

## CA125 as a Biomarker for Identifying Disease Severity and Right Ventricular Dysfunction in Obstructive Sleep Apnea

### ABSTRACT

**Background:** Obstructive sleep apnea (OSA) is associated with increased cardiovascular risk, particularly through right ventricular (RV) dysfunction. Cancer antigen 125 (CA125), a biomarker traditionally used in ovarian cancer, has shown potential as an indicator of RV dysfunction. This study aims to compare CA125 levels between OSA patients and controls and to evaluate its association with disease severity and subclinical RV dysfunction.

**Methods:** This cross-sectional study included sixty OSA patients, divided into severe (apnea-hypopnea index [AHI]  $\geq 30$ ) and non-severe groups, and sixty age- and sex-matched controls. Cancer antigen 125 levels were assessed together with echocardiographic markers. Regression analysis identified predictors of severe OSA, and receiver operating characteristic (ROC) analysis assessed the diagnostic performance of CA125.

**Results:** Cancer antigen 125 levels were significantly elevated in severe OSA patients compared to non-severe and control groups (median 34.3 vs. 12.9 vs. 10.3 U/mL,  $P < .001$ ). Cancer antigen 125 correlated with RV fractional area change (RV-FAC) ( $r = -0.496$ ,  $P < .001$ ), tricuspid annular plane systolic excursion (TAPSE) ( $r = -0.285$ ,  $P = .027$ ), and AHI ( $r = 0.581$ ,  $P < .001$ ). Regression analysis identified CA125 (odds ratio [OR] = 1.259, 95% confidence interval [CI]: 1.102-1.438,  $P = .001$ ) and TAPSE (OR = 0.425, 95% CI: 0.217-0.834,  $P = .013$ ) as independent predictors of severe OSA. ROC analysis showed that CA125 could effectively predict RV dysfunction (area under the curve [AUC] = 0.857) and severe OSA (AUC = 0.804).

**Conclusion:** Elevated CA125 levels are associated with increased disease severity and subclinical RV dysfunction in OSA, suggesting its potential as a biomarker for early cardiac involvement.

**Keywords:** Biomarker, cancer antigen 125, cardiovascular risk, obstructive sleep apnea, right ventricular dysfunction

### INTRODUCTION

Obstructive sleep apnea (OSA) is a condition characterized by recurring episodes of upper airway obstruction during sleep, which can result in reduced oxygen levels and disturbances in sleep continuity.<sup>1</sup> The sporadic drops in oxygen levels associated with OSA have been correlated with increased sympathetic nervous system activation, changes in intrathoracic pressure, vascular inflammation, and elevated oxidative stress. These physiological changes may play a role in the development of myocardial injury and cardiovascular issues.<sup>2,3</sup>

OSA is increasingly recognized as an important factor in the development of various cardiovascular disorders, including heart failure (HF).<sup>4</sup> Research has thoughtfully explored the impact of OSA on both the structural and functional characteristics of the right ventricle (RV). The findings indicate that individuals with OSA may experience RV remodeling and dysfunction, even in the absence of overt HF symptoms.<sup>5,6</sup> Given that RV dysfunction is a well-documented indicator of adverse cardiovascular outcomes, early detection of subclinical RV involvement in OSA may offer an opportunity for improved risk stratification and management.<sup>4</sup>

### ORIGINAL INVESTIGATION

İlke Erbay<sup>1</sup> 

Rabia Hande Avcı<sup>2</sup> 

Naile Eriş Gündül<sup>1</sup> 

Murat Altuntaş<sup>3</sup> 

Ahmet Furkan Süner<sup>4</sup> 

Pelin Aladağ<sup>1</sup> 

Uğur Köktürk<sup>1</sup> 

Ahmet Avcı<sup>1</sup> 

<sup>1</sup>Department of Cardiology, Bülent Ecevit University Faculty of Medicine, Zonguldak, Türkiye

<sup>2</sup>Department of Pulmonology, Karabük University Training and Research Hospital, Karabük, Türkiye

<sup>3</sup>Department of Pulmonology, Uzunmehmet Chest and Occupational Health Diseases Hospital, Zonguldak, Türkiye

<sup>4</sup>Department of Public Health, Çaycuma District Health Directorate, Zonguldak, Türkiye

**Corresponding author:** İlke Erbay  
✉ ilkeerbay@gmail.com

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Cancer antigen 125 (CA125) is a biomarker predominantly linked to ovarian cancer due to its secretion from Müllerian epithelial cells. However, emerging research suggests that CA125 may also be elevated in patients experiencing various cardiovascular conditions, particularly those characterized by fluid overload and right HF.<sup>7,8</sup> This observation highlights the potential of CA125 as a valuable biomarker for right heart dysfunction, which may reflect underlying hemodynamic changes in these patients.<sup>9,10</sup> Given that CA125 levels rise in response to serosal and cardiac congestion, it is plausible that CA125 may serve as an indirect marker reflecting early right-sided cardiac involvement in patients with advanced OSA. However, the potential association between CA125 levels, early RV involvement, and the clinical severity of OSA remains to be fully elucidated.

