**Peer Review File**

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**Reviewer A**

Comment 1: I agree with the authors that establishing the independent impact of OSA on cardiovascular outcomes is important. The manuscript explores this interesting topic. Below I included my comments and suggestions.
The primary research question was to identify differences in cardiovascular outcome between subjects with OSA vs. without OSA. In the secondary analyses, authors explored the impact of BP control on the associations between OSA and cardiovascular outcome by examining interaction term. They concluded that the interaction term was not significant; however, it was not clear to me whether the original variables (presence of OSA, BP control variable) were significant predictors of cardiovascular outcome in the model that included interaction term. Please elaborate on the statistical model that was tested and interpretation of the findings.
**Reply:** Thank you for question. We analyzed the interaction of presence of OSA and BP control status on the extended MACCE by Cox regression model, no significance of the association between the interaction and MACCE was observed, while the presence of OSA showed as a risk factor of extended MACCE. Further, we reviewed the manuscript and added how the interaction was tested in the model in the "statistical analysis" section.
**Changes in the text:** We added "The multiplicative interaction between presence of OSA and BP control status (controlled or uncontrolled) was also tested in a Cox model" to explain how the interaction was tested in the model in the "statistical analysis" section (see Page11, Line204, 205). Also, we modified interpretation of the findings (see Page13, Line249,250, Page15, Line294, 295).

Comment 2: If the interested is in the OSA, authors could expand the finding by using severity of OSA. For example, without OSA, mild OSA, moderate to severe OSA may help identify dose-response relationship. This can further strengthen the findings.
**Reply:** Thank you for your suggestion. We analyzed the relationship between the severity of OSA and extended MACCE, as shown in the table below. It could be seen that as the severity of OSA increases in the crude model, the risk of extended MACCE gradually increases. However, after adjusting for gender and age, only the association between severe OSA and extended MACCE was observed, while in the full model, no significant difference was observed in this relationship.
**Changes in the text:** None.

| | Crude model | | Partially adjusted model | | Full model | |
|---|---|---|---|---|---|---|
| | HR (95%CI) | P value | HR(95%CI) | P value | HR(95%CI) | P value |
| without OSA | 1.0 | | 1.0 | | 1.0 | |
| mild OSA | 1.36(1.00-1.83) | 0.048 | 1.14(0.84-1.54) | 0.412 | 1.08(0.79-1.46) | 0.634 |
| moderate OSA | 1.63(1.20-2.20) | 0.002 | 1.22(0.90-1.65) | 0.211 | 1.09(0.80-1.49) | 0.579 |
| severe OSA | 1.86(1.38-2.51) | <0.001 | 1.40(1.03-1.89) | 0.033 | 1.18(0.86-1.62) | 0.314 |

Partially adjusted model: adjusted for age and sex.

Fully adjusted model: adjusted for age, sex, body mass index, baseline systolic blood pressure, diastolic blood pressure, low-density lipoprotein cholesterol, eGFR, smoking, type 2 diabetes, history of coronary heart diseases, lipid-lowering drugs, antidiabetic drugs, and antiplatelet drugs.

Comment 3: Authors might want to consider having a native English speaker review the manuscript.

**Reply:** Thank you for your suggestion. Actually, we had Charles Worth company conduct language polishing before submitting the manuscript. However, if necessary, we may use the AME Editing Service for medical writing service further.

**Changes in the text:** none.

**Minor revisions**

Comment 4: Please review the content of Highlight Box and make sure that the message reflects the findings of the data. For example, “Antihypertensive therapy would partially reduce the risk of cardiac events in patients with hypertension and OSA.” Antihypertensive therapy or Controlled blood pressure.

**Reply:** Thank you for your suggestion. We have once again discussed and summarized the main findings of this meeting. 'Controlled blood pressure' does indeed reflect our research results more accurately than 'Antihypertensive therapy'.

**Changes in the text:** We have modified our text as advised (see Page 5, line 60)

Comment 5: Please make sure “extended MACCE” and “MACCE” are appropriately used throughout the manuscript.

