate is also observed in the female population. It has been known that surgical treatment in early-stage lung cancer patients increases survival rates; however, this becomes more complex in the older age group. The effectiveness and success of surgical treatment in advanced-stage lung cancer patients, especially those over eighty years old, remains a controversial topic in light of current research and clinical practices.<sup>3-5</sup>

This study aims to comprehensively evaluate the factors affecting surgical success in elderly lung cancer patients.

**Corresponding Author:** Mesut BUZ, mesutbuzmd@gmail.com





## METHODS

The study was conducted with authorization from the Kartal Dr. Lütfi Kırdar City Hospital Clinical Researches Ethics Committee (Date: 27.04.2023, Decision No: 2023/514/248/16). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective analysis, undertaken between January 2018 and December 2021, involves lobectomy and pneumonectomy surgeries performed on patients aged 70 or older. Patients who underwent lobectomy or pneumonectomy and were aged 70 or older were included in the study. Patients who underwent segmentectomy or had incomplete data prior to the operation were excluded. Data were retrospectively collected from the hospital information system.

The demographic information, smoking history, comorbidities, pulmonary function test results, echocardiography outcomes, preoperative complete blood count, and albumin levels of the selected patients were recorded. Recognizing the impact of nutritional status on surgical outcomes, patients identified with significant albumin deficiencies (e.g., albumin levels below 3.5 g/dl) underwent a tailored preoperative nutritional support protocol. This included albumin replacement therapy and nutritional supplementation, aiming to optimize their condition ahead of surgery.

Patients with a hemoglobin level of 10 g/dl or lower received a preoperative erythrocyte suspension transfusion. All operations were overseen by an experienced anesthesia team. Postoperative needs for erythrocyte suspension transfusion, the number of drains and drainage volume, definitive pathological diagnosis and stage, length of hospital stay, complications, and mortality rates were recorded.

### Statistical Analysis

This study delineates the application of descriptive statistics, including mean, standard deviation, median, and range (minimum-maximum values), alongside frequencies and proportions for data characterization. The suitability of data for normal distribution was initially evaluated via the Kolmogorov-Smirnov test. However, acknowledging the complexity of normality assessment, it is proposed that future analyses incorporate additional measures such as skewness, kurtosis, and visual inspection methods (histograms, detrended Q-Q plots). Quantitative independent variables were analyzed using the Mann-Whitney U test due to its non-parametric nature, whereas qualitative independent variables were examined through the Chi-square test, with Fisher's exact test applied under specific conditions. Statistical procedures were executed using SPSS software (Version 29, Chicago, IL, USA). The American Society of Anesthesiologists (ASA) Physical Status Classification

System is utilized to assess the preoperative physical fitness of patients undergoing surgery. It categorizes patients into six groups based on their physical health, ranging from ASA I, indicating a healthy patient, to ASA VI, denoting a brain-dead patient. This system helps in predicting perioperative risks and tailoring anesthesia management. In this study, the ASA score was used to evaluate the baseline health status of patients undergoing surgical treatment.

## RESULTS

The ages of the operated patients ranged from 70 to 86, with an average age of 73.3. Of the 103 patients included in the study, 86 were male (83.5%) and 17 were female (16.5%). 85 of the operations (82.5%) were thoracotomies, while 18 (17.5%) were VATS (Video Assisted Thoracoscopic Surgery). 6 patients (5.8%) underwent pneumonectomy, and 97 patients (94.2%) underwent lobectomy. 82 patients (79.6%) had comorbidities. The demographic data of the patients, preoperative FEV1 value, EF value, comorbidities, and ASA (American Society of Anesthesiologists) scores are summarized in **Table 1**.

	Min-Max	Median	Mean±SD/n-%
Age	70.0 - 86.0	73.0	73.4 ± 3.4
Gender	Female		17 16.5%
	Male		86 83.5%
ASA Score	I		17 16.5%
	II		53 51.5%
	III		33 32.0%
Smoking	20.0 - 150.0	40.0	38.7 ± 16.9
Smoking	(-)		27 26.2%
	(+)		76 73.8%
Ejection fraction	50.0 - 67.0	60.0	61.1 ± 3.8
FEV1 %	60.0 - 126.0	84.0	83.7 ± 13.8
Drainage	0.0 - 2800.0	700.0	771.8 ± 495.9
Hemogram-preop	7.9 - 14.0	11.0	10.8 ± 1.5
Albumin	10.0 - 43.0	34.0	33.8 ± 5.4
Diagnosis			
Squamous			46 44.7%
Adenocarcinoma			42 40.8%
Adenosquamous			4 3.9%
Large cell neuroendocrine carcinoma			4 3.9%
Pleomorphic carcinoma			4 3.9%
Carcinosarcoma			1 1.0%
Combined small cell			1 1.0%
Neuroendocrine tumor			1 1.0%

Min: Minimum, Max: Maximum, SD: Standard deviation, FEV1: Forced expiratory volume 1

Preoperatively, 51.2% of the patients were classified as ASA 2, and 32.0% as ASA 3. The smoking rate was 73.8%. The most common pathological diagnosis was squamous

cell carcinoma at 44.7%, followed by adenocarcinoma at 40.8%. There were 47 patients (45.6%) in stage 1A, 26 (25.2%) in stage 1B, 11 (10.7%) in stage 2A, 10 (9.7%) in stage 2B, and 9 (8.7%) in stage 3A. 3 patients (2.9%) had chest wall resection and 11 patients (10.7%) were operated post neoadjuvant therapy. 49 patients (47.6%) experienced complications and 9 patients (8.7%) had surgical mortality within 30 days. The most common complication was prolonged air leak (42.9%), followed by pneumonia (26.5%). The average length of hospital stay was 9.1 days. The data on the type of operation and stage of patients are summarized in Table 2, and the types of complications, length of hospital stay, and mortality data are summarized in Table 3.

	n	%	
<b>Operation</b>			
Right lower bilobectomy	1	1.0%	
Right lower lobectomy	23	22.3%	
Right middle lobectomy	3	2.9%	
Right pneumonectomy	2	1.9%	
Right upper bilobectomy	3	2.9%	
Right upper lobectomy	34	33.0%	
Left lower lobectomy	7	6.8%	
Left pneumonectomy	4	3.9%	
Left upper lobectomy	24	23.3%	
Video-assisted thoracoscopic surgery	(+)	18	17.5%
	(-)	85	82.5%
Thoracotomy	(+)	85	82.5%
	(-)	18	17.5%
Neoadjuvant	(-)	92	89.3%
	(+)	11	10.7%
Chemotherapy	6	54.5%	
Chemotherapy+radiotherapy	5	45.5%	
Number of drains	I	60	58.3%
	II	43	41.7%
Erythrocyte replacement	(-)	89	86.4%
	(+)	14	13.6%
Complication	(-)	54	52.4%
	(+)	49	47.6%
Prolonged air leak	20	40.8%	
Atelectasis	3	6.1%	
Pneumonia	14	28.6%	
Hematoma	2	4.1%	
Atrial fibrillation	4	8.2%	
Bronchopleural fistula	1	2.0%	
Embolism	1	2.0%	
Other	11	22.4%	

Complication	n	%
Acute kidney failure	1	2.0%
Atrial fibrillation	2	4.1%
Arrhythmia	1	2.0%
Atelectasis	3	6.1%
Bronchopleural fistula	1	2.0%
Bradycardia	1	2.0%
Subcutaneous emphysema	2	4.1%
Couldn't extubate	2	4.1%
Hematoma	3	6.1%
Hemoptysis	1	2.0%
Liver enzyme elevation	2	4.1%
Pleurisy	1	2.0%
Pneumonia	13	26.5%
Pulmonary embolism	1	2.0%
Cerebrovascular accident	1	2.0%
Prolonged air leak	21	42.9%
Vocal cord paralysis	2	4.1%

No significant relationship was found between patients' demographic data and complications. Patients with a high American Society of Anesthesiologists (ASA) score had a higher frequency of complications (p=0.015).

Smoking was not found to significantly lead to complications. When evaluating the percentage and liters of FEV1 separately, no significant difference was found in the group with complications. Preoperative low complete blood count and albumin levels had a significant impact on the development of complications (p=0.026 and p=0.017, respectively). The presence of comorbidities, especially diabetes mellitus (DM) and chronic obstructive pulmonary disease (COPD), significantly increased the complication rate compared to other comorbidities (p=0.006 and p=0.025, respectively). The presence of secondary malignancies was not found to increase the complication rate.

No significant difference was observed in the distribution of definitive pathological diagnosis and stage between groups with and without complications. No significant difference was found in complication development among VATS lobectomy, thoracotomy, chest wall operations, and operations after neoadjuvant therapy. The need for postoperative erythrocyte suspension (ES) transfusion did not differ between the groups with and without complications. It was found that the group with complications had a longer hospital stay (p<0.001) and a higher mortality rate (p=0.001). The data on complications and their significance ratios are summarized in Tables 4 and 5.



Table 4. Analysis of factors influencing postoperative complications

		Complication (+)							
		Average±SD/n-%			Average±SD/n-%				
Age		73.3	±	3.2	73.5	±	3.6	0.754	m
Gender	Female	11		20.4%	6		12.2%	0.267	X <sup>2</sup>
	Male	43		79.6%	43		87.8%		
ASA score	I	14		25.9%	3		6.1%	0.015	X <sup>2</sup>
	II	27		50.0%	26		53.1%		
	III	13		24.1%	20		40.8%		
Smoking		40.0	±	20.5	37.4	±	12.8	0.737	m
	(-)	17		31.5%	10		20.4%	0.202	X <sup>2</sup>
	(+)	37		68.5%	39		79.6%		
Ejection fraction		61.4	±	3.9	60.7	±	3.8	0.335	m
FEV1 %		84.3	±	13.9	83.1	±	13.8	0.744	m
Drainage		596.3	±	375.2	965.3	±	542.6	0.000	m
Hemoglobin		11.1	±	1.5	10.5	±	1.4	0.026	m
Albumin		34.6	±	6.1	32.9	±	4.6	0.017	m
Comorbidity	(-)	17		31.5%	4		8.2%	0.003	X <sup>2</sup>
	(+)	37		68.5%	45		91.8%		
Diabetes mellitus		5		9.3%	15		30.6%	0.006	X <sup>2</sup>
Hypertension		19		35.2%	23		46.9%	0.225	X <sup>2</sup>
Coronary artery disease		11		20.4%	14		28.6%	0.332	X <sup>2</sup>
Congestive heart failure		1		1.9%	1		2.0%	1.000	X <sup>2</sup>
Kidney failure		4		7.4%	4		8.2%	0.886	X <sup>2</sup>
Chronic obstructive pulmonary disease		6		11.1%	14		28.6%	0.025	X <sup>2</sup>
Second malignancy		8		14.8%	6		12.2%	0.704	X <sup>2</sup>
Diagnosis									
Adenocarcinoma		20		37.0%	22		44.9%	0.417	X <sup>2</sup>
Adenosquamous		4		7.4%	0		0.0%	0.119	X <sup>2</sup>
Large cell neuroendocrine carcinoma		2		3.7%	2		4.1%	1.000	X <sup>2</sup>
Carcinosarcoma		1		1.9%	0		0.0%	1.000	X <sup>2</sup>
Combined small cell		0		0.0%	1		2.0%	0.476	X <sup>2</sup>
Neuroendocrine tumor		1		1.9%	0		0.0%	1.000	X <sup>2</sup>
Pleomorphic carcinoma		2		3.7%	2		4.1%	1.000	X <sup>2</sup>
Squamous		24		44.4%	22		44.9%	1.347	X <sup>2</sup>
2									
Stage	1A	30		55.6%	17		34.7%	0.105	X <sup>2</sup>
	1B	11		20.4%	15		30.6%		
	2A	3		5.6%	8		16.3%		
	2B	4		7.4%	6		12.2%		
	3A	6		11.1%	3		6.1%		

SD: Standard deviation, ASA: The American Society of Anesthesiologists, m: Mann-Whitney U test, X<sup>2</sup>: Chi-square test, FEV1: Forced expiratory volume 1

**Table 5.** Impact of comorbidities on surgical outcomes

		Complication (-)		Complication (+)		P			
		Average $\pm$ SD/n-%	Median	Average $\pm$ SD/n-%	Median				
Video-assisted thoracoscopic surgery	(+)	9	16.7%	9	18.4%	0.820	X <sup>2</sup>		
	(-)	45	83.3%	40	81.6%				
Thoracotomy	(+)	45	83.3%	40	81.6%	0.820	X <sup>2</sup>		
	(-)	9	16.7%	9	18.4%				
Chest wall	(+)	1	1.9%	2	4.1%	0.604	X <sup>2</sup>		
	(-)	53	98.1%	47	95.9%				
Neoadjuvant	(-)	46	85.2%	46	93.9%	0.154	X <sup>2</sup>		
	(+)	8	14.8%	3	6.1%				
Chemotherapy		4	50.0%	2	66.7%				
Chemotherapy+radiotherapy		4	50.0%	1	33.3%				
Number of drains	I	35	64.8%	25	51.0%	0.156	X <sup>2</sup>		
	II	19	35.2%	24	49.0%				
Erythrocyte replacement	(-)	49	90.7%	40	81.6%	0.178	X <sup>2</sup>		
	(+)	5	9.3%	9	18.4%				
Length of the hospital stay		6.6	1.5	7.0	11.8	5.5	10.0	0.001	m
Mortality	(-)	54	100.0%	40	81.6%	0.001	X <sup>2</sup>		
	(+)	0	0.0%	9	18.4%				

SD: Standard deviation, m: Mann-Whitney U test, X<sup>2</sup>: Chi-square test

## DISCUSSION

It is known that the frequency of cancer increases with advancing age and cancer surgery in older ages becomes more challenging due to increased comorbidities and decreased physical condition.<sup>1</sup> In this study, surgical outcomes for patients aged 70 and above were evaluated, and parameters affecting the development of complications were examined.

In patients undergoing lobectomy, age, ASA score, male gender, Zubrod score, diabetes, renal function disorders, induction therapy, FEV1 value, and smoking have been shown to be risk factors.<sup>6</sup> A study in France reported risk factors for mortality including age, gender, dyspnea score, ASA score, performance status, priority of surgery, diagnosis, comorbidities, and surgical procedure.<sup>7</sup> Hino and colleagues<sup>8</sup> have indicated that male gender and pathological diagnosis are associated with poor prognosis, and Licker and colleagues<sup>9</sup> have found that a low FEV1 value and the diagnosis of COPD increase the development of complications. In our study, no relationship was found between gender or pathological diagnosis and prognosis. However, a significant correlation was identified between a high ASA score and increased rates of complications and mortality. Similarly, smoking and diagnoses of COPD were found to increase complications and mortality.

In the study by Jingjing Shao and colleagues<sup>10</sup>, it was found that insufficient preoperative nutrition in lung resection is associated with poor prognosis.

Similarly, Sheng Wei and colleagues<sup>11</sup> demonstrated the relationship between nutrition, immunity, and survival in cancer patients using the HALP score. Our study also found a correlation between low albumin levels and complications, indicating that preoperative serum albumin could be a predictor for postoperative outcomes. Additionally, the study by Hiroyuki Ogawa and team<sup>12</sup> revealed that HgA1c levels are associated with recurrence-free and overall survival, with lower overall survival in patients with HgA1c levels above 8. Our findings also reflect the negative short-term impacts of diabetes due to its adverse effects on wound healing and the immune system. Marcus Taylor and colleagues<sup>13</sup> research on preoperative anemia found it to be independently associated with overall survival.

Our study similarly concludes that lower preoperative hemoglobin levels are linked to increased complications. Studies on early-stage lung cancer resection in the elderly generally report positive results<sup>14-16</sup>, but there's a lack of research on advanced stages. In our study, no significant difference in stages was observed, although many patients were in the early stages. Igor Saftic and colleagues<sup>17</sup> identified pneumonia and prolonged air leak as common complications. Kutluk and colleagues<sup>18</sup> reported a three-month mortality rate of 6.4%. Dominguez-Ventura and colleagues<sup>19</sup> reported a 30-day mortality rate of 6%. Pages and colleagues<sup>20</sup> found VATS lobectomy to be safer than thoracotomy in patients over 80, with 16.7% undergoing VATS and

83.2% undergoing thoracotomy. Our study found a slightly higher mortality rate, likely related to the high comorbidity of included patients.

### Limitations

This study's significant limitations include potential data inadequacies and inconsistencies due to its retrospective design. Being single-centered limits the generalizability of the results. The specific characteristics of patients aged 70 and above make the findings particularly relevant to this age group but may limit applicability to the general population. The limited number of patients may not provide sufficient data for rare conditions or detailed subgroup analyses.

### CONCLUSION

This study examines surgical outcomes in patients over 70 with lung cancer, highlighting the impact of high comorbidity indices and preoperative nutritional status. Notably, preoperative levels of albumin and hemoglobin are crucial for predicting postoperative complication risks. Comorbidities such as diabetes and COPD necessitate careful attention due to their risk enhancement. Surgical techniques like VATS and thoracotomy show similar postoperative outcomes. While these findings contribute to decision-making in this field, the study's retrospective nature and single-center approach suggest a need for more comprehensive research.

### ETHICAL DECLARATIONS

#### Ethics Committee Approval

The study was carried out with the permission of Kartal Dr. Lütfi Kırdar City Hospital Clinical Researches Ethics Committee (Date: 27.04.2023, Decision No: 2023/514/248/16).

#### Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

#### Referee Evaluation Process

Externally peer-reviewed.

#### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

#### Financial Disclosure

The authors declared that this study has received no financial support.

#### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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# Atherogenic plasma index is associated with ischemic cerebrovascular events due to carotid artery disease

✉ Muzaffer Aslan<sup>1</sup>, ✉ Doğaç Okşen<sup>2</sup>, ✉ Yunus Emre Yavuz<sup>1</sup>, ✉ Çağdaş Kaynak<sup>1</sup>

<sup>1</sup>Department of Cardiology, Faculty of Medicine, Siirt Training and Research Hospital, Siirt, Türkiye

<sup>2</sup>Department of Cardiology, Faculty of Medicine, Altınbaş University, İstanbul, Türkiye

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## ABSTRACT

**Aims:** Low molecular weight lipoprotein (LDL) and triglyceride (Tg), among cardiovascular disease risk factors, are replaced by markers with higher sensitivity and specificity. The atherogenic plasma index (API) has a strong predictive power for cardiovascular diseases. In our study, we aimed to compare the predictive power of API and other lipid parameters in detecting carotid artery disease (CAS) in patients with ischemic stroke.

**Methods:** A total of 878 individuals were analyzed, and 583 patients with ischemic stroke were enrolled in this study. The patients were divided into two groups according to the presence or absence of carotid artery disease in the Doppler ultrasound examination. Demographic data and lipid parameters were compared between both groups.

**Results:** The mean age of the patients with CAS was statistically significantly higher than the other group (74.33±11.27 vs 70.11±13.57; p=0.002). The Tg/HDL ratio was higher in patients with CAS than those without (3.80±2.83 vs 3.69±2.57; p=0.048). API was found to be statistically significantly higher in the group of patients with CAS compared to the other group (0.67±0.32 vs 0.48±0.25; p=0.024). Tg/HDL ratio and API were determined as predictive parameters for CAS in patients with ischemic cerebrovascular stroke. [OR: 1.345 (0.712-1.437); p=0.048, OR: 7.21 (0.881-8.056); p=0.023].

**Conclusion:** Conflicting results regarding the relation between atherosclerosis and conventional lipid parameters led to more specific subgroups being investigated. API shows a good correlation with the highly sensitive LDL subfraction in terms of atherosclerosis. API is a feasible variable predicting the presence of CAS in patients with ischemic stroke.

**Keywords:** Low-density lipoproteins, small dense low-density lipoproteins, atherogenic plasma indexes, carotid artery disease

## INTRODUCTION

Ischemic stroke is the second most common cardiovascular disease, leading to mortality and morbidity.<sup>1</sup> Carotid atherosclerosis is the main cause of ischemic stroke. It occurs when the atherosclerotic plaque rupture is complicated by intra-plaque bleeding, superficial ulceration, and thrombus formation.<sup>2</sup>

The first step in the development of ischemic stroke is the formation of atherosclerosis. Risk factors for atherosclerosis increase the risk of stroke. Lipid parameters are one of the leading factors among these factors. Low-density lipoproteins (LDL) cause increased risk, while high-density lipoproteins (HDL) have a protective effect. Given the structural differences between lipoprotein subgroups and apolipoproteins with different densities, it remains unclear which subgroups show a more reliable correlation between stroke and lipids.<sup>3</sup> Resolving the link between atherogenic lipoproteins and stroke has clinical importance in terms of protection from cerebrovascular diseases. Clarifying the relationship between

atherogenic lipids and the pathogenesis of stroke is important for the reconstruction of preventive treatment approaches. Extensive randomized studies have shown that the use of statins reduces the risk of ischemic stroke.<sup>4</sup> On the other hand, the view of managing all atherosclerotic processes with LDL cholesterol alone is getting weaker. The idea of a complete evaluation of high triglyceride (Tg), HDL, and LDL has led to the development of an atherogenic plasma index (API). API was defined by Dobiasova et al.<sup>5</sup> as the logarithm of Tg to HDL in base 10. Since its definition, it has been closely correlated with atherosclerosis and cardiovascular diseases.<sup>6,7</sup> Atherogenic lipoproteins are characterized by an increase in the concentration of small-density LDL and large VLDL and a decrease in HDL concentration. This profile is an indicator of high risk for coronary and carotid artery diseases. API defines the atherogenic index of plasma, reflecting lipid subgroups. High API value has been associated with cardio-metabolic events.<sup>8</sup>

**Corresponding Author:** Yunus Emre YAVUZ, yemre9194@gmail.com



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In our study, we hypothesized that API might have a determining role in carotid atherosclerosis in patients with ischemic stroke. Our study aims to investigate the effect of lipid subgroups in predicting carotid artery disease/stenosis (CAS) in the etiology of stroke in patients with ischemic stroke.

## METHODS

The study was initiated with the approval of the Siirt University Medical Faculty Clinical Researches Ethics Committee (Date: 13.12.2022, Decision No: 62448). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. A total of 878 patients admitted to our center with a cerebrovascular event and hospitalized between 2018 and 2022 were retrospectively analyzed through computer system records. Among these patients, 610 patients were included in the study. Twenty-seven patients were excluded from the study due to the inadequacy of the system records, death during the examinations, and simultaneous hemorrhage.

The study encompassed 583 patients who were diagnosed with ischemic cerebrovascular stroke. These patients were bifurcated into two groups: those who had carotid artery stenosis and those who did not. The system was used to gather demographic characteristics and laboratory data of the patients. The recorded information included age, gender, hypertension (HT), atrial fibrillation (AF), Diabetes mellitus (DM), obesity, peripheral artery disease, heart failure (ejection fraction <45%), peripheral artery disease, coronary artery disease, smoking, and laboratory parameters.

To minimize the effect of circadian rhythm on blood tests, blood samples were taken early in the morning after at least 10 hours of fasting. Total cholesterol, TG, and HDL concentrations were measured in the biochemistry laboratory using enzymatic methods. LDL was calculated according to the Friedewald formula.

All biochemical analyses were done with fresh blood samples. AIP was found by calculating the base ten logarithmic transformations of the ratio of TG to HDL (TG/HDL) in accordance with the formula defined by Dobiasova et al.<sup>5</sup>

Doppler ultrasound was used to diagnose CAS. Doppler ultrasonography measurements were taken from the distal segment of the common carotid artery on both sides, with carotid B-mode Doppler ultrasound performed by two experienced radiologists. Intima-media thickness (IMT) is one of the parameters used to determine atherosclerosis. The distal 1 cm part of the common carotid artery, internal carotid artery, and bifurcation

were scanned with 2D Doppler. The radiologist who took the imaging obtained different sections using anterior, posterior, and lateral angles.<sup>9</sup> Among these sections, the thickest IMT distance was selected. The atherosclerotic plaque was defined as a focal thickening with a minimum thickness of at least 1.3 mm, at least 50% greater than the surrounding vessel wall. It showed a reliability coefficient of 0.85 for the common carotid artery. The differences between radiologists were evaluated by using Pearson's correlation coefficients. The difference for each operator was less than 0.05.

## Statistical Analysis

Statistical analysis was conducted using the SPSS 22.0 software package from IBM Corp. Continuous variables were expressed as mean±standard deviation, and percentages were used for categorical variables. Non-normally distributed variables were presented as median (minimum-maximum) values. The distribution characteristics of variables were determined using the Kolmogorov-Smirnov and Shapiro-Wilks tests. Changes observed in non-normally distributed variables were analyzed using the Friedman test. The differences between continuous variables were assessed using a paired sample t-test. The Spearman correlation coefficient was used to examine the correlation of the analysis. A probability (p) value of less than 0.05 was considered statistically significant.