The aim of this study was to investigate whether serum CA125 levels are associated with OSA severity and early RV dysfunction in patients without overt HF.

## METHODS

### Study Populations

The present retrospective cross-sectional study comprised sixty patients diagnostically confirmed with OSA, encompassing a range of disease severities (mild, moderate, and severe) and an age- and sex-matched control group of sixty subjects without OSA. All patients had previously measured CA125 levels, as it is part of the institutional protocol for cardiopulmonary evaluation in patients diagnosed with OSA, particularly to assess potential right heart involvement. Data were collected between January 2023 and September 2024 at Uzunmehmet Chest and Occupational Health Diseases Hospital and Bülent Ecevit University Hospital. Diagnosis of OSA was confirmed through polysomnography based on the "International consensus document on obstructive sleep apnea,"<sup>11</sup> and patients were categorized into different stages of OSA severity. Within 1 month of diagnosis, these patients underwent cardiac evaluation at the cardiology outpatient clinic, including echocardiographic assessments and laboratory tests. Participants were excluded if they had a left

ventricular ejection fraction (LVEF) lower than 50%, grade 3-4 diastolic dysfunction, or severe valvular heart disease. Those with clinical signs of right heart failure, such as jugular venous distension, hepatojugular reflux, or pretibial edema, were not included. Additional exclusion criteria included a history of acute coronary syndrome, previous percutaneous coronary intervention, or significant stenosis (>50%) in an epicardial coronary artery. Patients with pulmonary embolism, severe respiratory disease, renal or hepatic impairment, active malignancy, prior use of continuous positive airway pressure (CPAP) therapy, or missing echocardiographic or CA125 data within 1 month of polysomnography were also excluded.

The control group included age- and sex-matched individuals without OSA who underwent identical cardiac and laboratory assessments.

### Sample Collection

The medical history and various parameters of each participant were carefully recorded. Peripheral blood samples were kindly collected from participants in the morning following an overnight fast. B-type natriuretic peptide (BNP) levels were assessed using chemiluminescent immunoassay kits (Beckman Coulter Access 2, Fullerton, CA, USA). Simultaneously, the concentrations of CA125 were evaluated using the same chemiluminescent immunoassay technique, adhering to the established upper threshold of 35 U/mL for standardization.

### Echocardiographic Evaluation

A thorough transthoracic echocardiographic assessment was conducted for all participants, employing standardized imaging views and methodologies in accordance with established clinical guidelines.<sup>12</sup> This assessment was carried out by two experienced cardiologists who were unaware of the study protocol, ensuring an unbiased evaluation. The imaging utilized the Affiniti 50 system (Philips, Eindhoven, The Netherlands) with a 2.5-5 MHz transducer. Estimated using the modified Simpson method derived from apical 4-chamber views. Additionally, the systolic pulmonary artery pressure (sPAP) was estimated based on validated echocardiographic equations.<sup>13</sup> Tricuspid regurgitation was classified into three categories: none/mild, moderate, and severe, using color flow Doppler techniques. For participants without symptoms of HF, RV dysfunction was assessed based on echocardiographic parameters including tricuspid annular plane systolic excursion (TAPSE), tricuspid lateral s' velocity, and RV fractional area change (RV-FAC).<sup>14,15</sup> Right ventricular dysfunction was defined as the presence of at least 1 abnormal value: TAPSE < 17 mm, tricuspid lateral s' velocity < 10 cm/s, or RV-FAC < 35%.<sup>15</sup>

### Polysomnographic Assessment

An experienced specialist diagnosed OSA through overnight polysomnographic monitoring using the Alice 6 LDx Diagnostic Sleep System (Philips Respironics, Murrysville, PA, USA). The apnea-hypopnea index (AHI), which quantifies the frequency of apnea and hypopnea events per hour of sleep, was recorded and analyzed. Apnea was defined as a complete absence of airflow through the nose and mouth

## HIGHLIGHTS

- Obstructive sleep apnea (OSA) is associated with increased cardiovascular risk, particularly through right ventricular (RV) dysfunction.
- In this cross-sectional study, cancer antigen 125 (CA125), a biomarker traditionally used in ovarian cancer, was evaluated alongside echocardiographic markers of RV function in sixty OSA patients (severe and non-severe) and sixty controls.
- Cancer antigen 125 levels were significantly higher in severe OSA patients and correlated with disease severity (apnea-hypopnea index) and RV dysfunction.
- Regression and ROC analyses identified CA125 as an independent predictor of severe OSA and RV dysfunction, highlighting its potential as a biomarker for early detection of subclinical cardiac involvement.

