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Posted Date: 5 February 2025

doi: 10.20944/preprints202502.0319.v1

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Article

Are There Gender-Based Differences in COPD Patients with Type 2 Respiratory Failure? Impact on Clinical Practice

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ABSTRACT: Purpose: To contribute to clinical practice by identifying gender-based differences in patients diagnosed with COPD who are monitored in the intensive care unit due to type 2 respiratory failure. Materials and Methods: The study was planned as a prospective, observational, and cross-sectional investigation. A total of 258 patients, 91 females and 167 males, were included in the study between 2023 and 2024. Demographic data and clinical parameters of COPD patients admitted to intensive care due to hypercapnic respiratory failure and treated with NIMV were compared between genders. Results: The number of male patients was higher than female patients, while the mean age of female patients was higher than that of males. Body mass index (BMI), morbid obesity, atrial fibrillation, renal disease, heart failure, hypertension, hypothyroidism, Charlson Comorbidity Index (CCI), and cardiothoracic ratio were found to be significantly higher in female patients. Emphysema and steroid use in treatment were more common in male patients. In laboratory analyses conducted at the time of admission, the average D-dimer and BNP levels were higher in female patients. The mean pCO₂ level assessed prior to discharge was also higher in female patients. Conclusion: Heart failure and risk factors that may lead to heart failure are more prominent in female COPD patients with type 2 respiratory failure. Despite the lower number of female patients compared to males, the significantly higher comorbidity burden in females as per CCI scores suggests that medical processes may be more challenging to manage in females. We believe that these findings will contribute to clinical practice and provide clinicians with insights for patient management.

Keywords: Hypercapnia; NIMV; BPAP; comorbidity; sex; female

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) ranks among the leading causes of morbidity and mortality globally (1). COPD is the third leading cause of death in the United States (2). The prevalence and burden of COPD are expected to increase in the coming decades due to continued exposure to risk factors and an aging global population (3). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) reports an overall prevalence of COPD at 11.8% in men and 8.5% in women (4), with significantly higher prevalence in men than women (5). However, from 2001 to 2019, COPD prevalence has been steadily rising among women (6). Although COPD is still primarily considered a "male disease," mortality rates among men have been decreasing in some countries, such as the United States and the United Kingdom, while remaining relatively unchanged among women (7,8).

Hypercapnic respiratory failure, also known as type 2 respiratory failure, is characterized by an increase in arterial carbon dioxide (CO₂) pressure (PaCO₂). CO₂ levels in arterial blood are directly

proportional to CO₂ production and inversely proportional to alveolar ventilation. Increased dead space and decreased minute ventilation are common causes of hypercapnia (9). During exacerbations, ventilation-perfusion (VA/Q) mismatches occur, potentially leading to arterial hypoxemia with or without hypercapnia (10). Hypercapnia should always be suspected in individuals at risk of hypoventilation (e.g., sedative use, history of sleep apnea) or with increased physiological dead space and limited pulmonary reserve (e.g., COPD exacerbation) presenting with symptoms such as dyspnea or altered mental status (9). Acute or acute-on-chronic hypercapnia may develop during exacerbations or in response to oxygen therapy in some COPD patients (9). Immediate admission to the intensive care unit (ICU) may be necessary for some cases. Ventilatory support during a COPD exacerbation can be provided via noninvasive (nasal or facial mask) or invasive ventilation (11). Noninvasive mechanical ventilation (NIMV) is the preferred first-line treatment for acute respiratory failure due to COPD exacerbations, with an 80-85% success rate in hypercapnic patients (12).

Many funding agencies in Europe and North America have implemented policies to encourage or mandate the consideration of sex and gender in medical research at all levels (13). Despite significant advances in intensive care medicine, limited attention has been given to gender differences in the management and outcomes of ICU patients (14). Although half of the global population comprises women, they account for only 35-45% of ICU patients (15). Clinical presentations, comorbidities, and prognoses may differ by gender, potentially affecting treatment decisions (16). A review of the literature reveals numerous studies on gender-COPD and gender-ICU topics. However, no study has specifically compared COPD patients with type 2 respiratory failure treated with NIMV based on gender. This study aims to identify gender-based differences in patients with hypercapnic respiratory failure treated with NIMV and to contribute findings to clinical practice.