## RESULTS

Among the 878 patients who were admitted to the hospital with a cerebrovascular accident, 583 patients were included in the study among the patients who had an ischemic stroke. The mean age of the patients with CAS was statistically significantly higher than the other group (74.33±11.27 vs 70.11±13.57; p=0.002). Gender and rates of chronic diseases other than atrial fibrillation (AF) were similar. AF was more common in the patient group without CAS (29.4% vs 36.1%; p=0.006). The incidence of coronary artery disease was significantly higher in the patient group with CAS (24.7% vs 16.3%; p=0.039). No statistically significant difference was observed between hemogram and biochemistry parameters. Although LDL and T-COL levels were higher in the CAS group, the difference was not statistically significant. The Tg/HDL ratio was found to be higher in patients with CAS than those without (3.80±2.83 vs 3.69±2.57; p=0.048). API was found to be statistically significantly higher in the group of patients with CAS compared to the other group (0.67±0.32 vs 0.48±0.25; p=0.024). Other and all results are shown in [Table 1](#).

Tg/HDL, API, LDL/HDL, and MON/HDL parameters were evaluated with binary logistic regression analysis

**Table 1.** Comparison of demography, hemogram and lipid parameters in the population of ischemic stroke patients with and without carotid artery disease

Variables	CAS (442)	NO (141)	P value
Age	74.33±11.27	70.11±13.57	0.002
Male sex	50.7% (n:224)	48.2% (n:68)	0.612
Hypertension	40.0 (n:177)	36.9 (n:52)	0.503
Diabetes mellitus	29.9 (n:132)	26.2 (n:37)	0.409
AF	29.4 (130)	36.1 (51)	0.006
Morbid obesity	3.2 (14)	5.7 (8)	0.174
PAD	6.6 (29)	4.3 (6)	0.316
HF	15 (66)	8.5 (12)	0.054
CAD	24.7 (109)	16.3 (23)	0.039
Smoking	10.9 (48)	7.1 (10)	0.193
Hgb	13.66±1.82	13.51±2.07	0.487
WBC	9.28±2.93	9.19±4.10	0.815
PLT	241.08±78.94	248.94±78.93	0.324
RDW	50.87±8.74	50.55±11.12	0.768
NEU	6.24±3.04	6.30±3.60	0.879
LYMP	2.25±1.02	2.07±1.14	0.099
MON	0.54±0.25	1.12±1.78	0.615
T-COL	184.83±51.39	178.02±44.71	0.145
TG	147.18±78.65	142.98±77.84	0.594
HDL- C	43.52±12.30	44.24±12.31	0.418
LDL- C	116.46±40.69	111.25±37.22	0.175
TG/HDL	3.80±2.83	3.69±2.57	0.048
API	0.67±0.32	0.48±0.25	0.024
LDL/HDL	2.85±1.24	2.75±1.21	0.422
MON/HDL	0.013±0.08	0.032±0.40	0.211

Abbreviations: CAS: Carotid artery disease, CAD: Coronary artery disease, AF: Atrial fibrillation, PAD: Peripheral artery disease, HF: Heart failure, Hgb: Hemoglobin, WBC: White blood cell count, PLT: Platelet count, RDW: Red cell distribution width, NEU: Neutrophil count, LYMP: Lymphocyte count, MON: Monocyte count, T-COL: Total cholesterol, TG: Triglycerides, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, API: Atherogenic plasma index

to determine the lipid parameters predicting CAS in patients with ischemic stroke. Tg/HDL ratio and API were determined as predictive parameters for CAS in patients with ischemic cerebrovascular stroke [OR: 1.345 (0.712-1.437); p=0.048, OR: 7.21 (0.881-8.056); p=0.023] (Table 2).

**Table 2.** Binary logistic regression–lipid parameters independently associated with ischemic SVO due to carotid artery disease

Variable	P value	Exp (B)	OR 95% CI
Tg/HDL	0.048	1.345	0.712–1.437
API	0.023	7.21	0.881–8.056
LDL/HDL	0.732	1.033	0.859–1.241
MON/HDL	0.820	0.545	0.070–4.929

Nagelkerke R square=0.504, Cox&Snell R square=0.337

## DISCUSSION

Cardiovascular diseases continue to be the most important cause of morbidity and mortality despite all the advancements in the medical treatment field. It is known that some of the events that occur are preventable with appropriate treatment goals. Ischemic stroke, which has a significant share in cardiovascular diseases, has been the subject of many studies in terms of etiology. Different lipid parameters and mathematical combinations of lipid subgroups have been reported as predictive variables. Despite extensive studies, there is no consensus on a lipid subgroup. In our study, we investigated the CAS predictive powers of lipids in patients with ischemic stroke. The motivation of this study was the hypothesis that API is indicative of the atherogenic dyslipidemia profile.

Lipid parameters that predict CAS in the etiology of ischemic stroke were evaluated in this study. Among the lipid parameters, API was observed as a statistically significant variable for predicting CAS in patients with ischemic stroke.

Plaque formation on the carotid artery is one of the most important predictors of ischemic stroke. Doppler ultrasound, which has an important role in determining the plaque, also gives information about the morphology of the plaque. It is known that echolucent plaques cause complicated ischemic stroke more frequently. Echogenic plaques contain more fibrous tissue and tend to calcify. This makes the plate more stable. Echolucent plaques are rich in lipids. Population-based studies have reported that people with echolucent plaques have lower HDL cholesterol levels.<sup>10</sup> In literature conducted from the past to the present, significant correlations have been established between the development of atherosclerosis and different lipid parameters in the etiology of CAS.

Current evidence is that LDL, Tg, and apoB molecules increase the risk of stroke. Circulating lipoproteins contain varying degrees of cholesterol and Tg. This leads to uncertainty in the measurement of the level of atherogenic lipoproteins.<sup>11</sup> According to the Mendelian randomization study, which consisted of MEGASTROKE data from 514,791 participants, univariate analyses showed that high Tg, LDL, apoB, and low HDL levels cause an increased risk of ischemic stroke. However, multivariate analyses reported that the potency of Tg and LDL decreased relative to apoB and even attenuated to null after mutual adjustment.<sup>3</sup> In a study of 402 patients examining the correlation between serum lipids and carotid plaque formation in the Chinese patient population, a significant correlation was observed between the LDL/HDL ratio and the increase in carotid intima-media thickness.<sup>12</sup>

The effects of LDL and HDL levels on early carotid atherosclerosis were investigated in a series of 825 patients by Tamada et al.<sup>13</sup> There was no statistically significant correlation between LDL cholesterol and carotid plaque score in multivariate analyses. However, LDL/HDL ratio was significantly associated with increased carotid plaque scores in both genders. A cross-sectional study conducted with 10,900 patients reported that TC/HDL, Tg/HDL, and LDL/HDL ratios were positively correlated with peripheral arterial diseases. Despite the high number of patients in the study, using only the ankle-brachial index for diagnosing peripheral artery disease created a limitation in the study.<sup>14</sup> On the other hand, in a cross-sectional study of 302 patients by Nimkuntod et al.<sup>15</sup>, the LDL/HDL ratio for carotid plaque formation was not found to be statistically significant. In the same study, the presence of carotid plaque was observed in correlation with age, gender, and Tg levels. In a cross-sectional designed MRI study involving 6143 individuals, 24% (n: 1456) of patients had small vessel disease. Hypercholesterolemia was observed to be associated with a decreased small vessel disease risk rate after other risk factors such as age and hypertension were adjusted.<sup>16</sup>

Heretofore, many predictive parameters have been studied to identify individuals at high cardiovascular risk. Ideal parameters for risk analysis should be low-cost, fast, specific, and non-invasive. According to the prospective study of Framingham offspring data, sdLDL demonstrated a strong association with atherosclerotic cardiovascular diseases.<sup>17</sup> A strong correlation has been demonstrated between small, dense, low-density lipoproteins (sdLDL) and CAS. Shoji et al.<sup>18</sup> previously investigated the correlation between carotid atherosclerosis and various lipid parameters in 326 consecutive subjects. Compared to LDL, apo B, apo A-I, non-HDL, and Tg levels, sdLDL levels have the highest correlation with carotid atherosclerosis (Spearman's  $r=0.441$ ,  $P<0.001$ ). According to the prospective study of Framingham offspring data, sdLDL demonstrated a strong association with atherosclerotic cardiovascular diseases.<sup>17</sup> Although sdLDL, which shows different lipid and protein components with the smallest molecular sizes and high affinity for proteoglycans in the arterial wall among LDL sub-fractions, is considered an ideal marker, it is very costly to determine the level by quantitative measurement.

Determination of sdLDL levels by lipoprotein separation is not a feasible method in daily practice. For this reason, studies have focused on searching for more cost-effective markers to correlate with sdLDL with similar sensitivity levels. Dobiasova et al.<sup>5</sup> aimed to determine atherogenic lipoprotein particles based on Tg and HDL plasma concentrations and obtained a statistically significant correlation with the studies. While conventional assessment of lipoprotein particle size distribution requires gradient

gel electrophoresis, this described method accurately estimates sdLDL using routine serum lipid values.

There are many studies examining the correlations between lipid parameters and ischemic cerebrovascular diseases. Small-density lipoproteins support subclinical inflammation and atherosclerosis process by increasing oxidative stress, disrupting the endothelial structure, damaging cell DNA, and increasing lipid peroxidation activity. In our study, when Tg and HDL were evaluated apart from each other, no significant difference was observed in the levels of the CAS group. Tg/HDL was demonstrated as a predictor of CAS in patients with ischemic stroke in univariate and multivariate statistical analyses. In the literature, API has been presented as a parameter with similar predictive power but lower cost as sdLDL, the highly atherogenic LDL subgroup. In our study, API was observed as a predictor of CAS in individuals with ischemic stroke, correlating with previous studies.

### Limitations

Our study has some limitations as well as strengths, such as the relatively high number of patients demonstrating the effects of API on CAS in ischemic SVO patients. Although the demographic characteristics were similar, the average age of the CAS group was statistically significantly higher since no propensity matching was performed in the patient recruitment. Lipid fractions such as lipoprotein a, apoprotein, and sdLDL could not be included in the study due to cost reasons. Another limitation of the study is that the data of patients with ischemic stroke were collected and designed retrospectively.

### CONCLUSION

Today, when hyperlipidemia treatments are still discussed in the prevention of atherosclerosis, the search for more specific parameters other than classical lipid molecules continues. Our study aimed to determine the predictive variables of CAS in patients with ischemic stroke by examining the ratios of API and other non-classical parameters. Accordingly, API was demonstrated as a strong CAS predictor. In the study, more specific variables were observed as a result of the equations made with the lipid parameters that are frequently used in daily practice. Further prospective studies investigating the effects of API and other parameters on cardiovascular events may provide more effective data for the clinical approach.

### ETHICAL DECLARATIONS

#### Ethics Committee Approval

The study was carried out with the permission of Siirt University Medical Faculty Clinical Researches Ethics Committee (Date: 13.12.2022, Decision No: 62448).



## Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

## Referee Evaluation Process

Externally peer-reviewed.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.

## Financial Disclosure

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## Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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# The relationship of serotonin level with syndrome X and coronary artery disease

İbrahim Aktaş<sup>1</sup>, Hasan Arı<sup>2</sup>, Mehmet Demir<sup>2</sup>, Yasemin Üstündağ<sup>2</sup>

<sup>1</sup>Department of Cardiology, Malatya Training and Research Hospital, Malatya, Türkiye

<sup>2</sup>Department of Cardiology, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Türkiye

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## ABSTRACT

**Aims:** Platelets secrete serotonin (5-hydroxytryptamine) which has several effects on the vascular wall and promotes thrombogenesis, mitogenesis, and proliferation of smooth muscle cells. We thought serotonin which relation with coronary artery disease (CAD) has been shown in various data might be important for etiology and diagnosis of cardiac syndrome X (CSX) which's physiopathology has not been elucidated yet. The aim of the study is to investigate relationship between serotonin level with CSX and stabile coronary artery disease.

**Methods:** Serum serotonin levels were measured by micro ELİSA procedure in three group of patients who underwent coronary angiography. First group consisted of 30 patients (17 male, 13 female, mean age 60.5±6.1) who has diagnosed CSX, second group consisted 22 patients (11 male, 11 female, mean age 60.5±6.1) who has diagnosed stabile coronary artery disease and third group consisted 28 patients (10 male, 18 female, mean age 56.6±10) comprised the control group. All three groups of patients demographic, biochemical, hematological and echocardiographic data were recorded.

**Results:** The three groups were similar with respect to age, sex, body mass index and the frequencies of diabetes mellitus and smoking(p>.016). We detected average serum serotonin levels 49.7 ng/ml in syndrome X group, 41.8 ng/ml in CAD group and 44.8 ng/ml in control group. These values are not statistically significant between the groups monitored(p=.91).

**Conclusion:** The serotonin level of of CSX patients, stabile coronary artery disease patients and control group patients were measured in the serum which seperated from peripheral venous blood. Statistically significant difference in serum serotonin levels couldn't be detected between these three group.

**Keywords:** Serotonin, cardiac syndrome X, coronary artery disease

## INTRODUCTION

Coronary artery disease (CAD) is defined as ischemia-induced pathological events that occur as a result of the myocardium not being fed due to occlusion in the coronary arteries. Many factors have a role in the etiology of CAD and atherosclerosis is the most blamed.

In a significant part of the patient group who went to the emergency room with chest pain and underwent coronary angiography, coronary angiography is found to be normal and vasospasm in the epicardial coronary arteries was not detected. Although there are many studies on the pathogenesis of cardiac syndrome X (CSX), the etiology of it has not been clearly revealed. In the formation of myocardial ischemia in patients with CSX, many hypotheses have been developed, such as mediation by  $\alpha$  receptors,<sup>1</sup> coronary microvascular dysfunction, overestimation of cardiac pain,<sup>2</sup> increased vasoconstrictor response in smooth muscle cells due to

the increase in membrane Na-H (sodium-hydrogen) exchanger channel activity, increased release of local vasoconstrictor autocooids such as angiotensin and endothelin, abnormal neural stimulation, and cardiac sympathetic dysfunction.<sup>3</sup>

Activated platelets release varying amounts of serotonin, which causes vasoconstriction and platelet aggregation.<sup>4</sup> Serotonin is a potent smooth muscle stimulant and vasoconstrictor. The release of vasodilator agents such as prostacyclin and prostaglandin E2 decreases with the release of local vasoconstrictor substances such as serotonin.<sup>5</sup> Serotonin level has been shown to be associated with CAD in various publications.<sup>6</sup>

Despite the fact that the role of serotonin in the physiopathogenesis of CAD has been the subject of various studies, the relationship between serotonin and CSX has

**Corresponding Author:** İbrahim AKTAŞ, ibrahim.aktas@ozal.edu.tr



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not been studied yet. It has not yet been possible to clearly explain the cause of angina and the pathophysiology of angina in CSX patients. Alpha-receptor-mediated vasoconstriction in arterioles has been blamed in the mechanism of myocardial ischemia in CSX patients.<sup>1</sup> We thought that serotonin, which is known to be a vasoconstrictor agent, may be an important mediator in the etiology of CSX.

The aim of this study to investigate the relationship between serotonin level and CSX, which has not been examined in the literature before. Moreover, although studies have been conducted on it before, we were able to re-evaluate the relationship of serotonin level with CAD.

## METHODS

### Ethics

Upon obtaining the approval of Uludağ University Faculty of Medicine Clinical Researches Ethics Committee (Date: 26.05.2015, Decision No: 2015-11/27), the research was initiated. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

### Patients

In this study, among the patients who went to Bursa Yüksek İhtisas Training and Research Hospital Cardiology Clinic and underwent elective coronary angiography for various reasons, 3 patient groups consisting of 30 patients with a diagnosis of syndrome X (group 1: Patients with angina chest pain, positive exercise tests suggestive of myocardial ischemia, and <50% stenosis lesions of the epicardial coronary arteries), 28 patients with normal coronary follow-up and non-cardiac evaluation (group 2: Patients with non-cardiac chest pain, negative stress tests that may indicate myocardial ischemia, and normal coronary angiography on coronary angiography), and 22 patients with stable coronary artery disease with obstructive coronary artery stenosis (group 3: A group of stable coronary artery patients with anginal complaints and a >70% stenosis lesion as a result of coronary angiography) were evaluated.

Patients over the age of 35 were included in the study, regardless of gender. The patient groups that were not included in the study due to exclusion criteria are listed in [Table 1](#). Demographic characteristics, weight, height, concomitant diseases, habits, medications, blood tests, echo and ECG findings, exercise tests, coronary lesion status of the patients were examined in detail and recorded.

### Effort Test

The patients were subjected to the maximal effort test according to the Bruce protocol. In cases where there is at

Table 1. Exclusion criteria of the study

Left ventricular systolic dysfunction (ejection fraction)	Chronic obstructive pulmonary disease
Presence of valvular heart disease or hypertensive heart disease	Liver or kidney dysfunction
Patients with previous percutaneous intervention	thyroid dysfunction
Patients diagnosed with depression or using antidepressant agents	Those who have had a cerebrovascular accident
Patients with thrombocytopenia or thrombocytosis	Current signs of infection
Presence of ECG findings that complicate the interpretation of the effort test	Patients with acute pericarditis or myocarditis
Presence of diagnosis of malignancy	Presence of permanent pacemaker, bundle branch block, severe atrio-ventricular conduction defects
	Hypertrophic or dilated cardiomyopathy
	>75 years old patient group

least 1 mm horizontal and down sloping ST segment depression in at least 2 consecutive leads 80 ms after the J point, chest pain during the exertion test, and a decrease of 10 mmHg or more in systolic blood pressure compared to the initial blood pressure, the effort test was considered positive. Duke treadmill score (DTS) was calculated for each patient. A DTS score above +5 was considered low risk, between 4 and -10 was considered medium risk, and -11 and below was considered high risk for coronary artery disease.

### Echocardiography

All patients included in the study was subjected to transthoracic echocardiography by the same operator. Echocardiographic examination was performed using Vivid 7 Pro® (GE healthcare) echocardiography device and a 3.5 Mhz transducer. In parasternal long axis images, left ventricular systolic and end-diastolic widths, posterior wall and septum thicknesses, and left ventricular ejection fraction (IF) were measured with M-Mode. Apical four-chamber, apical five-chamber, parasternal long axis and parasternal short axis images were obtained by two-dimensional and color Doppler examination. Measurements were taken in apical four-chamber and apical five-chamber images using tissue Doppler, continuous wave, and pulsed wave Doppler.

### Coronary Angiography

Selective coronary angiography were performed via the right femoral artery, using the Seldinger technique, using 6F Judkins catheters. Vasospastic angina was ruled out to rule out vasospastic angina by using a hyperventilation test (explained to breathe quickly and deeply for 5 minutes) during angiography.

### Serum Serotonin Measurement

Venous blood samples were collected from all three patient groups between 9 am and noon during their outpatient follow-up. After the collected blood was centrifuged at 5000 rpm for 10 minutes, its serums were separated and stored in eppendorfs at -22 °C. When all the blood was ready, serotonin measurements were performed in one go in the biochemistry laboratory of our hospital. Serum

serotonin levels were measured using the commercial kit DAS-ELISA (double-antibody sandwich enzyme-linked immunosorbent assay) from Sunred Biotechnology.

In summary, 40 µl of serum was added to wells coated with human serotonin monoclonal antibody, then 10 µl of biotin-labeled ST-antibody and 50 µl of streptavidin-HRP were added to form an immune complex. The wells were washed 5 times with 350 µl of washing solution to remove unbound enzymes after incubation for 60 minutes at 37 °C. Then, 100 µl of chromogen solution A and B (1:1 ratio) was added to each well. This mixture was incubated for 10 minutes at 25 37 °C in an orbital mixer in the dark. Afterwards, 50 µl of stopper solution was added and the absorption levels at 450 nm were measured within 15 minutes. The amount of serotonin was calculated from the calibration curve and the results were expressed in nanograms/milliliter. The manufacturer reported intraday and interday coefficients of variation as <10% and <12%, respectively, and sensitivity as 0.38 ng/ml.

### Statistical Analysis

SPSS 22.0 computer software was used for the statistical analysis of the cases. Numerical variables are shown as mean±standard deviation, and categorical variables as percentages. Shapiro-Wilk test and skewness-kurtosis coefficients were analyzed for normality analysis. Accordingly, the comparison of the groups was performed with the Kruskal-Wallis test for continuous variables and with Chi-square or Fisher's exact test for categorical variables. Since the number of groups compared was 3, the Bonferroni correction was performed and the p<.016 value was considered significant in the statistical measurements.

## RESULTS

A total of 80 patients with similar demographics, 30 of them constituting the CSX group (group 1), 22 stable coronary artery patients with occlusive lesion on CAG (group 3), and 28 control group patients with negative exertion test (group 2), whose coronary arteries were normal and evaluated as non-cardiac, were included in the study.

There was no statistically significant difference between the groups in the evaluation performed in terms of gender, age and body mass index (BMI) of all 3 patient groups included in the study. When patients were examined in terms of coronary artery disease risk factors, the number of patients with hypertension was found to be 9 (30%) in the CSX patient group, 18 (81.8%) in the CAD group, and 8 (28.6%) in the control group. The number of hypertensive patients in the CAD group was

statistically significantly higher (p<.001). Presence of diabetes, hyperlipidemia, smoking and CAD heredity, which are other CAD risk factors, are similar in all 3 groups (p>0.016).

Against the possibility of affecting the serotonin level, blood pressure and pulse/minute counts were measured just before taking the serotonin sample from the venous blood of the patients participating in the study, and it was understood that there was no statistical difference between the 3 groups in terms of the relevant results.

Demographic and clinical characteristics of all three patient groups are summarized in [Table 2](#).

Table 2. Demographic and clinical characteristics of the groups				
	Group 1 (n=30) (Syndrome X)	Group 2 (n=28) (Control)	Group 3 (n=22) (CAD)	P
Age (years)	54.6±11.4	56.6±10	60.5±6.1	.08
Male gender, n (%)	17 (56.7)	10 (35.7)	11 (50)	.26
Female gender, n (%)	13 (43.3)	18 (64.3)	11 (50)	.26
BMI (kg/m <sup>2</sup> )	28.6±3.6	29.9±3.88	30±3.4	.32
DM, n (%)	6 (20)	5 (17.9)	8 (36.4)	.25
HT, n (%)	9 (30)	8 (28.6)	18 (81.8)	<.001*
HL, n (%)	9 (30)	6 (21.4)	6 (27.3)	.75
Smoking, n (%)	8 (26.7)	14 (50)	5 (22.7)	.07
Heredity, n (%)	8 (26.7)	9 (32.1)	14 (63.6)	.017
SBP (mmHg)	122.58 ±12.72	120.88 ±13.1	128.18±11.70	.08
DBP (mmHg)	80.34±6.39	78.57±5.75	84.09±5.90	.018
MHR (Beats/min)	77±10	75±13	77±10	.31

\*p<.016, CAD: Coronary artery disease, BMI: Body mass index, DM: Diabetes mellitus, HT: Hypertension, HL: Hyperlipidemia, SBP: Systolic blood pressure, DBP: Diastolic blood pressure MHR: Mean heart rate

Statistically similar features were observed when the left ventricular ejection fraction (LVEF), left ventricular ejection fraction (LVEF), left ventricular systolic and end-diastolic diameters (LVDSC, LVSS), left ventricular interventricular septum and posterior wall diameters were measured and analyzed echocardiographically in all 3 patient groups ([Table 3](#)).

As a result of the study, the hematological and biochemical data of the groups are summarized in [Table 4](#). In terms of white blood cell count, hemoglobin and platelet counts, no significant difference was observed between the groups. Renal function tests, electrolytes, lipid parameters, brain natriuretic peptide (BNP) and Hs-CRP values obtained from the patients were found to be similar in all 3 groups, and the results are summarized in the [Table 4](#).