**Reply:** Thanks, we revisited the full text, especially the "extended MACCE" and "MACCE".

**Changes in the text:** we have modified our text as advised (e.g.see Page 12, line 226)

Comment 6: Line 80 – Please define the study design beyond observational study such as prospective vs. retrospective.
**Reply 1:** We additionally defined the types of study. Our study is a retrospective cohort study.
**Changes in the text:** we have modified our text as advised (see Page 7, line 106)

Comment 7: Line 86 – Even though the study inclusion and exclusion criteria were reported in another paper, I recommend including the information to help the readers who the study population is. In reference 20, it was stated that UROSAH inclusion criteria were as follows: hypertensive patients with suspected OSA. Please explain on how you defined the inclusion criteria of "suspected OSA." Also, adding information on screened subjects vs. excluded subjects to Supplement figure 1 could be helpful.
**Reply:** We added the inclusion and exclusion criteria in the "Method" section, and add ed the information on screened subjects vs. excluded subjects to Supplement figure 1. As, well, we explain the inclusion criteria of "suspected OSA.
**Changes in the text:** we added inclusion and exclusion criteria in the "Method" section (see Page 8, Line110-131.) and modified "Supplement Figure 1" to "Figure S1" and added our information on screened subjects as advised.

Comment 8: Please clarify if the study subjects were outpatients or inpatient. The paper mentions that subjects visited the hypertension center; however, later the subjects were referred to as "inpatients".
**Reply 1:** All the participants in our cohort were hospitalized inpatients in our hypertension center, we have revised in the manuscript.
**Changes in the text:** we have modified in the revised manuscript (see Page 7, line 108-109)

Comment 9: Line 87 All inpatients were assessed for BP level, target organ damage, complications, and screening of secondary hypertension.
**Reply 1:** We have added the assessment in detail, which included office blood pressure measurement, evaluation of hypertension target organ damage and complications including heart, brain, kidney, vascular and retinopathy, and screening for secondary hypertension at our center.
**Changes in the text:** we have added our text (see Page 8, line 125-129).

Comment 10: Line 91 Totally, 3329 inpatients were enrolled. > In total, 3329 subjects were included.
**Reply 1:** We're sorry that we didn't describe it clearly in the manuscript, which confused you. Initially, we consecutively included 3605 hospitalized hypertensive

patients with suspected OSA, and all patients underwent full-night polysomonography monitoring to identify OSA. 276 subjects who were lost to follow-up were not included, and finally 3329 subjects who completed follow-up were included for analysis.
**Changes in the text:** we have modified our text (see Page 7, line 108-109, Page 8, line 132,133) and Supplementary figure S1(see Figure S1 in the revised version).

Comment 11: Line 100 When was blood pressure to define subgroups collected? From the paper, baseline assessment did not include BP measurement (line 96). It seems like the latest BP reading from the chart was used (see Line 112 Additionally, data on the latest BP level and treatment of OSA (ie, CPAP) after the initial diagnosis). Please clarify.
**Reply 1:** All admitted patients were measured and recorded by trained nurses, which was described in our previous study [Reference 20], and the data were analyzed in Table 1. We defined subgroups by mean level of BP in follow-up (Table 3).
**Changes in the text:** we added the measurement of blood pressure **in the revised manuscript** (see Page 8-9, line 141-144).

Comment 12: Line 112 treatment of OSA (ie, CPAP) after initial diagnosis were collected. However, in the latter part of the manuscript, OSA treatments included CPAP, oral appliance, and surgery. Please clarify. Also, how did the authors define regular CPAP treatment presented in Table 1?
**Reply:** We collected information on OSA treatment at follow-up, including treatment modality (CPAP, oral appliance, and surgery), frequency and duration of treatment, etc. Regular CPAP treatment was defined as average treatment ≥4 hours/night for >70% of the entire follow-up period, or on average of ≥4 hours per night (CPAP devices only provide cumulative hours of use).
**Reference:** Xu PH, Hui C, Lui M, et al. Incident type 2 diabetes in OSA and effect of CPAP treatment: a retrospective clinic cohort study. Chest 2019;156:743-753. Doi:10.1016/j.chest.2019.04.130
**Changes in the text:** We added the information as to the OSA-specific treatment (see Page 9, line 163) and the definition of regular CPAP treatment (see Page9-10, Line 164-166) in the revised manuscript and added the reference (see reference 23).

