Original Article

Serum levels of carbohydrate antigen 125 in patients with heart failure and obstructive sleep apnea syndrome: a retrospective analysis

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Background: Obstructive sleep apnea syndrome (OSAS) combined with heart failure (HF) has become a serious disease that threatens human health. Therapeutic interventions targeting OSAS have been shown to improve outcomes in patients with HF, so the identification of severe OSAS in HF is critical. Carbohydrate antigen 125 (CA125) is associated with inflammation and volume overload. The levels of CA125 are elevated in the serum of patients with HF and might be further elevated in patients with HF and OSAS. The aim of this study was to measure CA125 levels in patients with HF with and without OSAS and to analyze affecting factors.

Methods: In this single-center retrospective cohort study, a total of 95 patients diagnosed with HF hospitalized in Zhongda Hospital from April 2021 to April 2022 were recruited, including 55 patients with OSAS and 40 patients without OSAS. Participants with a history of central sleep apnea syndrome, severe chronic obstructive pulmonary disease, tumors, severe infection, or who were pregnant were excluded. The histories of the participants were recorded, and laboratory examinations were performed. Binary logistic regression analysis was performed to determine the relationship between serum CA125 levels and OSAS in patients with HF.

Results: The serum CA125 levels were higher in the HF + OSAS group than in the HF group (29.60 *vs.* 9.68 U/mL, P<0.001). According to the univariate analysis, CA125 (>35 U/mL) was significantly related to pleural effusion, acute HF, apnea-hypopnea index (AHI), left ventricular ejection fraction (LVEF) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. Finally, the AHI demonstrated statistical significance in multiple analyses (OR 1.070, 95% CI: 1.019–1.124, P=0.006). Spearman rank correlation coefficient analysis showed that CA125 was positively correlated with AHI, and Ln(CA125) (Ln is the natural logarithm based on e) gradually increased with increasing AHI (r=0.551, P<0.0001).

Conclusions: The levels of CA125 were further increased in patients with HF and OSAS, and CA125 (>35 U/mL) was positively correlated with AHI. As a biomarker associated with inflammation and congestion, serum CA125 may have certain value in the diagnosis of patients with HF combined with OSAS.

Keywords: Carbohydrate antigen 125 (CA125); obstructive sleep apnea syndrome (OSAS); heart failure (HF); correlative factor

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Introduction

Heart failure (HF) is a major global health problem that is estimated to affect at least 64.3 million people worldwide, and the clinically diagnosed prevalence of known HF in the general adult population is 1–2% (1). Obstructive sleep apnea syndrome (OSAS) has been reported in over 50% of patients with HF (2). OSAS combined with HF has become a serious disease threatening human health, which has aroused widespread concern in society. Therapeutic interventions targeting OSAS have been shown to improve outcomes in patients with HF, so the identification of severe OSAS in HF is critical for management and outcomes (3). Previous studies have mainly explored the pathophysiological mechanism of OSAS and HF, while there have been few studies on serological predictors.

Carbohydrate antigen 125 (CA125), a high molecular weight transmembrane glycoprotein, is most commonly associated with ovarian cancer (4). A large body of evidence shows that serum CA125 has been involved in the pathophysiological processes of HF (1,5). The exact mechanism of elevated serum CA125 concentrations in patients with HF has not yet been fully elucidated. Increasing data suggest that inflammation has arisen as a possible culprit, as associations between CA125 and proinflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and interleukin-10 (IL-10), have been established (6). Notably, inflammation and volume overload in HF mutually interact, enhancing each other's activity in a two-way fashion, thus forming a positive feedback loop that results in elevated serum CA125 levels (7,8).

Elevated CA125 levels are associated with inflammation and volume overload (6), and OSAS is a chronic, low-grade inflammatory disease (9) that aggravates HF through hypoxia, inflammation and neurohumoral mechanisms (10,11). Thus, OSAS may further increase serum CA125 levels in patients with HF. Unfortunately, no clinical studies have investigated the association between serum CA125 levels and OSAS in patients with HF.

