BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form ([http://bmjopen.bmj.com/site/about/resources/checklist.pdf](http://bmjopen.bmj.com/site/about/resources/checklist.pdf)) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

| TITLE (PROVISIONAL) | Association Between Comorbid Sleep Apnea–Hypopnea Syndrome and Prognosis of Intensive Care Patients: A Retrospective Cohort Study |
|---------------------|--------------------------------------------------------------------------------------------------------------------------|
| AUTHORS             | Wang, Hongxia; Shao, Guangqiang; Rong, Lei; Ji, Yang; Zhang, Keke; Liu, Min; Ma, Ling |

### VERSION 1 – REVIEW

| REVIEWER           | Bonsignore, Maria R  
|--------------------| University of Palermo |
| REVIEW RETURNED    | 03-Mar-2021 |

| GENERAL COMMENTS | This paper asks an interesting and clinically important question, and similar to smaller previous articles, concludes that OSAHS seems to exert a protective effect on 30-day mortality after admission to ICU compared to patients without OSAHS. The paper is well written and balanced, and the propensity score analysis reinforces the conclusions. However, in this and the previous reports, it is unclear whether there might be subgroups of patients who show a high risk instead of a protective effect. I am thinking of morbidly obese patients in particular, could you stratify your sample by BMI classes? In addition, there are some reports highlighting poorer outcomes in patients with COVID-19 infection who showed a high risk for sleep disordered breathing (Peker et al, Effect of High-Risk Obstructive Sleep Apnea on Clinical Outcomes in Adults with Coronavirus Disease 2019: A Multicenter, Prospective, Observational Cohort Study, Ann Am Thorac Soc 2021, in press). In addition, sleep apnea seems associated with a more severe COVID-19 disease (Strausz S, Kiiskinen T, Broberg M, et al. Sleep apnoea is a risk factor for severe COVID-19. BMJ Open Resp Res 2021;8:e000845. doi:10.1136/ bmjresp-2020-000845). Finally, the research letter by Cade et al in the Am J Respir Crit Care Med 2021 (in press, doi: 10.1164/rccm.202006-2252LE) suggests that OSA is associated with higher mortality for COVID-19. I would add such information to the discussion, to underline that more work is needed in order to assess the role of OSA severity and the possible role of CPAP treatment (not considered in your analysis) in ICU outcomes in OSA vs non-OSA patients. Another point of interest raising my curiosity in your paper was the high number of "elective" ICU admission in the OSA group. Does this indicate post-surgical admissions? Could this contribute to the lower mortality? I acknowledge that after propensity score matching, percentages of patients with elective ICU admissions were not different. |

| REVIEWER           | Bouloukaki, Izolde |
The manuscript by Dr Wang and colleagues focuses on identification (by critical care database) of the prevalence of sleep apnea–hypopnea syndrome (SAHS) in an intensive care unit population and investigate the association between SAHS and prognosis of these patients. The authors found an increase in mortality in patients with SAHS compared to patients without SAHS. Unfortunately, this manuscript contains only superficial information with many important limitations, already stated by the authors, such as missing details in SAHS diagnosis and severity. Furthermore, there is no data on SAHS treatment status before ICU admission, which is a major limitation in order to have a valid analysis and conclusion. Discussion section also needs improvement.

**VERSION 1 – AUTHOR RESPONSE**

Reviewer 1

1. comment: However, in this and the previous reports, it is unclear whether there might be subgroups of patients who show a high risk instead than a protective effect. I am thinking of morbidly obese patients in particular, could you stratify your sample by BMI classes?

Response to this comment: Thank you very much for the good advice. We divided the samples according to BMI classes and compared the outcomes in the patients with or without OSAHS. The study from Bailly S. revealed that OSA has a significant impact on the length of ICU stay for patients with BMI over 40 kg/m2 (IRR: 1.56 [1.05; 2.32], p = .03) (Reference #26 in our manuscript). We set the BMI equal to 40 kg/m2 as the boundary layer to determine the difference in our study, and found that the results are following the same trend. In the BMI subgroups, most patients with comorbid SAHS had a lower 30-day mortality, ICU mortality, and in-hospital mortality, compared with those without SAHS (Table 3). The results have been rewrite and marked in red.

2. comment: In addition, there are some reports highlighting poorer outcomes in patients with COVID-19 infection who showed a high risk for sleep disordered breathing (Peker et al, Effect of High-Risk Obstructive Sleep Apnea on Clinical Outcomes in Adults with Coronavirus Disease 2019: A Multicenter, Prospective, Observational Cohort Study, Ann Am Thorac Soc 2021, in press). In addition, sleep apnea seems associated with a more severe COVID-19 disease (Strausz S, Kiiskinen T, Broberg M, et al. Sleep apnoea is a risk factor for severe COVID-19. BMJ Open Resp Res 2021;8:e000845. doi:10.1136/ bmjresp-2020-000845). Finally, the research letter by Cade et al in the Am J Respir Crit Care Med 2021 (in press, doi: 10.1164/rcrm.202006-2252LE) suggests that OSA is associated with higher mortality for COVID-19. I would add such information to the discussion, to underline that more work is needed in order to assess the role of OSA severity and the possible role of CPAP treatment (not considered in your analysis) in ICU outcomes in OSA vs non-OSA patients.

