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GUSTATORY AND OLFACTORY DYSFUNCTION IN HOSPITALIZED PATIENTS WITH COVID-19 PNEUMONIA A PROSPECTIVE STUDY

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Running title: Olfactory and gustatory dysfunction in COVID-19 Pneumonia.

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ABSTRACT

Importance: Identifying undetected clinical signs is imperative in the prevention of SARS-CoV-2.

Objective: To establish the prevalence of clinical gustatory and olfactory dysfunction in COVID-19 pneumonia patients. Clinical outcomes and recovery rates associated with gustatory and olfactory dysfunction were also assessed.

Design: A prospective study was performed in 80 COVID-19 pneumonia hospitalized patients. Patients were reevaluated daily at wards until discharge, gustatory and olfactory dysfunction symptoms were retrospectively collected from ER charts after first assessment. Follow-up was performed in telemedicine consultation.

Setting: The study was performed in a single-center hospitalization ward at a University hospital.

Participants: Consecutive patients with hospitalization criteria of COVID-19 pneumonia were eligible and those unable to talk, previous gustatory and olfactory dysfunction, and negative SARS-CoVID-19 PCR were excluded.

Interventions: Systematic assessment of gustatory and olfactory symptoms with standardized questions.

Outcome(s): Gustatory and olfactory dysfunction prevalence in COVID-19 pneumonia patients.

Results: Among the 80 individuals 62.5% were male, the median age was 57-years and 50% (n=40) had comorbidities. The prevalence of gustatory and olfactory dysfunction was 73.8% (n=59) [CI-95%, (63.8-83.8)], although only 26.3% (n=21) of the patients self-reported symptoms in the ER. Gustatory and olfactory changes were observed in 58.8% (n=47) and 55% (n=44) of cases, respectively and were the first symptoms in 25% (n=20) of patients. Anosmia was associated with

ageusia, OR:7 (CI-95%, 2.3-21.8 p=0.001). There was an association between hyporexia and gustatory dysfunction, OR:4.1 [CI-95%, 1.23-13.67 p=0.016]. No differences in clinical outcomes were observed when patients with and without gustatory and olfactory dysfunction were compared. Recovery rates of gustatory and olfactory dysfunction were 20% (n=10) and 85% (n=42), at day 7 and 45 respectively.

Conclusion: The prevalence of gustatory and olfactory dysfunction in COVID-19 pneumonia was much higher that detected by self-reporting. Presence of gustatory and olfactory dysfunction was not a predictor of clinical outcome.

Article Summary

- Prospective study design in consecutive patients with COVID-19 pneumonia.
- Prospective recovery rates of gustatory and olfactory function in COVID-19 pneumonia patients.
- Lack of validated olfactory and gustatory questionnaires.
- Lack of olfactory and gustatory quantitative assessment.
- The selected population represents mostly hospitalized patients excluding milder cases

Introduction

SARS-CoV-2 is causing a pandemic with more than 2.9 million reported cases and it has caused more than 1900000 deaths so far **(1)**. In the absence of an effective vaccine, basic strategies to avoid the spread of highly contagious infections include the early recognition of cases. Therefore it is highly important to identify potential undetected early clinical signs, given the possibility of early transmission as described in several studies (2-4)**.** In this scenario, establishing contact tracing of suspected cases with key clinical findings is of utmost importance according to the latest recommendations of the world health organization **(5)**. In addition, prompt diagnosis and treatment of any potentially severe viral infection is essential to improve the clinical outcomes.

Gustatory and olfactory dysfunction is an unrecognized condition not well defined in general medical practice, in which it it is very difficult to establish causal relationships firmly. Among the etiologies, viruses are the most common ones; *Coronavirus, Influenza,* and *Picornavirus* have been detected in nasal secretions in smell studies, with a wide range of severity and even permanent loss of smell and taste **(6)**. The consequences of gustatory and olfactory dysfunction compromise the quality of life and the mood state **(7)**.

In the initial reports of the pandemic in Wuhan area, gustatory and olfactory dysfunction were not described **(8-10)** while a small retrospective study performed in Milan estimated a prevalence of gustatory and olfactory dysfunction around 34% of the patients hospitalized with COVID-19 infection **(11**). Several reports from isolated sudden onset anosmia have also recently described in COVID-19 patients **(12,13)**. A recently published

multicenter-crossectional study performed in France and Belgium reported a prevalence of 85% of smell and gustatory dysfunction in mild cases **(14).** However, the incidence in severe cases requiring hospital admission needs to be defined. Since the onset of the pandemic in Barcelona, there are a great number of self-reported gustatory and olfactory symptoms in hospitalized pneumonia patients with a confirmed COVID-19 in our health care center. The present study aims to estimate the prevalence, clinical traits, and evolution of gustatory and olfactory dysfunction in patients hospitalized for COVID-19 associated pneumonia.

Materials and methods

Study design

We performed a prospective assessment to patients consecutively admitted to a dedicated ward where attending physicians evaluated gustatory and olfactory dysfunction. After the initial evaluation a retrospective review of the ER charts prior admission was also reported to determine self-report. The study was conducted in the hospital clinic of Barcelona, a tertiary University reference center. The study populations were patients with COVID-19 pneumonia admitted from february 28th to april 24th in one of the hospitalization wards. Data collection was performed on april 30th.

The main objective of this study was to determine the proportion of gustatory and olfactory dysfunction in hospitalized patients with the diagnosis of COVID-19 pneumonia. Secondary endpoints were; to characterize clinical traits, to describe laboratory values, to recognize factors associated with gustatory and olfactory dysfunction, to explore potential differential outcomes between patients with and without gustatory and olfactory dysfunction and to examine gustatory and olfactory recovery rates trough time.

Patients

SARS-CoV-2 infection was confirmed by either viral by real-time polymerase chain reaction (PCR) detection in a nasopharyngeal swab or clinical and radiological characteristics according to the ECDC criteria **(15)**, which states the following: 1) acute respiratory tract infection (sudden onset of cough, fever, shortness of breath), 2) severe acute respiratory infection (fever and at least one sign/symptom of respiratory disease (e.g., cough, fever,

shortness breath) requiring hospitalization with unilateral or bilateral interstitial infiltrate in the chest-X ray. This clinical definition was implemented by the 15th of March onwards when the percentage of positive microbiologically documented cases was higher than 70% from the total of the collected samples. Patients with prior dysfunctions, unable to talk, with mental impairment and with negative SASRS-CoV-2 results were excluded from the analysis. Inclusion of consecutive patients from the same ward were established to avoid selection bias, also patients with direct admission to the ICU, and posterior discharge to the ward were excluded to avoid memory bias.