lasting at least 10 seconds, while hypopnea was characterized by a minimum 50% reduction in airflow for at least 10 seconds, accompanied by a drop of 4% or more in oxygen saturation, as measured by pulse oximetry. The diagnosis of OSA was established when individuals exhibited more than 30 apnea or hypopnea episodes over 6 hours or had an AHI of  $\geq 5$  events per hour.<sup>16</sup> In this study, patients in the OSA group were divided into two groups: severe OSA (AHI  $\geq 30$ ) and non-severe OSA (AHI  $< 30$ ), in line with standard classifications used in the literature.<sup>17,18</sup>

### Statistical Analysis

All statistical analyses were conducted using SPSS software (version 26.0, IBM Corp., Armonk, NY, USA). Continuous variables were assessed for normality using the Kolmogorov-Smirnov test. Normally distributed data were expressed as mean  $\pm$  SD and compared using the independent samples t-test. Non-normally distributed variables were presented as median and interquartile range (IQR) and analyzed using the Mann-Whitney U test. Categorical variables were expressed as counts and percentages and compared using the chi-square or Fisher's exact test, where appropriate. Correlations between CA125 levels and echocardiographic parameters were evaluated using Spearman's or Pearson's correlation coefficients, based on data distribution. Multiple logistic regression analysis was performed using forward selection to identify independent predictors of severe OSA (AHI  $\geq 30$ ) within the model. Receiver operating characteristic (ROC) curve analysis was performed to assess the diagnostic performance of CA125 levels in identifying echocardiographic RV dysfunction and severe OSA. Figures 2-4 were generated using GraphPad Prism 10 software. For all analyses, a *P*-value  $< .05$  was considered statistically significant.

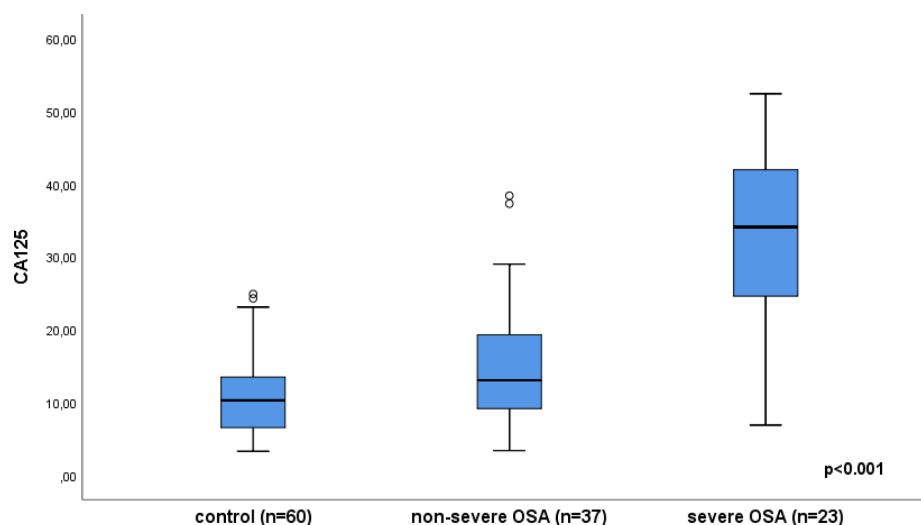
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## RESULTS

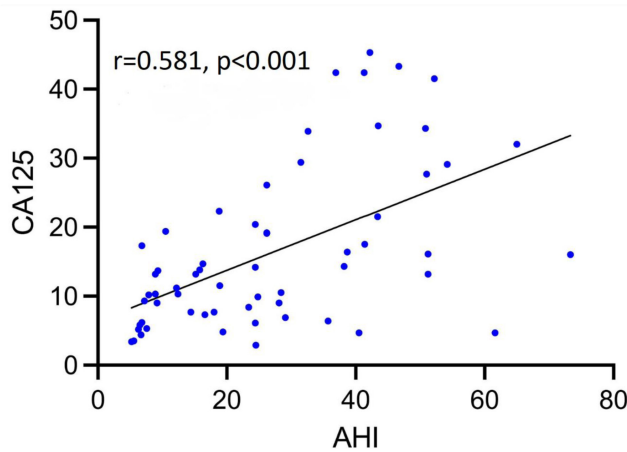
Table 1 provides an overview of the demographic, echocardiographic, and laboratory characteristics of the participants. The percentage of male participants was 51.7% in the OSA group and 45.0% in the control group, with no statistically significant difference observed between the two groups ( $P = .465$ ). The average age of individuals in the OSA and control groups was  $44.9 \pm 11.5$  years and  $46.7 \pm 11.4$  years, respectively, showing no meaningful statistical variation ( $P = .399$ ). In contrast, body mass index (BMI) and smoking prevalence were significantly elevated among OSA patients compared to controls ( $P < .001$  for both). Cancer antigen 125 levels were also notably higher in individuals with OSA (median: 18.3 U/mL; interquartile range (IQR): 10.4-33.4) than in control subjects (median: 10.3 U/mL; IQR: 6.5-13.6,  $P < .001$ ). Moreover, patients diagnosed with severe OSA exhibited significantly elevated CA125 levels in comparison to both non-severe OSA patients and control subjects ( $P < .001$  for all, Figure 1).