Comment 13: Line 118 I assume the patients were recruited as outpatients. What is the definition of “cardiac rehospitalization”? What is the reason to use rehospitalization rather than index hospitalization in this study?
**Reply:** we’re sorry to confuse you. All patients were hospitalized inpatients with hypertension in our Hypertension Center. According to the MACCE definition, we’d like to say that readmission due to unstable angina and heart failure, we have modified

the expression of "cardiac rehospitalization". Since the extended MACCE we observed in this study used composite outcomes rather than the total number of events, so we used "rehospitalization" rather than "index hospitalization".
**Changes in the text:** We have modified the expression in the revised manuscript. (See Page10, Line 174)

Comment 14: Line 118 revascularization – what procedures are included under this term? Please clarify.
**Reply:** The revascularization included percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG).
**Changes in the text:** We added the information of revacularization in the revised manuscript (see Page 10, Line 173-174)

Comment 15: Line 119 death from heart – please clarify.
**Reply: I**t should be "Death from heart diseases"
**Changes in the text:** Death from heart diseases (see Page10, Line 176)

Comment 16: Line 124 The international classification of diseases (ICD-10) classification code was used to classify 75 cases of deadly disease. What are deadly diseases?
**Reply:** ICD-10 are used to classify 75 cases of the causes of death.
**Changes in the text:** we modified the text (see Page 10, Line 184)

Comment 17: Line 156 –the crude incidence of overall outcomes was xxx. It seems that "overall outcomes" is the primary outcome defined as extended MACCE. Please use the defined term consistently throughout the manuscript.
**Reply:** Thank you. You are right. **"**Overall outcomes**"** should be "extended MACCE".
**Changes in the text:** We have modified the term "Overall outcomes**"** should be "extended MACCE" (see Page12, Line 222-223).

Comment 18: Statistical analysis – How was normality defined or tested?
**Reply:** Skewness-kurtosis method are used to perform test of normality.
**Changes in the text:** we added the text in the Statistical analysis (see Page 11, Line 190).

Comment 19: Line 156 What is crude incidence of overall outcomes? Please define "overall outcomes".
**Reply: "**Overall outcomes**"** should be "extended MACCE"
**Changes in the text:** We have modified the term "Overall outcomes**"** should be

“extended MACCE” (see Page12, Line222-223)

Comment 20: Line 175 the interaction between OSA status and BP level was not significant for extended MACCE…. Please review the “statistical analysis” section and explain how this interaction was tested in the model. Also, no interaction does not mean there is an independent effect. Please review your interpretation of the findings.
Line 214 Our data did not observe a significant interaction between OSA and BP levels regarding MACCE except for cardiac events, indicating an independent potential effect of OSA on CVDs. Please compare this statement with line 175.
**Reply:** Thank you for your reminder. We analyzed the interaction of presence of OSA and BP control status on extended MACCE, but no significance was observed. Further, we reviewed the manuscript and added how the interaction was tested in the model in the “statistical analysis” section.
**Changes in the text:** We added how the interaction was tested in the model in the “statistical analysis” section (see Page11, Line 201-202). Also, we modified interpretation of the findings (see Page 13, Line 246-248).

Comment 21: Line 219 Hence, our results support that using CPAP along with other antihypertensive regimens is important in treating hypertension and reducing CVDs mortality. Please review this statement, as this study did not explore the impact of CPAP therapy on study outcomes.
**Reply:** The sentence that **“**using CPAP along with other antihypertensive regimens is important in treating hypertension and reducing CVDs mortality**”**is the conclusion of Reference 29 we cited, and we’d like to say that our findings support this view.
**Changes in the text:** we deleted this sentence and the reference 29 in the revised manuscript (see Page 21, Line 453-454).

Comment 22: Table 1. SaO2 (arterial blood oxygen saturation) vs. SpO2 (pulse oximetry value).
**Reply:** Thank you for your carefully check. In the PSG monitoring indicators, the arterial blood oxygen saturation ($SaO_2$) that obtained by the pulse oxygen monitoring were used to assess the degree of hypoxia in OSA patients, including mean arterial oxygen saturation and lowest blood oxygen saturation. Therefore, $SaO_2$ is used in Table 1 rather than pulse oximetry value ($SpO_2$).
**Changes in the text:** we have modified the Abbreviations in Table 1(see Page 23, line 480)

Comment 23: Please review the title of Table 2,3. It does not match the content of Table 2. Please add abbreviations for MACCE, CI, and BP.