Response to this comment: Thank you very much for providing us with three studies about sleep apnea during the COVID-19 pandemic. We have carefully read the articles, except the third one which is not completely available online. According to your suggestion, we have discussed the similarities, differences, and conclusions of these three studies and also underlined that further studies are needed. The changes we made are marked in red in our revised manuscript.

3. comment: Another point of interest raising my curiosity in your paper was the high number of "elective" ICU admission in the OSA group. Does this indicate post-surgical admissions? Could this contribute to the lower mortality? I acknowledge that after propensity score matching, percentages of patients with elective ICU admissions were not different.

Response to this comment: Sorry for our negligence of "elective" ICU admission in the OSA group.
We extracted the information about the patients who had undergone surgery from database based on the keywords “operation” and “surgery”, and we found it difficult to identify those patients who were transferred to ICU after surgery. We have deleted all the "elective" ICU admission patients and analyzed the clinical outcomes again. The results are shown in the table below, which provide a same conclusion. Moreover, the propensity score matching showed the same results, thus, this type of patients would not lead to low mortality.

All Patients (n=27576) Without SAHS
(n=26100) With SAHS
(n=1476) P-value
Age (years) 64.12±17.90 64.25±18.10 61.93±13.72 <0.001
Males 15482 (56.14%) 14515 (55.61 %) 967 (65.51%) <0.001
Females 12094 (43.86%) 11585 (43.74%) 509 (34.49 %)
BMI 23.6 (19.77,26.33) 23.23 (19.66,25.9) 31.18 (24.75,35.39) <0.001
Type of admission
EMERGENCY 26595 (96.44%) 25162 (96.41%) 1433 (97.09%) 0.17
URGENT 981 (3.56%) 938 (3.59 %) 43 (2.91 %)
Outcome
30-day mortality 4194 (15.21%) 4096 (15.69%) 98 (6.64%) <0.001
ICU mortality 2460 (8.92%) 2406 (9.22 %) 54 (3.66 %) <0.001
Hospital mortality 3280 (11.89%) 3205 (12.28 %) 75 (5.08%) <0.001
Length of ICU stay (days) 4.79 (1.66,5.0) 4.78 (1.67,5.0) 5.10 (1.6,5.12) 0.23
Length of hospital stay (days) 10.85 (4.58,13.16) 10.85 (4.58,13.12) 10.91 (4.83,13.81) 0.054

Reviewer 2
1. Comments: this manuscript contains only superficial information with many important limitations, already stated by the authors, such as missing details in SAHS diagnosis and severity. Furthermore, there is no data on SAHS treatment status before ICU admission, which is a major limitation in order to have a valid analysis and conclusion. Discussion section also needs improvement.

Response to comments: Thank you very much for your comments. We agreed that there are some limitations in our study. For SAHS diagnosis, we extracted information based on the patient’s diagnosis according to (ICD-9-CM) codes: 32720, 32721, 32723, 32724, 3275, 3276, 232727, and 78057, which were described in the section of “Study population and data extraction” in our manuscript. The lack of disease severity and analysis of CPAP treatment is indeed the defects of our study. A recent study by Cade et al. (in press, doi: 10.1164/rccm.202006-2252LE) revealed no significant difference between patients with CPAP treatment in the year prior and those without CPAP treatment, which has been added in the discussion of this manuscript. Our study is a retrospective cohort study base on a relatively considerable sample size, and we have tried our best to adjust various confounding factors to obtain a relatively reliable conclusion, which has a certain values for clinical work and future research.

The manuscript has been revised and improved, while these changes will not influence the content and framework of the paper. All the changes are marked in red in the revised manuscript. We hope that the revised manuscript could be approved for publication in your journal.

Once again, special thanks to you for the constructive comments and suggestions.
The manuscript was improved by revision. However, the authors should stress more that the limitations cannot justify their conclusions and more detailed studies are welcome to clearly define the research question. I also would suggest the authors' to properly proof read the manuscript to rule out minor inconsistencies. Language improvements are suggested.

| GENERAL COMMENTS |
|--------------------------------------------------|
| The manuscript was improved by revision. However, the authors should stress more that the limitations cannot justify their conclusions and more detailed studies are welcome to clearly define the research question. I also would suggest the authors' to properly proof read the manuscript to rule out minor inconsistencies. Language improvements are suggested. |

**VERSION 2 – AUTHOR RESPONSE**

1. **comment**: However, the authors should stress more that the limitations cannot justify their conclusions and more detailed studies are welcome to clearly define the research question.

   **Response to this comment**: For this question, we had an in-depth discussion in our team. We think it is not appropriate to justify the conclusion because of its limitations but we agreed that the limitations have an impact on the conclusion. After discussion, we added this sentence “These limitations led to a decline in the accuracy of our conclusions” to the limitation section to emphasize the effect of limitations on the conclusion, which is marked in red in our revised manuscript.

2. **comment**: I also would suggest the authors' to properly proof read the manuscript to rule out minor inconsistencies. Language improvements are suggested.

   **Response to this comment**: We are so sorry for our carelessness. We have carefully checked the errors and made the corrections in the whole manuscript. The language has been modified by native language experts. See the attachment for the editing certificate.