MATERIALS-METHODS

Study Design, Inclusion, and Exclusion Criteria

Our study is prospective, observational, and cross-sectional. Patients admitted to the second-level pulmonary ICU between March 30, 2023, and March 30, 2024, for type 2 respiratory failure and clinically stabilized with noninvasive mechanical ventilation before discharge were included. 91 female and 167 male patients were enrolled in the study. Exclusion criteria included patients with type 1 respiratory failure alone, patients without a COPD diagnosis, those requiring intubation after noninvasive mechanical ventilation, patients transferred to third-level ICUs, COVID-19 PCR-positive patients transferred to COVID ICUs, patients who died during hospitalization for unrelated reasons, and patients with chronic hypercapnia previously using home BPAP.

Data Collection and Study Protocol

Informed consent was obtained from patients prior to data collection. Patient files and the hospital information management system served as data sources. In addition to demographic data, comorbidities, treatments received, long-term device use reports, length of stay, and routine laboratory parameters were recorded.

Statistical analysis

The data were analyzed using the Statistical Package for Social Sciences (SPSS) Windows 27.0 software (Chicago, IL, USA). The normality of data distribution was evaluated using the Kolmogorov-Smirnov test and histograms. Numerical data with normal distribution were presented as mean $\pm$ standard deviation, while non-normally distributed numerical data were presented as median and minimum-maximum values (IQR 25%-75%). Categorical variables were expressed as numbers (n) and percentages (%). Categorical variables were compared using the Chi-square or Fisher's Exact test, while continuous variables were compared using the Student's t-test or Mann-

Whitney U test. The Kruskal-Wallis analysis was used to compare more than two continuous variables. A p-value <0.05 was considered statistically significant for all tests.

Ethical Considerations

Ethical approval for the study was obtained from the Ethics Committee of Ankara Sanatorium Training and Research Hospital (Date: 22.02.2023; No: 2012-KAEK-15/2644).

RESULTS

Table 1 compares the gender distribution and ages of the patients. The study was conducted with a total of 258 patients. Of these, 91 (35.3%) were female and 167 (64.7%) were male (p<0.01). The mean age of the patients was 69±10 years. The mean age of female patients was 72±12 years, significantly higher than that of male patients (68±8 years, p=0.003) (Table 1).

Table 1. Demographic Distribution of Patients.

	General	Female	Male	P
n (%)	258 (%100)	91 (%35.3)	167 (%64.7)	<0.01
Age	69±10	72±12	68±8	0.03

Table 2 evaluates the comorbidities, treatments, and hospital stay durations of the patients. When comorbidities were compared by gender: Body mass index (BMI) (p<0.001), morbid obesity (p<0.001), atrial fibrillation (p=0.023), renal disease (p=0.027), neurological diseases (p=0.005), heart failure (p<0.001), hypertension (p<0.001), hypothyroidism (p=0.024), Charlson Comorbidity Index (CCI) (p=0.02), and cardiothoracic ratio (p<0.001) were significantly higher in female patients compared to males (Table 2). Emphysema was significantly higher in male patients compared to females (p<0.001) (Table 2).

No significant differences were found in the gender comparison of patients prescribed long-term BPAP at home (p=0.730) or long-term oxygen therapy at home (p=0.765) (Table 2).

When comparing treatments (antibiotics, steroids, antidepressants, anxiolytics, nutritional support), the number of male patients receiving steroid therapy was significantly higher than female patients (p=0.004) (Table 2).

There were no significant differences in hospital stay durations between genders (p=0.926) (Table 2).

Table 2. Comparison of Comorbidities, Treatments, and Hospital Stay Durations by Gender.

	General 258 (100%)	Female 91 (35.3%)	Male 167 (64.7%)	p
Kyphoscoliosis	8 (3.1%)	5 (5.5%)	3 (1.8%)	0.102
Morbid obesity	26 (10.1%)	17 (18.7%)	9 (5.4%)	<0.001
OSAS	13 (5%)	6 (6.6%)	7 (4.2%)	0.400
Hypertension	147 (57%)	65 (71.4%)	82 (49.1%)	<0.001
Diabetes Mellitus	81 (31.4%)	32 (35.2%)	49 (29.3%)	0.336
Coronary artery disease	52 (20.2%)	20 (22.0%)	32 (19.2%)	0.591
Atrial fibrillation	39 (15.1%)	20 (22.0%)	19 (11.4%)	0.023