No patients in the OSA group exhibited clinical symptoms indicative of RV failure; however, TAPSE, tricuspid lateral s', and RV-FAC measurements were significantly reduced in individuals with severe OSA compared to those with non-severe OSA ( $P < .001$ ,  $P = .010$ , and  $P < .001$ , respectively; Table 2). The prevalence of RV dysfunction was notably higher among severe OSA patients (43.5% vs. 8.1%,  $P = .001$ ). Concentrations of CA125 and BNP were significantly elevated in the severe OSA group compared to the non-severe group. The median CA125 level was found to be 34.3 U/mL in the severe OSA group, whereas it was 10.3 U/mL in the non-severe group ( $P < .001$ ). Similarly, BNP levels were found to be higher in the severe OSA group ( $86.1 \pm 41.0$  pg/mL vs.  $57.6 \pm 25.1$  pg/mL,  $P = .005$ ).

In OSA patients, the results of the correlation analysis between other variables and CA125 are shown in Table 3. Serum CA125 was significantly associated with sPAP ( $r = 0.362$ ,  $P = .004$ ), TAPSE ( $r = -0.285$ ,  $P = .027$ ), tricuspid



**Figure 1.** Comparison of cancer antigen 125 levels between control, non-severe obstructive sleep apnea (OSA), and severe OSA groups.

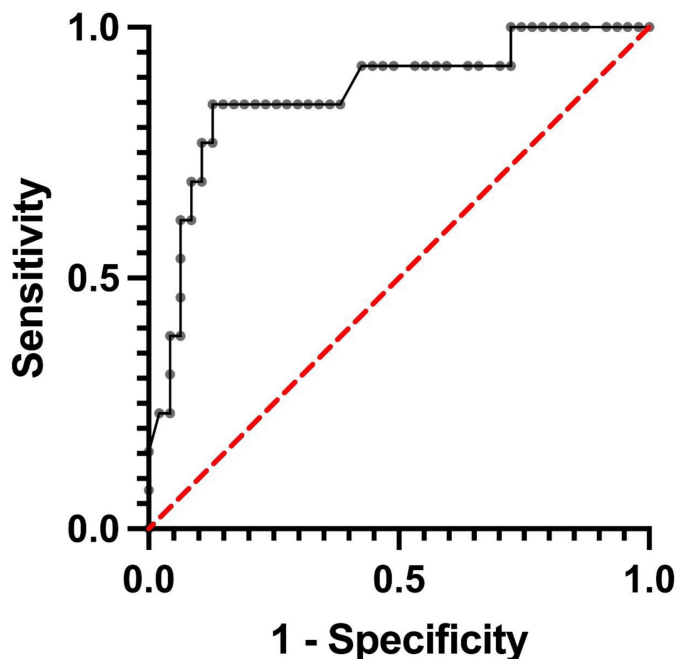


**Figure 2. Correlation between apnea-hypopnea index and cancer antigen 125 ( $r = 0.581$ ,  $P < .001$ ).**

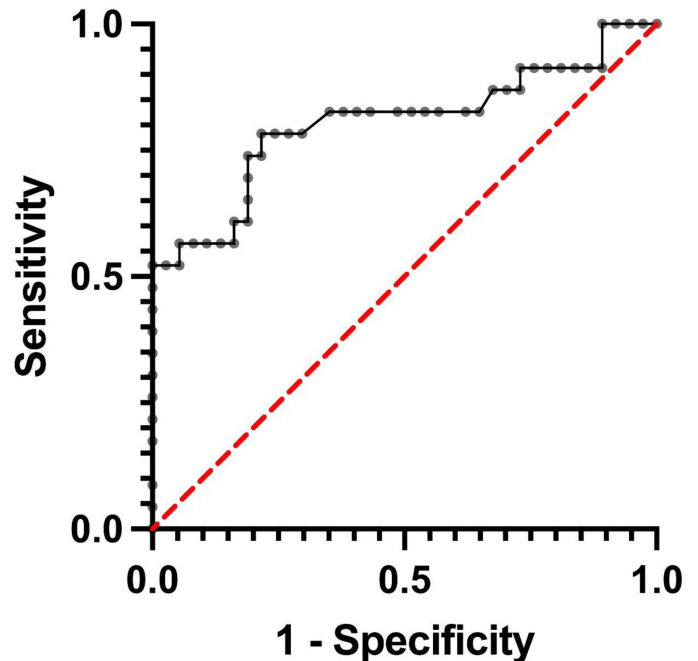
lateral  $s'$  ( $r = -0.329$ ,  $P = .010$ ), RV-FAC ( $r = -0.496$ ,  $P < .001$ ), AHI ( $r = -0.581$ ,  $P < .001$ ) and lowest and mean oxygen saturation ( $r = -0.470$ ;  $r = -0.452$ ,  $P < .001$  for both). Figure 2 shows that the natural logarithm of CA125 increased progressively with higher AHI values.