Data Collection

Directed anamnesis was performed to each patient upon arrival to the ward, including baseline characteristics, demographics and classical pneumonia signs. Patients were asked for gustatory and olfactory dysfunction symptoms such as: ageusia, dysgeusia, anosmia and hyposmia. The following questions were asked systematically to all patients; have you noticed any sudden and recent changes in smell and taste? If it was positive, was this the first symptom?, is there a total reduction of taste and smell, is there a partial reduction of taste and smell?, do the symptoms have disappeared?, when does symptoms disappear?. Gustatory and olfactory dysfunction was reevaluated at the moment of discharge and post-discharge by telemedicine consultations where they were asked if, they had resolution of the symptoms, if there was a partial or total recovery?, and when the symptoms resolved. During admission further laboratory tests (liver enzymes, creatinine, C-reactive protein, D-dimer, leucocytes count, CD4, CD8, CD3 count ferritin, and procalcitonin) were performed to all patients. The last follow-up date was on April 24th.

For data collection, variables were extracted from electronic health records in the SAP 740 Hospital Information System© (Societas Europaea, Walldorf, Germany). The results obtained were included in a database created with the program MICROSOFT EXCEL© for later analysis with the statistical package SPSS v18.0© (IBM corporation, Armonk, New York, USA).

Statistical analysis

The primary endpoint of the study was the proportion of patients with gustatory and olfactory dysfunction presented in percentages with a confidence level of 95% and a confidence interval of 10.5. For analyzing categorical variables compared between groups the Fisher's exact test was performed; significant p values were shown in Odds ratios and confidence intervals. The significance level was p-value <0.05. The inferential analysis of continuous variables, such as laboratory values, was performed using parametric tests (Student's t-test); Pearson test was performed to correlate the duration of the symptoms and inflammatory markers. Missing data was reduced by using an operator manual at the start of the study and carefully collecting the data. The missed data was managed with the listwise selection approach.

Sample Size calculation

An estimated sample size of 80 patients would allow an accuracy of 10.5% with a confidence interval of 95% for an expected prevalence of 33% as shown in the previous study by Giacomelli et al. **(11)**

Ethics.

The hospital's research ethics committee and the competent Spanish authorities approved the protocol describing the project proposed by the researcher (approval number HCB/2020/0458).The processing, reporting, and transfer of personal data for all participating subjects complied with the provisions in Organic Act 15/1999 of 13 December (Spanish Royal Decree 1720/2007 of 21 December), and the current Regulation EU 2016/679 of the European Parliament and the European Council at April 27, 2016, being mandatory after May 25, 2018, on the Protection of Personal Data and guarantee of digital rights. The patients either signed written consent or when it was not possible due to the pandemic and isolation measure an oral consent was given by the patient and it was recorded in the Electronic Clinical Documentation.

Patient and public involvement: The patients were not involved in the study described.

Results

Baseline characteristics

Of the 1738 patients with COVID-19 who have been admitted in the hospital from February 28th to April 24th, 1371 were hospitalized in several hospitalization wards and 337 in the ICU. The analysis of gustatory and olfactory dysfunction was prospectively performed in 80 patients as it is shown in the flow chart, [Figure 1]. The median (IQR) age was 57 (43-70) years old, 62.5 % were males. Eleven patients (14%) were health care workers. The origin was mostly European 71% (n=57) and Latin American 25% (n=20). Comorbidities were present in 50% (n=40) of patients. The median (IQR) time from symptoms onset to hospital admission was 8 (5-10) days, and the median (IQR) length of stay (LOS) was 8 (5-12.5) days [Table 1].

Gustatory and olfactory dysfunction

The main clinical symptoms reported by patients are depicted in table 1. The prevalence of gustatory and olfactory dysfunction was found in this sample to be 73.8 % (n=59) [95 % (CI 63.8% to 83.8 %]. Separately, gustatory and olfactory dysfunction was present in 58.8% (n=47) and 55% (n=44) of cases, respectively. Anosmia was the most frequent symptom present in 46.3% (n=37), followed by dysgeusia in 41.3 % (n=33), ageusia in 28.3% (n=23) and hyposmia in 15% (n=12). In 21% (n=7) of the patients with dysgeusia, it was described as salty taste. There was an association between the coexistence of ageusia and anosmia, OR: 7 [IC: 95 2.26 to 21.8 p= 0.001]. Gustatory and olfactory dysfunction was the first symptom in 25% (n=20) of the cases. Only in one case, gustatory and olfactory dysfunction appeared 7 days after admission; the rest of the patients had gustatory and olfactory

symptoms before hospital admission. In the ER only 26.3 % (n=21) of the patients reported olfactory-gustatory dysfunction. ER physicians were more likely to report positive clinical findings rather than negative findings (90.5% vs. 9.5%), OR: 4.6 [0.97-21.95 IC: 95 p= 0.039].Among the classical pneumonia symptoms fever was present in 89% (n=71) of the patients and it was the most frequent consulting symptom in the ER 53.8% (n=43). The second most common symptom was coughing 77.5% (n=62), followed by dyspnea 58.8% (47%), asthenia 56.3% (n=45), myalgia 50% (n=40), hyporexia 38% (n=33); vomiting 8.8 % (n=7) and skin lesions 6.3% (n=5) were uncommon [Figure 2]. There was an association between hyporexia with gustative dysfunction, OR: 4.1 [1.23 to 13.67 IC: 95 p= 0.016], also there was association between cough and presence of gustatory and olfactory dysfunction, OR: 1.2 [0.12 to12.86 IC: 95, p= 0.046]. [Table 1].

Among laboratory abnormalities, CRP values were elevated at admission in 91.8% cases, along with lymphopenia 98.8%, other common findings were elevation of lactate dehydrogenase 76.2%, D-Dimer 66.2 %, and hyperferritinemia 63.2%. [table 2].

There were differences between AST and ALT values between those with gustatory-olfactory dysfunction and those without symptoms [(33 vs. 61 UI/l) p=0.019 and (28 vs. 49) p= 0.003], respectively. No differences in the others laboratory findings were found between the studied groups [Table 2].

Treatment prescribed

All the patients received hydroxicloroquine and azithromycin, about 91.3 % (n=73) of the patients received Lopinavir boosted with ritonavir, 38.8% (n=31), Interleukin blockers and

30.4% (n=24) corticosteroids. A few started teicoplanin 18.8% (n=15), and Interferon 7.6% (n=6). Oxygen supplementation was required in 69.8% (n=55) of the patients and 10% (5%) required intubation. No differences were detected between study groups [Table 3].

Clinical outcomes

A total of 90% (n=73) patients were discharged at the moment of this publication and 13.8% (n=11) required ICU during the admission, none of them died. After discharge 87% (n=67) had a telemedicine follow-up to check on their status. There were not readmission episodes.

There was no association between outcomes in patients with gustatory and olfactory dysfunction and those without gustatory and olfactory dysfunction, in terms of ICU admission, LOS, SpO2/FiO2 ratio, oxygen supplementation, respiratory distress or organizing pneumonia. Pulmonary embolism was associated with the absence of gustatory and olfactory dysfunction (21% vs 0) p=0.0001. [Table 3].