Kidney disease	72 (27.9%)	33 (36.2%)	39 (23.3%)	0.027
Neurological disease	7 (2.7%)	6 (6.6%)	1 (0.6%)	0.005
Depression/anxiety	44 (17.1%)	17 (18.7%)	27 (16.2%)	0.609
Bronchiectasis	19 (7.4%)	3 (3.3%)	16 (9.6%)	0.065
Pneumonia	17 (6.6%)	8 (8.8%)	9 (5.4%)	0.294
History of previous tuberculosis	12 (4.7%)	2 (2.2%)	10 (6.0%)	0.168
Pulmonary embolism	16 (6.2%)	8 (8.8%)	8 (4.8%)	0.204
Heart failure	124 (48.1%)	59 (64.8%)	65 (38.9%)	<0.001
Lung cancer	22 (8.5%)	4 (4.4%)	18 (10.8%)	0.080
Hypothyroidism	18 (7.0%)	11 (12.8%)	7 (4.7%)	0.024
Emphysema	69 (26.7%)	5 (5.5%)	64 (38.3%)	<0.001
Anemia	65 (25.2%)	27 (29.7%)	38 (22.9%)	0.233
Body mass index (Mean±SD)	28±8	31±9	27±7	<0.001
Charlson comorbidity index (Mean±SD)	5±2	5±2	4±1	0.002
Cardiothoracic ratio (Mean±SD)	0.56±0.09	0.61±0.07	0.53±0.09	<0.001
Length of stay (Mean±Sd)	9±5	10±7	9±7	0.926
Systemic steroid treatment	184 (71.3%)	55 (60.4%)	129 (77.2%)	0.004
Antibiotic treatment	222 (86%)	77 (84.6%)	145(68.8%)	0.625
Anxiolytic/antidepressant treatment	38 (14.7%)	14 (15.4%)	24 (14.4%)	0.827
Nutritional support	19 (7.4%)	6 (6.6%)	13 (7.8%)	0.727
Number of patients prescribed BPAP at home	138 (53.5%)	50 (54.9%)	88 (52.7%)	0.730
Number of patients prescribed OC at home	91 (35.3%)	31 (34.1%)	60 (35.9%)	0.765

* Kruskal Wallis analysis was performed. OSAS: Obstructive Sleep Apnea Syndrome, BPAP: Bilevel positive airway pressure, OC: Oxygen concentrator.

Table 3 evaluates the laboratory parameters of the patients. In the analysis of laboratory parameters at admission, the average D-dimer value ($p=0.036$) and brain natriuretic peptide (BNP) value ($p=0.04$) were significantly higher in female patients compared to males (Table 3). No significant differences were found in the comparison of pH compensation-decompensation in blood gas analysis at admission by gender (Table 3).

In hemogram analyses conducted at admission and prior to discharge, the mean hemoglobin levels were significantly higher in male patients compared to females ($p<0.001$, $p<0.001$) (Table 3).

In blood gas analyses performed before discharge, the mean partial carbon dioxide pressure ($p\text{CO}_2$) ($p=0.036$), actual bicarbonate (aHCO_3) ($p=0.031$), actual base excess (aBe) ($p=0.021$), and standard base excess (SBE) ($p=0.035$) values were significantly higher in female patients compared to

males. Additionally, in the biochemistry analysis, the mean sodium levels (p=0.003) were significantly higher in female patients (Table 3).

Although not shown in the table: The lymphocyte/WBC ratio at admission, lymphocyte/WBC ratio at discharge, monocyte/WBC ratio at admission, monocyte/WBC ratio at discharge, neutrophil/WBC ratio at admission, neutrophil/WBC ratio at discharge, eosinophil/WBC ratio at admission, eosinophil/WBC ratio at discharge, basophil/WBC ratio at admission, and basophil/WBC ratio at discharge showed no significant differences between males and females (p=0.25, p=0.19, p=0.34, p=0.96, p=0.52, p=0.09, p=0.75, p=0.37, p=0.89, p=0.24, respectively). Additionally, no significant differences were found in blood group parameters (A, B, O, AB) when compared by gender (p=0.92).

Table 3. Analysis of Laboratory Parameters by Gender .