**Reply:** We reviewed the title of Table 2,3 and corrected the titles. Also, we added the abbreviations for MACCE, CI, and BP. MACCE: Major adverse cardiovascular and cerebrovascular events; CI, confidence interval; BP: blood pressure.
**Changes in the text:** We added abbreviations for MACCE, CI, and BP (see Page 3, line 20-23, Page 4, Line 41-44).

Comment 24: Please review Table S1. Remove "adjusted" right below "stroke" and "all cause death".
**Reply:** We reviewed Table S1. The "adjusted" right below "stroke" and "all cause death" in Table S1 has been removed and the abbreviations for OSA and CI are added.
**Changes in the text:** We remove "adjusted" right below "stroke" and "all cause death" in Table S1. (See Page 1, Line 3).

Comment 25: Table S3 defines BP control variables as BP controlled < 140/90 vs. BP controlled ≥140/90 mmHg. Based on line 101-103, the latter variable should be BP uncontrolled SBP ≥140 mmHg or DBP ≥90 mmHg. Please review.
**Reply:** Thank you for your carefully check, we reviewed the table and corrected the variable.
**Changes in the text:** We revised "BP controlled ≥140/90mmHg" to "BP uncontrolled SBP ≥140 mmHg or DBP ≥90 mmHg". (See Page 2, table S3, the first column).

**Reviewer B**

Yao et al have performed an interesting study aimed to explore the impact of OSA on the risk of CVD outcomes in a large-scale Asian cohort under antihypertensive treatment. They included 3,329 hypertensive patients with 415 incident MACCE after a median follow-up of 7 years. The authors concluded that hypertensive OSA patients increased CV risk compared with non-OSA hypertensive patients especially those with uncontrolled hypertension. Very interesting research about the interaction between OSA, hyertension ant its control and CVE
I have some comments.
Comments 1: Please add in the abstract how many patients suffered from OSA as well as the IQR of follow-up.
**Reply:** Thank you for your comment.
**Changes in the text:** We added "A total of 3329 hypertension patients were enrolled, in which 2585 patients (about 77.6%) suffered from OSA. During a median follow-up period of 7.0 years, 415 patients developed extended MACCE "in the abstract (see Page 4, line 43, 44).

Comments 2: The composite outcome include all-cause death. I would like to see whether the results were the same inclusion only cardiovascular deaths (fatal and non-fatal CVE) as well as fatal cardio- and cerebrovascular death as separate variable (not only all-cause mortality).

**Reply:** Thank you for your suggestion. The fatal CVE were included in our "cardiac events" variable.

**Changes in the text:** None.

Comments 3: Conclusions (abstract): Please remove "undeniable" and tone down the conclusions. This is not a RCT or a very large observational study without limitations.

**Reply:** Thank you. We have removed "undeniable".

**Changes in the text:** We have removed "undeniable" in the abstract and the conclusion of the main text. (See Page 4, line 53).

Comments 4: It is important to recognized that the results should not be extrapolated to other zones of the world since this is an exclusively an Asian study.

**Reply:** I agree with you.

**Changes in the text:** We added this text to the "limitation" section. (See Page 16, line 331-333).

Comments 5: It is very important that the authors clearly point out whether the study is prospective or retrospective.

**Reply:** Thank you. This study is a retrospective cohort study. We added to the "Method--- Study design and subjects" section in the revised manuscript.

**Changes in the text:** We added "retrospective study" in the "Method---Study design and subjects" section (see Page 6, line 103-105).

Comments 6: Adherence to treatment. What happen with antihypertensive treatment? Finally other limitation is the lack of information about the class of hypertensive drugs used

**Reply:** Thank you. Due to the retrospective study, some patients were only able to obtain recent information as to the antihypertensive medication during our follow-up, so the class of hypertensive drugs used was not analyzed.

**Changes in the text:** We added" lack of information about the class of hypertensive drugs used" in the "limitation" section (see Page 16, line 333, 334).

Comments 7: Patients were recruited from hypertensive centers, so I have to assume that these patients have more severe hypertension. Is this a selection bias?