In this study, we detected the levels of CA125 in HF patients with and without OSAS and discussed the relevant clinical factors of CA125 (>35 U/mL) to determine the predictive indicators of HF combined with OSAS and further achieve early intervention and precise treatment for HF. We present this article in accordance with the STROBE reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-23-323/rc).

Highlight box

Key findings

- The levels of carbohydrate antigen 125 (CA125) were further increased in patients with heart failure (HF) and obstructive sleep apnea syndrome (OSAS), and CA125 (>35 U/mL) was positively correlated with apnea-hypopnea index.

What is known and what is new?

- The identification of severe OSAS in HF is critical to improve outcomes. Previous studies mainly focused on the pathophysiological mechanism of the two, while there are few studies on serological predictors.
- This study is the first study to investigate the correlation between serum CA125 levels and OSAS in patients with HF.

What is the implication, and what should change now?

- As a biomarker associated with inflammation and congestion, serum CA125 may have certain value in the diagnosis of patients with HF combined with OSAS.
- Our findings need to be confirmed in larger prospective studies.

Methods

Study population

Information for HF patients with and without OSAS was retrospectively recorded from the patient's electronic documentation system in our center from April 2021 to April 2022. Finally, a total of 55 patients with OSAS were retrospectively enrolled in the HF and OSAS group (HF + OSAS group). Another 40 patients without OSAS were enrolled in the HF group (HF group). HF was diagnosed based on the "2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure" (12). OSAS was diagnosed based on the "International consensus document on obstructive sleep apnea" (13). The exclusion criteria in our study were as follows: (I) central sleep apnea syndrome; (II) pregnancy; (III) severe chronic obstructive pulmonary disease; (IV) tumors; and (V) severe infection. A flow chart displaying the enrolment process is shown in *Figure 1*. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics committee for Clinical Research of Zhongda Hospital, Affiliated to Southeast University (No. 2020ZDSYLL278-P01) and informed consent was obtained from all the patients.

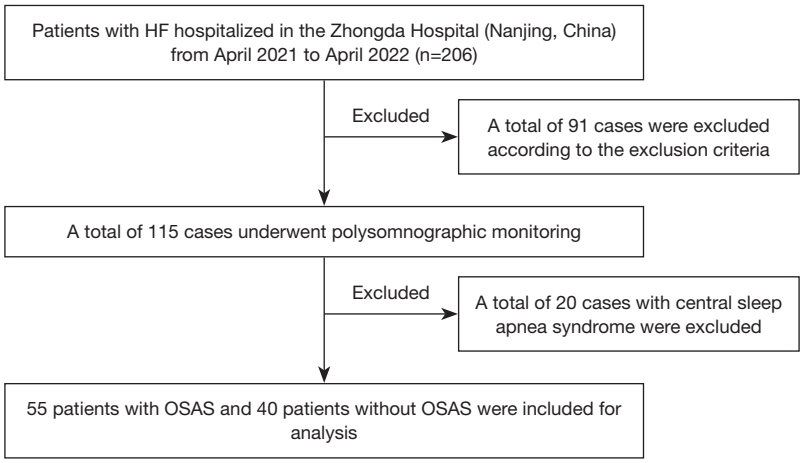

Figure 1 Flow diagram of patient enrollment and exclusion. HF, heart failure; OSAS, obstructive sleep apnea syndrome.

Study process

Medical history and vital signs of all participants were recorded. All blood samples were taken from peripheral veins fasting for at least 8 h in the morning. N-terminal pro-B-type natriuretic peptide (NT-proBNP) was measured together within the first 24–48 h after admission by the dry immunofluorescence method using a fluorescence quantitative analyzer (Model: AQT90; Test kit: Radiometer Medical Equipment Co., Ltd., Shanghai, China) according to standard operation procedures. All patients underwent comprehensive transthoracic echocardiography according to published guidelines using standard views and techniques (14). The left ventricular ejection fraction (LVEF) was measured by an experienced sonographer with an ultrasound diagnostic device (U.S. GE Vivid7 full-digital color Doppler ultrasound diagnostic apparatus).