Laboratory Parameters	General	Female	Male	p
	258 (%100)	91 (35.3%)	167 (64.7%)	
Compensation in Hospitalization				0.761
Compensated (PH=7.35-7.45) n (%)	187 (72.5%)	67 (73.6%)	120 (71.9%)	
Decompensated (PH<7.35) n (%)	71 (27.5%)	24 (26.4%)	47 (28.1%)	
Admission PH	7.29±0.08	7.28±0.07	7.29±0.08	0.686
Discharged PH	7.46±0.05	7.47±0.04	7.46±0.05	0.402
Admission PaCO2	79.1±15.7	77.5±15.2	79.8±16.0	0.239
Discharged PaCO2	50.4±7.7	51.6±6.1	49.8±7.4	0.036
Admission aHCO3	37.8±7.7	37.0±9.0	38.3±6.9	0.160
Discharged aHCO3	36.1±5.3	37.0±5.3	35.7±5.3	0.031
Admission sHCO3	31.9±7.3	31.9±8.0	31.9±6.8	0.680
Discharged sHCO3	34.5±4.9	35.3±4.4	34.1±5.1	0.038
Admission aBe	8.5±7.6	8.2±8.4	8.6±7.1	0.679
Discharged aBe	11.0±5.3	11.7±4.3	10.6±5.8	0.021
Admission sBe	11.3±7.9	10.4±8.7	11.8±7.3	0.208
Discharged sBe	12.9±6.3	13±5	12±6	0.035
Admission CRP	77±88	62±76	86±94	0.086
Discharged CRP	24±29	20±22	25±32	0.792
Admission BUN	59±34	66±35	55±33	0.006
Discharged BUN	52±25	52±23	52±25	0.848
Admission creatinine	1.15±0.59	1.16±0.52	1.15±0.63	0.591
Discharged creatinine	0.94±0.50	0.87±0.27	0.98±0.59	0.136
Admission sodium	138.6±4.8	139.0±4.2	138.4±5.1	0.500
Discharged sodium	138.6±3.4	139.4±3.4	138.2±3.4	0.003
Admission potassium	4.58±0.78	4.56±0.72	4.60±0.81	0.237
Discharged potassium	4.19±0.63	4.14±0.58	4.21±0.67	0.229
Admission chloride	96.5±6.7	96.3±6.3	96.7±7.0	0.399
Discharged chloride	96.1±4.3	95.9±4.7	96.1±4.1	0.683

Admission magnesium	2.03±0.35	2.00±0.35	2.04±0.36	0.636
Discharge magnesium	1.95±0.24	1.91±0.26	1.96±0.22	0.183
Admission calcium	8.76±0.76	8.67±0.85	8.81±0.70	0.594
Discharge calcium	8.69±0.60	8.73±0.61	8.67±0.60	0.501
Admission Albumin	3.50±0.52	3.48±0.50	3.51±0.54	0.518
Discharge Albumin	3.16±0.45	3.14±0.39	3.17±0.48	0.465
Admission leukocyte	10.92±4.39	11.01±4.27	10.87±4.46	0.753
Dischage leukocyte	9.08±3.41	8.68±2.91	9.30±3.64	0.294
Admission lymphocyte	1.27±1.06	1.36±0.98	1.22±1.10	0.127
Discharge lymphocyte	1.36±1.39	1.29±0.73	1.40±1.65	0.680
Admission monocyte	0.611±0.254	0.601±0.352	0.616±0.376	0.695
Discharge monocyte	0.589±0.254	0.573±0.234	0.598±0.265	0.618
Admission neutrophil	8.81±3.94	8.78±3.91	8.83±3.97	0.827
Discharge neutrophil	7.05±2.96	6.62±2.76	7.29±3.05	0.119
Admission eosinophil	0.082±0.185	0.073±0.118	0.087±0.213	0.938
Discharge eosinophil	0.123±0.154	0.144±0.191	0.111±0.129	0.485
Admission basophil	0.037±0.035	0.036±0.026	0.038±0.039	0.599
Discharge basophil	0.028±0.022	0.029±0.024	0.027±0.021	0.493
Admission hemoglobin	13.2±2.6	12.1±2.3	13.8±2.6	<0.001
Discharge hemoglobin	12.2±2.6	11.4±2.2	12.7±2.7	<0.001
Admission platelet	244±92	253±94	239±91	0.162
Discharge platelet	233±87	229±90	234±85	0.456
Admission procalcitonin	0.81±4.90	0.35±0.99	1.07±6.06	0.510
Discharge procalcitonin	0.11±0.27	0.10±0.24	0.11±0.28	0.822
Admission D-dimer	2497±4667	3535±6411	1933±3255	0.036
Admission troponin	347±1660	249±697	401±2005	0.702
Admission BNP	355±519	469±603	294±458	0.004
Admission T4	0.98±0.23	0.95±0.21	0.99±0.24	0.381
Admission TSH	2.05±9.32	3.42±15	1.27±2	0.640