Table 3. Echocardiographic data of groups

	Group 1 (n=30) (Syndrome X)	Group 2 (n=28) (Control)	Group 3 (n=22) (CAD)	p
SVEF (%)	59.66±4.21	58.25±3.40	60.54±3.48	.18
LVEDD (mm)	46.96±2.80	47.61±3.26	47.27±2.09	.63
LVESD (mm)	29.37±2.84	29.73±3.07	28.50±2.50	.54
IVS (mm)	9.96±2.02	9.73±2.70	10.45±0.80	.83
PW (mm)	9.51±1.78	8.96±2.97	10.13±0.46	.11

CAD: Coronary artery disease, LVEF: Left ventricular ejection fraction, LVEDD: Left ventricular end-diastolic diameter, LVESD: Left ventricular end-systolic diameter, IVS: Interventricular septum diameter, PW: posterior wall diameter

Table 4. Hematological and biochemical data of groups

	Group 1 (n=30) (Syndrome X)	Group 2 (n=28) (Control)	Group 3 (n=22) (CAD)	p
Wbc (×10 <sup>3</sup> )	7367±2110	7375±2210	7090±2090	.89
Hemoglobin (gr/dl)	12.8±1.4	12.5±1.3	12.5±1.2	.80
Platelet	237670±70500	218600±57700	234040±77600	.86
Urea (mg/dl)	14.6±4.3	14.2±4.2	15.1±4.8	.85
S. crea (mg/dl)	0.69±0.21	0.66±0.16	0.71±0.17	.47
Sodium (mEq/L)	138±2	137±2	139±3	.02
Potassium (mEq/L)	4.3±0.4	4.1±0.2	4.4±0.4	.03
T. cholesterol (mg/dl)	184±33	188±40	168±46	.17
LDL-C (mg/dl)	112±29	115±35	101±37	.23
HDL-C (mg/dl)	47±14	44±9	42±16	.30
Triglyceride (mg/dl)	151±74	135±79	123±50	.45
BNP (pg/mg)	33.3±29.6	28.5±23.9	58.7±55.2	.04
Hs-CRP (mg/L)	6.45±11.9	6.87±8.54	7.38±5.81	.10

Wbc: White blood cell count, S. crea: Serum creatinin, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, T. cholesterol: Total cholesterol, Hs-CRP: High-sensitivity C-reactive protein, BNP: Brain natriuretic peptide, CAD: Coronary artery disease

Medications used by all three groups when recruited to the study are listed in Table 5. The number of patients using acetylsalicylic acid (ASA) was 7 (23.3%) in the syndrome X group, 22 (100%) in the CAD group, and 5 (17.9%) in the control group. There was a statistically significant excess of ASA use in the CAD group compared to the other groups (p<.001). The use of other drugs used by the patients and listed in the table was found to be at similar rates in all 3 groups.

We found that the mean serum serotonin levels were 49.7 ng/ml in the syndrome X group, 41.8 ng/ml in the CAD group and 44.8 ng/ml in the control group. These values

Table 5. Medications taken by the groups

	Group 1 (n=30) (Syndrome X)	Group 2 (n=28) (Control)	Group 3 (n=22) (CAD)	p
ASA, n (%)	7 (23.3)	5 (17.9)	22 (100)	<.001*
Beta blocker n (%)	2 (6.7)	3 (10.7)	3 (13.6)	.70
ACEI n (%)	6 (20)	6 (21.4)	9 (40.9)	.18
CCB, n (%)	3 (10)	4 (14.3)	3 (13.6)	.87
Statin, n (%)	4 (13.3)	0	2 (9.1)	.14
Metformin, n (%)	5 (16.7)	5 (17.9)	5 (22.7)	.84
Sulfonylurea, n (%)	3 (10)	2 (7.1)	0	.32

\*p<.016, CAD : Coronary artery disease, ASA : Acetylsalicylic acid, ACEI : Angiotensin converting enzyme inhibitor, CCB : Calcium channel blocker

were not statistically significant between the groups (p=.91). Statistical analysis of serotonin levels between groups is summarized in Table 6. In Figure (Central Illustration), serum serotonin levels between groups are given.

Table 6. Relationship between groups in terms of serum serotonin levels

	Group 1 (n=30) (Syndrome X)	Group 2 (n=28) (Control)	Group 3 (n=22) (CAD)	p
Serotonin (ng/ml)	49.7	44.8	41.8	.91

CAD : Coronary artery disease

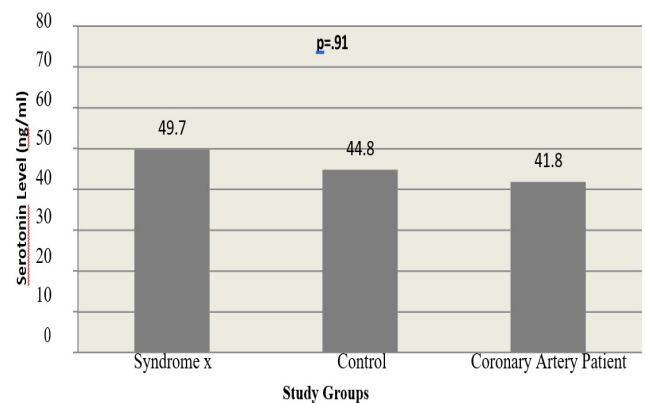


Figure (Central Illustration). Comparison of serum serotonin levels between groups

## DISCUSSION

In this study, we aimed to review the relationship between coronary artery disease and serotonin levels and to examine the relationship between CSX disease, whose etiopathogenesis has not been clearly elucidated and whose relationship with serotonin has not been studied before, and serotonin.

More than 95% of serotonin in the human body is synthesized from enterochromaffin cells in the intestinal system, and the remaining part is synthesized from the raphe

nucleus and neuroendothelial cells in the brain.<sup>7</sup> Serotonin is not synthesized in platelets. These cells take serotonin from the plasma and store it. Experimental studies have suggested that platelets are associated with the development of atherosclerosis.<sup>8-10</sup> Some experimental studies in animals indicate that platelets are activated and aggregated in cases of coronary artery stenosis or endothelial damage.<sup>4,11,12</sup> Activated platelets release various amounts of serotonin, causing vasoconstriction<sup>4,11,13</sup> and cyclic flow reduction, leading to recurrent aggregation.<sup>4</sup> Moreover, serotonin stimulates the proliferation and migration of arterial smooth muscle cells through growth factor.<sup>14,15</sup> These effects are blocked by ketanserin, a specific serotonin receptor antagonist.<sup>14,16</sup> Serotonin has been shown to increase the proliferation of vascular endothelial cells.<sup>17,18</sup>

Various studies have indicated that platelet derivatives such as serotonin and thromboxane A<sub>2</sub> have an important role in the physiopathogenesis of acute coronary syndrome.<sup>19,20</sup> In particular, increased serum serotonin concentrations were observed in blood collected from the coronary sinuses of patients with complex coronary lesions.<sup>21</sup> Similarly, blood serum obtained from the coronary sinus of patients with coronary artery disease has been shown to cause vasoconstriction in canine coronary arteries *in vitro*. This vasoconstrictor effect was abolished by serotonin receptor blockers.<sup>22</sup> In many previous studies, the vasoactive effects of serotonin were studied in animals with normal epicardial coronary arteries. Brum et al.<sup>23</sup> and Lamping et al.<sup>24</sup> reported that serotonin exerts a dose-dependent vasoconstrictor effect in damaged coronary artery endothelium of dogs. Chu and Cobb,<sup>25</sup> on the other hand, revealed that serotonin has a dose-dependent (consisting of vasodilation and vasoconstriction, respectively) biphasic effect in canine coronaries without endothelial damage. In addition, *in vitro* studies have shown that serotonin causes vasodilation in intact coronary arteries and vasoconstriction in damaged coronary endothelium.<sup>26,27</sup>

By binding to the 5-HT receptor on endothelial cells, serotonin stimulates the release of the relaxation factor, and by binding to the 5-HT<sub>2</sub> receptors on the vascular smooth muscles, it stimulates their contraction.<sup>28</sup> If the vascular endothelium is normal, the relaxation factor is dominant and leads to vasodilation.<sup>29</sup> However, if the endothelium is damaged or dysfunctional, as in coronary artery disease, vasoconstriction via 5-HT<sub>2</sub> receptors becomes dominant.<sup>29-31</sup> The platelet antiaggregation effect of sarpogrelate, which is a 5-HT<sub>2</sub> receptor blocker, and its anti-anginal activity by increasing collateral circulation have been demonstrated in studies conducted.<sup>32,33</sup>

Serotonin levels of 96 patients with coronary artery disease and control group of 25 patients with normal coronary artery disease compared by Vikenes et al.<sup>6</sup> Serotonin

levels were measured in the platelet-rich plasma of blood samples collected via the venous route, and the serotonin level was statistically significantly higher in the coronary artery disease group. In their study, Van den Berg et al.<sup>21</sup> investigated whether there was a difference between the serotonin levels of 39 patients with stable coronary artery disease with occlusive lesions and 13 patients with normal coronary artery control group. Blood samples were collected from 2 places, from the aorta and the coronary sinus of the patients, and their serotonin levels were studied. There was no difference between the two groups in terms of serotonin levels in blood samples collected from the aorta and coronary sinus. The difference between the coronary sinus serotonin concentration and the aortic serotonin concentration levels was found to be significantly higher in the coronary artery disease group. This data supports that serotonin is released into the coronary circulation in patients with occlusive coronary artery disease.

Despite coronary angiography without flow-limiting stenosis, CSX is characterized by typical anginal pain diagnosed after exclusion of non-cardiac pain. It is still a hopeless syndrome for both patients and physicians due to the lack of a standard diagnostic criteria, lack of consensus on pathophysiology, and ineffective treatment options. Various theories have been proposed to explain the pathophysiological abnormality, such as abnormal coronary flow reserve, insulin resistance, abnormal autonomic control, increased sodium hydrogen exchange activity, abnormal cardiac sensitivity, and microvascular spasm.<sup>34</sup> The most proven and accepted ideas are endothelial dysfunction and inflammation, and increased pain sensitivity.<sup>35</sup> Endothelial dysfunction disrupts the vasoconstriction/vasodilation balance, reduces the release of anti-inflammatory and antithrombotic factors and decreases the availability of nitric oxide.<sup>36</sup>

Previously, the relationship between coronary artery disease and serotonin has been the subject of many studies, as mentioned above. In this study, we aimed to review the relationship between coronary artery disease and serotonin levels and to examine the relationship between CSX disease, whose etiopathogenesis has not been clearly elucidated and whose relationship with serotonin has not been studied before, and serotonin.

Previously, the relationship between coronary artery disease and serotonin has been the subject of many studies, as mentioned above. We could not detect any difference in serotonin levels between the coronary artery patients and the control group. As we mentioned above, the study conducted by Van den Berg et al.<sup>21</sup> on 39 patients is in line with the results of our study. Van den Berg et al.<sup>21</sup> found no significant difference in serotonin levels between the blood taken from the central aorta of both groups. Similarly,



serotonin levels of blood taken from the coronary sinuses were similar in both groups. The difference between aortic serotonin levels and coronary sinus serotonin levels was found to be significantly higher in patients with coronary artery disease.

In the study of Vikenes et al.<sup>6</sup>, which we mentioned before, on 121 patients, unlike the results of our study, serotonin levels were found to be higher in coronary artery patients compared to the control group. In this study, as in our study, blood was obtained by peripheral venous route, but the serotonin level was studied from platelet-rich plasma, not from serum. Serotonin is known to be very rapidly metabolized and rapidly reabsorbed after release. Therefore, the relatively low levels of free circulating levels make it more meaningful to study serotonin levels from whole blood or platelet-rich plasma, not serum. Studying serotonin levels from serum is one of the limitations of our study. Measurement of serotonin levels in serum in our study may be one of the reasons underlying the inconsistency between the results of the study conducted by Vikenes et al.<sup>6</sup> and the study we conducted.

Studies that indicate that serotonin levels may play an important role in the etiology, diagnosis and treatment strategy of coronary artery disease in the aforementioned previous studies encouraged us to examine the relationship between CSX and serotonin, the physiopathogenesis of which has not yet been fully elucidated.

Endothelial dysfunction, one of the most frequently accused mechanisms in the etiology of cardiac syndrome X, may be causing serotonin's inability to vasodilate over 5-HT in the impaired endothelium, as in CAD, and develop ischemia as a result of the vasoconstriction effect on vascular smooth muscle (via 5-HT<sub>2</sub>). Based on this, we speculated that serotonin or 5-HT receptor blockers may have a role in the etiopathogenesis, diagnosis and treatment of CSX disease, which is known as a sub-branch of the stable coronary artery disease group and has a good prognosis but adversely affects the quality of life. We compared the serum serotonin levels of patients with CSX and the control group. No difference was observed between serum serotonin levels of both groups. As mentioned above, the measurement of serotonin level from serum, not whole blood or platelet-rich plasma, may have played a role in the emergence of this result. Moreover, the rapid metabolism and reabsorption of serotonin may explain the similarity of serotonin levels measured in peripheral blood between the two groups. Measurement of serotonin levels from the coronary sinuses or coronary arteries, as previously performed in animal studies, could change the course of the study. This can be considered among the important limitations of our study.

## CONCLUSION

The relationship between CAD and serotonin has been examined in many previous studies. However, to the best of our knowledge, this study is the first to examine the relationship between cardiac syndrome X, which is predominantly caused by microvascular dysfunction, and serotonin, a vasoactive molecule. In this study, no significant difference was found between serotonin levels in coronary artery patients, syndrome X patients and the control group. It has not been possible to show the relationship of serotonin level with coronary artery disease and syndrome X.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was carried out with the permission of Uludağ University Faculty of Medicine Clinical Researches Ethics Committee (Date: 26.05.2015, Decision No: 2015-11/27).

### Informed Consent

All patients signed and free and informed consent form.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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# Analysis of maxillary sinus volume of a group of population living on the southern border of Southeastern Anatolia

✉ Mehmet Emin Doğan, ✉ Nurbanu Uluşık

Department of Dentomaxillofacial Radiology, Faculty of Dentistry, Harran University, Şanlıurfa, Türkiye

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## ABSTRACT

**Aims:** This study aimed to assess the maxillary sinus volume (MSV) of people living in the south of the southeastern region of Anatolia by cone beam computed tomography (CBCT) in accordance with gender and age groups.

**Methods:** 400 maxillary sinus CBCT images of 200 patients were analyzed. To examine the correlation of maxillary sinus volume with age, all data were divided into six subgroups according to age. IRYS 15.1 software was used to obtain multiplanar images and volume measurement. SPSS package program version 25 was used to analyze the data. The Kolmogorov-Smirnov test was used to examine whether the data had a normal dispersion.

**Results:** In this study, 200 individuals, 110 (55%) women and 90 (45%) men, were included. When MSV was examined in accordance with age groups, statistically no remarkable difference was observed between the groups ( $p>0.05$ ). In the comparison between men and women patients, a statistically important difference was showed in the right and left MSV, with men having a higher mean sinus volume than women ( $p<0.05$ ).

**Conclusion:** MSV in men was found higher than in women. The mean MSV gradually decreases with age. However, in this study, no significant difference was observed in the average right and left MSV between age groups.

**Keywords:** Computed tomography, age group, gender, volume, maxillary sinus

## INTRODUCTION

The maxillary sinus is an important paranasal sinus within the four pairs of paranasal sinuses. These are air cavities in the bone, connected to the nasal cavity through their ostium and surrounded by mucosa.<sup>1</sup> Maxillary sinuses, which continue to develop after birth, are formed in the 3rd and 4th intrauterine months.<sup>2</sup> The development of the maxillary sinus, which has the largest volume of the paranasal sinuses and is of the greatest interest to dentists due to its proximity to the teeth, starts in the 10th week of intrauterine life and reaches a volume of 6-8 cm<sup>3</sup> in the postnatal period. The first period in which it develops most rapidly volumetrically and becomes pneumatized is between the ages of 0-3, and the second period is between the ages of 7-12.<sup>3,4</sup> The adult size is 14-18 cm<sup>3</sup> on average, but it reaches this size around 18-20 years of age.<sup>4,5</sup>

At the base of the maxillary sinus is the alveolar bone of upper jaw, and at its ceiling is the lower wall of the orbit. It opens into the nasal cavity through the hiatus semilunaris.<sup>6</sup> The base of the maxillary sinus is flush with the floor of the nasal cavity until around age 12. With the eruption of persistent teeth, this level is displaced

towards the top of the alveolar crest.<sup>3</sup> MSV may change as a result of systemic or pathological conditions. Alveolar bone resorption and sinus pneumatization, especially following tooth loss in the posterior region, cause the sinus to extend.<sup>6</sup> This situation can be explained by the periosteum in the Schneiderian membrane showing osteoclastic activity that triggers bone resorption.<sup>7</sup>

2D and 3D imaging techniques are used to evaluate the maxillary sinuses. In the initial diagnosis phase, evaluation is made with clinical examination and conventional radiography techniques.<sup>8</sup> 2D imaging techniques include Water's radiography, Caldwell, submentovertex, lateral sinus radiography and panoramic radiography. Among these techniques, Water's radiography provides the best visualization of the maxillary sinus. However, unwanted superpositions in 2D radiographs make it difficult to visualize the area to be examined. In this case, computed tomography (CT), one of the 3-dimensional techniques, has been evaluated as the gold standard in imaging the maxillary sinuses.<sup>9</sup> CT allows us to investigate the anatomy, variations, pathologies of the maxillary sinus

**Corresponding Author:** Mehmet Emin DOĞAN, meminemindogan@gmail.com



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and surrounding anatomical formations such as the nasal cavity in detail. These images are examined in axial, coronal and sagittal sections, allowing measurements to be made with determined parameters.<sup>10</sup> CBCT, which is more commonly used in dentistry than CT, is widely used due to its lower patient dose, more practical patient positioning, short exposure time, preventing movement artifacts, fewer metal artifacts, and better resolution.<sup>11-13</sup>

Panoramic radiography, CT, CBCT and magnetic resonance techniques are used to visualize maxillary sinus volumes (MSVs). Material ejection into the sinus, stereology (point counting method) and ellipsoid formula can be used to measure the MSV. However, in recent years, 3D techniques allow image processing and volume measurement using Hounsfield unit (HU) values. The area to be examined can be marked and tissue area, volume and density measurements can be made.<sup>14</sup> CBCT is more advantageous than CT in MSV measurements because it provides better image resolution and provides detailed images with less radiation.<sup>11</sup>

Unlike the existing studies in the literature that examine the MSV using 3D techniques,<sup>4,14-18</sup> there are a restricted number of studies examining the effect of environmental temperature on volume values.<sup>19,20</sup> Studies examining the effect of climate on MSV have been conducted in two different regions in Türkiye.<sup>21,22</sup>

This study aimed to evaluate the MSV of people living in the south of the southeastern region of Anatolia in accordance with gender and age groups using CBCT images.

The null hypothesis (H<sub>0</sub>) environmental temperature does not affect maxillary sinus volume according to age and gender.

## METHODS

In this study, 400 maxillary sinus CBCT images of 200 patients, aged between 10 and 81, who were born and raised in Şanlıurfa and who applied to Harran University Faculty of Dentistry Dentomaxillofacial Radiology for diverse causes, were included. The research protocol was approved by Harran University Clinical Researches Ethics Committee (Date: 11.12.2023, Decision No: 23.23.08). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Informed consent form was obtained from the participants and they were informed about the scope of the study. These patients were divided into 6 subgroups with respect to age [10-19 age (n:34), 20-29 age (n:34), 30-39 age (n:36), 40-49 age (n:32), 50-59 age (n:35), 60 and over (n:29)] and MSVs were measured and the relationship with gender was analyzed.

To obtain the images, were used Castellini X Radius Trio Plus (Imola, Italy) CBCT images of all patients were taken with the same device, and images were obtained in sagittal, axial and coronal planes with the IRYS 15.1 software program. Midface fractures that disrupt the integrity of the maxillary sinus, pathological formations in the sinus, anatomical variations, patients with craniofacial anomalies, patients who have undergone a surgical operation involving the maxillary sinus, patients with systemic diseases affecting bone and images containing distorted artifacts were excluded from the study.

The manually examined region was drawn on the axially planned maxillary sections of the IRYS software and the details of the Hu products were displayed (Figure 1). In the volume properties, the Hu value was marked between the minimum sine and the average (Figure 2). The area is limited so that air, soft tissue, bone marrow centers of the surrounding bone tissue and nasal cavity cannot enter. For intra-observer agreement, 20% of the data was remeasured and intraclass correlation was calculated.

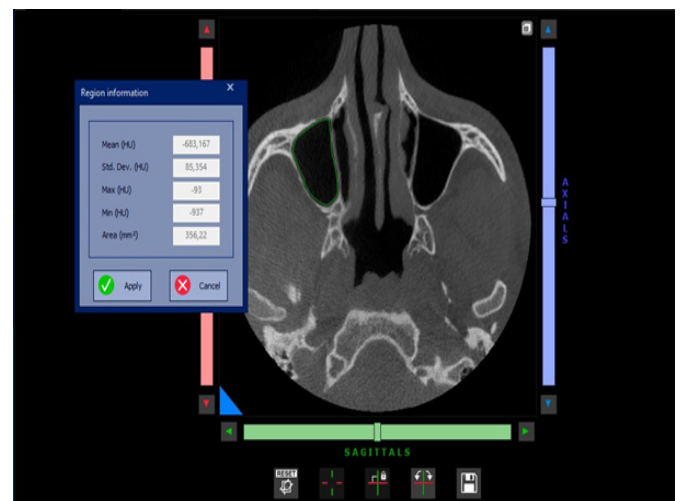


Figure 1. Drawing of the examined region and Hu values

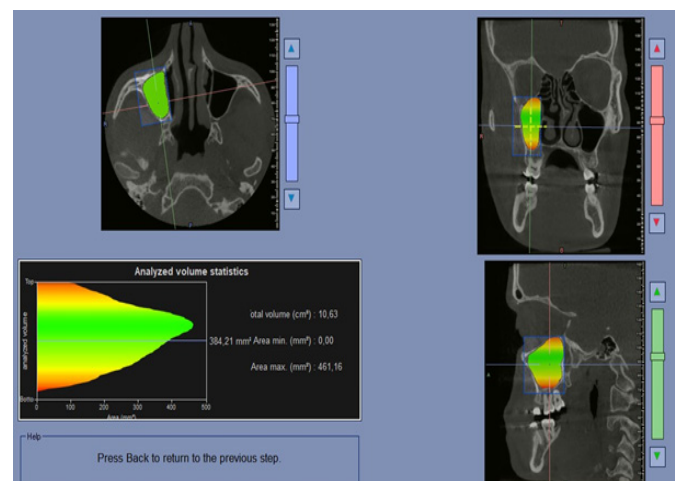


Figure 2. Determination of sinus boundaries in semi-automatic volume chambers



## Statistical Analysis

The data obtained were analyzed using the SPSS 25 (Armonk, NY, IBM) package program. Whether the variables had a normal distribution was calculated with the Kolmogorov-Smirnov test. One-way analysis of variance (ANOVA) was performed to determine the difference between the groups in terms of right and left MSV values. If significant differences between group means were present, post-hoc pairwise multiple comparisons were made using the Tukey test. We tested Mann Whitney to compare the right and left average maximum sinus volume with respect to gender. Intra-observer agreement was calculated with the intraclass correlation coefficient test.  $P < 0.05$  was admitted as the importance grade.

## RESULTS

In this study, 400 maxillary sinuses belonging to a total of 200 participants, 110 women (55%) and 90 men (45%), were examined, and the MSV was calculated by dividing it into 6 subgroups according to age and its relationship with gender was evaluated. Group 1 between the ages of 10-19, group 2 between the ages of 20-29, group 3 between the ages of 30-39, group 4 between the ages of 40-49, group 4 between the ages of 50-59, those aged 60 and over were named group 6. Right and left mean sinus volume values are shown in Table 1. Intra-observer agreement intraclass correlation coefficient was detected high level (1.00). No significant difference was found between age groups in terms of combined regulation of MSVs ( $p > 0.05$ ). When comparing the right and left average MSV, it was significantly higher in men than in women ( $p < 0.05$ ) (Table 2).

**Table 1. Distribution of right and left maxillary sinus volume between age groups**

Maxillary sinus volume (cm <sup>3</sup> )	Groups	Mean	SD	p value
Right maxillary sinus	Group 1	12.99	4.76	0.116
	Group 2	12.88	4.45	
	Group 3	11.91	3.67	
	Group 4	11.13	4.33	
	Group 5	11.31	4.45	
	Group 6	10.62	4.52	
Left maxillary sinus	Group 1	13.62	5.15	0.165
	Group 2	13.90	4.17	
	Group 3	11.93	4.15	
	Group 4	12.16	4.18	
	Group 5	11.62	4.88	
	Group 6	11.71	5.17	

SD: Standard deviation

**Table 2. Distribution of right and left maxillary sinus volume in female and male**

Gender	Female	Male
n	110	90
Right maxillar sinus volume (cm <sup>3</sup> )	9.72	14.44
Left maxillary sinus volume (cm <sup>3</sup> )	10.39	15.09
p value	0.000*	0.000*

\*: Statistically significant ( $p < 0.05$ )

## DISCUSSION

In this study, MSV was calculated comparatively between different age groups. No statistically remarkable difference was showed in the analysis between groups. Considering the relationship with gender, the statistical difference and the fact that the number of men is less than the number of women may cause this result.

Ariji et al.<sup>23</sup> calculated MSVs in axial CT images of 115 patients. While the MSV increased until the age of 20, it decreased thereafter. They found that sinus volume changes with age correlated with skeletal size and physique. No substantial difference was found between genders or between right and left MSVs. In study, the average MSV was highest in the 10-19 age group and decreased in older participants, which is similar to this study. Urooge et al.<sup>24</sup> examined the effect of sexual dimorphism on the maxillary sinus with CBCT, they found no difference in sinus volume between genders. In this study, the sinus volume of men was found to be higher than that of women. Finding different results from our study may be due to the effect of racial and regional differences.