#### Predictors of Severe Obstructive Sleep Apnea

Regression analysis for predictors of severe OSA (Table 4) identified that in univariate analysis, age, BMI, diabetes mellitus, LVEF, LA diameter, RA diameter, sPAP, TAPSE, tricuspid lateral  $s'$ , RV-FAC, CA125, and BNP were significantly associated with severe OSA. In multiple logistic regression analysis, only TAPSE (odds ratio [OR] = 0.425, 95% confidence interval



**Figure 3. Receiver operating characteristic curve for the identification of echocardiographic right ventricular dysfunction with cancer antigen 125 levels in patients with obstructive sleep apnea (AUC = 0.857,  $P < .011$ ).**



**Figure 4. Receiver operating characteristic curve for identification of severe obstructive sleep apnea with cancer antigen 125 levels (area under the curve = 0.804,  $P < .001$ ).**

[CI]: 0.217-0.834,  $P = .013$ ) and CA125 (OR = 1.259, 95% CI: 1.102-1.438,  $P = .001$ ) remained significant predictors of severe OSA.

#### Predictive role of Cancer Antigen 125

The optimal cut-off value for CA125 to detect echocardiographic RV dysfunction was 19.4 U/mL, with a sensitivity of 78.6% and specificity of 89.6% (AUC = 0.857,  $P < .001$ ; Figure 3). The optimal cut-off for predicting severe OSA was 14.3 U/mL, with a sensitivity of 78.3% and specificity of 78.4% (AUC = 0.804,  $P < .001$ ; Figure 4).

#### DISCUSSION

This study is among the first to investigate the relationship between CA125 levels, disease severity, and RV function in patients with OSA who do not exhibit overt HF. The findings demonstrated that CA125 levels increased in parallel with OSA severity and were significantly higher in patients with severe OSA. Furthermore, CA125 levels showed a moderate positive correlation with AHI, suggesting a link between CA125 and the extent of respiratory disturbance during sleep. Echocardiographic assessment revealed that RV functional parameters were significantly lower in the severe OSA group, consistent with a greater burden of subclinical RV dysfunction. These findings suggest that elevated CA125 levels may reflect early RV involvement in advanced OSA.

In OSA, recurrent episodes of both apnea and hypopnea during sleep result in upper airway obstruction, leading to periods of hypoxia, hypercapnia, and intrathoracic pressure fluctuations.<sup>19</sup> These effects, combined with frequent arousals, activate the sympathetic nervous system, disrupt autonomic function, and stimulate the renin-angiotensin-aldosterone system, leading to myocardial remodeling and

**Table 1. Baseline Demographic, Echocardiographic and Laboratory Characteristics of the OSA and Control Group**

Variables	OSA (n=60)	Control (n=60)	P
Age, years	44.9 ± 11.5	46.7 ± 11.4	.399
Male, n(%)	31 (51.7)	27 (45.0)	.465
BMI (kg/m <sup>2</sup> )	32.9 (26.0-36.3)	27.0 (24.3-30.2)	<.001
Smoking, n (%) <sup>a</sup>	36 (60.0)	10 (16.7)	<.001
Hypertension, n (%)	25 (41.7)	14 (23.3)	.032
Diabetes mellitus, n (%)	17 (28.3)	12 (20.0)	.286
COPD, n (%)	18 (30.0)	4 (6.7)	.001
AF, n (%)	5 (8.3)	3 (5.0)	.464
<b>Echocardiographic Parameters</b>			
LVEF (%)	61.6 ± 3.3	62.7 ± 2.5	.041
LV Edd (mm)	46.6 ± 3.8	45.6 ± 2.6	.105
LV Esd (mm)	31.0 ± 5.9	28.7 ± 4.2	.014
IVS (mm)	11.0 (10.0-12.0)	10.0 (9.0-10.4)	<.001
Posterior wall (mm)	10.0 (9.5-11.0)	9.0 (9.0-10.4)	.001
LA diameter (mm)	36.2 ± 4.2	34.0 ± 3.6	.003
RA diameter (mm)	32.6 ± 4.6	30.8 ± 3.8	.022
Pulmonary artery diameter (mm)	21.3 ± 2.9	19.6 ± 1.9	<.001
sPAP (mm Hg)	29.1 ± 5.0	25.6 ± 4.3	<.001
TAPSE (mm)	22.1 ± 3.7	23.3 ± 2.3	.033
Tricuspid lateral s' (cm/s)	14.5 ± 2.0	15.5 ± 2.2	.011
RV-FAC (%)	44.7 ± 6.0	47.0 ± 4.4	.021
<b>Laboratory Parameters</b>			
CA125 (U/mL)	18.3 (10.4-33.4)	10.3 (6.5-13.6)	<.001
BNP (pg/mL)	68.5 ± 34.7	57.0 ± 22.8	.033
eGFR (mL/min/1.73 m <sup>2</sup> )	91.3 ± 18.9	94.4 ± 15.8	.329
Hb (g/dL)	13.8 ± 1.5	12.9 ± 1.5	.002