PaCO2: Partial arterial carbon dioxide pressure, aHCO3:Actual bicarbonate, aBe: Actual base excess, sBe: Standard base excess, BNP: Brain Natriuretic Peptide, TSH: Thyroid Stimulating Hormone.

Discussion

Our study is the first to compare clinical parameters by gender in COPD patients treated with NIMV and other medical therapies for type 2 respiratory failure in the intensive care unit and subsequently discharged. The number of male patients was higher than that of females. The mean age of female patients was significantly higher than that of males. BMI, morbid obesity, atrial fibrillation, renal disease, heart failure, hypertension, hypothyroidism, Charlson Comorbidity Index (CCI), BNP, BUN, D-dimer, cardiothoracic ratio assessed on the first day of hospitalization, and pCO2 measured before discharge were significantly higher in females. The presence of emphysema and the use of steroids in treatment were significantly more common in males. No significant gender differences were observed in patients prescribed long-term BPAP or oxygen therapy for home use.

A study examining the epidemiology of COPD in Türkiye using health insurance data found that 56.2% of physician-diagnosed COPD patients were male and 43.8% were female (17). Another

study on COPD exacerbations in Türkiye reported that 85% of the patients were male, while 15% were female (18). Studies examining ICU patients have shown that the number of male patients is consistently higher (16,19–24). In our study, consistent with the literature, the number of male patients was significantly higher than that of females.

A meta-analysis evaluating hospital admissions due to COPD exacerbations showed that gender distribution varied widely, with mean ages ranging from 63.0 ± 14.5 to 76.3 ± 10.6 years (25). Studies by Zetterstein et al. on ICU patients and Grabicki et al. on COPD patients found no differences in the mean age between males and females (18,22). However, Todorov et al. reported a significantly higher mean age in female ICU patients compared to males [75 (64;82) years in women vs. 68 (58;77) years in men, $p < 0.001$] (26). In our study, the mean age of females was significantly higher than that of males.

Comorbidities are common in all stages of COPD, from mild to severe (1). A study evaluating COPD patients by gender found that comorbidity burden, based on the Charlson Comorbidity Index, was higher in women with severe and very severe COPD (27). A study on ICU patients found fewer comorbidities in females than in males (5.4 vs. 6.4, $p = 0.002$) (19). Among four studies examining CCI by gender, three found no significant differences (21,28,29), while one reported a higher comorbidity burden in males (22). In our study, CCI was higher in females than in males.

Cardiovascular diseases are common and significant comorbidities in COPD (1). The prevalence of systolic and diastolic heart failure in COPD patients ranges from 20% to 70% (30). COPD is frequently associated with cardiac arrhythmias, which contribute to increased dyspnea (31). Atrial fibrillation is common in COPD and can exacerbate dyspnea (32). Hypertension is likely the most common comorbidity in COPD and can significantly impact disease progression (33). Grabicki et al. found that cardiovascular diseases were more prevalent in females, while coronary artery disease was more common in males (16). A study conducted in northern Sweden on COPD patients found a higher prevalence of cardiovascular disease in males (34). Roche et al. found no gender differences in hypertension, ischemic heart disease, or left heart failure (35). Todorov et al. reported no significant differences between genders in arrhythmias and heart failure (26). In our study, heart failure, hypertension, atrial fibrillation, increased cardiothoracic ratio (a radiological indicator of heart failure), and elevated BNP (a laboratory marker of heart failure) were significantly more common in females. No significant differences were observed between genders in coronary artery disease.