CA125 measurement

Venous blood samples were collected from 6:00 AM to 8:00 AM after overnight fasting for CA125 measurement. CA125 was measured using a chemiluminescent microparticle immunoassay (Model: MAGLUMI2000Plus; Test kit: Shenzhen Xinye Biomedical Engineering Co., Ltd., Shenzhen, China), and the upper limit of normal for CA125 was 35 U/mL. CA125 is one of the optional tests in our center. For those with recent CA125 results from outpatient visits or prior hospitalization, we may not repeat the test during admission.

Polysomnographic (PSG) analysis

All participants were monitored with PSG monitoring by an experienced expert with the polysomnographic monitoring device (Version: SF-A9; Manufacturer: Hunan Wanmai Medical Technology Co., Ltd., Shaoyang, China), and the apnea-hypopnea index (AHI) was reviewed and recorded separately by two experienced experts. AHI refers to the average number of apnea and hypopnea events per hour during a night's sleep. Apnea is defined as the cessation of oronasal airflow for ≥10 s, and hypopnea refers to a reduction of ≥50% in oronasal airflow for ≥10 s, accompanied by a decrease in blood oxygen saturation of at least 4% measured by pulse oximetry. OSAS refers to more than 30 episodes of repeated apnea and hypopnea during 7 hours of nocturnal sleep or AHI ≥5 times/h.

Statistical analysis

Continuous variables that satisfy a normal distribution are expressed as the mean and standard deviation, and continuous variables that do not satisfy a normal distribution are expressed as the median and quartile. Categorical data are presented as numbers and percentages. Comparisons between two groups were performed using an independent sample *t*-test, the Kruskal-Wallis *H*-test, the Mann-Whitney *U* test or the chi-square test, as appropriate. We used univariate and multivariate logistic regression analyses to define the clinical characteristics of HF with OSAS and risk factors for CA125 (>35 U/mL).

Table 1 Baseline characteristics of HF patients with or without OSAS

Variables	Total (n=95)	HF group (n=40)	HF + OSAS group (n=55)	P value
Female, sex	79/95 (83.2)	35/40 (87.5)	44/55 (80.0)	0.335
Age, years	72.0±11.4	68.6±11.4	74.4±10.9	0.013*
Hypertension	70/95 (73.7)	27/40 (67.5)	43/55 (78.2)	0.243
Diabetes	39/95 (41.1)	15/40 (37.5)	24/55 (43.6)	0.548
Atrial fibrillation	39/95 (41.1)	12/40 (30.0)	27/55 (49.1)	0.062
Renal dysfunction	18/95 (18.9)	6/40 (15.0)	12/55 (21.8)	0.402
Pleural effusion	27/95 (28.4)	6/40 (15.0)	21/55 (38.2)	0.013*
Acute heart failure	38/95 (40.0)	15/40 (37.5)	23/55 (41.8)	0.671
LVEF, %	59.6±12.1	62.2±10.9	57.7±12.6	0.073
CA125, U/mL	18.10 [9.27, 38.20]	9.68 [7.32, 13.30]	29.60 [19.00, 48.10]	<0.001**
NT-proBNP, pg/mL	1,590 [515, 3,700]	494 [83, 2,000]	2,380 [1,320, 4,750]	<0.001**

Data are expressed as mean ± standard deviation, n/N (%) or median [quartile]. *, P value less than 0.05; **, P value less than 0.001. HF, heart failure; OSAS, obstructive sleep apnea syndrome; LVEF, left ventricular ejection fraction; CA125, carbohydrate antigen 125; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

The correlation variables that were statistically significant in univariate analyses were identified as independent factors in multivariate analyses. Spearman correlation analyses were used to evaluate the relationship between Ln(CA125) (Ln is the natural logarithm based on e) and the AHI. A two-sided P value <0.05 was considered statistically significant for all analyses. All analyses were performed using SPSS software version 24 (IBM Corporation, Armonk, NY, USA).