Gustatory and olfactory outcomes

From the 59 patients with gustatory-olfactory dysfunction were 50 were reassessed for follow-up. At day 7 after discharge 20% (n=10) had recovered gustatory and olfactory function, in days 14, 30 and 45 recovery rates were 28% (n=14), 56% (n=28) and 84% (n=42) respectively. The median time of recovery was 14 days (7-30), [Figure 3].

The time of olfactory-gustatory recovery was positively correlated with age r: 0.48 p= 0.03 and ferritin levels r: 0.353 p=0.037. There was no correlation with severity degree of respiratory function or any other abnormal laboratory values.

Discussion

This is a prospective study evaluating the prevalence of gustatory and olfactory dysfunction in hospitalized patients. We found a prevalence of 74% in all patients admitted to a hospital ward with COVID-19 pneumonia who could be questioned. In a previous study in hospitalized patients overall prevalence was reported to be 33% **(11).** The main reason for this discrepancy could be related to: first, the retrospective design of that study, second the reassessment of the ER electronic health records in hospitalization wards demonstrated an unrecognized prevalence of gustatory and olfactory dysfunction of 53% in this prospective cohort. In fact, short communications reports in Italy already acknowledge a self-reported prevalence of gustatory and olfactory dysfunction in retrospective charts of 19 % **(16).**

In our cohort, gustatory and olfactory dysfunction syndrome was almost as prevalent as fever and cough, the classical symptoms of viral pneumonia. In the context of flu-like symptoms along with gustatory- olfactory dysfunction syndrome, the possibility of COVID-19 must be addressed. In a recent case-control study gustatory and olfactory dysfunction was 10 times higher in patients with PCR positive results than those with negative results **(17).**

Our study reported 55% of anosmia, in contrast, Lechein et al, reported anosmia in 86% patients in the setting of a symptom-oriented otorhinolaryngology specialized consultation; they were younger patients, without comorbidities and most of them were health care providers as opposed to our older and more comorbid cohort of hospitalized

patients. An Iranian case-control study reported olfactory changes in nearly 98% of de COVID-19 patients with a median age of 46 years evaluated by quantitative testing of the sense of smell. This study suggests that hyposmia quantitative testing might serve as a rapid alternative diagnostic to screen for SARS-CoV-2 **(18)**. The role of this test in older patients remains unclear due to the related age changes in the smell function **(19).**

Similar clinical signs and symptoms were observed between patients with and without gustatory and olfactory dysfunction. Coughing was observed more frequently in patients with gustatory and olfactory dysfunction but a more severe respiratory syndrome was not observed. Gustatory dysfunction was associated with hyporexia, which might be particularly relevant for patient's quality of life and activities of daily life especially if it is persistent (**20-21**).

There were no major alterations in laboratory values. A mild to moderate elevation of the liver enzymes were common in the absence of GOD symptoms, no case of acute liver failure was reported. Although it is difficult to establish an explanation for these findings, it could be due to inflammatory changes in the liver, or related to a different tissue expression of receptors and entry molecules. ACE2 and TMPRSS2 are expressed in cells from multiple tissues including olfactory cells and liver, the degree in which tropism might affect different tissues is not well established **(22).**

Clinical outcomes were similar in both groups, except for the presence of pulmonary embolism in 20% of patients without gustatory and olfactory dysfunction symptoms, it could not be excluded from the presence confounding factors associated with pulmonary

embolism such as tromboprophylaxis **(23),** and further investigation should be implemented to validate these results.

Lechein et al, reported that recovery olfactory rates were 72% on day 8. Since our study represented olfactory and gustatory outcomes together establishing comparisons might be difficult, however, we found recovery rates of just 20% on day 7 and 84% on day 45. Another possibility for this discrepancy might be the older age of our cohort and the more severe clinical manifestations of COVID-19.

Although no correlation between etiopathogenic factors and the length of gustatory and olfactory function recovery has been made so far, the inflammatory reaction process might play a role. Our data support that higher levels of ferritin and older age are associated with longer recovery rates. Ferritin levels have been reported in previous studies to be markedly higher in severe cases than in moderate cases of COVID-19 with longer recovery rates and also older age was associated with higher disease severity (**24-26**).

Strengths and weaknesses of the study

The main limitation of this study was, the lack of validated olfactory and gustatory questionnaires based on the smell and taste component which could give a more standardized approach and the impossibility to perform olfactory-gustatory testing using quantitative measurements, still a standardized non-validated questionnaire was implemented and used systematically in all patients. Consecutive patients were included in this study to minimize selection bias, although selection could still be a cause of bias in

our data. The selected population represents mostly hospitalized patients excluding milder cases without pulmonary involvement and the most critical with direct admission to the ICU unit.

Conclusions and policy implications

There is high prevalence of gustatory and olfactory dysfunction in COVID-19 pneumonia hospitalized patients. Self-report rates are low in our population. To improve surveillance in this pandemic it is strongly suggested redefine case definition for COVID-19 in international guidelines.

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Transparency statement: All the information displayed in the present manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Data sharing statement: Extra data will be available by emailing ajinciar@clinic.cat

Patient and public involvement: The patients were not involved in the study described; there will be enlisting of patients in disseminating the research findings to the general population in primary care settings.

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Table 1. Baseline characteristics according to the presence of gustatory and olfactory dysfunction in patients with COVID-19 pneumonia.

VARIABLE	COHORT	GOD	Absence of GOD	p Value
N	80	59	21	
Median (IQR) Age	57 (42-70)	58 (44-69)	55 (38-72)	0.782
Male, n (%)	50 (63)	34 (59)	15 (71)	0.325
RT-PCR (+) nasopharyngeal swab, n (%)	73 (91.2)	55 (93)	19 (86)	0.985
European, n (%)	57 (71)	37 (64)	14 (67)	0.940
Coexisting illness, n (%)	40 (50)	27 (47)	12 (57)	0.370
Hypertension, n (%)	22 (29)	17 (29)	5 (23)	0.738
Diabetes, n (%)	8 (10)	6 (10)	2 (10)	0.932
Pulmonary disease, n (%)	8 (10)	7 (14)	1 (5)	0.168
Oncologic disease, n (%)	5 (6)	2 (3)	3 (14)	0.76
Heart disease, n (%)	5(6)	3 (5)	2 (11)	0.453
Health Care Worker, n (%)	11(14)	3 (14)	3 (14)	0,934
Median (IQR) days from onset to ER	8 (5.25-10)	8 (5-11)	7 (5.5-9)	0.135
Fever, n (%)	71 (89)	52 (88)	19 (91)	0.771
Cough, n (%)	62 (78)	49 (83)	13(62)	**0.046**
Shortness of breath, n (%)	52 (65)	35 (59)	17 (81)	0.074
Asthenia, n (%)	45 (56)	33 (56)	12 (57)	0.934
Myalgia, n (%)	40 (50)	34 (53)	9 (43)	0.147
Diarrhea, n (%)	35 (44)	25 (42)	10 (48)	0.677
hyporexia, n (%)	33(38)	29 (49)	4 (19)	**0.016**
Headache, n (%)	28 (35)	24 (41)	4 (19)	0.061
Arthralgia, n (%)	10(13)	8(14)	2 (10)	0.545
Chest Pain, n (%)	9 (11)	6 (10)	3 (14)	0.608
Odynophagia n, (%)	7 (9)	6 (10)	1 (5)	0.451
Vomiting, n (%)	7 (9)	6 (10)	1 (5)	0.451
Rash, n (%)	5 (6)	5 (9)	0	0.168

IQR: interquartilic range. GOD, Gustatory and olfactory dysfunction.

