

Peer Review File

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Reviewer A

Thank you for your manuscript entitled “Serum levels of carbohydrate antigen 125 in patients with heart failure and 4 obstructive sleep apnea syndrome: a retrospective analysis”. The manuscript gives new insight of CA125 as new cardiac biomarker in a population of patients with OSAS. CA125 has become popular over the last decade in the monitoring of acute and chronic heart failure in adults. The study is conducted in a fashion of a feasibility study to give retrospective preliminary data on CA125 levels in patients with OSAS and HF compared to HF patients without OSAS. The methodology of the study is appropriate and even in the light of small sample size the comparison of groups is correct. The study is of interest for the reader. Nevertheless, I have raised some questions and major/ minor comments to be answered/ corrected.

Many thanks for your hard work in reviewing this article. Your professional suggestions have revealed many limitations of this manuscript and have been of great help to us. This article has been carefully revised according to your valuable advice. Here, we have appended detailed responses to your comments.

Please kindly see below for our responses:

Major Comments

Abstract

Line 21: Please rephrase this sentence “A total of 95 patients with HF were recruited for our monocentric 22 observational study,...“ as it is not clear for the reader that patients were included retrospectively. Sounds more as prospective inclusion.

Reply:

Thank you for your valuable suggestions. We have rephrased this sentence. Please kindly check it (See page 1, Line 17-18).

What is new?

See minor comments.

Introduction

See minor comments.

Methods

Line 88: Please include “Finally, a total of 55 patients with OSAS were retrospectively enrolled in the HF and OSAS group (HF+ OSAS group) “ for better understanding of the retrospective design of the study.

Reply:

Thank you for your valuable suggestions. We have revised this sentence according to your suggestions. Please kindly check it (see Page 4, Line 77-79).

Line 98: Please avoid explanation which suggest “prospective” enrollment of the patients. Please screen the manuscript related to this issue and rephrase the relevant sentences. Think about using “...were retrospective recorded from patient’s charts/ electronic documentation system at the following timepoints :.....”

Reply:

Thank you for your valuable suggestions. We have carefully reviewed the full text and rephrased the relevant sentences according to your suggestions. Please kindly check it (see Page 4, Line 75-79).

Please verify in the methods section how is your standard procedure of “Biomarker” monitoring in patients with OSAS. When and in which situation do you measure “NTproBNP” and “CA125”.

Reply:

Thank you for your valuable suggestions. We have added detailed measurement methods of “NTproBNP” and “CA125” to the article. Please kindly check it (see Page 5, Line 89-93 and Line 100-103).

Are there routine guidelines to measure it? As this is a retrospective study it is important to mention the routine practice in a short paragraph or 1-2 sentences. Also explain how echocardiographic assessment of the patients is performed. Routine echo in every patient? Was the echo performed by cardiologists?

Reply:

Thank you for your valuable suggestions. We have included guidelines for the measurement of echocardiography, the details of which are described in the article. Please kindly check it (see Page 5, Line 93-97).

Results

See minor comments.

Discussion

Overall, the discussion section is well written. In particular, the section beginning from Line 240 – 290 gives a good connection of the relevant findings and puts the findings in the right context. This section from Line 208 -217 gives redundant information in comparison to the following section from Line 240-290. Please reorganize the discussion to avoid redundant information. Think about putting the key findings in first place of the discussion, by following explanation of OSAS and HF and then your major section with explanation of link between OSAS + HF + CA125 and points I), II) and III).

Reply:

Thank you for your valuable suggestions. Following your suggestions, we have removed redundant information about the relationship between AHI and inflammatory factors. In addition, we have reorganized the relevant texts according to the importance of the content discussed. First, we explain the relationship between OSAS and HF and introduce the importance of serum markers for their diagnosis (see Page 9-10, Line 175-200). Then, we described the research status and influencing factors of CA125 in cardiovascular field (see Page 10, Line 201-211). Finally, CA125 was significantly elevated in patients with OSAS and HF in

this study, and we explained the reasons for this result in detail (see Page 10-12, Line 212-265). Please kindly check it.

A short section prior to the limitations of what is planned in the future and how an integration of CA125 measurements in patients with OSAS can be implemented in the clinical routine would be interesting for the reader.

Reply:

Thank you for your valuable suggestions. Due to data limitations, the diagnostic threshold of 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. We have discussed this in the "Limitations" section (see Page 13, Line 273-276).

Are there information about right heart dysfunction/ right heart function and CA125 measurements for this population? As patients with OSAS are at risk for PH and right heart failure.

Reply:

Thank you for your valuable suggestions. As you said, OSAS is a risk factor for pulmonary hypertension and right heart failure. 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 study found that pleural effusion was related to CA125, and the proportion of pleural effusion in patients with HF combined with OSAS was significantly higher than those without OSAS. Pleural effusion reflected the degree of right heart failure to a certain extent. Therefore, CA125 is associated with right heart dysfunction, which has also been confirmed in previous studies (Miñana Gem et al., 2020). We have added this to the discussion section. Please kindly check it (see Page 9-10, Line 182-188 and Line 206-209).