Results

Increased CA125 levels in HF patients with OSAS

A total of 95 patients with HF were recruited, including 55 patients with OSAS in the HF + OSAS group (n=55, 74.4±10.9 years) and 40 patients without OSAS in the HF group (n=40, 68.6±11.4 years). The other clinical characteristics of all participants are shown in *Table 1*. There were no significant differences in the proportions of female sex, hypertension, diabetes, atrial fibrillation, renal dysfunction, or acute HF between the two groups. The LVEF was similar in the two groups (P=0.073). Patients with OSAS were older than patients without OSAS (74.4±10.9 *vs.* 68.6±11.4, P=0.013) and had a higher proportion of pleural effusion (38.2% *vs.* 15.0%, P=0.013). Moreover, the levels of CA125 and NT-proBNP in the HF + OSAS group were higher than those in the HF group (29.60 *vs.* 9.68 U/mL, P<0.001; 2,380 *vs.* 494 pg/mL, P<0.001, respectively). Clinical characteristics associated with OSAS in patients with HF are displayed in *Table 2*. In the univariate analysis, age, atrial fibrillation, pleural effusion, LVEF, NT-proBNP and CA125 levels were included in the equation (P<0.1). Finally, CA125 levels (OR 1.110, 95% CI: 1.043–1.181, P=0.001) demonstrated statistical significance in multiple analyses (*Table 2*).

Correlations between CA125 (>35 U/mL) and study variables in all subjects

The correlation analysis results of other variables and CA125 (>35 U/mL) are displayed in *Table 3*. There was no significant correlation between CA125 (>35 U/mL) and female sex (P=0.09), age (P=0.132), hypertension (P=0.406), diabetes (P=0.901), atrial fibrillation (P=0.412) or renal dysfunction (P=0.876). Serum CA125 (>35 U/mL) was significantly related to pleural effusion (P<0.001), acute HF (P<0.001), AHI (P<0.001), LVEF (P=0.009) and NT-proBNP levels (P<0.001). In the univariate analysis, pleural effusion, acute HF, AHI, LVEF and NT-proBNP levels were included in the equation (P<0.05). Finally, the AHI demonstrated statistical significance in multiple analyses (OR 1.070, 95% CI: 1.019–1.124, P=0.006) (*Table 3*). Spearman rank correlation coefficient analysis showed that CA125 was positively correlated with the AHI. As shown

Table 2 Clinical characteristics associated with patients with HF and OSAS

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Female, sex	0.571 (0.182–1.798)	0.332		
Age, years	1.049 (1.009–1.090)	0.017	1.025 (0.972–1.082)	0.362
Hypertension	0.580 (0.231–1.455)	0.245		
Diabetes	0.775 (0.337–1.782)	0.549		
Atrial fibrillation	0.444 (0.188–1.049)	0.064	0.563 (0.167–1.896)	0.354
Renal dysfunction	0.632 (0.215–1.859)	0.405		
Pleural effusion	0.286 (0.103–0.796)	0.017	1.781 (0.391–8.109)	0.455
Acute heart failure	0.835 (0.362–1.924)	0.672		
LVEF, %	0.968 (0.934–1.003)	0.076	0.995 (0.948–1.045)	0.846
CA125, U/mL	1.110 (1.055–1.169)	<0.0001	1.110 (1.043–1.181)	0.001*
NT-proBNP, pg/mL	1.000 (1.000–1.001)	0.004	1.000 (1.000–1.000)	0.944

*, P value less than 0.05. HF, heart failure; OSAS, obstructive sleep apnea syndrome; OR, odds ratio; CI, confidence interval; LVEF, left ventricular ejection fraction; CA125, carbohydrate antigen 125; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Table 3 Higher AHI values are associated with CA125 (>35 U/mL)

