PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	GUSTATORY AND OLFACTORY DYSFUNCTION IN HOSPITALIZED PATIENTS WITH COVID-19 PNEUMONIA: A PROSPECTIVE STUDY
AUTHORS	Inciarte, Alexy; Cardozo, Celia; Chumbita, Mariana; ALCUBILLA, Pau; Torres, Berta; González Cordón, Ana; Rico, Veronica; Aguero, Daiana; García-Pouton, Nicole; Hernández-Meneses, Marta; ALBIACH, Laia; Meira, Fernanda; De la Mora, Lorena; Linares, laura; Puerta-Alcalde, Pedro; Macaya, Irene; Mensa, Josep; Laguno, Montse; AMBROSIONI, Juan; Ramos, Angela; Morata, Laura; Bodro, Marta; Moreno-García, Estela; Moreno, Antonio; Sola, Montse; Rojas, Jhon; Leal, Lorna; Torres, Manuel; Garcia-Vidal, Carolina; Martínez, Jose Antonio; Alobid, Isam; Soriano, Alex; Garcia, Felipe

VERSION 1 – REVIEW

REVIEWER	Vaira, Luigi A Sassari University Hospital
REVIEW RETURNED	21-Jun-2020

GENERAL COMMENTS	thanks for the opportunity to review this manuscript. I apologize for any mistakes; English is not my native language. the authors prospectively evaluate the gustatory and olfactory function of 80 COVID patients in order to establish: frequency, correlation with the clinical outcome, recovery times. although the frequency is now well established by studies based on psychophysical tests, as far as I know, there are no prospective studies in the literature. this study methodology is fundamental for evaluating recovery time. Furthermore, this study fits perfectly into the ongoing debate on the prognostic value of chemosensitive disorders. Another strong point is to evaluate only patients with moderate and severe forms of COVID-19 and pneumonia. There are very few studies analyzing this patient population In my opinion, this article is worthy of publication, but could be improved with some revisions. I would like to give some suggestions to the authors. Title: i would add ":" or "." After "pneumonia" and before "a prospective study"

	Abstract (and text): please spell out "ER" in full before using the acronym for the first time. Abstracts, results, line 48. "The prevalence of gustatory and olfactory dysfunction was 73.8%" I would change in "73.8% of the patients had a taste and / or smell disorder" OR "the prevalence of chemosensitive dysfunctions was 73.8%". Summary: SARS-CoV-2, COVID-19, ER, ICU (in the methods section) please spell out in full before using the acronym for the first time. Introduction (line 6-9): the number of cases and deaths is continuously increasing; I would add the date to which the reported data refer. Methods, "patients" section, line 45-50 (SARS-CoV-2 infection was confirmed by either viral PCR detection in a nasopharyngeal swab OR clinical and radiological…). I understand that positivity has been confirmed in some patients through nasopharyngeal swab while in others only through clinical criteria. If so, I would add in the study limitations that not all patients had PCR confirmation of infection. On the contrary, if all patients included in the study were to have a positive swab, please specify it better (change OR in AND). Methods "data collection" section. In the abstract, the authors say that chemosensitive functions were assessed daily. In this section, it appears that they have been assessed only upon admission, discharge and post-discharge for an unspecified period. It is necessary to specify better if the evaluation took place daily and how long the observation period lasted. Statistical analysis. Line 20-21, "with a confidence level of 95% and a confidence interval of 10.5" Is that correct? Discussion (page 14 line 7-29): it is true that the frequency of chemosensitive disorders reported in this study are different from those of Giacomelli et al. but it is similar to that found by many other authors (10.1002/hed.26269; 10.1002/HED.26204; 10.1016/j.medmal.2020.04.006; 10.1016/S1473-3099(20)30293-0; 10.1001/jama.2020.6771). The fundamental point is that there is a difference between the data that we get from the ER and what we would have if we asked patients if they have chemosensitive problems. Trivially, the patient who arrives in ER with severe dyspnea does not report having anosmia if we do not ask him. This is demonstrated very well by the results obtained by the authors and confirms that all studies that are based only on the analysis of patient medical records (e.g big epidemiological studies) are not accurate in determining the frequency of

	chemosensitive dysfunctions. Discussion (page 15 line 50 to page 16 line 6). In the abstract the most important conclusion is that the presence of a chemosensitive disorder does not influence the prognosis. I would also better underline this concept in the discussion by inserting it in the debate currently underway in the literature between those who say that the presence of a chemosensitive disorder is related to a mild prognosis (10.1002/alr.22292) and those who say that chemosensitive disorders do not have a prognostic value (10.1002/alr.2287; 10.1002/alr.22608). the manuscript needs a revision of English, there are several typographical and some grammatical errors.