Patients with pulmonary etiologies and increased BMI are considered at risk for ICU admission (36). Pulmonary causes are the most frequent reasons for hospital admission in patients with elevated BMI (36). A study by Kumar et al. on ICU patients found that among patients with a BMI of 30–39, 51.4% were male and 48.6% were female; for a BMI of 40–49, 41.5% were male and 58.5% were female; for a BMI ≥ 50 , 41.9% were male and 58.1% were female (36). Grabicki et al. found that females had lower BMI than males (16). In contrast, Roche et al. reported higher BMI in females with COPD but no gender differences in obesity prevalence (35). In our study, females had significantly higher BMI than males, and the number of morbidly obese female patients was greater than that of males.

In our study, renal failure and hypothyroidism were significantly more common in females. Matera et al. reported a higher prevalence of renal disease in males (37), Grabicki et al. found thyroid diseases to be more common in females (16).

When we evaluated the relationship between increased BMI, hypothyroidism, renal failure, and heart failure, all three conditions were found to be associated with heart failure and increased heart failure risk. Heart failure often coexists with reduced renal function, and the relationship between the two conditions is bidirectional (38). Being overweight (BMI ≥ 25 kg/m²) and obesity (BMI ≥ 30 kg/m²) independently increase the risk of heart failure (39). Hypothyroidism is also a risk factor for heart failure (40).

Other laboratory parameters significantly higher in females were D-dimer levels assessed on admission and pCO₂ levels measured before discharge. Elevated D-dimer levels are known to correlate with renal failure (41). The higher pCO₂ levels before discharge in females may be due to the higher BMI and obesity prevalence, making hypercapnia more challenging to control in this

group. In males, parameters significantly higher than in females included steroid use and the presence of emphysema. Males and females may exhibit phenotypically different responses to tobacco smoke exposure, with males being more prone to the emphysematous phenotype and females to the airway-dominant phenotype. (42). A review of the literature revealed no studies comparing systemic steroid use between men and women. In our study, the higher prevalence of steroid use in men could be attributed to the prioritization of diuretic therapy in women due to the higher incidence of heart failure as a comorbidity, relegating the anti-inflammatory steroid therapy to secondary importance.

Limitations

1. As this was an observational study, only routinely evaluated parameters were examined. Additional tests (e.g., echocardiography, spirometry) could not be performed. 2. The study was conducted at a single center.

Conclusion

In our study examining gender-based differences in COPD patients treated with NIMV for type 2 respiratory failure, heart failure and risk factors for heart failure were found to be more prominent in female patients. Consistent with the literature, although the number of female patients was lower than that of males, the significantly higher comorbidity burden in females based on CCI scores suggests that medical processes may be more challenging to manage in women. We believe that these findings will contribute to clinical practice and provide clinicians with valuable insights into patient management.

Author Contributions: Conceptualization, Tarkan Ozdemir, Murat Yıldız, Maşide Arı, Güler Eraslan Doğanay, Mustafa Özgür Cırık and Çiğdem Özdilekcan; Methodology, Tarkan Ozdemir, Murat Yıldız, Maşide Arı and Emrah Arı; Software, Tarkan Ozdemir; Validation, Tarkan Ozdemir, Murat Yıldız and Maşide Arı; Formal analysis, Tarkan Ozdemir, Maşide Arı and Emrah Arı; Investigation, Tarkan Ozdemir, Murat Yıldız, Emrah Arı, Güler Eraslan Doğanay, Mustafa Özgür Cırık and Melek Doğanç; Resources, Tarkan Ozdemir; Data curation, Tarkan Ozdemir, Murat Yıldız, Güler Eraslan Doğanay, Mustafa Özgür Cırık, Melek Doğanç, Derya Kızılgöz and Yusuf Tuğrul Şipit; Writing – original draft, Tarkan Ozdemir; Writing – review & editing, Tarkan Ozdemir, Murat Yıldız, Maşide Arı, Emrah Arı, Güler Eraslan Doğanay, Mustafa Özgür Cırık, Melek Doğanç, Çiğdem Özdilekcan, Derya Kızılgöz and Yusuf Tuğrul Şipit; Supervision, Tarkan Ozdemir; Project administration, Tarkan Ozdemir.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Ankara Sanatorium Training and Research Hospital (Date: 22.02.2023; No: 2012-KAEK-15/2644).

Informed Consent Statement: Informed consent was obtained from patients prior to data collection

Data Availability Statement: The original contributions presented in this study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author(s).

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