Since this study was a retrospective study, on the one hand, sonographers did not deliberately retain cardiac parameters reflecting right heart function (such as right ventricular area change fraction (FAC), right ventricular ejection fraction (RVEF), tricuspid ring systolic velocity, etc.). On the other hand, pulmonary arterial pressure and degree of tricuspid regurgitation and other data were partially missing. Therefore, there is little information about serum CA125 level and right heart function in this study We have added it to the "Limitations" section (see Page 13, Line 271-272).

Reference:

Miñana G, de la Espriella R, Mollar A, et al. Factors associated with plasma antigen carbohydrate 125 and amino-terminal pro-B-type natriuretic peptide concentrations in acute heart failure. *Eur Heart J Acute Cardiovasc Care*, 2020, 9: 437-447.

Minor Comments

Line 36: Please specify abbreviation „LnCA125“and write out „Ln“

The sentence “Previous studies mainly focused on the pathophysiological mechanism of the two, while there were few studies on serological predictors.” makes no sense to me, as it is not clear what is meant by “two

Line 56-58: Please rephrase this sentence “Previous studies mainly focused on the pathophysiological mechanism of the two, while there were few studies on serological predictors...”(see comment above).

Reply:

Thank you for your valuable suggestions. To better understand the meaning of the expression, we have rewritten the word “TWO” to the specific word “OSAS and HF” (see Page 10, Line 198-200).

Line 95: This information is redundant, as it was mentioned before in the section “The study was approved by the local ethics committee of our faculty of medicine.

Reply:

Thank you for your valuable suggestions. We have removed this information that has been repeatedly expressed in the text in the “Methods” section. Please kindly check it.

Line 103/104: Think about using “device” instead of “apparatus”.

Reply:

Thank you for your valuable suggestions. We have replaced “apparatus” with “device” in the “Methods” section (see Page 5, Line 96).

Line 133: Please write out or explain “Ln” as “logarithmically transformed” prior to the abbreviation.

Reply:

Thank you for your valuable suggestions. We have made relevant explanations in the text where “Ln” first appears. Please kindly check it (see Page 6, Line 124-125).

Line 143: “,retrospectively; “ should by “,retrospectively.”

Between a word and words in parentheses there should be a space. Please check the manuscript.

Reply:

Thank you for your valuable suggestions. We have checked and corrected similar issues. Please kindly check it.

Line 145-149: “Female sex, Hypertension, Diabetes, Atrial fibrillation, Renal dysfunction, or Acute heart failure between the two groups.“ Please, write words as „Female sex, Hypertension...” lowercased and not capitalized, as these words are no

Reply:

Thank you for your valuable suggestions. We have changed the above vocabulary in the manuscript to lowercase form. Please kindly check it (see Page 6-7, Line 132-153 and Page 10, Line 206-209).

The sentence „While patients with OSAS were older (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) than patients without OSAS“ makes no sense to me. I think you missed some words at the end.

Reply:

Thank you for your valuable suggestions. We have revised the expression of this sentence in the text. Please kindly check it (see Page 6, Line 135-137).

Line 152-154: please check capitalized words.

Reply:

Thank you for your valuable suggestions. We have checked and revised all the capitalized words. Please kindly check it (see Page 6-7, Line 132-153 and Page 10, Line 206-209).

Reviewer B

The study evaluated Ca125 serum levels in patients with HF with OSAS and with HF without OSAS. HF is an important health problem, with significant morbidity and mortality that can be further complicated by OSAS.

It is a well written retrospective analysis that brings further insight in the association of Ca125 with congestion and inflammation in HF. Since, it is a low-cost serum marker it may help clinicians in the management of such a severe disease. Especially in low-income countries.

Many thanks for your hard work in reviewing this article. Your professional suggestions have revealed many limitations of this manuscript and have been of great help to us. This article has been carefully revised according to your valuable advice. Here, we have appended detailed responses to your comments.

Please kindly see below for our responses:

It only concerned me that the group with OSAS and HF had a higher prevalence of HF pleural effusion than the groups of patients with HF only. Maybe this should be mentioned in the limitations section.

Reply:

Thank you for your valuable suggestions. 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. Therefore, we found that the group with OSAS and HF had a higher prevalence of pleural effusion than the group without OSAS. We have explained this in the discussion section. Please kindly check it (see Page 9, Line 182-188).

In the discussion section, in line 167, I was in doubt of what "in the central vein " meant. Is it the cava vein ?

Reply:

Thank you for your valuable suggestions. I'm sorry we didn't make that clear in the article. In fact, "in the central vein" really means "in the systemic vein". We have corrected it in the article. Please kindly check it (see Page 10, Line 210).

In line 212, is it a ";" or a "." ?

Reply:

Thank you for your valuable suggestions. We are very sorry for mistakenly writing "." as ";" . We have corrected it in the article. Please kindly check it (see Page11, Line 215).

In the discussion section, lines 204 to 243 is an only paragraph, could it be fractioned it more paragraphs ?

Reply:

Thank you for your valuable advice. We have reorganized the relevant text according to the importance of the discussed content and described them in separate paragraphs. First, we explain the relationship between OSAS and HF and introduce the importance of serum markers for their diagnosis (see Page 9-10, Line 175-200). Then, we described the research status and influencing factors of CA125 in cardiovascular field (see Page 10, Line 201-211). Finally, CA125 was significantly elevated in patients with OSAS and HF in this study, and we explained the reasons for this result in detail (see Page 10-12, Line 212-265). Please kindly review it.