Table 2. Laboratory values according to the presence of gustatory and olfactory dysfunction in patients with COVID-19 pneumonia. (n=80)

VARIABLES	COHORT	GOD	Absence of GOD	p Value
N	80	59	21	
CRP mg/dL [< 1.0]	9 (3-14)	8 (3-16)	10 (5-13)	0.838
LDH mg/dL [< 234]	310 (268-386)	309 (250-367)	342 (260-453)	0.109
Ferritin mg/dL [< 200]	716 (256-1322)	592 (241-1255)	1066 (300-1552)	0-093
AST UI/L [5.0 - 40.0]	39 (25-61)	33 (22-50)	61 (39-94)	**0.003**
ALT UI/L [5.0 - 40.0]	29 (20-68)	28 (19-55)	49 (27-102)	**0.019**
BT mg/dL [0.20 - 1.20]	0.64 (0.8-0.4)	0.6 (0.4-0.75)	0.8 (0.55-1.05)	0.560
LYM cells/mm^3 [4.00 - 11.00]	0.9 (0.6-1.3)	0.9 (0.6- 1.3)	0.8 (0.6-1.5)	0.820
D-Dimer ng/ml [< 500]	800 (400-1200)	700 (400-1100)	1000 (600-1800)	0.251
Platelets cells/mm^3 [130 - 400]	212 (168-266)	213(170-265)	209 (150-281)	0.735
Creatinine mg/dL [0.30 - 1.30]	0.6 (0.7-09)	0.78 (0.63-0.91)	0.86 (68-0.98)	0.630
Calcium meq/l[8.5 – 9.5]	8.2 (8-8.5)	8.2 (8-8.6)	8.1 (7.8 --8.3)	0.735
Cd4 Cels/µL [530 - 1300]	356 (248-579)	358.5 (258.7-630)	328 (225-464)	0.414
Cd8 Cels/µL [330 - 920]	225 (147-353)	241 (148 -256)	186 (140.7-396)	0.934
Cd3 Cels/µL [1000 - 2200]	630 (404-1014)	676 (459.5-1035)	496 (386-792)	0.310

CRP, C-re-active protein; LDH, Lactate deshidrogenase; AST, Aspartate tranferase ; ALT, Alanine transferase; BT, Total bilirubine; LYM, lymphocyte; NEU, neutrophil; CD4, CD4+ count;CD8, CD8+ count; GOD, Gustatory and olfactory dysfunction.

Table 3. Clinical outcomes according to the presence of gustatory and olfactory dysfunction in patients with COVID-19 pneumonia

VARIABLE	COHORT	GOD	Absence of GOD	p Value
N	80	59	21	
LOS (IQR)	8 (4-11.75)	8 (4.2-11)	7 (4-14)	0.836
SpO2/fiO2 ratio (IQR)	448 (245-247)	451 (257-471)	391 (197-471)	0.346
Lopinavir/ritonavir, n (%)	73 (94)	52 (91)	21 (100)	0.161
Interferon, n (%)	6 (8)	4 (7)	2 (10)	0.638
Corticosteroid, n (%)	24 (30)	15 (3)	9 (43)	0.147
Interleukin blocker, n (%)	33 (41)	22 (37)	11 (52)	0.228
ICU admission, n (%)	11 (14)	7 (12)	4 (19)	0.412
Complication n, (%)	32 (41)	20 (35)	12 (57)	0.07
Oxygen requirement, n (%)	55 (69)	40 (68)	15 (71)	0.758
Orotraqueal intubation, n (%)	8	5 (8.5)	3 (14)	0.867
Respiratory distress, n (%)	31	20 (34)	11 (52)	0.135
Pulmonary embolism, n (%)	5 (6)	0	5 (23)	0.0001
Organizing pneumonia, n (%)	10 (13)	5 (9)	5 (24)	0.068

LOS, length of stay; SpO2, peripheral capillary oxygen saturation; FiO2, Fraction of Inspired Oxygen; IQR, Interquartilic range; GOD, Gustatory and olfactory dysfunction.