Median values are given with interquartile ranges (the 25<sup>th</sup> and 75<sup>th</sup> percentiles).

AF, atrial fibrillation; BMI, body mass index; BNP, B-type natriuretic peptide; CA125, cancer antigen 125; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; Hb, Hemoglobin; IVS, interventricular septum; LA, left atrium; LVEF, left ventricular ejection fraction; LV Edd, left ventricular end-diastolic diameter; LV Esd, left ventricular end-systolic diameter; OSA, obstructive sleep apnea; RA, right atrium; RV-FAC, right ventricular fractional area change; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; Tricuspid lateral s', tricuspid lateral annular peak systolic velocity.

<sup>a</sup>Smoking defined as current smoker or ex-smoker.

fluid retention.<sup>20</sup> Chronic intermittent hypoxia also promotes pulmonary smooth muscle hypertrophy and vasoconstriction, increasing vascular resistance and gradually progressing to pulmonary arterial hypertension, RV hypertrophy, and potentially right HF.<sup>6,21,22</sup> In this study, echocardiographic indicators of RV function were significantly impaired in OSA patients compared to controls, even in the absence of overt HF symptoms.

Given the cardiovascular risks associated with OSA, reliable biomarkers are needed to assess cardiac involvement. CA125 was initially identified as a marker for ovarian cancer,

**Table 2. Baseline Demographic, Echocardiographic and Laboratory Characteristics of Severe and Non-Severe Obstructive Sleep Apnea Groups**

Variables	Severe OSA (AHI ≥ 30) (n=23)	Non-severe OSA (AHI < 30) (n=37)	P
Age, years	51.0 ± 12.5	41.1 ± 9.1	.002
Male, n(%)	11(47.8)	20 (54.0)	.639
BMI (kg/m <sup>2</sup> )	35.3 (30.5-37.3)	32.8 (24.8-35.5)	.046
Smoking, n(%) <sup>a</sup>	17 (73.9)	19 (51.3)	.083
Hypertension, n(%)	13 (56.5)	12 (32.4)	.066
Diabetes mellitus, n(%)	10 (43.5)	7 (18.9)	.040
COPD, n(%)	9 (39.1)	9 (24.3)	.224
AF, n(%)	3 (13.0)	2 (5.4)	.362
<b>Echocardiographic Parameters</b>			
LVEF (%)	60.0 (58.0-63.0)	64.0 (60.0-65.0)	.032
LV Edd (mm)	48.9 ± 3.8	45.1 ± 3.1	<.001
LV Esd (mm)	31.9 ± 7.8	30.5 ± 4.4	.431
IVS (mm)	11.3 ± 1.0	10.4 ± 1.3	.004
Posterior wall (mm)	11.0 (10.0-12.0)	10.0 (9.0-11.0)	.011
LA diameter (mm)	38.7 ± 4.4	34.6 ± 3.3	<.001
RA diameter (mm)	34.8 ± 4.9	31.2 ± 3.9	.005
Pulmonary artery diameter (mm)	23.2 ± 2.5	20.1 ± 2.5	<.001
sPAP (mm Hg)	33.0 (28.0-35.0)	26.0 (25.0-30.0)	<.001
TAPSE (mm)	19.9 ± 3.5	23.4 ± 3.1	<.001
Tricuspid lateral s' (cm/s)	13.6 ± 2.4	15.1 ± 1.6	.010
RV-FAC (%)	40.4 ± 5.1	47.3 ± 5.1	<.001
Presence of RV dysfunction, n(%)	10 (43.5)	3 (8.1)	.001
<b>Laboratory Parameters</b>			
CA125 (U/mL)	34.3 (27.7-42.4)	12.9 (8.4-19.3)	<.001
BNP (pg/mL)	86.1 ± 41.0	57.6 ± 25.1	.005
eGFR (mL/min/1.73 m <sup>2</sup> )	88.7 ± 18.8	92.8 ± 19.0	.416
Hb (g/dL)	14.4 ± 1.6	13.4 ± 1.3	.019
<b>Polysomnographic Parameters</b>			
AHI (events per hour)	43.4 (38.2-51.2)	15.2 (7.7-24.4)	<.001
Sleep duration (min)	399.0 (360.0-405.0)	400.3 (383.7-411.2)	.434
Lowest O <sub>2</sub> saturation (%)	71.4 ± 10.1	82.5 ± 3.7	<.001
Mean O <sub>2</sub> saturation (%)	89.0 (87.0-90.0)	92.0 (90.0-94.0)	<.001

Median values are given with interquartile ranges (the 25<sup>th</sup> and 75<sup>th</sup> percentiles).