Ekizoğlu et al.<sup>25</sup> Maxillary sinus volume was calculated using the ellipsoid formula on 380 maxillary sinus CT images of 140 patients (70 women, 70 men). Volume values were found to be higher in men than in women, and this result is compatible with this study. In another study, Sahlstrand-Johnson et al.<sup>15</sup> found no significant difference between age and sinus volume when they examined the right and left maxillary sinus CT images of 60 patients (32 women, 28 men). Similar to this study, the average sinus volume of men was found to be higher than that of women. In addition, maxillary sinus volume was measured automatically with the ellipsoid formula and volume measurement program, and the results of these two techniques were calculated to be compatible. It also includes measurements of the maximum wideness, depth and height of the maxillary sinus using the ellipsoid formula as the volume measurement method. However, the complex structure of the maxillary sinus may not reflect the accuracy of these millimetric values.



Değermenci et al.<sup>26</sup> calculated the MSV using the ellipsoid and stereological method (point counting method) in cranial CT. In their study of 361 individuals between the ages of 0 and 18, found that sinus volume was directly proportional to age and reached its maximum dimension at the age of 16. No substantial difference was found between gender and right-left side. In our study, a significant difference was found with respect to gender. The younger age groups in this study help us observe the maximum size of the maxillary sinus. While the older age groups in our study may provide information about the decrease in MSV with age, it is insufficient to examine the maximum size. Another study that calculates the volume using the stereological method is the study of Karakas et al.<sup>27</sup> in their study where they examined the paranasal sinuses with CT, it was determined that men had a larger sinus volume than women, and this result is compatible with this study.

Bornstein et al.,<sup>16</sup> who measured volume via CBCT systems calculated the right and left MSVs of 87 patients. The MSV in men was found to be larger than in women, and no significant relationship was found between both sides. These results were reported by Shresta et al.<sup>17</sup>, who used a separate 3D software program. It is compatible with the work of.

Aktuna Belgin et al.<sup>14</sup> divided 200 patients with right and left maxillary sinus CBCT images into five age groups and according to gender. In these images, MSVs were calculated in a different 3D software programme by limiting the HU values. No difference was found between right and left MSVs. While there was no significant difference between men and women, the MSV values of women in the 18-24 age group were lower than men. The method used and the relationship between the right and left sides are compatible with our study. Saccucci et al.<sup>28</sup>, who calculated volume using a 3-dimensional software programme, found no difference between genders, unlike this study. Saccucci et al.<sup>28</sup> they performed maxillary sinus volume calculations using 3D software in 52 patients (26 women, 26 men). Contrary to this study, no differences between genders were detected. This situation can be explained by the small sample size examined and the difference in ethnicity and climatic conditions.

Güleç et al.<sup>4</sup> scanned right and left CBCT images of 133 participants (49 males, 84 females) and measured MSVs. It was found that MSV did not differ significantly with respect to gender and age. Although the age distribution of the patients in our study was in parallel with the results of this study, the mean MSV was found to be larger in male patients in terms of gender. Unlike these two studies conducted in Anatolia, the changing

demographic structure as a result of high migration mobility in our region affects the results of our study. In addition, the mean MSV was found to be less in our study. The observation of smaller MSV in our region where the environmental temperature is high can be supported by the results of studies examining this issue in the literature.<sup>19,20</sup> MSV was found higher than our study in studies conducted in cities with hot climates such as Antalya and Adana in the south of Anatolia.<sup>21,22</sup> We think it may be due to differences in humidity in the air and differences in measurement techniques used. Tastemur et al.<sup>22</sup> in their MSV measurements in Sivas province, where the cold climate effect was observed, they concluded that the average sinus volume values are higher than in this region.

Sarilita et al.<sup>18</sup>, who examined 194 maxillary sinus images of 97 patients between the ages of 0 and 25 from the Indonesian population, calculated the sinus volume using different 3D software. While MSV increased until the age group of 16-20, these values decreased between the ages of 20-25. In our study, the average MSV in the 10-19 age range was higher than in the 20-29 age range, which is compatible with this study.

Cohen et al.<sup>29</sup> who measured volume using the software program of the CT device, divided the patients into two groups according to age: 25-64 years old and over 65 years old. MSV was found to decrease significantly in individuals over 65 years of age. MSV was calculated of men greater than of women. The fact that the sinus volume values of the 60 and over age group, the oldest population in this study, were lower, was consistent with this study.

### Limitations

Inability to know patients' blood calcium levels, growth hormone levels, not knowing whether individuals are treated for sinusitis. In studies with cold climates, higher measurements were made compared to this study. In future studies, it is recommended to compare the northern and southern regions to prove the effect of cold on MSV.

### CONCLUSION

In this study, MSV was evaluated numerically using CBCT images. The average MSV decreases with advancing age. However, no substantial difference was detected between age groups. MSV in men was found higher than in women. Lack of humidity and high temperature in the living area may cause the MSV to be smaller. The MSV data obtained in our study can be a resource for various orthodontic, maxillofacial surgery and medical specialties examining the head and neck region.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The research protocol was approved by Harran University Ethics Committee (Date: 11.12.2023, Decision No: 23.23.08).

### Informed Consent

All patients signed the free and informed consent form.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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# Long-term outcomes of cases after uvulopalatopharyngoplasty surgery: a retrospective study

Arzubetül Duran<sup>1</sup>, Ali Vefa Yüçetürk<sup>2</sup>

<sup>1</sup>Department of Otorhinolaryngology and Head&Neck Surgery, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Türkiye

<sup>2</sup>Department of Otorhinolaryngology and Head&Neck Surgery, İzmir Can Hospital, İzmir, Türkiye

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## ABSTRACT

**Aims:** This study aims to evaluate late-term postoperative anatomical, radiological, and polysomnographic study findings after uvulopalatopharyngoplasty surgery and describe the relationships between these findings.

**Methods:** This cross-sectional, retrospective study had a population of all cases undergone mentioned surgery in the department of otolaryngology at a university hospital between January 2005 and December 2008. Demographic variables (age, gender, time after the surgery), body mass indexes, Epworth Sleepiness Scale scores, anatomic variables (routine and non-routine examination findings and measurements), radiographic variables (computed tomography scans data), polysomnographic variables (Apnea-hypopnea indexes, mean and minimum oxygen saturations) were assessed. The results were reported as odds ratio (95% CI) and  $p < 0.05$  was considered to indicate statistical significance.

**Results:** The study sample was composed of 21 cases with available data. There were no statistically significant differences in the distribution of any of the study variables between subjects in different Obstructive Sleep Apnea Syndrome severity groups other than the higher age of the mild group. Severity categories were merged and compared, such as having the syndrome or having a moderate/severe syndrome. A resected uvula was more common in the moderate plus severe Obstructive Sleep Apnea Syndrome (apnea-hypopnea index  $> 15$ ) group (8 vs 2,  $p = .009$ ). The mean upper alveolar arcus width differed among apnea-hypopnea index  $< 15$  and apnea-hypopnea index  $> 15$  groups,  $4.15 \pm 0.21$  and  $3.93 \pm 0.26$ , respectively ( $p = 0.04$ ). There was no significant correlation between the Apnea-hypopnea index and the other variables but there were moderate to strong significant correlations between other variables.

**Conclusion:** Uvular length, uvular width and the measurement of the upper alveolar arcus (indicating the maxillary transverse width) differ in cases who have undergone uvulopalatopharyngoplasty surgery and fell into different Obstructive Sleep Apnea Syndrome severity groups determined by a polysomnographic study.

**Keywords:** Maxillary transverse width, obstructive sleep apnea syndrome (OSAS), polysomnography, uvula, uvulopalatopharyngoplasty (UPPP)

## INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is within the scope of sleep-related breathing disorders. It is characterized by recurrent episodes of upper airway obstruction during sleep with a decrease in blood oxygen ( $O_2$ ) saturation.<sup>1,2</sup> If snoring does not accompany OSAS, it is called primary snoring. While primary snoring causes social problems, OSAS can lead to symptoms that significantly reduce the quality of life and even life-threatening problems. The incidence of OSAS is between 0.8% and 4% by screening tests.<sup>3</sup> When sleep is interrupted, the cycle structure and sleep pattern change, and excessive daytime sleepiness occurs. Also, the rate of cardiovascular mortality and morbidity is

high in OSAS. It was only in the second half of the 20th century that snoring surgery was developed, and the research in the field of sleep revealed the relationship between apnea and upper airway obstruction that makes uvulopalatopharyngoplasty (UPPP) becomes widespread as a surgical technique other than tracheotomy in the treatment of OSAS.

UPPP is a surgical treatment method for primary snoring and OSAS. When we look at the literature regarding postoperative polysomnographic findings of the UPPP surgery, a 50% decrease was observed in 50% of the patients.<sup>4</sup> OSAS and its treatment remain up-to-date as an area where research continues.

**Corresponding Author:** Arzubetül DURAN, drabduran@gmail.com



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Although the UPPP operation has been performed for a long time, a multidisciplinary approach between clinics for the approach to sleep-related breathing disorders developed recently. This problem, which exists at the diagnosis stage of OSAS, is also encountered during the evaluation stage of the treatment. In some studies, postoperative success has been reported without polysomnographic examination,<sup>5</sup> and the existing postoperative findings mostly belong to the early period.

The study aims to answer the following clinical questions: "What are the late-term polysomnographic findings among patients underwent UPPP surgery? What are the relationships between those findings and anatomical factors observed clinically or radiologically?" Regarding the second question, we hypothesized that the frequency of anatomical and radiological examination results are equal in the OSAS groups defined according to the polysomnographic findings.

## METHODS

### Study Design and Ethics

The investigators designed and implemented this cross-sectional study as a medical expertise thesis in the field of otorhinolaryngology, permission was obtained from the relevant institution (2007-084). Ethics committee approval is not required for this study since this is produced from a medical expertise thesis before 2020. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The study population was composed of all cases undergone UPPP surgery in the department of otolaryngology at the Manisa Celal Bayar University Hospital between January 2005 and December 2008. Cases with body mass index (BMI) < 35 kg/m<sup>2</sup> at the time of surgery, cases with a polysomnographic sleep study at least 6 months after the surgery, and cases with a complete postoperative examination at least 6 months after the surgery were included. Cases with a history of smoking and nasal pathologies were excluded.

### Variables

Demographic variables (age, gender, time after the surgery), body mass index (BMI), Epworth sleepiness scale (ESS) scores, anatomic variables, radiographic variables, and polysomnographic variables were collected from hospital information system files.

The following were evaluated during the detailed examination of the patients (categorical anatomic variables): 1) presence of any craniofacial anomaly; 2) any nasal pathologies (mucosal color, septal deviation, turbinate hypertrophy, presence of any polyp/mass, nasal valve angles), 3) oropharyngeal examination including

the Mallampati index (I, II, III, IV), 4) evaluation of soft palate, uvula, tongue position, and lateral pharyngeal bands, 5) a flexible nasopharyngoscopy for the Müller maneuver (at the level of soft palate and tongue base) and the structure of the epiglottis (or presence of epiglottic collapse).

Continuous anatomic variables were 1) the neck circumference in cm (measurement above the prominentia thyroidea when the mouth is closed and the head is in a neutral position), 2) the distance between the mandible and the thyroid cartilage (With a closed mouth and head in a neutral position, the distance between the gnation and the prominentia thyroidea), 3) mandible to sternum distance (the distance between gnation and incisura jugularis in neutral position, mouth closed and head in neutral position), 4) maximum mouth opening in cm (distance between the lower and upper incisive teeth at the midline when the patient opens his mouth as wide as possible), 5) measurements of the width and length of the uvula, the distance between the hard palate and the root of the uvula (measurement of the distance of the posterior edge of the hard palate in the midline to the root of the uvula), 6) upper alveolar arch width measurement (distance between the last molar teeth in the upper alveolar arch in the horizontal plane), 7) palatal height (measurement of the distance of the point where the palate is at its most dome to the horizontal plane between the last upper molar teeth), 8) measurement of the distance from the posterior uvula/soft palate to the posterior pharyngeal wall with flexible nasopharyngoscopy. 9) Measurement of the distance from the base of the tongue to the posterior pharyngeal wall.

Radiological variables were recorded if present. These were the distance between the posterior end of the hard palate and the lower end of the uvula, the narrowest distance between the base of the tongue and the posterior wall of the pharynx, the distance between the most protruding part of the soft palate and the posterior wall of the pharynx, and the distance between the lower end of the soft palate and the superior of the nasopharynx were measured in the topogram. In addition, the air column area between the back surface of the soft palate and the back wall of the nasopharynx, the air column area between the lower end of the soft palate and the upper end of the epiglottis, and the boundaries of the soft palate area were manually drawn in the topogram. These areas were evaluated with an automatic area calculation program. In the axial plan, the boundaries of the smallest air column area in the sections where the soft palate was visible and the smallest air column area at the tongue root level were drawn manually and evaluated with an automatic area calculation program. Computed



tomography examinations of the cases were performed on the Siemens Somatom Emotion, Helical Computed Tomography device. Scans were performed with section thickness of 5 mm, table movement of 7.5 mm, 100 mAs, and 130 kV settings, and the region between the nasopharynx and C4-C5 was scanned. All images were obtained with the patient in the supine position and the head in a neutral position. The sections taken were perpendicular to the airway to obtain an accurate measurement of the airway area.

All-night polysomnography (PSG) recordings of the patients were made with a comprehensive portable polysomnography device (Somté PSG System, Compumedics Ltd., Abbotsford, Australia) in a single room of the hospital, without the supervision of a sleep technician. Pre-sleep evaluations and post-sleep evaluations were made under the supervision of a technician. According to the current classification, a Level II: Comprehensive portable PSG was performed.<sup>6</sup> The patient was awake and got ready for examination with a portable PSG in the sleep unit before the sleep study. Electrodes were connected according to the international 10-20 system, and the case recording were adjusted according to the algorithm. Electroencephalography (EEG), electrooculography (EOG), jaw electromyography (EMG), respiratory effort, oximetry, body position, air flow, pulse, and leg movements were recorded with a polysomnographic digital sleep system. The parameters evaluated with the PSG were total recording time, total sleep time, sleep efficiency, total rapid eye movement (REM) sleep, REM latency, duration of sleep stages and their ratio to total sleep time, number of apneas and hypopneas, mean duration of apnea/hypopnea (sec), the longest duration of apnea/hypopnea (sec), apnea index, apnea-hypopnea index (AHI), the proportion of sleep spent in the supine position, supine AHI, non-supine AHI, AHI in the REM period, AHI in the non-REM period, mean and minimum oxygen saturations.

### Surgical Procedure

Surgery was performed under general anesthesia with orotracheal intubation. The case was in a supine position with the head in hyperextension position, and a Davis Boyle mouth gag attached for exposure. To determine the amount of tissue that can be removed safely, the contact surface of the soft palate and the posterior pharynx wall was found by palpation with the Yankauer aspirator tip. Approximately 5-8 mm distal to this point, just superior to the musculus levator veli palatini, was marked with monopolar cautery as the upper surgical border. A tampon was placed in the nasopharynx. A total of 4-8 cc of lidocaine with adrenaline (20 mg Lidocaine Hydrochloride and 0.0125 mg Epinephrine base per 1 ml) diluted one-to-one with 0.9% NaCl

solution was infiltrated into the bilateral anterior plicas and uvula. If the patient was not tonsillectomized, the operation was started with a tonsillectomy. First, the anterior plica of the right tonsil was incised with a No. 15 scalpel, and dissection was performed with a tonsil spoon by entering lateral to the capsule. The tonsil was held with grasping forceps, and a right tonsillectomy was performed with unipolar cautery. A tampon was placed to provide hemostasis, starting from the lower pole and applying pressure to both poles. Then, left tonsillectomy was performed using the same technique. After waiting the necessary time for hemostasis, the bleeding foci observed in the tonsil area were held with a hemostatic Kelly forceps and cauterized with unipolar cautery. Then, a suspension suture was passed from the end of the uvula with 3/0 non-absorbable suture material suspending the uvula. If the patient had a tonsillectomy, a strip-shaped tissue approximately 2-3 mm wide was resected from bilateral anterior plicas with a No. 15 scalpel and tissue scissors.

An incision followed by a resection was made in a horizontal plane, forming a right angle with the anterior plica incision while considering the mark on the soft palate. Approximately 1-1.5 cm incisions were made on the posterior plicas, starting from the junction with the uvula and extending to the superior and the lateral directions obliquely, to ensure no tension during the suturing. The anterior and the posterior mucosa were sutured with 3/0 absorbable suture material, passing through the mucosa and constrictor pharyngeal muscle buried inside. To ensure that the oropharyngeal opening was rectangular, bilateral anterior and posterior plicas were sutured mutually with 3/0 absorbable suture material without closing the inferior parts of the tonsillar lodges. The inferior and posterior 1/3-2/3 portion of the uvula was resected, and the mucosa was approximated with absorbable sutures. The tampon from the nasopharynx was removed.

The cases were started on postoperative amoxicillin-clavulanate oral suspension as antibiotherapy and paracetamol oral suspension as analgesic for one week. Intramuscular analgesic (diclofenac sodium, 75 mg in 3 ml) was administered to patients on demand within the first 24 hours postoperatively. No significant early complications developed in cases hospitalized for an average of one day. It was recommended to follow a tonsil diet for one week.

### Statistical Analysis

Demographic variables (age, gender, time after the surgery), BMI, ESS scores, anatomic variables, radiographic variables, polysomnographic variables were characterized using descriptive statistics. Chi-square tests were performed for categorical variables.

Student's t-test was performed for continuous variables following the normal distribution or Mann-Whitney U test for continuous variables not following the normal distribution, while performing a bivariate analysis. A Pearson correlation coefficient was performed to evaluate the relationship between sturdy variables. The results were reported as odds ratio (95% CI) and P<.05 was considered to indicate statistical significance. SPSS 26 for Windows (SPSS Inc, IBM Corp, Armonk, NY) was used for all statistical analyses.

## RESULTS

During the retrospective search, 62 subjects were screened for eligibility. The final sample comprised 21 subjects with a mean age of 49.52±9.58 years and 19(90.5%) were male. The mean time between surgery and the PSG was 24.80 (±9.40) months. **Table 1** summarizes descriptive study variables and examination findings grouped by OSAS presence and severity. The mild OSAS group had a mean age of 60±9.1 years, which is higher than other groups

Table 1. Summary of descriptive study variables and examination findings grouped by OSAS presence and severity							
		All Sample (n=21)	Primary snoring (n=7)	Mild OSAS (n=4)	Moderate OSAS (n=2)	Severe OSAS (n=8)	p
Age		49.52 (±9.58)	46 (±9.6)	60 (±9.1)	54.5(±2.1)	46.13(±7.1)	0.04†
Sex	Male	19(90.5)	7(100)	4(100)	1(50)	7(87.5)	
	Female	2 (9.5)	0	0	1(50)	1(12.5)	
Body mass index		28.49 (±3.14)	27.64(±1.39)	28.30(±2.71)	31.37 (±5.58)	28.62(±3.97)	0.56
Surgery to PSG (mts)		24.80(±9.40)	21.5 (±7.0)	31.5(±6.2)	21.25 (±7.0)	24.2(±12.2)	0.43
ESS		6.57(± 5.38)	5.4(±3.1)	3 (±3.5)	6.5(±6.3)	9.3(±6.7)	0.24
Dental occlusion	Retrognathic	1 (4.8)	0	0	0	1(12.5)	
	Orthognathic	18(85.7)	6(87.5)	4(100)	2(100)	6(75)	
	Prognathic	2 (9.5)	1(14.3)	0	0	1(12.5)	
Mallampati score	1	9 (42.9)	2(28.6)	2(50)	0	5(62.5)	
	2	9 (42.9)	3(42.9)	2(50)	2(100)	2(25)	
	3	3 (14.3)	2(28.6)	0	0	1(12.5)	
Muller's maneuver at soft palate	0	1 (4.8)	0	0	1(50)	0	
	I	1 (4.8)	1(14.3)	0	0	0	
	II	8 (38.1)	3(42.9)	1(25)	0	4(50)	
	III	5 (23.8)	0	1(25)	1(50)	3(37.5)	
Muller's maneuver at base of tongue	IV	6 (28.6)	3(42.9)	2(50)	0	1(12.5)	
	I	1 (4.8)	1(14.3)	0	0	0	
	II	10(47.6)	3(42.3)	1(25)	1(50)	5(62.5)	
	III	5 (23.8)	0	2(50)	1(50)	2(25)	
Soft palate elongation	IV	5 (23.8)	3(42.3)	1(25)	0	1(12.5)	
	Normal	18(85.7)	5(71.4)	4(100)	2(100)	7(87.5)	
Soft palate thickness	Elongated	3 (14.3)	2 (28.6)	0	0	1(12.5)	
	Normal	19(90.5)	6(87.5)	3 (75)	2(100)	8(100)	
Soft palate webbing	Thickened	2 (9.5)	1(14.3)	1(25)	0	0	
	Normal	19(90.5)	6(87.5)	3 (75)	2(100)	8(100)	
Uvula examination	Webbing	2	1(14.3)	1(25)	0	0	
	Normal	11(52.4)	5(71.4)	4(100)	0	2(25)	
Uvula thickness	Resected	10(47.6)	2 (28.6)	0	2(100)	6(75)	
	Normal	9(42.9)	5(71.4)	3(75)	0	1(12.5)	
Tongue	Resected	10(47.6)	2 (28.6)	0	2(100)	6(75)	
	Thickened	2 (9.5)	0	1(25)	0	1(12.5)	
	Normal	13(61.9)	5(71.4)	3 (75)	1 (50)	4 (50)	
Lat. phary.bands	Macroglossic	8(38.1)	2 (28.6)	1(25)	1 (50)	4 (50)	
	Normal	15(71.4)	5(71.4)	4(100)	1(50)	5(62.5)	
Lat. phary.bands	Hypertrophic	6(28.6)	2 (28.6)	0	1(50)	3(37.5)	

Data was presented as n (percentage) for categorical variables, mean (± standard deviation) for continuous variables following the normal distribution, and median (Interquartile range) for continuous variables not following the normal distribution unless otherwise specified. p values for continuous variables are calculated by One-way ANOVA (analysis of variances) test, †: Tukey's post hoc comparison.  
Data was presented as n (percentage) for categorical variables.  
OSAS: Obstructive sleep apnea syndrome, PSG: Polysomnography, ESS: Epworth sleepiness scale score, Lat. phary.: Lateral pharyngeal

(p=0.04). There were no other statistically significant differences in the study variables between subjects in different OSAS severity groups. Categorical variables are not compared according to OSAS severity because of the small number of subjects and conceptually relevant cells are merged for further analysis.