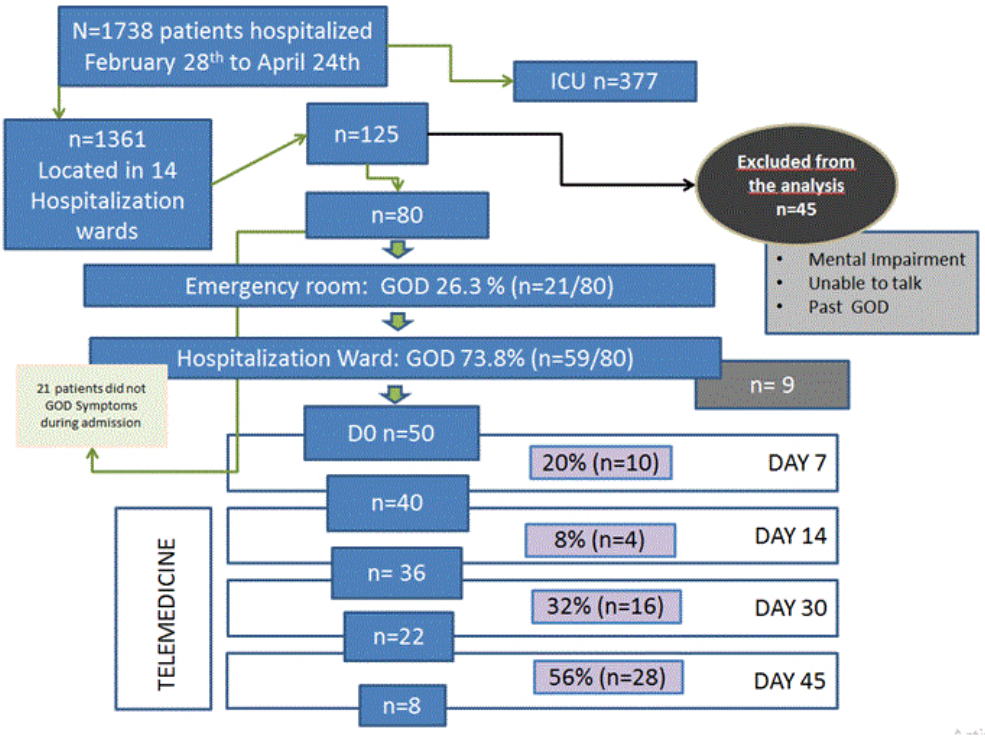
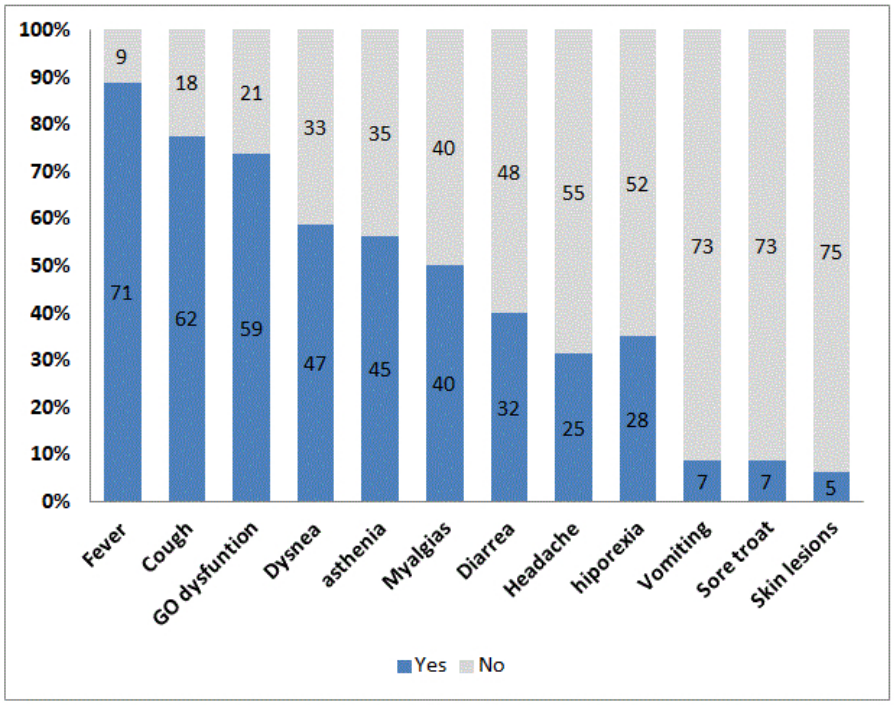


Figure 1. Study Flow Chart. Day 0: If the patient meets criteria is included in the study. Blue boxes represent individuals on follow-up with gustatory-olfactory dysfunction, lilac boxes represents individuals in which the recovery event develops. Gray boxes represent individuals lost to follow up. White boxes represent timelines and mode of follow-up.

244x190mm (72 x 72 DPI)

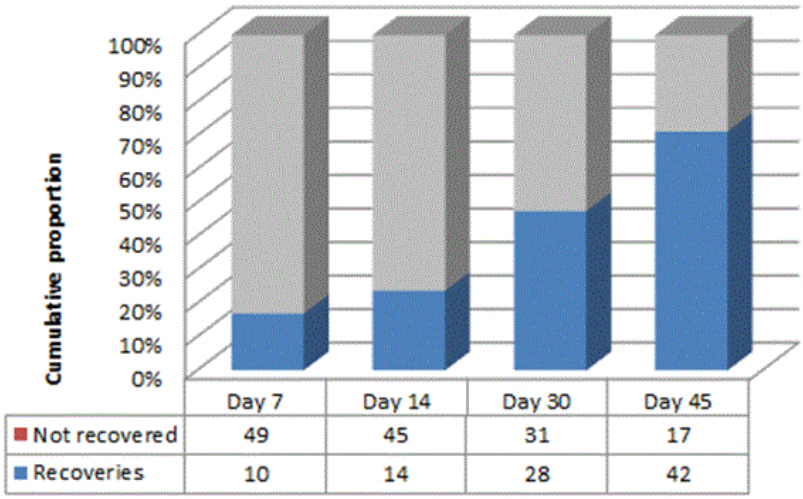
Figure 2. General symptoms in patients with COVID-19 pneumonia in absolute numbers (n=80)



GOD: Gustatory and olfactory dysfunction

244x189mm (72 x 72 DPI)

Figure 3. Recovery rates of gustatory-olfactory dysfunction trough time at follow up post – discharge n=50



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Section 1: What is already known on this topic?
• Self reported prevalence in Pneumonia population. • Prevalence in cross-sectional studies in mild disease forms in specific groups (health care workers) and specific consultation (ENT consultations) • One study retrospective study of recovery rates in pauci symptomatic patients.
Section 2: What this study adds?
• Prevalence of gustatory and olfactory symptoms in COVID-19 pneumonia population. • Prospective recovery rates in a more severe disease group (COVID-19 pneumonia patients) • Our study suggest there is no association between severity outcomes of patients with gustatory and olfactory dysfunction and those who don't
Implication: Support a more generalized consensus of gustatory and olfactory symptoms in case definition of COVID-19 in international organizations.

BMJ Open

GUSTATORY AND OLFACTORY DYSFUNCTION IN HOSPITALIZED PATIENTS WITH COVID-19 PNEUMONIA: A PROSPECTIVE STUDY

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GUSTATORY AND OLFACTORY DYSFUNCTION IN HOSPITALIZED PATIENTS WITH COVID-19 PNEUMONIA: A PROSPECTIVE STUDY

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Running title: Olfactory and gustatory dysfunction in COVID-19 pneumonia.

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ABSTRACT

Importance: Identifying undetected clinical signs is imperative in the prevention of SARS-CoV-2.

Objective: To establish the prevalence of clinical gustatory and olfactory dysfunction in patients with COVID-19 pneumonia. Clinical outcomes and recovery rates associated with gustatory and olfactory dysfunction were also assessed.

Design: A prospective study was performed in 80 patients admitted to Hospital Clínic of Barcelona (Spain) for COVID-19 pneumonia. Patients were reevaluated in the ward daily until discharge. Gustatory and olfactory dysfunction symptoms were retrospectively collected from emergency room (ER) charts after first assessments. Follow-up was performed in telemedicine consultation.

Setting: The single-center study was performed in a hospitalization ward at a university hospital.

Participants: Consecutive patients meeting hospitalization criteria for COVID-19 pneumonia were eligible. Study exclusion criteria were patients who could not speak, had previous gustatory and olfactory dysfunction or whose PCR tests for SARS-CoV-19 were negative.

Interventions: Systematic assessment of gustatory and olfactory symptoms with standardized questions.

Outcome(s): Prevalence of gustatory and olfactory dysfunction in patients with COVID-19 pneumonia.