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Female, sex	0.379 (0.124–1.162)	0.09		
Age, years	1.035 (0.990–1.083)	0.132		
Hypertension	1.600 (0.528–4.849)	0.406		
Diabetes	0.943 (0.372–2.391)	0.901		
Atrial fibrillation	1.470 (0.586–3.961)	0.412		
Renal dysfunction	1.096 (0.347–3.463)	0.876		
Pleural effusion	9.535 (3.371–26.973)	<0.001	2.933 (0.765–11.248)	0.117
Acute heart failure	6.429 (2.329–17.746)	<0.001	1.667 (0.301–9.240)	0.559
AHI	1.069 (1.031–1.109)	<0.001	1.070 (1.019–1.124)	0.006*
LVEF, %	0.948 (0.911–0.986)	0.009	0.980 (0.931–1.033)	0.457
NT-proBNP	1.000 (1.000–1.001)	<0.001	1.000 (1.000–1.001)	0.051

*, P value less than 0.05. AHI, apnea-hypopnea index; CA125, carbohydrate antigen 125; OR, odds ratio; CI, confidence interval; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

in *Figure 2*, Ln(CA125) gradually increased with increasing AHI (r=0.551, P<0.0001).

Discussion

OSAS refers to more than 30 episodes of repeated apnea and hypopnea during 7 hours of nocturnal sleep or sleep apnea hypopnea index ≥5 times/h. Upper airway obstruction causes hypoxemia, hypoxia, hypercapnia, and shifts in intrathoracic pressure, which, combined with frequent waking from sleep, further leads to sympathetic nervous system activation, autonomic dysfunction, renin-

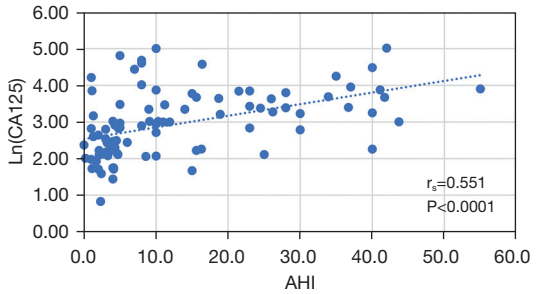

Figure 2 The correlation between logarithmically transformed Ln(CA125) and the AHI. CA125, carbohydrate antigen 125; AHI, apnea-hypopnea index.

angiotonin aldosterone system activation, resulting in myocardial remodeling and sodium and water retention (15). In addition, due to long-term chronic intermittent hypoxia, OSAS can cause hypertrophy and/or proliferation of lung smooth muscle cells, leading to contraction of pulmonary vessels and increased vascular resistance, which can gradually progress to pulmonary hypertension, right ventricular hypertrophy, and even right HF. When right HF occurs, systemic venous return is blocked, and fluid leakage in the chest increases, which leads to the occurrence of pleural effusion. This finding was consistent with the results of our study (16). OSAS is highly prevalent in patients with both HF with reduced ejection fraction and HF with preserved ejection fraction, and may contribute to the development of HF, which may reflect an important modifiable risk factor for patients with HF. The prevalence of OSAS among the HF population ranges from 20% to 60%, and the incidence of OSAS is generally higher in heart failure with preserved ejection fraction (HFpEF) patients (17,18). Observational data have shown that OSAS is independently associated with poor quality of life, excessive rehospitalization, and premature mortality in patients with HF (18). OSAS is an independent risk factor for cardiovascular disease morbidity and mortality (19). Therefore, exploring the indicators of disease assessment and prediction of HF combined with OSAS plays a key role in realizing early prevention and precision treatment. Previous studies have mainly focused on the pathophysiological mechanism of OSAS and HF, while there have been few studies on serological predictors.

CA125, also called mucin 16, is a glycoprotein synthesized by serous cells in response to mechanical stress in hyperemia or inflammatory stimulation. For decades, serum CA125 has been widely used as a biomarker for ovarian cancer screening, surveillance, and risk stratification (4). However, several recent studies have shown elevated serum CA125 levels in patients with cardiovascular diseases, such as HF, atrial fibrillation, pericardial disease, and ischemic heart disease (20,21). The findings of other researchers that have shown an association between CA125 and pleural effusion (22), left ventricle ejection fraction (23), acute HF (24), and NT-proBNP levels (6) are consistent with the results of our study. Neurohormonal and inflammatory activation, as well as increased volume and congestion in the systemic vein, seem to be the factors that increase the serum level of CA125 (25,26).