As the primary eligibility criteria were having a UPPP surgery, subject categories were merged and compared from a sleep surgery perspective. Table 2 summarizes descriptive study variables and examination findings grouped by OSAS presence (AHI>5 events/hour), and moderate OSAS plus severe OSAS presence (AHI>15

**Table 2. Summary of descriptive study variables and examination findings grouped by OSAS presence and moderate OSAS plus severe OSAS presence**

		All Sample (n=21)	AHI>5 (n=14)	AHI<5 vs >5 p	AHI<15 (n=11)	AHI>15 (n=10)	AHI<15 vs >15 p
Age		46 (±9.6)	51.29 (±9.60)	0.24	51.09 (±11.41)	47.80 (±7.28)	0.44
Gender	Male	7 (100)	12 (87.5)	0.53*	11 (100)	8 (80)	0.21*
	Female	0	2 (14.3)		0	2 (20)	
Body mass index		27.64 (±1.39)	28.92 (±3.70)	0.27	27.88 (±1.86)	29.17 (±4.13)	0.38
Surgery to PSG (mts)		21.5 (±7.0)	27 (12.25)	0.36##	8.17 (±2.46)	24.4 (±11.03)	0.85
ESS		5.4 (±3.1)	7.14 (±6.23)	0.50	4.54 (±3.35)	8.80 (±6.42)	0.06
Dental occlusion	Retrognathic	0	1 (7.1)	0.68	0	1 (10)	0.55
	Orthognathic	6 (87.5)	12 (85.5)		10 (90.9)	8 (80)	
	Prognathic	1 (14.3)	1 (7.1)		1 (9.1)	1 (10)	
Mallampati score	1	2 (28.6)	7 (50)	0.36	4 (36.4)	5 (50)	0.77
	2	3 (42.9)	6 (42.9)		5 (45.5)	4 (40)	
	3	2 (28.6)	1 (7.1)		2 (18.2)	1 (10)	
Muller's maneuver at soft palate	0	0	1 (7.1)	0.21	0	1 (10)	0.16
	I	1 (14.3)	0		1 (9.1)	0	
	II	3 (42.9)	5 (37.5)		4 (36.4)	4 (40)	
	III	0	5 (37.5)		1 (9.1)	4 (40)	
	IV	3 (42.9)	3 (21.4)		5 (45.5)	1 (10)	
Muller's maneuver at base of tongue	I	1 (14.3)	0	0.10	1 (9.1)	0	0.33
	II	3 (42.3)	7 (50)		4 (36.4)	6 (60)	
	III	0	5 (37.5)		2 (18.2)	3 (30)	
	IV	3(42.3)	2 (14.3)		4 (36.4)	1 (10)	
Soft palate elongation	Normal	5(71.4)	13 (92.9)	0.24*	9 (81.2)	9 (90)	1.00*
	Elongated	2 (28.6)	1 (7.1)		2 (18.2)	1 (10)	
Soft palate thickness	Normal	6 (87.5)	13 (92.9)	1.00*	9 (81.2)	10 (100)	0.47*
	Thickened	1 (14.3)	1 (7.1)		2 (18.2)	0 (0)	
Soft palate webbing	Normal	6 (87.5)	13 (92.9)	1.00*	9 (81.2)	10 (100)	0.47*
	Webbing	1 (14.3)	1 (7.1)		2 (18.2)	0	
Uvula examination	Normal	5 (71.4)	6 (42.9)	0.36*	9 (81.2)	2 (20)	0.009*
	Resected	2 (28.6)	8 (51.7)		2 (18.2)	8 (80)	
Uvula thickness	Normal	5 (71.4)	4 (28.6)	0.15	8 (72.7)	1 (10)	0.011
	Resected	2 (28.6)	8 (51.7)		2 (18.2)	8 (80)	
	Thickened	0	2 (14.3)		1 (9.1)	1 (10)	
Tongue	Normal	5 (71.4)	8 (51.7)	0.65*	8 (72.7)	5 (50)	0.38*
	Macroglossic	2 (28.6)	6 (42.9)		3 (27.3)	5 (50)	
Lateral pharyngeal bands	Normal	5 (71.4)	10 (71.4)	1.00*	9 (81.2)	6 (60)	0.36*
	Hypertrophic	2 (28.6)	4 (28.6)		2 (18.2)	4 (40)	

Data presented as n (percentage) for categorical variables, mean (± standard deviation) for continuous variables following the normal distribution, and median [Interquartile range] for continuous variables not following the normal distribution unless otherwise specified. p values for categorical variables are the two-tailed p-value computed using the t distribution, Pearson Chi-Square unless otherwise specified. \*, Fisher's exact test. p values for continuous variables are calculated by Student's t-test unless otherwise specified, \*\*: Mann-Whitney U test. AHI: Apnea-hypopnea index, PSG: Polysomnography, OSAS: Obstructive sleep apnea syndrome, ESS: Epworth Sleepiness scale score, PSG: Polysomnography.

events/hour). There were no statistically significant differences in the distribution of any of the study variables between subjects in primary snoring (AHI<5 events/hour) and OSAS (AHI>5 events/hour) groups. On the other hand, the ESS Score of subjects in the primary snoring plus mild OSAS (AHI<15 events/hour) and moderate plus severe OSAS (AHI>15 events/hour) groups were 4.54 (±3.35) and 8.80 (±6.42), respectively (p=0.06). A resected uvula was more common in the moderate plus severe OSAS (AHI>15 events/hour) group.

After the descriptive examination variables, **Table 3** summarizes examination measurements grouped by OSAS presence (AHI>5 events/hour), OSAS severity, and moderate OSAS plus severe OSAS presence (AHI>15 events/hour). The average SaO<sub>2</sub> % was different between groups as expected. Uvular width and uvular length were constant in the moderate OSAS group, which is 0 mm. Similar to examination findings, resected uvulas in the moderate plus severe OSAS (AHI>15 events/hour) group

caused a difference in mean uvular width and uvular length, 0 [6.00] mm and 0 [1.00] mm, respectively (p=0.005 and p=0.003). Upper alveolar arcus width was different among AHI<15 events/hour and AHI>15 events/hour groups 4.15 (±0.21) and 3.93 (±0.26), respectively (p=0.05).

**Table 4** summarizes CT scan-related variables, grouped for OSAS presence and severity. No Mild OSAS cases had CT scans. There were no statistically significant differences in the study variables between subjects in the groups.

In **Table 5**, correlations between study variables are summarized. Pearson correlation coefficient was performed to evaluate the relationship between the age and the other study variables. The results indicated that the relationships were not significant. There were a few significant strong relationships between some descriptive variables, previously described and reported as the pathophysiology of OSAS.

**Table 3. Summary of examination measurements grouped by OSAS presence, OSAS severity, and moderate OSAS plus severe OSAS presence**

	All (n=21)	Primary snoring, AHI<5 (n=7)	Mild OSAS (n=4)	Moderate OSAS (n=2)	Severe OSAS (n=8)	p	AHI>5 (n=14)	AHI<5 vs >5 p	AHI<15 (n=11)	AHI>15 (n=10)	AHI<15 vs >15 p
Average SaO <sub>2</sub> %	92.0 (± 3.5)	94.0 (±2.5)	92.7 (±1.7)	93.5 (±0.7)	89.5 (±4.2)	0.07	91 (±3.67)	0.06	93.54 (±2.25)	90.3 (±4.08)	0.43
Minimum SaO <sub>2</sub> %	57.00 [90.50]	85.00 [90.00]	39.50 [84.25]	68 [0]	31.00 [68.25]	0.65#	59.5 [79.00]	0.28##	79.00 [86.00]	42.20 [72.25]	0.42##
Neck circ. (cm)	41.28 (±3.44)	41.21 (±2.03)	41.25 (±4.29)	39.75 (±0.35)	41.75 (±4.62)	0.92	41.32 (±4.03)	0.94	41.22 (±2.83)	41.35 (±4.17)	0.93
Mand. to thyroid (cm)	6.00 [0.75]	7.00 [1.50]	7.00 [0.75]	8.25 [.]	6.25 [1.00]	0.06#	6.8 (±0.81)	0.70	7.00 (±0.63)	6.8 (± 0.94)	0.57
Mand. to sternum (cm)	11.50 [2.00]	12.00 [1.50]	12.25 [1.00]	13.50 [.]	12.00 [3.00]	0.83#	12.67 (±0.81)	0.67	12.36 (±0.83)	12.80 (± 2.14)	0.55
Interincisive width (cm)	4.76 (±0.75)	5.00 (±1.00)	4.87 (±0.62)	5.00 (±0.00)	4.43 (±0.62)	0.50	5 [1.00]	0.68##	5.00 [1.00]	5.00 [1.00]	0.22
Uvular width (mm)	0 [5.00]	6.00 [7.00]	6.00 [10.25]	0	0 [6.00]		0[5.25]	0.17##	6.00 [2.00]	0 [6.00]	<b>0.005##</b>
Uvular length (mm)	0 [5.00]	5.00 [10.00]	5.00 [3.00]	0	0 [5.00]		0 [5.00]	0.12##	5.00 [3.00]	0 [1.00]	<b>0.005##</b>
Alveolar arcus width (cm)	4.04 (±0.26)	4.11 (±0.23)	4.22 (±0.18)	4.20 (±0.42)	3.86 (±0.19)	0.058	4.01 (±0.27)	0.42	4.15 (±0.21)	3.93 (± 0.26)	0.04
Palatal height (cm)	2.65 (±0.35)	2.82 (±0.42)	2.62 (±0.25)	2.75 (±0.35)	2.48 (±0.30)	0.32	2.50 [0.40]	0.17##	2.75 (±0.36)	2.54 (±0.31)	0.17
Hard palate to proximal uvula (cm)	3.42 (±0.41)	3.30 (± 0.40)	3.47 (±0.05)	3.25 (±0.35)	3.56 (±0.54)	0.62	3.45 [0.23]	0.19##	3.36 (±0.32)	3.50 (±0.50)	0.46
Retrophar. dist. (mm)	6.00 (±1.84)	6.14 (±1.46)	5.50 (±2.08)	9.00 (±1.41)	5.37 (±1.59)	0.07	5.92 (±2.05)	0.80	5.90 (±1.64)	6.10 (± 2.13)	0.82
BOT to posterior pharyngeal dist. (mm)	7.14 (±1.82)	6.71 (±1.88)	6.25 (±0.95)	9.00 (±2.82)	7.50 (±1.77)	0.30	7.35 (±1.82)	0.46	6.54 (±1.57)	7..80 (±1..93)	0.11

Data presented as mean (± standard deviation) for continuous variables following the normal distribution, median [Interquartile range] for continuous variables not following the normal distribution unless otherwise specified. Uvular width and uvular length were constant in the moderate OSAS group, which is 0 mm. p values are Student's t-test unless otherwise specified, OSAS: Obstructive sleep apnea syndrome, #: Kruskal-Wallis Test, ##: Mann-Whitney U test, SaO<sub>2</sub>: Oxygen saturation, Circ.: Circumference, Mand.: Mandible, Retrophar.: Retropharyngeal, Dist.: Distance, BOT: Base of tongue.



**Table 4.**Computed tomography scan related variables, grouped for OSAS presence and severity

	All (n=9)	Primary Snoring (n=3)	Moderate OSAS (n=1)	Severe OSAS (n=5)	p	AHI>15 (n=6)	AHI<15 vs >15 p
Hard palate-distal soft palate (mm)	29.57 (±5.44)	31.86 (±6.72)	28.60	28.40 (±5.54)	0.73	28.43 (±4.95)	0.40
Minimum distance, BOT-posterior pharyngeal wall (mm)	7.18 (±3.63)	5.83 (±3.55)	13.80	6.68 (±2.73)	0.14	7.86 (±3.80)	0.46
Minimum distance, soft palate-posterior pharyngeal wall (mm)	3.42 (±1.30)	3.60 (±1.40)	4.70	3.06 (±1.35)	0.56	3.3 (±1.38)	0.79
Distal soft palate-superior nasopharyngeal wall (mm)	37.16 (±7.22)	39.36 (±5.15)	32.40	36.80 (±9.03)	0.75	36.06 (±8.27)	0.55
Air column area, posterior surface of the soft palate - posterior nasopharyngeal wall (cm <sup>2</sup> )	1.63 (±0.59)	2.16 (±0.79)	1.39	1.36 (±0.28)	0.17	1.36 (±0.25)	0.05
Air column area, distal soft palate-superior edge of the epiglottis(cm <sup>2</sup> )	3.08 (±0.50)	3.33 (±0.39)	3.30	2.88 (±0.57)	0.49	2.95 (±0.54)	0.32
Sagittal area, soft palate (cm <sup>2</sup> )	3.12 (±0.95)	3.22 (±0.65)	2.60	3.17 (±1.23)	0.87	3.08 (±1.13)	0.85
Minimum air column area, axial, BOT level (cm <sup>2</sup> )	2.26 (±0.84)	2.33 (±1.11)	3.18	2.03 (±0.71)	0.51	2.22 (±0.79)	0.86
Minimum air column area, axial, soft palate level (cm <sup>2</sup> )	1.35 (±0.71)	1.94 (±0.58)	1.18	1.03 (± 0.66)	0.22	1.06 (±0.60 )	0.07

Data presented as mean (± standard deviation). One-way ANOVA(analysis of variances) test compared means of OSAS severity groups. For comparing AHI <15 vs AHI>15 groups, we run Student's t-test. All data are calculated on CT scans. No Mild OSAS cases had CT scans. OSAS: Obstructive sleep apnea syndrome, BOT: Base of tongue.

**Table 5.**Correlations betweenstudy variables

	Age	Body mass index	ESS	Surgery to PSG time(mts)	AHI	Average SaO <sub>2</sub> %	Minimum SaO <sub>2</sub> %	Neck circ. (cm)	Interincisive width (cm)	Mand. to thyroid (cm)	Mand.to sternum (cm)	Uvular width (mm)	Uvular length (mm)	Alveolar arcus Width(cm)	Palatal height (cm)	Hard palate-prox. uvula(cm)	Retrophar. dist. (mm)
Body mass index	r																
	p	.38															
ESS	r		.57														
	p	.28	.006														
Surgery to PSG time (mts)	r																
	p	.22	.49	.25													
AHI (Ev/h)	r																
	p	.49	.84	.11	.65												
Average SaO <sub>2</sub> %	r																
	p	.55	.87	.30	.33	.001											
Minimum SaO <sub>2</sub> %	r*						.44										
	p	.79	.60	.91	.76	.28	.04										
Neck circ. (cm)	r																
	p	.60	.19	.24	.41	.16	.001	.86									
Interincisive width (cm)	r																
	p	.86	.13	.16	.95	.13	.12	.45	.02								
Mand. to thyroid (cm)	r*																
	p	.80	.99	.19	.36	.19	.41	.89	.85	.05							

**Table 5.**Correlations betweenstudy variables (Continued)

	Age	Body mass index	ESS	Surgery to PSG time (mts)	AHI	Average SaO <sub>2</sub> %	Minimum SaO <sub>2</sub> %	Neck circ. (cm)	Interincisive width (cm)	Mand. to thyroid (cm)	Mand.to sternum (cm)	Uvular width (mm)	Uvular length (mm)	Alveolar arcus Width(cm)	Palatal height (cm)	Hard palate-prox. uvula (cm)	Retrophar. dist. (mm)
Mand.to sternum (cm)	r*																
	p	.82	.73	.84	.54	.89	.86	.24	.63	.76	.15						
Uvular width (mm)	r*																
	P	.60	.55	.19	.07	.07	.85	.41	.22	.63	.81	.71					
Uvular length (mm)	r*			.48	-.43							.96					
	p	.49	.90	.25	.02	.05	.71	.62	.41	.58	.97	.58	.001				
Alveolar arcus width (cm)	r		.44									.58	.46				
	p	.14	.04	.70	.61	.05	.64	.55	.24	.40	.46	.86	.005	.03			
Palatal height (cm)	r								.43	.23							
	p	.58	.90	.77	.35	.15	.15	.65	.64	.04	.30	.58	.34	.64	.58		
Hard palate-prox. uvula (cm)	r		.45	.43								-.46					
	p	.47	.03	.04	.51	.87	.53	.12	.79	.94	.33	.03	.66	.52	.90	.29	
Retrophar. dist. (mm)	r																
	p	.95	.31	.48	.51	.81	.67	.97	.73	.93	.32	.85	.82	.68	.85	.62	.18
BOT to post. pharyn. dist.(mm)	r		.45			-.46											
	p	.89	.24	.04	.99	.20	.03	.41	.13	.84	.67	.21	.67	.66	.34	.78	.80

r: Pearson correlation, r\*:Spearman's rho, p: Significance, ESS: Epworth sleepiness scale score, PSG: Polysomnography, AHI: Apnea hypopnea index (event/hour), SaO<sub>2</sub>: Oxygen saturation, Circ.: Circumference, Mand.: Mandible, Retrophar.: Retropharyngeal, Dist.: Distance, BOT: Base of tongue

There was a significant moderate negative relationship between inter-incisive width and neck circumference,  $r=-.49$ ;  $p=.02$ . Also, inter-incisive width was correlated with mandible to thyroid distance moderately ( $r=.42$ ;  $p=0.05$ ). Likewise, there was a significant moderate positive relationship between inter-incisive width and palatal height,  $r=.43$ ;  $p=.04$ . Uvular width and uvular length were correlated strongly, as expected. There were significant moderate positive relationships between upper alveolar arcus width and BMI and uvular length ( $r=.44$ ;  $p=.04$  and  $r=.46$ ;  $p=.03$  respectively). There was a significant strong positive relationship between upper alveolar arcus width and uvular width ( $r=.58$ ;  $p=.005$ ). We measured the distance between the distal hard palate to the proximal uvula for assessing the prolapsus of the soft palate. There were significant moderate positive relationships between this measurement and BMI and uvular length ( $r=.45$ ;  $p=.03$  and  $r=.43$ ;  $p=.04$  respectively). There was a significant moderate negative relationship between the mentioned distance and mandible to sternum distance,  $r=-.46$ ;  $p=.03$ . There was a significant moderate positive relationship between the distance from the base of the tongue to the posterior pharyngeal wall and the ESS score,  $r=.45$ ;  $p=.04$ . There was a significant

moderate negative relationship between the distance from the base of tongue to the posterior pharyngeal wall and the average SaO<sub>2</sub>%,  $r=-.46$ ;  $p=.03$ .

## DISCUSSION

The UPPP surgery has been performed for decades. We conducted this study to examine the relationship between late-term polysomnographic findings and clinical/radiological examination characteristics. The study hypothesized that the frequency of anatomical and radiological examination findings was the same in OSAS groups defined by polysomnographic findings. Study findings were diversified using specific examination measurements not used in the routine otorhinolaryngological examination of OSAS cases.

The results of this study confirm the hypothesis that when patients who underwent UPPP surgery were grouped according to late-term polysomnography findings, there was no difference between the groups except for uvula findings, in general. Both uvular examination and uvular measurement findings were significantly different in cases with  $AHI>5$  events/hour and  $AHI>15$  events/hour cases, indicating that

uvular resection is more common in the OSAS group and the moderate plus severe OSAS group. However, the correlation coefficients performed to evaluate the relationship between uvular measurements and the AHI indicated that the relationships were not significant. Based on the results of this study, it seems that the resection of the uvula does not prevent cases from having moderate or severe OSAS.

Another significantly different measurement was the width of the upper alveolar arcus, which is narrower in the AHI>15 events/hour group. Although this measurement was not significantly correlated to the AHI, it was significantly correlated to the BMI, the uvular width, and the uvular length. The correlation coefficient results indicated that the relationship between all the other non-routine measurements and the AHI wasn't significant.

Due to the complexity and heterogeneity in its pathophysiology, OSAS presents a challenge for clinicians involved in its evaluation and management. With the definition of OSAS phenotypes by Eckert et al.,<sup>7</sup> the pathophysiology has become more understandable. However, each country, region, and clinic may have differences in health management, socio-economic standards, cultural perception, social and health priority, understanding, and awareness about primary snoring and OSAS as a problem and the need for diagnosis and treatment. Several consensus statements and guidelines for the evaluation and management of adult OSAS patients have been published in the last 3 decades throughout the world. These summarize and consolidate the available knowledge on the diagnosis and treatment of OSAS.<sup>9</sup> Yet, most of these did not elaborate on specific indications of surgical treatments in detail.

Therefore, in a recent study establishing a panel of otolaryngology/head and neck surgery experts in snoring and OSA to develop statements on diagnosing and treating snoring and OSAS in adults, surgical treatment and various aspects of palatal surgery are discussed.<sup>10</sup> The presence of a long soft palate/large uvula and a large tongue are stated to be important risk factors with a consensus of 100%. Uvular length is still a point to check in preoperative sleep surgery patients. However, in this study uvula length was significantly longer in the group with AHI 0–15 events/hour than in the AHI>15 events/hour group.

An overnight polysomnographic study is the most reliable confirmatory investigation for OSAS diagnosis nevertheless the precise localization of the site of obstruction of the airflow cannot be detected in this way. Imaging modalities such as X-ray cephalometry, sleep videofluoroscopy, CT scanning, and magnetic resonance imaging (MRI) have been used to detect the obstruction site and other structural abnormalities. A meta-analysis of 25 studies has shown a strong correlation between certain craniofacial morphology variables in adult

subjects with OSAS.<sup>11</sup> Although there was no significant difference between the cephalometric measurements of the groups in this study, when the current literature is searched, it is clear that clinical cephalometric studies are still worth conducting to elucidate the exact relationship between craniofacial features and OSAS.

A narrow maxilla in its transverse dimensions is known to be associated with upper airway obstruction. As most of the radiological data were limited to studies using lateral cephalogram(s), observations related to transverse dimensions that require postero-anterior cephalometric analysis would not be commented upon. Because of that, we measured the upper alveolar width to assess maxillary transverse deficiency and found a narrower mean maxillary width in the AHI>15 events/hour group. However, in a recent study, the maxillary transverse deficiency was identified by a reduction in radiological measurement of inter-premolar distance and intermolar distance, no association was found between the maxillary measurements and obstructive sleep apnea severity.<sup>12</sup> We could not compare our examination findings to CT measurements because of the small number of cases with CT scans. Likewise, no other studies to compare our results of clinical measurements of maxillary transverse width exist.

### Limitations

This study's main limitation was that no preoperative data was available before the UPPP surgery to compare the postoperative results. Another limitation is that we reached postoperative data in 21 cases out of 62 cases (33.8%). These were because of the retrospective design of the study, as not every case operated on admitted back with a complaint necessitating a PSG. Also, we had CT scan data of 9 cases. Radiological imaging was not indicated for a postoperative follow-up, and these data were from any other indications of a neck CT scan. However, our data includes non-routine measurements and examinations of late results of a common sleep surgery technique.

### CONCLUSION

Uvular length, uvular width and the measurement of the upper alveolar arcus (indicating the maxilla's transverse width) differ in cases who have undergone UPPP surgery and fell into different OSAS severity groups determined by a PSG. These characteristics are still a curious topic among sleep surgeons and are worth studying in future research.

### ETHICAL DECLARATIONS

#### Ethics Committee Approval

Institutional approval was obtained. Ethics committee approval is not required for this study since this is produced from a medical expertise thesis before 2020.

### Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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# Adjuvant denosumab treatment in patients with resectable high-risk giant cell tumor of bone

Arif Akyıldız<sup>1</sup>, Rashad Ismayilov<sup>2</sup>, Deniz Can Güven<sup>2</sup>, Elvin Chalabiyev<sup>1</sup>,  
Najmaddin Abdurrahimli<sup>3</sup>, Sercan Aksoy<sup>1</sup>

<sup>1</sup>Division of Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Hacettepe University, Ankara, Türkiye

<sup>2</sup>Department of Internal Medicine, Faculty of Medicine, Hacettepe University, Ankara, Türkiye

<sup>3</sup>Department of Radiology, Faculty of Medicine, Hacettepe University, Ankara, Türkiye

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## ABSTRACT

**Aims:** Giant cell tumor of bone (GCTB) is an uncommon, benign, but aggressive osteolytic skeletal neoplasm of young adults. Although denosumab is frequently used in neoadjuvant treatment and metastatic unresectable disease in these patients, its role in adjuvant therapy is unclear. In this study, we evaluated the efficacy and safety of denosumab as an adjuvant therapy in patients with resectable high-risk GCTB.

**Methods:** Patients with resectable high-risk GCTB over the age of 16 who received postoperative denosumab between January 2013 and September 2022 were included. Demographic and clinical characteristics of the patients, tumor localization, prior treatments, response to denosumab treatment, and adverse effects of the drug were analyzed retrospectively.

**Results:** A total of 18 patients (10 women) with a median age of 23 (16-45) years were recruited. The median follow-up time was 7.1 (4.2-8.7) years and the median denosumab treatment duration was 12 (12-90) months. One (6%) patient experienced a partial response, and 17 (94%) patients had stable disease. Grade 1 or 2 hypophosphatemia was the most frequent adverse effect (16.7%, n=3). No patients stopped therapy due to side effects, and no grade 3 or 4 incident were observed.

**Conclusion:** Postoperative denosumab may also be useful in the adjuvant treatment of patients with high-risk resectable GCTB.

**Keywords:** Giant cell tumor of bone, denosumab, adjuvant drug therapy

## INTRODUCTION

Giant cell tumor of bone (GCTB) is a relatively rare, benign, but locally aggressive osteolytic skeletal neoplasm affecting young adults.<sup>1,2</sup> GCTB accounts for 3 to 5% of all primary bone tumors.<sup>3,4</sup> Although considered a benign tumor, GCTB represents a spectrum of neoplasms with unpredictable behavior based on clinical, radiological, and histologic characteristics. GCTB can erode bones and spread into the surrounding soft tissue, producing discomfort, significant morbidity, and occasionally metastasis. Curative surgery, either curettage or resection, is the standard treatment; nevertheless, some areas may not be amenable to resection, and local recurrence can occur at any site.<sup>5</sup> Even after curettage, GCTB tends to recur locally. Furthermore, distant metastases, which most frequently spread to the lungs, occur in about 2-3% of cases.<sup>6,7</sup>

GCTB is composed of osteoclast-like giant cells and mononuclear stromal cells.<sup>8</sup> Although it is assumed that the neoplastic component is generated from the

stromal compartment, the precise cellular origin remains unknown. Because of their proliferative abilities, spindle-like stromal cells constitute the neoplastic component of GCTB.<sup>8</sup> Besides these, receptor activator of nuclear factor kappa B ligand (RANKL) appears to have a crucial role in the pathophysiology of GCTB.<sup>9,10</sup> Stromal cells express RANKL, while giant cells express RANK, and elevated levels of RANKL lead to more bone lysis and destruction.<sup>11,12</sup> However, the fundamental cause of the elevated RANKL expression by stromal cells remained unclear. Nevertheless, the most persuasive evidence for the role of RANKL signalling in the pathophysiology of GCTB comes from numerous phase II trials with denosumab, which shown that blocking RANKL signalling is a potent and effective therapy in this disease.<sup>13-16</sup> Denosumab, a RANKL-inhibiting human monoclonal antibody, is approved for the treatment of adults and skeletally mature adolescents with metastatic

**Corresponding Author:** Rashad Ismayilov, ismayilov\_r@hotmail.com



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or unresectable GCTB or when surgical resection is anticipated to result in significant morbidity.<sup>17</sup> However, data on the use of denosumab in the adjuvant setting are very limited.<sup>18,19</sup> Therefore, we aimed to evaluate the efficacy and safety of postoperative denosumab in patients with resectable high-risk primary GCTB in real-life.