Results: Of the 80 study subjects, 62.5% were male and the median age was 57 years. Half of the cohort (n=40) presented with comorbidities. The prevalence of chemosensitive disorder was 73.8%(n=59) [CI-95%,(63.8-83.8)], although self-reported symptoms were recorded in only 26.3%(n=21) of patients in the ER. Gustatory and olfactory dysfunction were observed in

58.8%(n=47) and 55%(n=44) of cases, respectively. They were also the first symptoms in 25%(n=20) of patients. Anosmia was associated with ageusia, OR:7(CI-95%,2.3-21.8 p=0.001). No differences in clinical outcomes were observed when patients with and without gustatory and olfactory dysfunction were compared. Recovery rates were 20%(n=10) and 85%(n=42) at day 7 and 45, respectively.

Conclusion: The prevalence of gustatory and olfactory dysfunction in COVID-19 pneumonia was much higher than in self-report. Presence of gustatory and olfactory dysfunction was not a predictor of clinical outcomes.

Article Summary

- Prospective study design in consecutive patients with COVID-19 pneumonia.
- Prospective recovery rates of gustatory and olfactory function in patients with COVID-19 pneumonia.
- Lack of validated questionnaires of olfactory and gustatory function.
- Lack of quantitative assessments of olfactory and gustatory function.
- The selected population primarily represents hospitalized patients, excluding milder cases.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in a pandemic with more than 26 million reported cases and, as last reported in September 2020, 800000 deaths **(1)**. With no effective vaccine available, basic preventive strategies against transmission of the highly contagious virus include the early recognition of potential clinical signs. Such a strategy could minimize the possibility of early transmission, as has been described in several studies **(2-4).** Similarly, per the latest recommendations of the World Health Organization, establishing contact tracing of suspected cases could provide key clinical findings related to SARS-CoV-2 and mitigate risk of transmission **(5)**. Lastly, prompt diagnosis and treatment of possibly severe viral infection could improve clinical outcomes.

Within this context, gustatory and olfactory dysfunction is an unrecognized and poorly defined condition, for which establishing strong causal relationships is challenging. Viruses, however, are the most frequent pathogens with respect to etiology. For example, *Coronavirus, Influenza* and *Picornavirus* have been detected in nasal secretions in smell studies, with various degrees of severity and an even permanent loss of smell and taste **(6)**. Consequently, gustatory and olfactory dysfunction leads to a decrease in the quality of life and mood state **(7)**.

When initial reports of the SARS-CoV-2 outbreak in Wuhan area were published, gustatory and olfactory dysfunction were not described **(8-10).** However, a small retrospective study performed in Milan estimated a prevalence of gustatory and olfactory dysfunction

of around 34% of hospitalized patients with coronavirus disease 2019 (COVID-19) infection **(11)**. Similarly, several other reports of isolated sudden onset anosmia have recently been described in patients with COVID-19 **(12,13)**. Finally, a multicenter, cross-sectional study performed in France and Belgium reported a prevalence of gustatory and olfactory dysfunction of 85% in mild cases of COVID-19 **(14).**

However, incidence of gustatory and olfactory dysfunction has yet to be defined in severe cases of COVID-19 requiring hospital admission. Since the onset of the pandemic in Barcelona, a great number of gustatory and olfactory symptoms have been self-reported by patients admitted to our health care center for confirmed COVID-19 pneumonia. The present study aims to estimate the prevalence, clinical traits and evolution of gustatory and olfactory dysfunction in patients hospitalized for COVID-19 pneumonia.

Materials and methods

Study design

We performed a prospective assessment on patients consecutively admitted to a dedicated ward where attending physicians evaluated gustatory and olfactory dysfunction. After initial evaluations, a retrospective review of ER charts prior to admission was also performed to determine self-report. Negative findings were determined by the absence of the studied symptoms on ER charts, whereas positive findings were determined by the presence of studied symptoms on ER charts. The study was conducted at Hospital Clínic of Barcelona, a tertiary university reference center. The study population comprised patients with COVID-19 pneumonia admitted to a hospitalization ward between February 28th and April 24th, 2020. Data collection was performed on April 30th, 2020.

The main objective of this study was to determine the proportion of gustatory and olfactory dysfunction in hospitalized patients with confirmed COVID-19 pneumonia. Secondary endpoints were to define clinical traits, describe laboratory values, identify factors associated with gustatory and olfactory dysfunction, explore potential differential outcomes between patients with and without gustatory and olfactory dysfunction, and examine time to recovery rates from gustatory and olfactory dysfunction.

Patients

SARS-CoV-2 infection was confirmed by either real-time polymerase chain reaction (PCR) viral detection in a nasopharyngeal swab or by clinical and radiological characteristics set

forth by ECDC criteria **(15)**, including: 1) acute respiratory tract infection (sudden onset of cough, fever and shortness of breath) and 2) severe acute respiratory infection [fever and at least one sign/symptom of respiratory disease (e.g., cough, fever or shortness breath)] requiring hospitalization with unilateral or bilateral interstitial infiltrate in the chest X-ray. This clinical definition was set on March 15th, 2020, when the percentage of microbiologically-confirmed cases of COVID-19 from all collected samples was higher than 70%. Patients with prior dysfunction, unable to speak, with mental impairment or who tested negative for SARS-CoV-2 were excluded from the analysis. Additionally, to avoid memory bias, patients with direct admission to the intensive care unit (ICU) or posterior discharge to the ward were excluded. Inclusion of consecutive patients from the same ward was established to avoid selection bias.

Data Collection

Directed anamnesis was performed in each patient upon arrival to the ward, including baseline characteristics, demographics and classic pneumonia signs. Patients were asked about gustatory and olfactory dysfunction symptoms, such as ageusia, dysgeusia, anosmia and hyposmia on a daily basis until discharge. The following questions were asked systematically to all patients: 1) have you noticed any sudden and recent changes in smell and taste?; 2) If the response was affirmative, was this the first symptom?; 3) is there a total loss of taste and smell; 4) is there a partial loss of taste and smell?; 5) have the symptoms disappeared?; and, 6) when did the symptoms disappear? Gustatory and olfactory dysfunction were reevaluated during telemedicine consultations on a weekly basis after discharge. The following questions were then asked systematically to all

discharged patients: 1) was there resolution of symptoms?; 2) was there partial or total recovery?; and, 3) when did symptoms resolve? Additional laboratory tests (liver enzymes, creatinine, C-reactive protein, leukocyte count, CD4, CD8 and CD3 count, ferritin and D-dimer levels, and procalcitonin) were performed in all patients. The last follow-up date was April 24th, 2020.

For data collection, variables were extracted from electronic health records in the SAP 740 Hospital Information System© (Societas Europaea, Walldorf, Germany). The results obtained were included in a database created with MICROSOFT EXCEL© for later analysis with statistical package SPSS v18.0© (IBM corporation, Armonk, New York, USA).