This study is also the first to investigate the correlation between serum CA125 levels and OSAS in patients with HF. We found that compared with patients without OSAS, serum CA125 levels in patients with HF combined with OSAS were further increased (29.60 *vs.* 9.68 U/mL, P<0.001). We also found that CA125 (>35 U/mL) was positively correlated with AHI (P<0.001) and that Ln(CA125) gradually increased with increasing AHI (r_s=0.551, P<0.0001). There may be several explanations for the association between serum CA125 levels and OSAS in patients with HF, and these are discussed below.

(I) Inflammation: upper airway tissue biopsies in patients with OSAS showed increased subepithelial edema and inflammatory cell infiltration (27). Several studies have shown that patients with OSAS have elevated levels of systemic inflammatory biomarkers, including proinflammatory cytokines such as IL-6, C-reactive protein (CRP), and TNF-α (9,27). The levels of inflammatory markers, such as TNF-α and IL-6, increase during hypoxia, and the key inflammatory signaling pathway regulator nuclear factor-κB (NF-κB) is activated during oxidative stress. Furthermore, there is increased activation of NF-κB during exposure to intermittent hypoxia in in-vitro models in patients with OSAS (9,28). This provides strong evidence for the upregulation of inflammatory pathways during intermittent hypoxia. When HF is present, there may be an additional upregulation of this inflammatory state. As CA125 positively correlates with TNF-α, IL-6 and CRP levels (6), it may serve as a marker of the presence of underlying low-grade inflammation in this study population, which partly explains the further increased CA125 levels in patients with HF combined with OSAS compared with those without OSAS in this study.

(II) Volume overload: another possible mechanism

by which OSAS is associated with elevated serum CA125 levels in patients with HF is activation of the renin-angiotensin-aldosterone system (RAAS). Meta-analyses of 13 studies evaluating the role of OSAS on RAAS components have reported that patients with OSAS had elevated plasma levels of angiotensin II (Ang II) compared to control individuals and patients combined with hypertension had elevated aldosterone plasma levels (11). Meta-analysis studies have shown that the severity of OSAS is positively correlated with Ang II and aldosterone levels. The elevated Ang II levels in patients with OSAS increase aldosterone levels in the body, which leads to a large amount of water and sodium retention, resulting in a significant increase in the volume load of the heart. Moreover, one characteristic of OSAS is repeated attempts to breathe into a blocked airway, which results in significant changes in chest pressure and dilating strain on the vascular system. This leads to increased venous return and right heart volume and pressure overload (11,29). A literature search revealed that hyperemia, serous effusion, and inflammatory stimulation can promote the release of serum CA125, and the mechanism may be related to the response of serous mesenchymal cells to serous effusion and/or proinflammatory stimulation (6). When OSAS coexists with HF, which is a complex congestive pathophysiological process with an underlying inflammatory cascade, CA125 levels in the body are further elevated.

(III) Aggravated HF: chronic intermittent hypoxia is the main pathological feature of OSAS and plays an important role in promoting the development of HF. Relevant studies have shown that long-term chronic intermittent hypoxia can lead to myocardial fibrosis, ventricular hypertrophy, and ventricular dysfunction (13,30). Studies have found that the sympathetic nerve in patients with OSAS is overactive (30,31), and the RAAS system can be further activated due to the overexcited state of the sympathetic nervous system. This results in increased capacity load of the heart and thus promotes the development of HF. In addition, the activation of the RAAS also participates in cardiac remodeling through the production of growth factors, the expression of proto-oncogenes and the synthesis of the extracellular matrix (32). Therefore, when OSAS is present, HF is further worsened, leading to a further increase in CA125 levels.