## METHODS

### Ethics

This research was conducted in compliance with the Helsinki Declaration of 1964 and its subsequent amendments. All participants were informed in detail about the research and written informed consent was obtained from all of the subjects. The study was authorized by Hacettepe University Non-interventional Clinical Researches Ethics Committee (Date: 10.01.2023, Decision No: GO 12/1326).

### Patients

We retrospectively evaluated patients with histologically confirmed localized GCTB over the age of 16 years who received postoperative denosumab between January 2013 and September 2022. Demographic and clinical characteristics of the patients, tumor localization, previous treatments, response to therapy, and drug-related side effects were recorded. R0 resection was not achieved in any of the patients who underwent wide excision without surgical adjuvants. Postoperative residual tissues were diagnosed with magnetic resonance imaging (MRI). Before the treatment, all patients were evaluated by a multidisciplinary team. Denosumab (120 mg) was injected subcutaneously every 28 days, with additional injections on days 8 and 15 in the first month. Calcium (600 mg/day) and vitamin D (400 IU/day) supplements were also given to all patients. Following denosumab therapy, patients were followed using MRI or computed tomography scans of the area of interest, as appropriate. Response rates were assessed according to "Response Evaluation Criteria In Solid Tumors" (RECIST) 1.1. The radiographic findings were classified into four groups: complete response, partial response, stable disease, and progressive disease. The "Common Terminology Criteria for Adverse Events" (CTCAE; version 3.0) were used to evaluate adverse events and laboratory abnormalities.

### Statistical Analysis

Statistical analyzes were performed using SPSS version 28 software. Due to the small number of participants, only descriptive statistics were presented with frequency (%) and median (min-max).

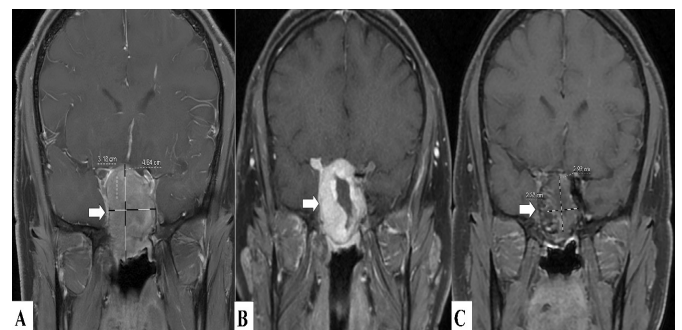
## RESULTS

A total of 18 patients (10 women and 8 men) with a median age of 23 (16-45) years were recruited. The median age at

diagnosis was 15.5 (4-39) years. The Eastern Cooperative Oncology Group Performance Status was grade 1 in 12 (66.6%) and grade 2 in 6 (33.3%) patients. The primary lesions were located in lower limb (33.3%, n=6), vertebrae (27.8%, n=5), pelvic bone (16.7%, n=3), skull (11.1%, n=2), and upper limb (11.1%, n=2). Ten (55.6%) patients had Campanacci class 2 and 8 (44.4%) had class 3 tumors. Previous treatments were radiation therapy (22.2%, n=4) and arterial embolization (5.5%, n=1), as shown in [Table](#).

Table. Baseline characteristics of patients.	
Characteristics	Frequency (%), n=18
Age, median (min-max), years	23 (16-45)
Age at diagnosis, median (min-max), years	15.5 (4-39)
<b>Sex</b>	
Women	10 (55.6)
Men	8 (44.4)
<b>ECOG PS</b>	
Grade 1	12 (66.6)
Grade 2	6 (33.3)
<b>Tumor location</b>	
Lower limb	6 (33.3)
Vertebrae	5 (27.8)
Pelvic bone	3 (16.7)
Skull	2 (11.1)
Upper limb	2 (11.1)
<b>Campanacci classification</b>	
Stage I	0 (0)
Stage II	10 (55.6)
Stage III	8 (44.4)
<b>Previous therapies</b>	
Radiation therapy	4 (22.2)
Arterial embolization	1 (5.5)
min: Minimum, max: Maximum, ECOG PS: The Eastern Cooperative Oncology Group Performance Status	

The median follow-up time was 7.1 (4.2-8.7) years and the median denosumab treatment duration was 12 (12-90) months. While 17 (94%) patients had stable disease, partial response was obtained in 1 (6%) patient ([Figure 1](#)). No complete response or progression was observed.



**Figure 1.** Brain magnetic resonance imaging-T1 series. a) A 4.64x3.18 cm solid lesion with irregular borders and lobulated contours, located in the midline clival, compressing the chiasm and prechiasmatic segments of the optic nerves. b) One month after transsphenoidal partial excision surgery. c) Significant reduction in lesion size (2.93x2.33 cm) after seven months of adjuvant denosumab.

Denosumab was generally well tolerated and no grade 3 or 4 side effects were encountered. Grade 1 or 2 side effects consisted of hypophosphatemia (16.7%, n=3) and

hypercalcemia (11.1%, n=2). No patient had discontinued therapy due to side effects.

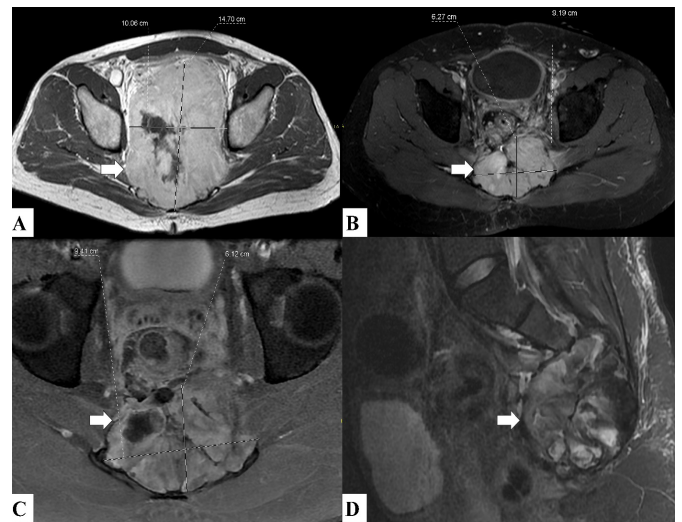
## DISCUSSION

This study represents the results of adjuvant denosumab therapy in patients with high-risk resectable GCTB. Our findings demonstrate that denosumab is effective and safe option in this group. Denosumab's therapeutic effect is related to its activities against RANKL.<sup>20,21</sup> GCTB is distinguished by stromal cells expressing RANKL and osteoclast-like giant cells expressing RANK. Denosumab works by binding to RANKL, which results in a significant reduction or elimination of osteoclast-like giant cells. As a consequence, osteolysis is stopped, and the proliferative stroma of the tumor is replaced by non-proliferative new bone that is differentiated and densely woven.<sup>12</sup>

The first studies of denosumab in GCTB revealed that administration of denosumab resulted in a significant reduction in the number of giant tumor cells and histological differentiation of highly proliferative stromal tumor cells into non-proliferative osteoid bone matrix, woven bone, or mature bone.<sup>12,13</sup> After the discovery of the antitumor effect of denosumab, many clinical studies were conducted in patients with GCTB. Especially, denosumab was approved in the neoadjuvant setting based on many non-randomized phase II trials and observational studies. When taken prior to extensive en-bloc resection, it reduces tumor burden and local recurrence rates while increasing surgical downstaging rates.<sup>16,22,23</sup>

Denosumab is also used chronically in the metastatic disease and unresectable tumors. The length of therapy, negative consequences from prolonged use, and the possibility of treatment interruption, however, are still open issues.<sup>24</sup> On the other hand, data on the use of denosumab in adjuvant setting are very limited. There is only one retrospective observational study in the literature on this subject. In that study, Errani et al.<sup>19</sup> compared 222 GCTB patients who underwent curettage alone with 25 patients who received curettage plus adjuvant denosumab. They observed local recurrence rate 16% in the first group and 60% in the denosumab group ( $p < 0.001$ ). In addition, denosumab use was shown as an independent poor risk factor for relapse-free survival in the multiple regression model (HR: 4.78, 95% CI: 2.45-9.35). In our study, on the contrary, stable disease was observed in 94% of patients and partial response was achieved in 6% of patients during a similar follow-up period of approximately 7 years. Significant differences between that research and ours include the inclusion of only extremity tumors and the use of adjuvant phenol applications as well as analysis with historical controls. In the group of patients with a high risk of recurrence, it needs to be studied whether adding denosumab in the adjuvant setting is beneficial. The duration of denosumab therapy is

also controversial. According to our data, denosumab could be used as adjuvant therapy in patients with postoperative residual disease. We administered it as an adjuvant for at least a year. Additionally, in a patient with GCBT in the sacral region, the adjuvant denosumab was used for 90 months, considering the postoperative residual disease and the risk of serious morbidity in the occasion of recurrence (Figure 2). Since data on adjuvant denosumab therapy and treatment duration are limited, adjuvant therapy could be given on a patient-by-patient basis. Prospective studies are needed to clarify which patient group would benefit from adjuvant therapy more.



**Figure 2.** Pelvic magnetic resonance imaging-T1 series. a) A 14.7x10.06 cm giant cell tumor of bone involving the sacral vertebrae, extending to the presacral region and compressing the rectum. b) Postoperative first month appearance of the mass. c-d) Stable disease after 90 months of adjuvant denosumab treatment.

Treatment with denosumab is generally well tolerated, with a low frequency of significant adverse effects. Hypophosphatemia, which occurred in 5% of patients, was one of the most common side effects of denosumab in one clinical trial.<sup>25</sup> In our study, 3 (16.7%) patients had hypophosphatemia and all of them were easily managed with phosphorus replacement. In a study of 97 patients, Palmerini et al.<sup>25</sup> observed that jaw necrosis was the most common complication (11%), and also atypical femoral fracture (4%) was another serious adverse effect. In another research of 138 GCTB patients treated with denosumab, one patient (0.7%) had jaw osteonecrosis.<sup>22</sup> Although different rates of side effects were reported in various studies, we did not observe serious side effects, perhaps due to the small number of patients in our study. However, several studies, including our data, support that denosumab is safe and well tolerated in GCBT patients.

## Limitations

Our study has some limitations such as retrospective design and the relatively small sample size. Additionally, factors influencing survival and treatment response could not be investigated because of the small number of patients and the low incidence of events.



## CONCLUSION

Denosumab therapy in GCTB is associated with a high tumor control rate with a favorable profile. It is authorized for use in metastatic, irresectable cancer and neoadjuvant settings. Our study supports that denosumab may also be useful in the adjuvant treatment of high-risk resectable patients.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was carried out with the permission of Hacettepe University Non-interventional Clinical Researches Ethics Committee (Date: 10.01.2023, Decision No: GO 12/1326).

### Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions



All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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# Evaluation of rabies risk contact cases

 Murat Solmaz<sup>1</sup>,  Özhan Orhan<sup>2</sup>

<sup>1</sup>Department of Pediatrics, Batman İluh State Hospital, Batman, Türkiye

<sup>2</sup>Department of Pediatrics, Faculty of Medicine, Mardin Artuklu University, Mardin, Türkiye

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## ABSTRACT

**Aims:** Rabies is a disease with fatal complications, often caused by a bite from an infected animal. The aim of this study was to retrospectively investigate the cases admitted due to rabies risk contact.

**Methods:** The study included 928 patients admitted to public hospitals in Batman in the last 1 year due to animal bites and risky contact. The cases included in the study were evaluated according to age, gender, residential area, season of application, place of bite, type of animal bitten and vaccination status.

**Results:** 31.8% of the applicants were under 18 years of age. 63.5% of the applicants were male. According to the season of application, the highest number of applications was in summer with 32.4%, while the lowest number of applications was in winter with 18.8%. When evaluated according to residential areas, there were more applications from urban areas. Animal bites were 53.8% cat bites, 35.5% dog bites, 10.8% horse, donkey and cow bites. 94.5% of cases fully completed the vaccination program.

**Conclusion:** Rabies is a major public health problem. Necessary measures should be taken to reduce the number of risky contact cases. Necessary shelters for animals, centers where they can be treated should be provided, and a preventive vaccination program for animals should be carried out in full.

**Keywords:** Rabies risk contact, cat bite, vaccination, public health

## INTRODUCTION

Rabies is a neurotropic RNA virus belonging to the lyssavirus genus of the rabdoviridae family. It can cause encephalitis, an acute and fatal condition involving the central nervous system.<sup>1</sup> Every year, people are bitten by animals at risk of rabies all over the world. Rabies is most commonly caused by being bitten by an infected animal and the wound is exposed to the animal's saliva. It can be transmitted through contact with damaged skin, scratching by an animal, organ transplantation from an infected person, and rarely through aerosols.<sup>2</sup>

Rabies remains an important public health problem. In developing societies, dogs are the most common rabies-causing animals, whereas in developed societies wild animals are the most common rabies-causing animals. The disease causes acute encephalitis with a rapidly progressive and fatal course. Because of the high mortality rate of encephalitis, rapid diagnosis and treatment is extremely important.<sup>2,3</sup>

Most diseases in humans, including rabies, can be prevented by vaccination. Therefore, in case of any suspicion in humans, the necessary vaccination program should be carried out in full. The most important method of rabies prevention is vaccination of animals.<sup>3-5</sup> The aim

of this study was to retrospectively investigate the cases admitted due to rabies risk contact.

## METHODS

This study is a retrospective study. The study included 928 patients admitted to public hospitals in Batman between January 1, 2023 and December 31, 2023 due to animal bites and risky contact. Those who did not have rabies risky contact were not included in the study. The cases included in the study were evaluated according to age, gender, residential area, season of application, place of bite, type of animal bitten and vaccination status. All pediatric and adult patients were included in the study.

The study was carried out with the permission of the Mardin Artuklu University Non-interventional Clinical Researches Ethics Committee (Date: 13.02.2024, Decision No: 2024/2-15). We obtained an informed consent form from all patients for procedure. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

## Statistical Analysis

Statistical analysis are made using IBM-SPSS version 24. Frequency and percentage were used as descriptive measures in the analysis.

Corresponding Author: Özhan ORHAN, ozhan.orhan@hotmail.com.tr



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## RESULTS

The data on the cases admitted to public hospitals in Batman due to animal bites and risky contact are given in **Table**. 33% of the applicants were between the ages of 19-35 years and the group with the least number of applicants was between the ages of 1-8 years with 9.2%. 31.8% of the applicants were under 18 years of age. Of the applicants, 63.5% (589) were male and 36.5% (339) were female. When evaluated according to residential areas, 545 (58.8%) cases were from urban areas and 383 (41.2%) cases were from rural areas. When evaluated according to the season of presentation, summer was the most common season with 32.4% and winter was the least common season with 18.8%. Animal bites were 53.8% cat bites, 35.5% dog bites, 10.8% horse, donkey and cow bites. When the applied cases were evaluated according to the bite site, the hand was damaged in 27.4% (254) cases, the arm was damaged in 42% (390) cases, the leg was damaged in 29.2% (271) cases, the head and neck was damaged in 1.2% (11) cases, and the abdomen was damaged in 0.2% (2) cases. All patients received local wound care and were included in the vaccination program. 94.5% of the cases completed the vaccination program completely. No rabies infection developed in any of the cases included in the vaccination program.

Table. Characteristics of the admitted cases			
		n	(%)
Age	1-8 years	85	9.2
	9-18 years	210	22.6
	19-35 years	306	33.0
	36-50 years	203	21.9
	51-75 years	124	13.4
Gender	Female	339	36.5
	Male	589	63.5
Residential area	Urban	545	58.8
	Rural	383	41.2
Season of application	Spring	203	21.9
	Summer	301	32.4
	Autumn	250	26.9
	Winter	174	18.8
Bite site	Hand	254	27.4
	Arm	390	42.0
	Leg	271	29.2
	Neck	11	1.2
	Abdomen	2	0.2
Type of biting animal	Cat	499	53.8
	Dog	329	35.5
	Others	100	10.8
Vaccination status	Complete	875	94.3
	Incomplete	53	5.7

## DISCUSSION

In this study, 928 patients admitted to our hospitals due to rabies risk contact were analyzed. In our study, similar to the literature data, it was determined that there were more males among the patients admitted.<sup>6,7</sup> The main reason for this is that men generally spend more time outdoors and therefore interact with animals more frequently. This leads to a higher risk of being bitten or scratched.

According to the data of the World Health Organization and also according to many studies conducted in our country, it has been shown that many cases with a history of rabies contact are seen at a high rate of 28%-44% between the ages of 6-15.<sup>8,9</sup> In our study, in line with the literature, we observed that the rate of admissions under the age of 18 was 31.8%.

In the study of Krzowska-Firych et al.<sup>10</sup> involving 519 patients with rabies risk contact, most of the rabies risk contact cases were urban dwellers. In our study, similar to many other studies in the literature, the majority of those admitted to hospital with rabies risk contact cases were living in urban areas. The reason for this in our study reveals that there are deficiencies in the control of animals that cause contact in urban areas. In order to eliminate this situation, controlled supervision of animals living especially in cities should be provided by the relevant administrators.

While cases due to wild animals occur in developed societies, in developing societies such as Turkey, such cases are seen due to inadequate vaccination of domestic animals living in cities.<sup>11</sup> Especially dogs are the main source of rabies-related deaths in humans. In studies conducted in our country, dogs constitute the majority of rabies contact animals.<sup>12</sup> However, in our study, most of the contact cases were cats.

The study by Ren et al.<sup>13</sup> revealed that rabies contact cases are most common in summer and autumn months. Similarly, in the study by Yizengaw et al.<sup>14</sup> it was shown that cases were most frequently seen in the summer months. In our study, similar to these studies, it was observed that most of the cases occurred in summer and the least in winter. In summer, people spend more time outdoors than in winter, increasing the risk of contact with animals.

Animal contact may vary depending on the type of animal and the age of the case. In literature studies, extremities are the most commonly injured region. According to a study conducted by Ostanello et al.,<sup>15</sup> in most of the cases, 66.5% of the injuries were to the extremities. In our study, most of the injuries were extremities. We think that this is due to the high rate of contact with cats.

Local wound care was provided to all of our contact cases and nearly 95% of our cases were fully vaccinated in accordance with the national vaccination program.

### Limitations

The limiting feature of our study is that it was retrospective and conducted with data from the last year. Epidemiologic studies with larger data should be conducted on this subject.

### CONCLUSION

Rabies risk contact continues to be an important public problem. Trainings should be provided to raise awareness about rabies and how first intervention should be done. In order to reduce the number of risky contact cases, the necessary work should be carried out within the legal framework to prevent the uncontrolled reproduction of the stray animal population, especially in crowded settlements. Necessary shelters for animals, centers where they can be treated should be provided, and a preventive vaccination program for animals should be carried out in full.

### ETHICAL DECLARATIONS

#### Ethics Committee Approval

The study was carried out with the permission of Mardin Artuklu University Non-interventional Clinical Researches Ethics Committee (Date: 13.02.2024, Decision No: 2024/2-15).

#### Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

#### Referee Evaluation Process

Externally peer-reviewed.

#### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

#### Financial Disclosure

The authors declared that this study has received no financial support.

#### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

#### Acknowledgements

Authors thank all participants who agreed to participate in the study.

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# Etiology in resistant hypertension

Yaşar Culha<sup>1</sup>, Özkan Gülmez<sup>2</sup>, Banu İşbilen Başok<sup>3</sup>, Ferruh Kemal İşman<sup>4</sup>, Aytekin Oğuz<sup>5</sup>

<sup>1</sup>Division of Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Afyonkarahisar Health Sciences University, Afyonkarahisar, Türkiye

<sup>2</sup>Department of Internal Medicine, Yağlıdere State Hospital, Giresun, Türkiye

<sup>3</sup>Department of Medical Biochemistry, Health Sciences University İzmir Tepecik Training and Research Hospital, İzmir, Türkiye

<sup>4</sup>Department of Medical Biochemistry, Institute of Health Sciences, Istanbul Medeniyet University, İstanbul, Türkiye

<sup>5</sup>Department of Internal Medicine, Institute of Health Sciences, Istanbul Medeniyet University, İstanbul, Türkiye

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## ABSTRACT

**Aims:** Resistant hypertension is defined as blood pressure that remains above goal despite the concurrent use of 3 antihypertensive agents of different classes. In resistant hypertensive patients, revealing the cause of secondary hypertension may allow drug or surgical treatment for the correction of hypertension. Resistant hypertensive patients, a significant portion of the hypertensive population, is estimated to occur. We aimed to investigate general characteristics and factors that make it difficult to control blood pressure in resistant hypertensive patients and to identify the incidence of secondary hypertension and secondary hypertension causes that play a role in the etiology of resistant hypertension.

**Methods:** In the study, Turkish Republic Ministry of Health, İstanbul Medeniyet University Göztepe Training and Research Hospital Internal Medicine, Diabetes and Obesity clinic for any reason the applicant and resistant hypertension detected a total of 80 patients (32 men, 48 women, mean age: 62±10) were enrolled consecutively. The treatment characteristics of patients, as well as demographic, anthropometric, and biochemical data, were evaluated, and the cause of secondary hypertension and etiology distribution were determined.

**Results:** In resistant hypertensive patients, the frequency of secondary hypertension was 60% (men 71%, women 52%). The most common causes of secondary hypertension are primary hyperaldosteronism (45%), obstructive sleep apnea syndrome (15%), and thyroid disorders (11%), respectively. 40% of the cases were diabetic, and 77.7% obese. Left ventricular hypertrophy and proteinuria were the most frequently detected target organ damage (96% and 37.5%, respectively). The average salt consumption of 10.75 grams/day was observed (males 12.2 g/day for females 9.7 g/day). There was analgesic use in 41% of cases, and in 3 cases, cola intake.

**Conclusion:** Secondary hypertension was found to be 60% common. Compared to other studies in the literature, primary hyperaldosteronism and pheochromocytoma were more common causes of secondary hypertension, and the obstructive sleep apnea syndrome was lower than expected. Hypercortisolism is not detected, which can be considered a surprising finding.

**Keywords:** Resistant hypertension, etiology, secondary hypertension, primary hyperaldosteronism

## INTRODUCTION

Resistant hypertension is defined as the inability to reduce blood pressure to targeted levels despite lifestyle regulation and the use of at least three antihypertensive drugs (provided that one of them is a diuretic) in appropriate doses.<sup>1,2</sup> In addition, patients who are using four or more antihypertensive drugs and whose blood pressure goal may or may not be achieved are also classified as having resistant hypertension.<sup>1</sup> The prevalence of resistant hypertension in the general hypertensive population is not precisely known. Still, cross-sectional studies and hypertension outcome studies suggest that resistant hypertension is common.<sup>3,4</sup> The ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack) study gives us the

most appropriate information. In the ALLHAT study, which included a wide range of ethnically diverse participants (>33,000 cases), the blood pressure of 34% of the participants could not be controlled with an average of two drug treatments during approximately five years of follow-up.<sup>3,4</sup> When the study was completed, 27% of participants were taking three or more medications. In total, 49% of participants in the ALLHAT study had their blood pressure controlled with one or two drugs, indicating that 50% had their blood pressure controlled with three or more medications.

Age is the most crucial factor impeding blood pressure control in resistant hypertensive patients.<sup>1,5</sup> As age increases, blood pressure control becomes more difficult.<sup>1,5</sup>

**Corresponding Author:** Yaşar CULHA, drjasar@hotmail.com



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The second most important factor is left ventricular hypertrophy and weight (body mass index [BMI] >30 kg/m<sup>2</sup>).<sup>1</sup> Chronic kidney disease is the strongest indicator of treatment resistance, defined as creatinine level greater than 1.5 mg/dl. High basal blood pressure, high dietary salt intake, DM (diabetes mellitus), black race, female gender, and living in the Southeastern United States are among the factors that make blood pressure control difficult.<sup>6,7</sup> Excessive consumption of cola is also among the causes of hypertension.<sup>6</sup> In patients with resistant hypertension, the underlying cause may include inaccurate blood pressure measurement, white coat hypertension, treatment noncompliance, arteriosclerosis, lifestyle changes (excessive salt intake in the diet, obesity, alcohol, cigarettes, cola), drug-related causes (cocaine, licorice root, NSAIDs including selective cox-2 inhibitors, aspirin, paracetamol, oral contraceptives, corticosteroids, erythropoietin, sympathomimetics, cyclosporine-tacrolimus) and secondary causes of hypertension (obstructive sleep apnea syndrome, chronic kidney disease, renal artery stenosis, primary aldosteronism, diabetes, pheochromocytoma, Cushing syndrome, and aortic coarctation).<sup>1,6,7</sup> Also, Monogenic causes of hypertension in young adults should be considered as the underlying secondary cause.<sup>8</sup> These factors should be investigated.