**Reply:** Thank you. This study is a retrospective cohort study. We added to the "Method--- Study design and subjects" section in the revised manuscript.

**Changes in the text:** We added "retrospective study" in the "Method---Study design

and subjects" section (see Page 6, line 103-105).

Comment 8: The proportion of OSA patients is a bit confuse. Was there the aprox same percentage of mild, moderate and severe OSA patients. A bit strange distribution.

**Reply:** The number and percentage of mild, moderate and severe OSA in the study were as follow: patients without OSA, with mild OSA, moderate OSA and severe OSA were 744(22.3%), 981(29.5%), 829(24.9%) and 775(23.3%). We included patients who pursued for screening the causes of hypertension, and patients with suspected OSA. Therefore, although the prevalence of OSA is high, there is little difference in the distribution of patients with different severity of OSA.

**Changes in the text:** None.

Comment 9: Really, the definition of MACCE does not include all-cause death but cardiovascular death

AHT is a risk factor for both fatal and non-fatal cardiovascular events. However, this association is not the same depending on the cardiovascular event and this could at least in part explain the results (for example why the relationship between hipertensive OSA patients is stronger with coronary than cerebral vascular disease)

**Reply:** You are right. The definition of MACCE does not include all-cause death. So, we used" extended MACCE" in our study. And the "cardiac events" we used included the "cardiovascular death".

**Changes in the text:** None.

Comment 10: Lines 290-298 are not necessary. It enough with "One strength of our study was that all patients were evaluated with full PSG"

**Reply:** Thank you for your suggestion. We deleted Line 290-298.

**Changes in the text:** We deleted Line 290-298. (See Page16, Line310-320)

Comment 11: I think it would be very informative to calculate the association depending on the severity of OSA. What happened with moderate-to-severe OSA compared with no OSA-mild OSA?

**Reply:** Thank you for you suggestion. We analyzed the data as you suggested, but we did not find the significant association between extended MACCE and moderate-to-severe OSA compared with no OSA-mild OSA. Further study is required to explore the reasons.

| | Crude model | | Partially adjusted model | | Full model | |
|---|---|---|---|---|---|---|
| | HR (95%CI) | P value | HR (95%CI) | P value | HR (95%CI) | P value |

| | | | | | | |
|---|---|---|---|---|---|---|
| without OSA-mild OSA | 1.0 | | 1.0 | | 1.0 | |
| Moderate-to-severe OSA | 1.45(1.20-1.76) | <0.001 | 1.20(0.99-1.47) | 0.068 | 1.09(0.89-1.34) | 0.394 |

Partially adjusted model: adjusted for age and sex.

Fully adjusted model: adjusted for age, sex, body mass index, baseline systolic blood pressure, diastolic blood pressure, low-density lipoprotein cholesterol, eGFR, smoking, type 2 diabetes, history of coronary heart diseases, lipid-lowering drugs, antidiabetic drugs, and antiplatelet drugs.

**Changes in the text:** None.

Comment 12: What happen with a severe or symptomatic hypertensive OSA and his/her treatment with CPAP?

**Reply:** According to the follow-up treatment for OSA patients, overall, the subjective feelings of the patients, such as excessive daytime sleepiness and drowsiness, have significantly improved, and the sound of snoring has disappeared. However, most patients still need to take antihypertensive medication to control their blood pressure and meet the target goal. However, due to the low proportion of patients who regularly use CPAP treatment, we did not find a correlation between CPAP and cardiovascular outcomes. Therefore, no data was provided in this study.

**Changes in the text:** None.

Comment 13: The main hypothesis of the study, as far as I see, is to analyse whether OSA and hypertension (controlled or uncontrolled) are independent risk factor for CVE. My concern is that maybe it could be better if you had included in the model the AHT values (as quantitative variable) and AHI also as quantitative variable, so you had seen not only if both variables are independently associated with MACCE but also if this association quantitatively increase with the increase in BP levels and AHI values.

**Reply:** Thank you very much for your suggestion. We have tried to incorporate AHI as a quantitative variable into the model, but did not find an association between AHI and MACCE. As far as the BP was referred, it showed very tiny association between quantitative SBP and MACCE(HR:1.009). We consider that the treatment of hypertension may weaken this association. We will consider your suggestion in the future research.

**Changes in the text:** None.