REVIEWER	Tsivgoulis, Georgios University of Athens, School of Medicine, Athens, Greece
REVIEW RETURNED	22-Jul-2020

GENERAL COMMENTS	This is a prospective, cohort study with the aim to assess the prevalence of gustatory and olfactory dysfunction in hospitalized patients with COVID-19 associated pneumonia and to investigate their clinical outcomes and recovery rates. Certain issues exist that need to be addressed by the authors. 1. Patient assessment was based on questionnaires and was not established through objective or quantitative methods. 2. Gustatory dysfunction may have been confounded by loss or dysfunction of retronasal olfaction. 3. Patients were not assessed for the possibility of concurrent rhinosinusitis or rhinitis. 4. Although authors highlight the need of early recognition of mildly symptomatic COVID-19 patients for prompt transmission control, they have actually studied hospitalized patients only. 5. SARS-CoV-2 was not confirmed in all included patients with RT-PCR. 6. Not all patients completed follow up. 7. Patient population was limited. 8. Authors should include in the Methods section the details regarding the assessment of the correlation between negative and positive symptoms reported by ER physicians. 9. Language needs minor editing. Several typos and syntax errors exist throughout the manuscript. 10. Authors should correct the number of COVID-19 associated deaths worldwide reported in the Introduction.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Luigi Angelo Vaira
Institution and Country: University Hospital of Sassari, Italy
Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below
thanks for the opportunity to review this manuscript. I apologize for any mistakes; English is not my native language.

the authors prospectively evaluate the gustatory and olfactory function of 80 COVID patients in order to establish: frequency, correlation with the clinical outcome, recovery times. although the frequency is now well established by studies based on psychophysical tests, as far as I know, there are no prospective studies in the literature. this study methodology is fundamental for evaluating recovery time. Furthermore, this study fits perfectly into the ongoing debate on the prognostic value of chemosensitive disorders. Another strong point is to evaluate only patients with moderate and severe forms of COVID-19 and pneumonia. There are very few studies analyzing this patient population

In my opinion, this article is worthy of publication, but could be improved with some revisions. I would like to give some suggestions to the authors.

Thanks for your appreciation and offer

Title: i would add ":" or "." After "pneumonia" and before "a prospective study"
As clearly stated by the reviewer ":" was added after pneumonia.

Abstract (and text): please spell out "ER" in full before using the acronym for the first time. Abstracts, results, line 48. "The prevalence of gustatory and olfactory dysfunction was 73.8%" I would change in "73.8% of the patients had a taste and/or smell disorder" OR "the prevalence of chemosensitive dysfunctions was 73.8%".
As clearly stated by the reviewer "emergency room" was added before using the acronym and the prevalence of chemosensitive dysfunction was added to the abstract results section
Summary:

SARS-CoV-2, COVID-19, ER, ICU (in the methods section) please spell out in full before using the acronym for the first time.
As clearly stated by the reviewer "SARS-CoV-2, COVID-19, ER, ICU" was spelled out in full before using the acronym in the methods sections and introduction.

Introduction (line 6-9): the number of cases and deaths is continuously increasing; I would add the date to which the reported data refer.

As suggested by the reviewer reported data about the number of cases and death was added as follow "has resulted in a pandemic with more than 26 million reported cases and, as last reported in September 2020, 800000 deaths"

Methods, "patients" section, line 45-50 (SARS-CoV-2 infection was confirmed by either viral PCR detection in a nasopharyngeal swab OR clinical and radiological…). I

understand that positivity has been confirmed in some patients through nasopharyngeal swab while in others only through clinical criteria. If so, I would add in the study limitations that not all patients had PCR confirmation of infection. On the contrary, if all patients included in the study were to have a positive swab, please specify it better (change OR in AND).

Thank you for raising these points. As suggested by the reviewer the sentence "not all the patients received PCR confirmation of the infection" was added to study limitations.

Methods "data collection" section. In the abstract, the authors say that chemosensitive functions were assessed daily. In this section, it appears that they have been assessed only upon admission, discharge, and post-discharge for an unspecified period. It is necessary to specify better if the evaluation took place daily and how long the observation period lasted.
As the reviewer suggested; the timelines of chemosensitive functions were further detailed in the data collection section, as follows "Patients were asked about gustatory and olfactory dysfunction symptoms, such as ageusia, dysgeusia, anosmia, and hyposmia on a daily basis until discharge" ……. "Gustatory and olfactory dysfunction were reevaluated during telemedicine consultations on a weekly basis after discharge". .

Statistical analysis. Line 20-21, "with a confidence level of 95% and a confidence interval of 10.5" Is that correct?