Statistical analysis

The primary endpoint of the study was to determine the proportion of patients with gustatory and olfactory dysfunction, reflected in percentages with a confidence level of 95%. The Fisher's exact test was performed to analyze categorical variables between groups; significant p values were shown in odds ratios and confidence intervals. The significance level was set at a p-value <0.05. Inferential analysis of continuous variables, such as laboratory values, was performed using parametric tests (Student's t-test); Pearson test was performed to correlate the duration of symptoms and inflammatory markers. Missing data was reduced by the use of an operator manual at the start of the study and careful data collection. Missing data was managed with the listwise approach.

Sample size calculation

An estimated sample size of 80 patients would allow for an expected prevalence of 33% at a 10.5% accuracy rate and 95% confidence interval, as has been shown in a prior study by Giacomelli *et al.* **(11)**

Ethics

The hospital's research ethics committee and competent Spanish authorities approved the protocol describing the project proposed by the researcher (approval number HCB/2020/0458). Processing, reporting and transfer of personal data for all participating subjects complied with provisions in Organic Act 15/1999 of December 13th (Spanish Royal Decree 1720/2007 of December 21st) and in current Regulation EU 2016/679 of the European Parliament and the European Council on April 27th, 2016, being mandatory after May 25th, 2018, on the Protection of Personal Data and guarantee of digital rights. The patients either signed written consent or when not possible, due to the pandemic and isolation measures in place, provided oral consent. In such cases, oral consent was recorded in Electronic Clinical Documentation.

Patient and public involvement: The patients were not involved in the study described.

Results

Baseline characteristics

Of the 1738 patients with COVID-19 admitted to the hospital between February 28th and April 24th, 1371 were placed in several hospitalization wards and 337 in the intensive care unit (ICU). Analysis of gustatory and olfactory dysfunction was prospectively performed in 80 patients [Figure 1 flow chart]. The median (IQR) age was 57 (43-70) years and 62.5 % were males. Eleven (14%) patients were health care workers. Continent origin of patients comprised 71% (n=57) European primarily, and 25% (n=20) Latin American. Comorbidities were present in 50% (n=40) of patients. The median (IQR) time from symptom onset to hospital admission was 8 (5-10) days, and the median (IQR) length of stay (LOS) was 8 (5-12.5) days [Table 1].

Gustatory and olfactory dysfunction

The main clinical symptoms reported by patients are depicted in Table 1. The prevalence of gustatory and olfactory dysfunction was found to be 73.8 % (n=59) [95 % (CI 63.8% to 83.8 %] in this sample. Separately, gustatory and olfactory dysfunction was present in 58.8% (n=47) and 55% (n=44) of cases, respectively. Anosmia was the most frequent symptom present in 46.3% (n=37) of cases, followed by dysgeusia in 41.3 % (n=33), ageusia in 28.3% (n=23) and hyposmia in 15% (n=12). In 21% (n=7) of cases of dysgeusia, patients reported a salty taste. There was an association between ageusia and anosmia, OR: 7 [IC: 95 2.26 to 21.8 p= 0.001]. Gustatory and olfactory dysfunction was the first symptom to appear in 25% (n=20) of cases. Only one case presented with gustatory and olfactory dysfunction a7 days after admission; the remaining patients presented with

gustatory and olfactory symptoms prior to hospital admission. In the ER, only 26.3 % (n=21) of patients reported olfactory-gustatory dysfunction. ER physicians were more likely to report positive than negative clinical findings (90.5% vs. 9.5%, respectively), OR: 4.6 [0.97-21.95 IC: 95 p= 0.039]. Among classic pneumonia symptoms, fever was present in 89% (n=71) of patients. It was also the most frequent consulted symptom in 53.8% (n=43) of patients who visited the ER. The second most common symptom was coughing, being present in 77.5% (n=62) of cases, followed by dyspnea in 58.8% (47%), asthenia in 56.3% (n=45), myalgia in 50% (n=40), hyporexia in 38% (n=33), vomiting in 8.8 % (n=7) and skin lesions in 6.3% (n=5) [Figure 2]. Vomiting and skin lesions were uncommon. Furthermore, hyporexia was associated with gustative dysfunction, OR: 4.1 [1.23 to 13.67 IC: 95 p= 0.016]. An association between cough and the presence of gustatory and olfactory dysfunction was also observed, OR: 1.2 [0.12 to12.86 IC: 95, p= 0.046] [Table 1].

Per laboratory abnormalities, C-reactive protein (CRP) values were elevated upon admission in 91.8% of cases; lymphopenia was present in 98.8% of cases. Other common findings included elevated levels of lactate dehydrogenase (76.2% of cases), D-dimer (66.2%) and serum ferritin (63.2%) [Table 2].

Differences between AST and ALT values were observed between patients with gustatory-olfactory dysfunction and those without symptoms [(33 vs. 61 UI/l) p=0.019 and (28 vs. 49) p= 0.003, respectively]. No differences in other laboratory findings were found between the studied groups [Table 2].

Treatment prescribed

All patients received hydroxychloroquine and azithromycin. In approximately 91.3 % (n=73) of patients, lopinavir boosted with ritonavir was administered; 38.8% (n=31), interleukin blockers; and 30.4% (n=24), corticosteroids. In 18.8% (n=15) of patients, teicoplanin was administered, whereas in 7.6% (n=6) of patients, interferon was administered. Oxygen supplementation and intubation were required in 69.8% (n=55) and 10% (5%) of patients, respectively. No differences were observed between study groups [Table 3].

Clinical outcomes

A total of 90% (n=73) of patients were discharged upon completion of the study period and 13.8% (n=11) required ICU admission during hospitalization, of whom none died. After discharge, 87% (n=67) of patients were followed up via a telemedicine consultation for any possible changes in status. No readmission episodes were recorded.

In terms of ICU admission, LOS, SpO2/FiO2 ratio, oxygen supplementation, respiratory distress or organizing pneumonia. No association was observed in outcomes between patients with gustatory and olfactory dysfunction and patients without gustatory and olfactory dysfunction. Pulmonary embolism was associated with the absence of gustatory and olfactory dysfunction (21% vs 0) p=0.0001 [Table 3].

Gustatory and olfactory outcomes

Of the 59 patients with gustatory and olfactory dysfunction, 50 were reassessed for follow-up. At day 7 after discharge, 20% (n=10) of these patients had recovered gustatory

and olfactory function. Recovery rates at day 14, 30 and 45 were 28% (n=14), 56% (n=28) and 84% (n=42), respectively. The median time of olfactory-gustatory recovery was 14 (7-30) days [Figure 3].

Time of olfactory-gustatory recovery was positively correlated with age (r: 0.48 p= 0.03) and ferritin levels (r: 0.353 p=0.037). No correlations with severity of respiratory function or any other abnormal laboratory values were found.