AHI, apnea-hypopnea index; AF, atrial fibrillation; BMI, body mass index; BNP, B-type natriuretic peptide; CA125, cancer antigen 125; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; Hb, Hemoglobin; IVS, interventricular septum; LA, left atrium; LVEF, left ventricular ejection fraction; LV Edd, left ventricular end-diastolic diameter; LV Esd, left ventricular end-systolic diameter; OSA, obstructive sleep apnea; RA, right atrium; RV-FAC, right ventricular fractional area change; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; Tricuspid lateral s', tricuspid lateral annular peak systolic velocity.

<sup>a</sup>Smoking defined as current smoker or ex-smoker.



**Table 3. Correlation Analysis Between CA125 and Other Clinical, Echocardiographic and Laboratory Parameters in Obstructive Sleep Apnea Patients**

	Spearman Correlation (r)	P
Age, years	0.381	.003
BMI (kg/m <sup>2</sup> )	0.223	.087
LVEF (%)	-0.238	.067
LA diameter (mm)	0.415	.001
RA diameter (mm)	0.330	.010
Pulmonary artery diameter (mm)	0.317	.014
sPAP (mmHg)	0.362	.004
TAPSE (mm)	-0.285	.027
Tricuspid lateral s' (cm/s)	-0.329	.010
RV-FAC (%)	-0.496	<.001
BNP (pg/mL)	0.248	.056
AHI	0.581	<.001
Lowest O <sub>2</sub> saturation (%)	-0.470	<.001
Mean O <sub>2</sub> saturation (%)	-0.452	<.001

AHI, apnea-hypopnea index; BMI, body mass index; BNP, B-type natriuretic peptide; CA125, cancer antigen 125; LA, left atrium; LVEF, left ventricular ejection fraction; OSA, obstructive sleep apnea; RA, right atrium; RV-FAC, right ventricular fractional area change; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; Tricuspid lateral s', tricuspid lateral annular peak systolic velocity.

and recent studies have shown that it is also significantly elevated in chronic congestive HF.<sup>23-25</sup> Previous studies have shown that CA125 is a reliable marker of RV function, independent of RV chamber size.<sup>9,26</sup> In this study, the significantly higher prevalence of subclinical RV dysfunction in the severe OSA group may explain the elevated CA125 levels observed in this group.

Echocardiography remains an important non-invasive tool for the assessment of RV dysfunction. However, in OSA patients, RV assessment can be challenging due to factors such as high BMI, often requiring specialized expertise. These limitations have prompted interest in circulating biomarkers as adjunctive tools for assessing RV involvement. Natriuretic peptides have been widely studied in this context, and several reports have linked elevated BNP levels with OSA severity and right heart strain.<sup>27,28</sup> However, BNP can be influenced by several factors, including age, renal function and left-sided cardiac pathology, which may limit its specificity in detecting isolated RV dysfunction.<sup>29</sup> In this study, although BNP levels were elevated in patients with severe OSA, CA125 remained an independent predictor of severe OSA in regression analysis. This relationship appears to be mediated by the presence of subclinical RV dysfunction, which was more common in the severe OSA group. In support of this, CA125 levels showed significant correlations with key echocardiographic indicators of RV function, including TAPSE, RV-FAC and tricuspid lateral s' velocity. These findings suggest that CA125 elevation in advanced OSA may not simply reflect disease burden, but may specifically reflect early right-sided cardiac involvement.

**Table 4. Regression Analysis for Predictors of Severe OSA (AHI ≥ 30)**

	OR (95% CI)	P
<b>Univariate Analysis</b>		
Male (ref. female)	0.779 (0.275-2.211)	.639
Age, years	1.094 (1.031-1.161)	.003
BMI (kg/m <sup>2</sup> )	1.089 (1.003-1.182)	.043
Smoking (ref. no)	2.684 (0.865-8.327)	.087
Hypertension (ref. no)	2.708 (0.925-7.927)	.069
Diabetes mellitus (ref. no)	3.297 (1.029-10.566)	.045
LVEF (%)	0.843 (0.714-0.995)	.043
LA diameter (mm)	1.314 (1.117-1.545)	.001
RA diameter (mm)	1.205 (1.055-1.377)	.006
sPAP (mm Hg)	1.273 (1.111-1.459)	.001
TAPSE (mm)	0.702 (0.574-0.859)	.001
Tricuspid lateral s' (cm/s)	0.659 (0.485-0.896)	.008
RV-FAC (%)	0.708 (0.585-0.856)	<.001
CA125 (U/mL)	1.175 (1.090-1.264)	<.001
BNP (pg/mL)	1.030 (1.009-1.052)	.006
<b>Multiple Logistic Regression Analysis*</b>		
TAPSE (mm)	0.425 (0.217-0.834)	.013
CA125 (U/mL)	1.259 (1.102-1.438)	.001

Nagelkerke R<sup>2</sup>:0.787, variable selection in the model was performed using the forward method.