It is recommended to investigate secondary hypertension, especially in cases with high blood pressure that started before the age of 20 or after the age of 50, a sudden and unexplained increase in blood pressure, subclinical severe organ damage detected at diagnosis, and resistant hypertension.<sup>9</sup> Approximately 5-10% of hypertensive patients have a secondary cause.<sup>10,11</sup> Although this rate is thought to be higher in resistant HT, the total prevalence is unknown because studies on this are limited.<sup>1,7</sup> In a recent study by Pedrosa et al.,<sup>12</sup> the frequency of secondary HT in resistant HT was 65.6%. This study aims to investigate the causes of secondary hypertension in resistant hypertension patients who apply to the outpatient clinic.

## METHODS

In the study, a total of 80 patients with resistant hypertension who were admitted to the Internal Medicine, Diabetes, and Obesity Outpatient Clinics of the Ministry of Health Medeniyet University Göztepe Training and Research Hospital for any reason were prospectively routinely examined and examined, and further evaluations were made in terms of the etiology of resistant hypertension. The approval of "The Ethic Committee of Scientific Researches of the İstanbul Medeniyet University Göztepe Training and Research Hospital (Date: 27.11.2011, Decision No: 28/A) and the informed written consent of the patients were obtained for the study. The principles of the Declaration of Helsinki were followed throughout the study.

## Criteria for Inclusion in the Study

Those who were 18 years of age and over and, as in the definition of resistant hypertension, whose target blood pressure could not be reached despite using three different antihypertensive drugs (including one diuretic) or cases who are using four or more antihypertensive drugs and whose target blood pressure level is reached or not.<sup>1,5,6,12</sup> The target blood pressure value is 140/90 mmHg for the general hypertensive group and 130/80 mmHg for those with DM and chronic kidney disease. The guidelines emphasize the importance of detecting pseudo-resistance related to (1) BP measurement technique problems, (2) white coat hypertension, and (3) medication/lifestyle noncompliance. For example, the 2018 European guidelines for resistant HT require inadequate control of BP to be confirmed by ambulatory blood pressure measurements (ABPM) or home blood pressure measurements (HBPM) and adherence to therapy to be validated.<sup>13</sup>

## Exclusion Criteria

Patients with pregnancy, acute illness, or unfavorable clinical conditions.

## Study Design

Patients who applied to internal medicine outpatient clinics and met the study's inclusion criteria were randomly selected regardless of gender. Gender, age, height, weight, BMI, waist circumference, smoking, and alcohol use history of the patients recorded. The presence of comorbid diseases in the patients was recorded. Names, dosing, and the number of anti-hypertensive drugs they are taking were recorded. The biochemical and urine analyses recorded include fasting blood sugar, total cholesterol, triglyceride, HDL, LDL, urea, creatinine, sodium, potassium, HbA1c, complete urinalysis, TSH, free T4, morning serum cortisol, protein/creatinine ratio in spot urine, GFR (glomerular filtration rate), 24-hour urine sodium, plasma aldosterone level, plasma renin activity, metanephrine, and normetanephrine levels in the 24-hour urine. The use of drugs and other substances that may cause hypertension or disrupt its control were recorded.

The ankle-brachial index (ABI) has been used to detect peripheral artery disease (PAD). The ABI measurement was performed using a hand-inflatable sphygmomanometer and a hand-held, with the help of flow Doppler ultrasonography, tibialis anterior and tibialis posterior arteries; Systolic pressures of both brachial arteries were measured; lower extremity systolic pressures to the value with higher pressure in the upper extremities found by dividing.<sup>14</sup> The resulting ABI is normally between 1.0 and 1.3. An ABI of less than 0.90 is considered diagnostic of PAD. Mild disease correlates

with an ABI ranging from 0.70 to less than 0.90, whereas moderate disease correlates with an ABI ranging from 0.40 to less than 0.70, and severe disease is associated with an ABI of less than 0.40.<sup>14</sup>

To calculate the amount of salt consumed daily, the subjects were asked to collect their urine for 24 hours. The amount of sodium excreted in the urine was recorded in milliequivalents (mEq). Since 1 gram of salt contains 17 mEq of sodium, the total sodium excreted in the urine was divided by 17 to determine the amount of salt consumed in grams.

### Anthropometric Measurements

Waist circumference, fasting, standing, and mid-expiration were measured from the middle of the lower rib border and the anterior superior spina iliaca, naked, with a constant tension tape measure, and the value recorded in centimeters was taken. BMI (kg/m<sup>2</sup>) was calculated by dividing body weight in kilograms by height in square meters. BP indirect method, using Erkameter 3000 branded standard mercury table top sphygmomanometer, the last two of 3 measurements taken at 2-minute intervals from both arms in an upright sitting position with back support, after the patient has been rested for 5 minutes, without caffeine or tobacco use in the last 1 hour, without being allowed to talk. It was recorded by taking the average. Blood pressure levels are categorized based on the ESH-ESC 2007 hypertension guideline.<sup>2</sup> The patients measured their blood pressure two times a day for at least five days using their own devices to evaluate the white coat effect. Measurements in the morning and evening should be done during the following hours, after resting in a sitting position for at least 5 minutes, and by paying attention to the standard precautions recommended for measurement. Hypertension is diagnosed if the average HBPM values are  $\geq 135/85$  mmHg.<sup>15</sup>

Lower extremity pressures were measured for aortic coarctation, and a difference of more than 20 mmHg between upper extremity and lower extremity BP was considered significant.

### Laboratory Data

In Göztepe Training and Research Hospital Biochemistry Laboratory, biochemical and hormonal examination results were obtained from venous blood samples taken after a night fast of at least 12 hours, using enzymatic, calorimetric, and chemiluminescent immunoassay methods on the Abbott Aeroset Autoanalyzer and Immulite-1000 device. GFR was calculated with the Cockcroft-Gault formula.

### Evaluation of Conditions Affecting Blood Pressure

Patients were questioned about using additional medications and substances that would negatively affect

BP. The use of NSAID and non-NSAID analgesics >three doses per week<sup>1</sup>, steroids (oral, parenteral or inhaler), OKS (oral contraceptive), amphetamine, cocaine, erythropoietin, cyclosporine, tacrolimus, TCA (tricyclic antidepressant), licorice, and cola ( $\geq$  one can per day)<sup>6</sup> usage was questioned.

### OSAS Evaluation

According to the Epworth sleep scale, patients' answers to each question were given a score between 0 and 3, and the total score was recorded based on the answers to 8 questions in the scale. A score of 10 or more was considered a positive screening test for OSAS.<sup>16</sup>

### Left ventricular hypertrophy (LVH)

Inpatients without echocardiography, electrocardiography was performed according to the Sokolof-Lyon Criteria. In the electrocardiogram,

- i) The sum of the voltages of the S wave in V1 and the R wave in V5 or V6 in the horizontal plane is over 35 mm,
- ii) R wave greater than 26 mm in V5 or V6, or
- iii) An R wave greater than 14 mm in DI or 11 mm in aVL was compatible with LVH.

### Proteinuria

Microalbumin in 24-hour urine above 30 mg/day was considered microalbuminuria, and above 300 mg/day was considered macroalbuminuria.

### Thyroid Disorders

TSH levels between 4 and 10 IU/ml were considered subclinical hypothyroidism, levels above 10 IU/ml were considered overt hypothyroidism, and levels below 0.5 IU/ml were considered hyperthyroidism<sup>17</sup>.

### Primary Hyperaldosteronism

Blood samples for serum aldosterone and PRA were taken at least 2 hours after getting out of bed in the morning and during a 5-15 minute sitting period.<sup>18</sup> Aldosterone antagonist use, if any, was discontinued three weeks before the tests. The blood samples were centrifuged with an NF 2000 brand centrifuge device at 4000 rpm for 10 minutes and then stored in a deep freezer at -80 degrees. Serum aldosterone (SA) and PRA (plasma renin activity) were studied by the RIA (radioimmunoassay) method (kit manufacturer: Immunotech, Beckman Coulter Inc.), and serum aldosterone was determined as pg/ml and PRA as ng/ml/hour. SA was converted from pg/ml to ng/dl, and the SA/PRA ratio was calculated in SA ng/dl and PRA ng/ml/hour units. For primary hyperaldosteronism, patients with SA > 20 ng/dl and SA/PRA > 30 were considered to have a positive screening test.

### Pheochromocytoma

Metanephrine and normetanephrine in 24-hour urine were measured by HPLC (High-performance liquid

chromatography) method and as mcg/day. Metanephrine >400 mcg/day and normetanephrine >900 mcg/day values were considered positive screening tests for pheochromocytoma.<sup>19</sup>

### Cushing's Syndrome

Patients were screened with 8:00 a.m. cortisol. Morning cortisol >20 mcg/day was considered hypercortisolemia. In cases with morning cortisol >20 mcg/dl, the test was repeated a second time, and ACTH measurement was performed between 08:00 and 10:00 in the morning.

### Renovascular Disease

Renal US and renal Doppler US imaging of the patients were performed by doctors from the Department of Radiology at Göztepe Training and Research Hospital, and in Doppler US, a renal/aortic flow ratio of 3.5 and peak systolic velocity greater than two m/sec is positive for renal artery stenosis. It was evaluated as a finding. The renal parenchymal disease was staged as grade 0-3 according to Renal US, and changes in size were recorded.<sup>20</sup> If renal Doppler US findings support renal artery stenosis or the suspicion is still high, further examination was performed with gadolinium MR angiography for a definitive diagnosis. >50% stenosis in renal arteries was considered significant.

### Statistical Analysis

SPSS (Statistical Package for Social Sciences) for Windows 13.0 program was used. Descriptive statistical methods (Mean, Standard Deviation, ratio, frequency) were applied. Pearson correlation analysis was used to correlate mean blood pressure and obesity. The chi-square test was used to compare categorical variables, and the independent sample t-test was used for continuous variables. The results were evaluated at the 95% confidence interval, and the significance level was  $p < 0.05$ .

## RESULTS

The study included 80 resistant hypertension patients (32 men, 48 women, mean age:  $62 \pm 10$  years). The cases' mean systolic, diastolic, and mean arterial blood pressures were  $149 \pm 16$  mmHg,  $88 \pm 9$  mmHg, and  $108 \pm 10$  mmHg, respectively. The most common comorbidities were DM and CAD (40% and 16.3%, respectively) (Table 1).

While the average BMI of the cases is  $32.6 \text{ kg/m}^2$ , 46.8% of men are overweight with a BMI of  $25-29.9 \text{ kg/m}^2$ , and the majority of women, 47.9%, are in the obesity stage 1 category with a BMI of  $30-34.9 \text{ kg/m}^2$ . In total, 87.6% of women are in the obese (BMI  $\geq 30 \text{ kg/m}^2$ ) category. The obese case rate in men is 47.7%. While 44 (55%) of the cases were using three different anti-hypertensive drugs, 36 (45%) were using four or more anti-hypertensive drugs. The average number of medications used in all cases was 3.6.

**Table 1. Distribution of demographic, medical history, and comorbidity characteristics of the cases**

	n=80
Age, years $\pm$ SD	62 $\pm$ 10
Gender, male/female	32/48
Waist circumference (cm), mean $\pm$ SD	106.3 $\pm$ 10.3
BMI, kg/m <sup>2</sup> , mean (min-max.)	32.6 (21.5-45)
Tobacco use, n (%)	
Smoker	12 (15)
Non-smoker	68 (75)
Alcohol use, n (%)	
Drinking	2 (2.5)
Not drinking	78 (97.5)
Comorbidities, n (%)	
Diabetes mellitus	32 (40)
Coronary artery disease	13 (16.25)
Hypothyroidism	10 (12.5)
Chronic kidney disease	8 (10)
Heart failure	3 (3.75)
Chronic obstructive pulmonary disease	2 (2.5)
Arrhythmia	2 (2.5)
Hyperthyroidism	1 (1.25)

SD: Standard deviation, BMI: Body mass index, min: Minimum, max: Maximum

32 (40%) of the cases had stage 1, 25 (31%) had stage 2, and 5 (6%) had stage 3 arterial blood pressure values. However, arterial blood pressure was <140/90 mmHg in 18 (23%) cases (These patients meet the criteria for resistant hypertension as they are taking four or more antihypertensive medications). A white coat effect was detected in 14 (17%) cases when the average of home measurements (three measurements) was compared with office measurements.

While the average salt intake of all cases was found to be 10.75 g/day, the salt intake was 12.2 g/day in men and 9.7 g/day in women (Table 2).

**Table 2. 24-hour urine sodium averages of the cases according to gender and the estimated daily salt intake calculated accordingly**

	Gender	n	Mean	Standard deviation
24-hour urine sodium averages (mEq/day)	All cases	80	182.9	84.8
	Male	32	208.9	80.7
	Female	48	165.6	83.8
24-hour salt (NaCL) intake (g/day)	All cases	80	10.75	4.9
	Male	32	12.2	4.7
	Female	48	9.7	4.9

According to echocardiography or ECG findings, left ventricular hypertrophy (LVH) was detected in 30 (37.5%) cases. LVH was detected in 18 (37.5%) women and 12 (37.5%) men, and the proportions are equal ( $p=0.98$ ). PAH (peripheral artery disease) was detected in 24% of the cases. While microalbuminuria (30-300 mg/day) was detected in 77% of the cases, macroalbuminuria ( $\geq 300 \text{ mg/day}$ ) was detected in 19% of the cases, normoalbuminuria was detected in only 4% of the cases.



Stage-4 chronic kidney disease (GFR<30 ml/min) was detected in 4 (5%) of the cases. The sleep characteristics of the cases in terms of obstructive sleep apnea syndrome (OSAS) are given in Table 3. Accordingly, a positive screening test for OSAS was detected in 12 (15%) cases. Witnessed apnea was present in 10 (12.5%) of the cases.

**Table 3.** Epworth sleep scale evaluation of the cases, distribution of witnessed apnea and snoring.

	n=80
Epworth sleep scale positivity*, n (%)	12 (15)
Witnessed apnea, n (%)	10 (12.5)
Snoring, n (%)	61 (76.2)

\*: Cases scoring  $\geq 10$  points according to the Epworth sleep scale are considered to have a positive screening for OSAS.

According to TSH values in terms of thyroid functions cases, 6 (7%) had subclinical hypothyroidism, 3 (4%) had hyperthyroidism; Thyroid functions were found to be expected (euthyroid) in the remaining 71 (89%) cases. Overt hypothyroidism was not detected in any cases. Further examination was performed with gadolinium MR angiography for renal artery stenosis (RAS) in 10 cases. Renal artery stenosis (stenosis >50% was taken as renal artery stenosis) was detected in 4 of these 10 cases (5% of all cases). Stenosis was 90% in one of these cases, 70% in two, and 60% in one. According to renal ultrasonography, grade 1 renal parenchymal disease was detected in 7 (8.75%) cases, grade 2 renal parenchymal disease was detected in 1 case, and there was no renal parenchymal disease in the remaining 72 cases. According to the morning serum cortisol measurements of the cases, hypercortisolemia (cortisol >20 mcg/dl) was detected in 4 (5%) of the cases in the 1st measurement. However, these cases' second cortisol measurements were within normal limits. In addition, the morning ACTH measurements of the cases with high initial measurements were also found to be within normal limits (0-100 pg/ml).

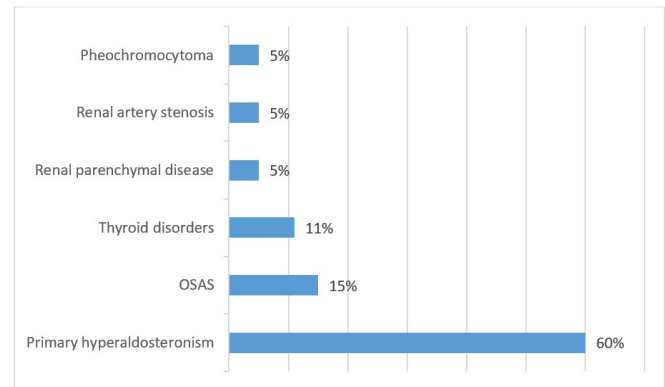
Primary hyperaldosteronism was detected in 36 (45%) of the cases. Secondary hypertension was present in 48 (60%) of all cases. While secondary hypertension was present in 23 (71%) of men, It was present in 25 (52%) of women (Table 4).

**Table 4.** Distribution of the presence of secondary HT in cases according to gender

	Secondary HT (present)	Secondary HT (absent)	Total
Male	23 (71%)	9 (29%)	32 (100%)
Female	25 (52%)	23 (48%)	48 (100%)
Total	48 (60%)	32 (40%)	80 (100%)

The most common causes of secondary hypertension in the cases were found to be primary hyperaldosteronism

(45%), OSAS (15%), and thyroid disorders (11%), respectively (Figure). Renal parenchymal disease, renal artery stenosis, and pheochromocytoma were detected at equal rates of 5%.



**Figure 1.** The frequency of causes for secondary hypertension

71 of 80 cases were using any type of diuretic (HCTZ, Indapamide, furosemide). Fifty-nine patients were using CCB (dihydropyridine+non-dihydropyridine), 55 patients were using ARB, 46 patients were using BB, 31 patients were using ACE inhibitors, 20 patients were using alpha-blockers, and two patients were using antihypertensive drugs from the other group. 55 of 71 cases using diuretics were using HCTZ. 26 of the cases use NSAID group analgesics and 7 of them use non-NSAID group analgesics. A total of 33 (41%) patients used analgesics. TCA (tricyclic antidepressant) was used in 5 cases, steroids in 3 instances, cola in 3 cases, OKS/HRT (oral contraceptive/hormone replacement therapy) in 2 cases, and erythropoietin in 1 case.

A weakly significant positive correlation was detected between BMI and MAP (mean arterial blood pressure) ( $r=0.237$   $p=0.034$ ). In other words, as BMI increases, MAP also increases.

## DISCUSSION

In our study, the frequency of secondary HT was found to be 60%. The frequency of secondary hypertension was found to be higher in men than in women. The frequency of secondary hypertension in the general hypertensive population is approximately 10%, but data on its frequency in the resistant hypertensive population are limited.<sup>13</sup> In a study by Pedrosa et al.,<sup>12</sup> the frequency of secondary HT in resistant HT was 65.6%. In our study, primary hyperaldosteronism (PHA) appears to be the most common cause of secondary hypertension. PHA was detected in 36 (45%) of the cases, and this rate is higher than in previous studies. Namely, in studies where SA/PRA was used as a screening test, PHA was found to be between 5-15% in the general hypertensive population,<sup>21,22</sup> and in recent years, there



are studies in which PHA was found to be between 20-30% in the resistant hypertensive population.<sup>1,7</sup> Common causes of secondary hypertension are OSAS, renal artery stenosis, chronic kidney disease, and PHA. More rare causes are pheochromocytomas, Cushing's syndrome, hyperparathyroidism, thyroid disorders, and aortic coarctation.<sup>1,7,23</sup> In many sources, the most common causes of secondary hypertension, especially in older ages, are shown to be renovascular and renal parenchymal diseases.<sup>10,11</sup> The frequency of renovascular HT in the hypertensive population over the age of 65 was found to be 7%; it is thought to be more common in resistant hypertensives.<sup>12,24</sup> Renal parenchymal disease in resistant hypertension: It is stated that it is seen at a rate of 2-5%.<sup>12,24,25</sup> OSAS has been identified as the most common cause of secondary HT in resistant HT (between 60% and 83%), with PHA accounting for 5-10%.<sup>12,26</sup>

It is known that beta-blocker group drugs may increase false positivity because they may reduce renin levels.<sup>27,28</sup> For this reason, it is recommended that this group of medications be discontinued two weeks before screening for PHA. However, this was not possible in a quarter of our patient group due to cardiac problems. It has also been reported that ACEIs, ARBs, diuretics, and dihydropyridine group CCBs may reduce the SA/PRA ratio and cause false negatives.<sup>18,28</sup> However, the fact that our cases already had resistant hypertension, a significant portion of them had stage-2 and 3 BP values, and that many cases were already using anti-hypertensive drugs from 4 or more groups (36 cases used  $\geq 4$  drugs) prevented these drugs from being discontinued. In our study, the diagnosis of cases with positive screening for PHA should be confirmed with salt suppression tests and radiological evaluations (computed tomography and/or magnetic resonance imaging). Due to cost, these additional examinations could not be performed within the scope of the study, but cases with positive screening tests were referred for further examination.

In recent years, studies have reported obstructive sleep apnea syndrome (OSAS) as the most common cause of secondary hypertension in resistant hypertensive patients.<sup>12</sup> Different studies have reported that the prevalence of OSAS in resistant hypertension varies between 60% and 83%.<sup>12,26</sup> We could not perform polysomnography to diagnose OSAS in our cases, but we scored according to the Epworth sleep scale, which is considered a screening test and shows daytime sleepiness. Accordingly, only 12 (15%) of the cases had a positive screening test according to the Epworth sleep scale. Thus, contrary to studies in recent years, a meager rate of positive screening for OSAS was detected in our cases. However, in studies where OSAS rates were high, polysomnography, the gold standard for diagnosis, was used.

Hypothyroidism is more common as a cause of secondary hypertension, especially in the 60s<sup>10</sup>. Approximately 3-5% of all patients with hypertension have hypothyroidism, but data on resistant hypertension are limited.<sup>29</sup> In a few studies, thyroid disease has been reported as a secondary cause of HT at a rate of 1-2%.<sup>23</sup> Thyroid disorder was detected in 11% of our cases, and this rate can be considered to be higher than expected. Hypothyroidism alone was detected in 7%.

Increased extracellular fluid load makes controlling blood pressure difficult in chronic kidney disease. This effect is more pronounced when GFR falls below 30 ml/min, which occurs in stage-4 kidney disease.<sup>23,24</sup> It is stated in the literature that renal parenchymal disease (GFR is taken as  $<30$  ml/min) is seen at a rate of 2-5% in resistant hypertension.<sup>23-25</sup> In our study, renal parenchymal disease was detected at a rate of 5%, similar to the literature.

It is stated that the incidence of renal artery stenosis increases, especially in hypertensive patients aged 65 and over.<sup>10</sup> While the rate of renovascular hypertension was below 1% in unselected patient groups, this rate was reported to be 10% in the hypertension patient group examined for diagnostic evaluation<sup>31</sup>. There are also studies indicating that it is detected in 2-5% of resistant hypertensive patients.<sup>12</sup> In our study, renal artery stenosis was detected in 4 (5%) cases, similar to the stated rates.

Pheochromocytoma, another cause of secondary hypertension, was detected in 4 (5%) patients. The frequency of pheochromocytoma in the general hypertensive population is between 0.1-0.6%.<sup>32</sup> Although its frequency in the resistant hypertensive population is unknown, publications in the form of case reports have increased in recent years. The rate found in our study appears to be higher than expected. Due to cost, radiological imaging (computed tomography and/or magnetic resonance imaging) could not be performed for pheochromocytoma within the scope of the study. Still, cases with positive screening tests were referred for further examination.

Although morning cortisol is not recommended for screening patients for Cushing's syndrome, it is widely used in outpatient clinic settings because it is easily applicable. It is more appropriate to repeat at least 2-3 measurements instead of a single measurement. The annual incidence of Cushing syndrome in the general population is 2 per million. It is detected at rates close to 2% in the screening of high-risk populations with obesity or adrenal incidentaloma.<sup>33</sup> Its frequency in resistant hypertension is unknown. Although most of our cases were obese, hypercortisolism was not detected in any of our cases. However, it may be more appropriate to screen these cases for Cushing's syndrome with further tests.

In the HYDRA (Hypertension and Diabetes Risk Screening and Awareness) study, which included 45125 primary care patients, a significant increase in the prevalence of hypertension was found as BMI increased.<sup>34</sup> In the same study, it was observed that as BMI increased, BP control became more complex, and there was a significant increase in the number of antihypertensive medications used. Similarly, in our study, 87.4% of the cases were obese, and it was determined that as BMI increased, mean arterial pressure (MAP) increased in direct proportion (r: 0.237 p: 0.034). Similar to other studies, this supports the idea that obesity is an essential factor that disrupts BP control in our cases.