Limitations

Several limitations need to be acknowledged. First, this study is a monocentric study, which may induce selection bias. Second, our study included patients with both acute and chronic HF, and even though the proportion of types was not significantly different between the two groups, we cannot completely rule out the influence of HF itself on the findings. Third, the echocardiogram results were not reviewed again by other sonographers and the right-side parameters of the echocardiogram were lacking. Last, due to data limitations, the diagnostic threshold of the serum CA125 level in patients with HF combined with OSAS and the long-term prognostic impact of CA125 in such patients have not been clarified, which may be one of the directions of future research.

Conclusions

Our study revealed that serum CA125 levels in patients with HF combined with OSAS were further increased compared with those in patients without OSAS. We also found that the CA125 level (>35 U/mL) was positively correlated with AHI. Serum CA125, as a biomarker associated with inflammation and congestion, may have certain value in the diagnosis of patients with HF and OSAS.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://cdt.amegroups.com/article/view/10.21037/cdt-23-323/rc

Data Sharing Statement: Available at https://cdt.amegroups.com/article/view/10.21037/cdt-23-323/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cdt.amegroups.com/article/view/10.21037/cdt-23-323/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics committee for Clinical Research of Zhongda Hospital, Affiliated to Southeast University (No. 2020ZDSYLL278-P01) and informed consent was provided by all the patients.

References

1. Kumric M, Kurir TT, Bozic J, et al. Carbohydrate Antigen 125: A Biomarker at the Crossroads of Congestion and Inflammation in Heart Failure. Card Fail Rev 2021;7:e19.
2. Schoebel C, Fietze I, Penzel T. Effects of optimized heart failure medication on central sleep apnea with Cheyne-Stokes respiration pattern in chronic heart failure with reduced left-ventricular ejection fraction. Annu Int Conf IEEE Eng Med Biol Soc 2019;2019:5723-6.
3. Lu T, Ma H, Shang L. Efficacy analysis of non-invasive positive pressure ventilation in elderly patients with heart failure complicated with obstructive sleep apnea syndrome. Technol Health Care 2023. [Epub ahead of print]. doi: 10.3233/THC-230554.
4. Zhang M, Cheng S, Jin Y, et al. Roles of CA125 in diagnosis, prediction, and oncogenesis of ovarian cancer. Biochim Biophys Acta Rev Cancer 2021;1875:188503.
5. Núñez J, de la Espriella R, Miñana G, et al. Antigen carbohydrate 125 as a biomarker in heart failure: a narrative review. Eur J Heart Fail 2021;23:1445-57.
6. Bulska-Będkowska W, Chełmecka E, Owczarek AJ, et al. CA125 as a Marker of Heart Failure in the Older Women: Population-Based Analysis. J Clin Med 2019;8:607.
7. Llàcer P, Bayés-Genís A, Núñez J. Carbohydrate antigen 125 in heart failure. New era in the monitoring and control of treatment. Med Clin (Barc) 2019;152:266-73.
8. Hartupee J, Mann DL. Neurohormonal activation in heart failure with reduced ejection fraction. Nat Rev Cardiol 2017;14:30-8.
9. Imani MM, Sadeghi M, Khazaie H, et al. Evaluation of Serum and Plasma Interleukin-6 Levels in Obstructive Sleep Apnea Syndrome: A Meta-Analysis and Meta-Regression. Front Immunol 2020;11:1343.
10. Cacciapuoti F, D'Onofrio A, Tarquinio LG, et al. Sleep-disordered breathing and heart failure: a vicious cycle of cardiovascular risk. Monaldi Arch Chest Dis 2023. [Epub ahead of print]. doi: 10.4081/monaldi.2023.2660.
11. Jin ZN, Wei YX. Meta-analysis of effects of obstructive sleep apnea on the renin-angiotensin-aldosterone system. J Geriatr Cardiol 2016;13:333-43.
12. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42:3599-726.
13. Mediano O, González Mangado N, Montserrat JM, et al. International Consensus Document on Obstructive Sleep Apnea. Documento internacional de consenso sobre apnea obstructiva del sueño. Arch Bronconeumol 2022;58:52-68.
14. Mitchell C, Rahko PS, Blauwet LA, et al. Guidelines for Performing a Comprehensive Transthoracic Echocardiographic Examination in Adults: Recommendations from the American Society of Echocardiography. J Am Soc Echocardiogr 2019;32:1-64.
15. Cai A, Wang L, Zhou Y. Hypertension and obstructive sleep apnea. Hypertens Res 2016;39:391-5.
16. Castillo-Galán S, Arenas GA, Iturriaga R. Contribution of STIM-Activated TRPC-ORAI Channels in Pulmonary Hypertension Induced by Chronic Sustained and Intermittent Hypoxia. Curr Vasc Pharmacol 2022;20:272-83.
17. Kishan S, Rao MS, Ramachandran P, et al. Prevalence and Patterns of Sleep-Disordered Breathing in Indian Heart Failure Population. Pulm Med 2021;2021:9978906.
18. Javaheri S, Barbe F, Campos-Rodriguez F, et al. Sleep Apnea: Types, Mechanisms, and Clinical Cardiovascular Consequences. J Am Coll Cardiol 2017;69:841-58.
19. Salari N, Khazaie H, Abolfathi M, et al. The effect of obstructive sleep apnea on the increased risk of