This sentence has been changed as follow: "olfactory dysfunction presented in percentages with a confidence level of 95%"

Discussion (page 14 line 7-29): it is true that the frequency of chemosensitive disorders reported in this study are different from those of Giacomelli et al. but it is similar to that found by many other authors (10.1002/hed.26269; 10.1002/HED.26204; 10.1016/j.medmal.2020.04.006; 10.1016/S1473-3099(20)30293-0; 10.1001/jama.2020.6771). The fundamental point is that there is a difference between the data that we get from the ER and what we would have if we asked patients if they have chemosensitive problems. Trivially, the patient who arrives in ER with severe dyspnea does not report having anosmia if we do not ask him. This is demonstrated very well by the results obtained by the authors and confirms that all studies that are based only on the analysis of patient medical records (e.g big epidemiological studies) are not accurate in determining the frequency of chemosensitive dysfunctions.
Indeed, that the frequency of chemosensitive disorders reported in this study are similar to those found by many other authors; Vaira et al, Klopfenstein et al, Spinato et al. which gives external validity to our study. Patients tend to disclose symptoms that are either more annoying or they consider more severe. Patients with a more severe disease are more prone to self-neglect chemosensory loss in the emergency room setting than outpatients patients

Discussion (page 15 line 50 to page 16 line 6). In the abstract, the most important conclusion is that the presence of a chemosensitive disorder does not influence prognosis. I would also better underline this concept in the discussion by inserting it in the debate currently underway in the literature between those who say that the presence of a chemosensitive disorder is related to a mild prognosis (10.1002/alr.22292) and those who say that chemosensitive disorders do not have a prognostic value

(10.1002/alr.2287; 10.1002/alr.22608).
Thank you for bringing this point to our attention. We have added a paragraph in the discussion section to address this issue as follows: "there is some debate as to whether or not the presence of chemosensory disorder is related to a better prognosis. In some studies, the absence of anosmia was associated with a mild-to-moderate COVID-19 infection and outpatient care. Other studies have concluded that there is no prognostic value; however, the persistence of olfactory dysfunction at day 20 is associated with a more severe disease course".

the manuscript needs a revision of English, there are several typographical and some grammatical errors.

As recommended a native English speaker colleague assisted with the quality of the English, typographical and grammatical errors were corrected throughout the manuscript

Reviewer: 2
Reviewer Name: Georgios Tsivgoulis
Institution and Country: Second Department of Neurology, National and Kapodistrian University of Athens,School of Medicine, Attikon University Hospital, Athens, Greece
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
This is a prospective, cohort study with the aim to assess the prevalence of gustatory and olfactory dysfunction in hospitalized patients with COVID-19 associated pneumonia and to investigate their clinical outcomes and recovery rates.
Certain issues exist that need to be addressed by the authors.
1. Patient assessment was based on questionnaires and was not established through objective or quantitative methods.
Thank you for point this out, as your clearly state the main limitation of the study was lack of quantitative assessment and this is highlighted in the first paragraph of our limitation section.

2. Gustatory dysfunction may have been confounded by loss or dysfunction of retronasal olfaction.
As reviewer suggested; "and the use of an accepted retro nasal olfaction test methods" was added to the limitation section,

3. Patients were not assessed for the possibility of concurrent rhinosinusitis or rhinitis.
We agree with the reviewer and had added that concurrent disease was rhinitis that observed in 3 patients and we have added this point in clinical symptoms on table 2.

4. Although authors highlight the need of early recognition of mildly symptomatic COVID-19 patients for prompt transmission control, they have actually studied

hospitalized patients only.
The following phrase was added in the limitation section "The conclusions of this study should be limited to the selected population that represents mostly hospitalized patients excluding milder cases without pulmonary involvement and the most critical with direct admission to the ICU unit"

5. SARS-CoV-2 was not confirmed in all included patients with RT-PCR.
The sentence "not all the patients received PCR confirmation of the infection" was added to study limitations.

6. Not all patients completed follow up.
The sentence "Not all patients completed follow up" was added to study limitations.

7. Patient population was limited.
The sentence "Patient population was limited" was added to study limitations.

8. Authors should include in the Methods section the details regarding the assessment of the correlation between negative and positive symptoms reported by ER physicians
The sentence "negative findings were determined by the absence of the studied symptoms on the ER charts and positive findings were determined by the presence of the studied symptoms on the ER chars" was added to materials and methods section.
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9. Language needs minor editing. Several typos and syntax errors exist throughout the manuscript.
As suggested by the reviewer minor typos and syntax errors were corrected throughout the manuscript.

10. Authors should correct the number of COVID-19 associated deaths worldwide reported in the Introduction.

As suggested by the reviewer the number of COVID-19 associated deaths worldwide was updated and corrected as follow: . "as last reported in September 2020, 800000 deaths"

VERSION 2 – REVIEW

REVIEWER	Vaira, Luigi A Sassari University Hospital
REVIEW RETURNED	26-Oct-2020

GENERAL COMMENTS	the authors responded satisfactorily to all observations