Type 2 DM and HT are standard in all societies and often coexist. It is estimated that approximately 50-70 million individuals in the USA have HT with insulin resistance.<sup>27</sup> In two separate studies conducted on resistant hypertensive patients, the coexistence of DM and HT was found to be 30% and 35%.<sup>23,35</sup> 40% of the cases in our study had DM, which is slightly above the stated rates. DM was found to be the most common comorbid condition in our cases.

The recommended adequate daily sodium intake corresponds to 3.8 g of sodium chloride per day, which may be difficult to achieve today.<sup>36</sup> The achievable target is less than 5 g per day (85 mEq/day) of sodium chloride.<sup>36,37</sup> It has been determined that daily salt consumption in Turkish society is approximately 18 g (SALTÜRK-2008). In the same study, daily salt consumption was 19.3 g in men and 16.8 g in women. The average salt consumption of the cases in our study corresponds to 10.75 g/day sodium chloride. Men's daily salt intake was higher than women's (12.2 grams versus 9.7 grams). This shows that salt intake was significantly above the recommended daily salt consumption in our cases and may have a severe role in the emergence of resistance to treatment.

In our study, NSAID and non-NSAID analgesic use was determined in the majority of the cases. Meta-analyses indicate that analgesic use increases mean arterial pressure by approximately five mmHg.<sup>1</sup> Tricyclic antidepressant use in 5 cases, steroid use in 3 cases, oral contraceptive use in 2 cases, and erythropoietin use in 1 case were detected as other drug uses that disrupted BP control. In 3 cases,  $\geq$  one can of cola was consumed daily. The study conducted by Winkelmayr et al.<sup>6</sup> showed that drinking  $\geq$ 1 can of cola per day, regardless of whether it is sugary or diet cola, increases BP statistically significantly. This shows that cola intake may harm BP control in our 3 cases.

Left ventricular hypertrophy (LVH) and proteinuria are essential factors that make BP control difficult in resistant hypertension.<sup>1,38</sup> In our study, proteinuria was detected

in 96% of our cases, and LVH was detected in 37.5%. In resistant HT studies, proteinuria is 30-35%, and LVH is detected at 20%.<sup>25</sup> Proteinuria and CVH are indicators of target organ damage seen at higher-than-expected rates in our study.

## CONCLUSION

As a result, the frequency of secondary HT was found to be 60%, which is higher than expected. The frequency of primary hyperaldosteronism and pheochromocytoma as secondary causes of HT was higher than other studies in the literature. In contrast, obstructive sleep apnea syndrome was lower than expected. The fact that hypercortisolism was never detected can be considered a surprising finding. It has been observed that the presence of obesity and diabetes and excessive dietary salt consumption are the most critical factors that make blood pressure control difficult in patients with resistant hypertension.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was initiated with the approval of the Istanbul Medeniyet University Göztepe Training and Research Hospital Clinical Researches Ethics Committee (Date: 27.11.2011, Decision No: 28/A)

### Informed Consent

Written consent was obtained from the patient participating in this study.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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# Dental caries from the past to the future: is it possible to reduce caries prevalence?

Enes Kara<sup>1</sup>, Buse İpek<sup>2</sup>

<sup>1</sup>Physiotherapy Programme, Vocational School of Health Services, Sakarya University, Sakarya, Türkiye

<sup>2</sup>Department of Restorative Dentistry, Faculty of Dentistry, İstanbul University, İstanbul, Türkiye

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## ABSTRACT

Dental caries is a significant oral health issue encountered globally. Unlike bone tissue, dental tissue lacks the capacity for self-renewal, leading to the permanence of pathological changes in teeth. Dental caries is primarily the result of acid production by microorganisms that metabolise sugary foods, which demineralises tooth enamel. If left untreated, caries can progress beyond the enamel and damage the dentin and pulp tissue. The development and spread of dental caries is influenced by an individual's dietary habits, oral hygiene practices and various socio-economic factors. Throughout history, dental decay has consistently posed a major health issue across both ancient and contemporary communities. The incidence of dental caries has been influenced by factors such as dietary preferences, oral hygiene routines, and shifts in societal lifestyles. In particular, increased consumption of fermentable carbohydrates significantly increases the risk of caries formation. Conversely, preventive measures such as fluoride applications and a balanced diet can substantially reduce the incidence of caries. Other factors impacting the risk of caries include the chemical composition of saliva, the individual's general health and various medical conditions. Fluoride applications, healthy eating habits and regular dental visits stand out as effective methods for preventing dental caries. Therefore, the success of dental caries prevention strategies depends on raising health awareness at the individual level and strengthening public health policies. This multifaceted approach will help to create healthier oral conditions for future generations.

**Keywords:** Dental caries, dental anthropology, diet, dental anatomy, caries prevalence

## INTRODUCTION

Bone tissue undergoes a continuous process of renewal, giving it a dynamic structure capable of self-regeneration. In contrast, dental tissues lack this regenerative capacity. Pathological conditions in bone are often characterised by an increase or decrease in bone mass, whereas pathological processes in teeth typically manifest as tissue loss. Dental caries has been identified as one of the most common infectious dental diseases leading to tissue loss in dental tissues.<sup>1</sup>

Dental plaque is a biofilm layer formed by microorganisms that adhere to and accumulate on the tooth surface. These microorganisms induce demineralization of the hard tissues of the teeth through the acidic products generated during the breakdown of carbohydrates in the teeth, leading to the formation of caries.<sup>1,2</sup>

The increase in acidity and decrease in pH in the oral environment results in damage to dental minerals and the initiation of dental caries. It can be said that dental caries develops as a consequence of the acid-base

imbalance that occurs throughout the day. In particular, bacteria such as *Streptococcus mutans*, *Streptococcus sanguis*, *Actinomyces viscosus*, *Actinomyces naeslundii* and *Lactobacillus acidophilus* are among the microorganisms that cause dental caries.<sup>3-8</sup>

Caries usually begins in the enamel layer, leading to loss of substance and disruption of enamel integrity. If left untreated, caries progresses to the dentin and then to the pulp tissue. Dental caries occurs in the enamel, cementum and dentin layers and is classified according to its location on the tooth surface, including types such as fissure caries, proximal caries, facial and lingual smooth surface caries and root caries.<sup>9,10</sup>

The teeth most commonly affected by caries are, in order, molars, premolars, incisors and canines, with first molars being particularly affected. More caries are observed in the maxillary teeth than in the mandibular teeth, which is attributed to the less effective action of saliva in the maxilla. When examining the localisation of caries,

**Corresponding Author:** Enes KARA, eneskara@sakarya.edu.tr



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the most common sites are the fissures on the occlusal surfaces and the lateral surfaces of the crowns.<sup>10</sup>

A strong correlation exists between dietary choices and the incidence of dental caries. The nature and quantity of carbohydrates consumed significantly impact the rate of dental caries within a population. Diets rich in carbohydrates and deficient in proteins are likely to contribute to a higher prevalence of dental decay.<sup>1</sup>

Dental caries has been a common chronic disease throughout history. Archaeological finds indicate the presence of caries in the teeth of prehistoric dinosaurs, reptiles and primitive mammals. A study of the teeth of an extinct species of mammal, *Microsyops latidens*, has revealed some of the oldest caries cavities ever discovered. The fruit-based diet of these mammals supports the conclusion that dental caries is directly related to dietary habits.<sup>11</sup>

Anthropological studies confirm the presence of dental caries in ancient societies. However, as civilisation has progressed, dental caries has become more prevalent in human life. Changes in dietary habits and the foods consumed are important factors influencing this process. Agriculture and industrialisation are among the factors that influence dietary patterns and thus the development of dental caries.<sup>12</sup>

## HISTORICAL CHANGES IN THE PREVALENCE OF DENTAL CARIES

Dental caries has been one of the most persistent health problems in human history since the first human-like beings appeared. Spanning a broad time frame from prehistoric times to modern societies, dental caries has maintained its status as one of the most prevalent diseases in human history. The frequency of dental caries in ancient societies provides valuable insights into the oral hygiene practices, dietary habits and economic structures of those communities or individuals.<sup>13-16</sup>

Primitive societies tend to have a low prevalence of dental caries, largely due to their protein-rich diets and the consumption of hard foods that promote chewing and mechanical cleaning.<sup>12</sup> In the Paleolithic and Mesolithic periods, hunter-gatherer societies had rare cases of dental caries, but the transition to agriculture in the Neolithic period brought significant dietary changes, leading to an increase in the incidence of dental caries.<sup>17-24</sup>

The introduction of agriculture and the tools used to grind and prepare food made food softer and stickier, which prolonged its presence on teeth and increased the risk of caries.

Bernal et al.<sup>26</sup> have proposed that the consumption of carbohydrates, fats and proteins is closely related to the

frequency of dental caries and that this relationship can be utilized to determine the economic activities of societies.<sup>1,25</sup>

Studies from the Middle Palaeolithic show a 0% rate of dental caries in Neanderthals, rising to 1% in the Upper Palaeolithic. With dietary changes in the Neolithic period, there was an increase in the prevalence of dental caries, which was higher in societies that transitioned to agriculture earlier. During the Chalcolithic period, which followed the Neolithic and the subsequent Metal Age, dental caries rates generally varied between 3-5%, reaching around 10% in advanced agricultural societies.<sup>23,27,28</sup>

Archaeological studies have revealed that the prevalence of dental caries remained low in European countries until the 19th century. However, between 1850 and 1960, an increase in dental caries rates was observed, in parallel with the increase in sugar cane imports from the Americas. This trend is associated with the availability of sugar in the early 20th century in developed and affluent countries. In England in the early 20th century, the rejection of volunteers for military service because of poor oral health was a warning sign for public health experts. Around the same time, the discovery by the dentist Frederic McKay of the effectiveness of fluoride in preventing dental decay led to the introduction of water fluoridation. After the 1970s, the dental caries epidemic declined significantly in Europe and other developed countries. However, there has been a continuing increase in the prevalence of dental caries in developing countries.<sup>23,29</sup>

## THE CONTEMPORARY PROBLEM OF DENTAL CARIES

The 2016 World Health Organization (WHO) Global Burden of Disease Study highlights that dental caries remains one of the most prevalent health problems today. The study found that approximately 2.4 billion people worldwide have dental caries in their permanent teeth, and that 480 million children have dental caries in their primary teeth. The Global Oral Health Status report, published in 2022, updated the number of caries cases in children to 514 million.<sup>30-32</sup> The global average prevalence of caries in primary teeth was estimated to be 43%, with 134 of the 194 WHO Member States having a prevalence of over 40% in primary teeth. In upper-middle-income countries, this rate reached 46%, while in high-income countries it fell to 38%. The highest number of caries cases was recorded in lower-middle-income countries (244 million cases) and the lowest in high-income countries (45 million cases). The majority (75%) of untreated primary caries was found in middle-income countries, where health systems and resources were often inadequate. The global average prevalence of permanent

dental decay was 29%, representing over 2 billion cases. The highest numbers of caries cases were found in lower-middle-income countries (816 million cases) and upper-middle-income countries (690 million cases). Middle-income countries accounted for 75% of untreated dental caries in permanent teeth.<sup>31,33</sup>

From 1990 to 2019, there was a 2.6% reduction in instances of dental caries, although the absolute number of cases rose by around 640 million. This escalation primarily stems from demographic expansions in low- and lower-middle-income nations. In contrast, upper-middle and high-income countries have seen a decline in cases, which may be attributed to heightened oral hygiene awareness and the adoption of preventive dental health strategies in these regions.<sup>33</sup>

### RISK FACTORS FOR DENTAL CARIES

Risk factors encompass environmental, behavioral, and biological components that influence the likelihood of disease development.<sup>34</sup> Identifying these factors is crucial in preventing dental caries, a largely preventable disease. Early recognition of these risk factors, before clinical symptoms manifest, is essential in minimizing the risk of subsequent episodes of the disease.<sup>35</sup>

Caries risk, which indicates the likelihood of an individual developing a carious lesion in a given period of time, serves as a marker for predicting the future occurrence of the disease. The risk of developing dental caries is closely linked to an individual's lifestyle, dietary habits and behavioural factors.<sup>36</sup>

Particularly, sugar consumption is a significant risk factor for dental caries. It is well-documented that high sugar intake correlates with increased caries activity, and that reducing sugar consumption can significantly decrease both the incidence and severity of dental caries.<sup>37</sup>

Other important factors influencing caries risk include an individual's socio-economic status, dietary habits, oral hygiene habits, fluoride intake, salivary flow rate, salivary pH and buffering capacity, general health status and genetic predisposition. The detailed study of these factors play a critical role in the development of strategic approaches to the prevention and management of dental caries.<sup>38</sup>

### EFFECTS OF DIETARY HABITS AND DIET ON CARIES RISK

The effect of fermentable carbohydrates on the pH of oral plaque was first documented by Stephan and Miller in 1943.<sup>39</sup> The frequent consumption of carbohydrates was thought to create an acidic environment in plaque, which favours the proliferation of cariogenic bacteria and contributes to the development of dental caries.<sup>40</sup>

Extensive research has documented a linear relationship between sugar consumption and dental caries.<sup>41</sup> However, starchy foods and fresh fruit have been observed to have less cariogenic properties. Foods that require intensive chewing stimulate salivary secretion and therefore have a lower cariogenic potential. For example, fibrous and hard fruits such as apples and carrots act as natural toothbrushes, cleaning the tooth surfaces during chewing. The use of sugar alcohols and artificial sweeteners such as xylitol, saccharin and aspartame instead of fermentable carbohydrates can reduce the risk of caries.<sup>42</sup> A diet rich in protein and vegetables and the consumption of dairy products has the potential to lower the risk of dental caries.<sup>37</sup>

Liquid foods move quickly through the mouth and have minimal contact with tooth surfaces. However, holding beverages in the mouth for extended periods and frequent consumption can increase the risk of dental caries. In particular, hard candies and lollipops left in the mouth for a long time can prolong the demineralization process due to the slow release of sugar.<sup>43</sup>

### SOCIOECONOMIC AND DEMOGRAPHIC FACTORS RELATED TO CARIES

Oral and dental health directly influences an individual's quality of life and overall health, and cannot be viewed in isolation from general health. Extensive research indicates that socioeconomic status is a key determinant in both the oral and general health outcomes of individuals.<sup>44</sup>

Research shows that individuals with lower socioeconomic levels have a higher prevalence of dental caries. Lower levels of education and cultural background can lead to a lack of knowledge about oral health, resulting in poor brushing habits and the continuation of unhealthy dietary patterns. Economic constraints make it difficult to access preventive and curative dental health services, increasing the risk of dental caries.<sup>45-47</sup>

A study conducted in Ankara in 1972 on 5684 children aged 6-14 years found that the prevalence of dental caries was 43.1% in children from urban areas with high socioeconomic status, but 50.5% in rural areas.<sup>48</sup>

Epidemiological studies suggest that age is associated with the prevalence of dental caries. Individuals may be more susceptible to caries development at certain stages of their lives. In particular, the period between the ages of 1-2 years, when *Mutans streptococci* are transmitted from mother to child, the completion of the primary dentition and the eruption of the first molars during the mixed dentition phase are periods when the risk of caries increases.

In both childhood and adulthood, females have been observed to have higher DMFT (Decayed, Missing, Filled Teeth) index scores than males.

Earlier eruption of large molars in girls compared to boys and a relatively higher frequency of eating in women are among the factors that can increase the risk of caries. Hormonal changes during female-specific periods such as menstruation, pregnancy and menopause can lead to changes in saliva flow rate and composition, increasing the risk of caries.<sup>49</sup>

## THE ROLE OF SALIVA COMPOSITION IN CARIES FORMATION

Saliva plays a crucial role in preserving the health of both soft and hard tissues within the oral cavity, and is considered a vital factor in the development of dental caries. The functions of saliva, such as its flow rate, antimicrobial properties, buffering capacity and ability to remove food from tooth surfaces, play an important role in preventing the development of caries.<sup>50,51</sup>

Scientific studies have shown that people with dental decay have a faster and more intense production of acid in their saliva than people without dental decay. These findings strongly support the effectiveness of the buffering capacity of saliva in preventing dental decay.

In addition, research has shown that a low buffering capacity of saliva reduces the neutralisation of acids in plaque, which negatively affects the remineralization of early enamel lesions and increases the risk of caries formation.<sup>52</sup>

## GENERAL MEDICAL FACTORS INFLUENCING CARIES FORMATION

Long-term and regular use of medicines containing sugars such as glucose, fructose or sucrose can increase the prevalence of dental caries. Classes of drugs such as antidepressants, antihistamines, anxiolytics and antipsychotics can reduce the rate of salivation, increasing the risk of caries.<sup>49</sup>

Autoimmune diseases and metabolic disorders also have a significant impact on the development of caries. For example, Sjögren's syndrome leads to reduced saliva production due to inflammation of the salivary glands and can disrupt the pH balance of the oral cavity, facilitating caries formation. Uncontrolled diabetes, due to high blood glucose levels, can cause changes in the composition of saliva, increasing the risk of caries.<sup>53</sup>

Cancer treatments, especially chemotherapy, can affect the mineralization of dental enamel, increasing the prevalence of dental caries. In addition, physical or mental disabilities can affect oral hygiene and thus increase the risk of dental caries.

Neurological conditions, such as Parkinson's disease, can make it difficult for individuals to maintain adequate oral

care, potentially triggering the formation of caries. Similarly, individuals with developmental disabilities, including those on the autism spectrum, may face challenges with dental care, which can increase the risk of caries.<sup>49</sup>

## DENTAL ANATOMY AND ITS RELATIONSHIP TO CARIES

Dental caries can start in different anatomical areas of the teeth, and there exists a set of classifications developed specific to these starting points. The spread of caries can vary depending on the anatomical characteristics of the site.<sup>9</sup>

### Occlusal Caries: Pit and Fissure Caries

Pits and fissures on the occlusal surfaces of teeth can create a favourable environment for caries formation due to factors such as plaque accumulation and microbial colonization. The difficulty of toothbrushes to reach these narrow and deep structures can lead to inadequate oral hygiene. While the pronounced pits and fissures in younger individuals may increase the risk of caries in this age group, the erosion of tooth surfaces with age may lead to the flattening of pits and fissures, potentially reducing the risk of caries in shallow fissures.<sup>54,55</sup>

### Smooth Surface Caries

Smooth surface caries, which affect buccal, lingual and interproximal surfaces, can provide a suitable environment for plaque accumulation and microbial colonization. These caries are more prevalent in areas that are difficult to clean, facilitating caries formation.<sup>56</sup>

### Root Surface Caries

The increased longevity of humans and the longer presence of teeth in the oral environment may lead to an increased incidence of root surface caries. Particularly in the elderly, root surface exposure may become more susceptible to plaque accumulation due to gingival recession. The low inorganic content and relatively thin structure of cementum indicate that if left untreated, caries can progress rapidly to the dentin. This emphasises the importance of caries treatment and early intervention.<sup>57</sup>

## PREVENTION OF DENTAL CARIES AND REDUCING ITS PREVALENCE IN FUTURE GENERATIONS FLUORIDE APPLICATIONS

Dental caries prevention is a multifaceted approach that involves various strategies to reduce the prevalence and incidence of caries. Effective prevention strategies include fluoride applications, dietary adjustments, and the expansion of preventive dentistry practices. Each of these components plays a crucial role in maintaining



dental health and preventing the development of caries. Below are detailed descriptions of these preventive measures.<sup>37</sup>

Fluoride is an essential mineral that plays a crucial role in maintaining dental health and preventing caries. When present in trace amounts, fluoride can increase the resistance of dental materials and create a protective barrier during the demineralization process, thereby reducing caries activity.<sup>58</sup>

Both systemic and topical applications of fluoride are considered to be among the most effective methods of preventing dental caries. Fluoridation of public water supplies is a strategy supported by numerous studies to reduce the prevalence of dental caries. International health authorities, such as the WHO, recommend an optimal fluoride concentration of 1.5 ppm in drinking water. However, high doses and prolonged exposure to fluoride can have adverse effects on the skeletal system, teeth, and other organs. Historically, systemic applications of fluoride, such as the fluoridation of public water, milk, and salt, have been widely used. However, since the second half of the 20th century, topical applications such as fluoridated toothpastes and mouthrinses have emerged as effective alternatives. Professional applications, including fluoride gels, solutions, and varnishes, have been developed and research has shown that there are no significant differences in effectiveness between these methods.<sup>59-63</sup>

There are numerous studies in the literature supporting the effectiveness of fluoride applications in preventing dental caries. In particular, topical fluoride varnishes have been highlighted as an effective method of caries prevention. A study by Ashkenazi et al.<sup>59</sup> highlighted the advantages of topical fluoride applications over systemic methods in terms of time and efficacy. Similarly, a study by Beltrán-Aguilar and colleagues in 2000 found that locally applied fluoride varnishes are an effective method of caries prevention.<sup>64</sup>

Fluoridated toothpaste, containing fluoride concentrations ranging from 1000 to 1250 ppm, has been shown to play a significant role in preventing dental caries across children, adolescents, and adults. Additionally, there is evidence indicating that adopting the habit of brushing teeth twice daily from a young age can significantly reduce the development of caries.<sup>65</sup>

Dietary habits play a significant role in the prevention of dental caries. Consuming a balanced diet that includes adequate minerals and nutrients is essential for maintaining dental health. Foods high in fermentable sugars and carbohydrates increase the risk of caries, whereas a diet rich in proteins, vegetables, and dairy products can help reduce this risk. Limiting the intake

of sugary foods and beverages, and ensuring regular consumption of foods that promote saliva production, such as fibrous fruits and vegetables, are important dietary strategies for caries prevention.<sup>37</sup>

## REGULATION OF DIETARY HABITS

During the critical stages of tooth development, dietary habits play a significant role in the resistance of teeth to caries. Particularly in infancy, an adequate intake of minerals and essential nutrients supports dental robustness. In this context, the intake of nutrients such as calcium, phosphorus and vitamins A, D and C is essential for tooth development. The available literature indicates that deficiencies in vitamins A and D, as well as calcium and phosphorus imbalances, can adversely affect dental development.<sup>66</sup>

After the eruption of teeth, the influence of dietary habits and consumption patterns on dental caries becomes more pronounced. In particular, the intake of fermentable sugars can increase the risk of dental caries. The consumption of such sugars and starchy foods is increasing in modern diets. The frequency and timing of consumption of cariogenic foods are critical factors in caries risk. Studies have documented the relationship between the physical form of sugars, their frequency of consumption, their amount and their adhesiveness and dental caries.<sup>37</sup>

Anticariogenic diets are considered an effective strategy for reducing caries. Dairy products such as milk and yoghurt, which contain caries-preventive components such as calcium, phosphate, casein and lipids, contribute to the regulation of saliva and plaque acidity and the remineralization of early carious lesions.<sup>67</sup>

Limiting the consumption of sugary liquid foods, cooking methods, sequence of consumption and combinations may also influence the risk of caries. Therefore, attention to the cariogenic potential of foods consumed together and modifications in consumption or cooking methods are important.<sup>37,68</sup>

## EXPANSION OF PREVENTIVE DENTISTRY PRACTICES

Dental caries is recognised as a significant public health problem worldwide. Particularly in countries where preventive dental care is not widely available, oral and dental health problems can lead to serious economic and social challenges.<sup>69-71</sup>

The main focus in tackling this problem is to address the mechanisms of caries formation and risk factors, and to improve the early stages of carious lesions through remineralization methods. The goal of this approach is to prevent caries and maintain oral and dental health throughout the population.<sup>38</sup>



Preventive dental services have become increasingly important, particularly since the 1930s, with practices aimed at maintaining oral and dental health in children. At the core of this strategy is the ability to maintain healthy hygiene and dietary habits acquired in childhood into adulthood, thereby preserving the overall oral health of individuals in the long term. Recently, this understanding has been extended to the wider community and has become more comprehensive.<sup>69-71</sup>

Widespread adoption and effective implementation of preventive dental practices are critical to improving community oral health and reducing common problems such as dental caries. Individual education, public awareness and active application of the principles of preventive dentistry are essential.<sup>38</sup>

## CONCLUSION

Dental caries is influenced not only by individual health and hygiene practices, but also by broader social and economic factors. Fluoride application, regulation of dietary habits and expansion of preventive dental services are emerging as important tools in the fight against dental caries.

Effective management of dental caries requires an integrated approach at the individual, community and policy levels. This approach is based on instilling healthy oral and dental care habits from an early age, encouraging regular dental check-ups and taking specific measures for high-risk groups. It is also essential to understand the impact of diet and eating habits on caries, and to reduce the consumption of fermentable sugars and increase the intake of caries preventive foods. Raising public awareness and education levels is a critical factor in the success of these initiatives.

In conclusion, a multidisciplinary approach is essential for the effective prevention and treatment of dental caries. It is crucial for health professionals and policy-makers to collaboratively develop and implement comprehensive strategies to address this health issue. Such concerted efforts are pivotal in decreasing the prevalence of dental caries, thereby enhancing the overall oral and dental health of the community.

## ETHICAL DECLARATIONS

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

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## Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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