AHI, apnea-hypopnea index; BMI, body mass index; BNP, B-type natriuretic peptide; CA125, cancer antigen 125; CI, confidence interval; LA, left atrium; LVEF, left ventricular ejection fraction; OR, odds ratio; OSA, obstructive sleep apnea; RA, right atrium; RV-FAC, right ventricular fractional area change; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; Tricuspid lateral s', tricuspid lateral annular peak systolic velocity.

\*The model included age, BMI, diabetes mellitus, LVEF, LA diameter, RA diameter, sPAP, TAPSE, tricuspid lateral s', RV-FAC, CA125 and BNP.

The elevation of CA125 levels in patients with severe OSA may be explained by several interrelated mechanisms. Intermittent hypoxia may induce systemic inflammation and oxidative stress, both of which are known to activate mesothelial cells and increase CA125 production.<sup>30-32</sup> In addition, repetitive changes in intrathoracic pressure and airway obstruction can increase venous return and lead to right-sided volume overload, resulting in serosal irritation and congestion. These physiological changes can lead to CA125 elevation even in the absence of clinically evident HF.<sup>9</sup> Elevated levels of inflammatory cytokines such as IL-6 and TNF- $\alpha$  have also been associated with CA125 secretion.<sup>33</sup> In addition, increased sympathetic activity and stimulation of the renin-angiotensin-aldosterone system may contribute to fluid retention and cardiac remodeling, thereby exacerbating the ongoing process of congestion and mesothelial stimulation.<sup>34,35</sup> These mechanisms are consistent with previous reports, including the study by Ge et al,<sup>31</sup> which demonstrated a positive association between CA125 levels and OSA severity in patients with HF. The study expands on these findings by showing a similar relationship in patients without overt HF and by supporting this association with echocardiographic evidence of subclinical RV dysfunction.

This study has several limitations. First, the sample size was relatively small, which may limit the generalizability of the findings. The cross-sectional design also limits the ability to establish causal relationships between CA125 levels and RV dysfunction in OSA patients. Longitudinal studies would be useful for evaluating the predictive value of CA125 over time. Although the OSA group was recruited from a single center, this limitation is compensated by the fact that Uzunmehmet Chest and Occupational Health Diseases Hospital is the only provider of polysomnography testing in the region and receives patient referrals from multiple centers.

Patients with significant LV dysfunction and advanced diastolic dysfunction were also excluded to focus on a population with preserved LV function. While this allows a clearer assessment of the role of CA125 in reflecting isolated RV dysfunction, it may limit the applicability of the findings to patients with concomitant LV impairment. Finally, CA125 is known to be elevated in several clinical conditions, such as malignancy and inflammation,<sup>36</sup> which may confound its specificity as a biomarker of RV dysfunction in OSA. Future studies could help to refine the specificity and clinical utility of CA125 in this context.

## CONCLUSION

This study identified echocardiographically defined RV dysfunction as a target before the onset of clinically apparent HF. The strong association between CA125 levels, advanced OSA and parameters of RV dysfunction suggests that CA125 may serve as a useful biomarker for the early detection of RV dysfunction in this population, even before the onset of clinical symptoms.

**Ethics Committee Approval:** The study was approved by the Ethics Committee of Bülent Ecevit University (No. 2024/05, date: March 6, 2024). In addition, permission to use data from Uzunmehmet Chest and Occupational Health Diseases Hospital was granted by Zonguldak Provincial Health Directorate (Document No. 62843600-663-07). The study was conducted in accordance with the principles of the Declaration of Helsinki.

**Informed Consent:** Verbal and Written informed consent was obtained from the patients who agreed to take part in the study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – I.E., R.H.A.; Design – I.E., R.H.A.; Supervision – U.K., A.A.; Resource – I.E., N.E.G., M.A.; Materials – I.E., N.E.G., M.A.; Data Collection and/or Processing – I.E., N.E.G., M.A.; Analysis and/or Interpretation – I.E., A.F.S., N.E.G., P.A., A.A.; Literature Search – I.E., P.A., A.A.; Writing – I.E., U.K., A.A.; Critical Reviews – U.K., A.A.

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