cardiovascular disease: a systematic review and meta-analysis. Neurol Sci 2022;43:219-31.
20. Falcão F, de Oliveira FRA, da Silva MCFC, et al. Carbohydrate antigen 125: a promising tool for risk stratification in heart diseases. Biomark Med 2018;12:367-81.
21. Cheung A, Gong M, Bellanti R, et al. Cancer antigen-125 and risk of atrial fibrillation: a systematic review and meta-analysis. Heart Asia 2018;10:e010970.
22. Li S, Ma H, Gan L, et al. Cancer antigen-125 levels correlate with pleural effusions and COPD-related complications in people living at high altitude. Medicine (Baltimore) 2018;97:e12993.
23. Yilmaz MB, Zorlu A, Tandogan I. Plasma CA-125 level is related to both sides of the heart: a retrospective analysis. Int J Cardiol 2011;149:80-2.
24. Ding Y, Wang Q, Yang Y, et al. Diagnostic value of copeptin and cancer antigen 125 in acute heart failure patients with atrial fibrillation and their correlations with short-term cardiovascular events. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2018;30:1024-8.
25. Hamdy NM. Relationship between pro-anti-inflammatory cytokines, T-cell activation and CA 125 in obese patients with heart failure. Med Sci Monit 2011;17:CR174-9.
26. Kosar F, Aksoy Y, Ozguntekin G, et al. Relationship between cytokines and tumour markers in patients with chronic heart failure. Eur J Heart Fail 2006;8:270-4.
27. Vicente E, Marin JM, Carrizo SJ, et al. Upper airway and systemic inflammation in obstructive sleep apnoea. Eur Respir J 2016;48:1108-17.
28. Dyugovskaya L, Lavie P, Lavie L. Phenotypic and functional characterization of blood gammadelta T cells in sleep apnea. Am J Respir Crit Care Med 2003;168:242-9.
29. Selim BJ, Ramar K. Management of Sleep Apnea Syndromes in Heart Failure. Sleep Med Clin 2017;12:107-21.
30. Ahmed AM, Nur SM, Xiaochen Y. Association between obstructive sleep apnea and resistant hypertension: systematic review and meta-analysis. Front Med (Lausanne) 2023;10:1200952.
31. Biffi A, Quarti-Trevano F, Bonzani M, et al. Neuroadrenergic activation in obstructive sleep apnoea syndrome: a new selected meta-analysis - revisited. J Hypertens 2022;40:15-23.
32. Mentz RJ, Stevens SR, DeVore AD, et al. Decongestion strategies and renin-angiotensin-aldosterone system activation in acute heart failure. JACC Heart Fail 2015;3:97-107.

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