Discussion

This is a prospective study evaluating the prevalence of gustatory and olfactory dysfunction in hospitalized patients. We found a prevalence of 74% in all patients admitted to a hospital ward with COVID-19 pneumonia who could be questioned. In a previous study in hospitalized patients, overall prevalence was reported at 33% **(11).** The main reasons for this discrepancy could be attributed to the retrospective design of that study and an unidentified prevalence of gustatory and olfactory dysfunction of 53% in this prospective cohort due to reassessment of ER electronic health records in hospitalization wards. In fact, brief communication reports in Italy have already acknowledged a self-reported prevalence of gustatory and olfactory dysfunction of 19 % in retrospective charts **(16).**

In our cohort, gustatory and olfactory dysfunction syndrome was almost as prevalent as fever and cough, two classic symptoms of viral pneumonia. Within the context of flu-like symptoms and gustatory-olfactory dysfunction syndrome, the possibility of COVID-19 infection is worth considering. In a recent case-control study, gustatory and olfactory

dysfunction were 10 times more common in patients with positive PCR testing results than in those who tested negative for the COVID-19 infection **(17).**

Our study reported anosmia in 55% of cases, whereas investigators Lechein *et al.* reported anosmia in 86% of cases within the setting of a symptom-oriented, otorhinolaryngology-specialized consultation. Patients in that study were younger, without comorbidities and primarily health care providers, contrasting our older cohort of hospitalized patients who presented with more comorbidities. Similarly, with results being obtained by quantitative testing of sense of smell, an Iranian case-control study reported olfactory changes in nearly 98% of patients with COVID-19 and a median age of 46 years. This study suggests that quantitative testing of hyposmia might serve as a rapid, alternative diagnostic approach for SARS-CoV-2 screening **(18)**. However, the role of this test in older patients remains unclear given age-related changes that occur in olfactory function **(19).**

Similar clinical signs and symptoms were observed between patients with and without gustatory and olfactory dysfunction. Coughing was observed more frequently in patients with gustatory and olfactory dysfunction, whereas a more severe respiratory syndrome was not. Gustatory dysfunction was associated with hyporexia, which could affect a patient's quality of life and daily activities especially in cases of persistence (**20-21**).

Additionally, no major alterations in laboratory values were observed. A mild-to-moderate elevation of liver enzymes were common in the absence of gustatory and olfactory dysfunction symptoms; no case of acute liver failure was reported. Although an explanation for these findings is difficult to provide, this observation may be due to

inflammatory changes in the liver or in relation to a different tissue expression of receptors and entry molecules. ACE2 and TMPRSS2 are expressed in cells from multiple tissues, including olfactory cells and liver; the degree to which tropism might affect different tissues has not been well established **(22).**

Clinical outcomes were similar in both groups, however pulmonary embolism occurs in 20% of patients without gustatory and olfactory dysfunction symptoms. Confounding factors associated with pulmonary embolism such as thromboprophylaxis could not be excluded **(23),** and 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 **(24)**. 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 **(**25). Disparity of these findings might be explained by bias, e.g., severe and critically ill patients who are vulnerable to self-neglect and by consequence, do not recognize chemosensory loss and older patients failing to recognize an acute chemosensory loss due to a prior, unidentified olfactory impairment related to senescence. Investigators Lechein *et al.* reported recovery rates of olfactory function at 72% on day 8. Since our study represented olfactory and gustatory outcomes together, performing comparisons might be difficult; nonetheless, we found recovery rates of 20% on day 7 and 84% on day 45. Lastly, another possibility for this discrepancy is the older age and more severe clinical manifestations of COVID-19 infection in our cohort.

Although no correlation between etiopathogenic factors and the length of gustatory and olfactory function recovery has been made thus far, the inflammatory response might play a role. Our data supports that higher levels of ferritin and older age are associated with longer recovery rates. Ferritin levels have been reported to be markedly higher in severe cases than in moderate cases of COVID-19 with longer recovery rates; older age was associated with higher disease severity (**26-28**).

Strengths and weaknesses of the study

The main limitation of this study was the lack of validated olfactory and gustatory questionnaires based on smell and taste components, which could have provided an even more standardized approach. Another limitation was the impossibility to perform olfactory-gustatory testing using quantitative measurements and to include accepted retronasal olfaction test methods. In spite of this, a standardized, non-validated questionnaire was implemented and used systematically in all patients. Consecutive patients were included in this study to minimize selection bias, although selection could be a cause of bias in our data.

The study population selected is limited, representing hospitalized patients mostly and excluding milder cases without pulmonary involvement and the most critical cases with direct ICU admission. Moreover, not all of the patients had microbiologically-confirmed cases of infection or underwent complete follow-up after hospital discharge.

Conclusions and policy implications

There is high prevalence of gustatory and olfactory dysfunction in hospitalized patients with COVID-19 pneumonia. Self-reporting rates are low in our population. To improve surveillance in this pandemic, it is strongly suggested to redefine case definitions for COVID-19 in international guidelines.

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Transparency statement: All the information displayed in the present manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Data sharing statement: Extra data will be available by emailing ajinciar@clinic.cat

Patient and public involvement: Patients were not involved in the study described; there will be an enlisting of patients to disseminate the research findings to the general population in primary care settings.

Table 1. Baseline characteristics according to the presence of gustatory and olfactory dysfunction in patients with COVID-19 pneumonia.

Variable	Cohort	GOD	Absence of GOD	p Value
N	80	59	21	
Median (IQR) Age	57 (42-70)	58 (44-69)	55 (38-72)	0.782
Male, n (%)	50 (63)	34 (59)	15 (71)	0.325
RT-PCR (+) nasopharyngeal swab, n (%)	73 (91.2)	55 (93)	19 (86)	0.985
European, n (%)	57 (71)	37 (64)	14 (67)	0.940
Co-existing illness, n (%)	40 (50)	27 (47)	12 (57)	0.370
Hypertension, n (%)	22 (29)	17 (29)	5 (23)	0.738
Diabetes, n (%)	8 (10)	6 (10)	2 (10)	0.932
Pulmonary disease, n (%)	8 (10)	7 (14)	1 (5)	0.168
Oncological disease, n (%)	5 (6)	2 (3)	3 (14)	0.76
Heart disease, n (%)	5(6)	3 (5)	2 (11)	0.453
Health care worker, n (%)	11(14)	3 (14)	3 (14)	0,934
Median (IQR) days from onset to ER	8 (5.25-10)	8 (5-11)	7 (5.5-9)	0.135
Fever, n (%)	71 (89)	52 (88)	19 (91)	0.771
Cough, n (%)	62 (78)	49 (83)	13(62)	**0.046**
Shortness of breath, n (%)	52 (65)	35 (59)	17 (81)	0.074
Asthenia, n (%)	45 (56)	33 (56)	12 (57)	0.934
Myalgia, n (%)	40 (50)	34 (53)	9 (43)	0.147
Diarrhea, n (%)	35 (44)	25 (42)	10 (48)	0.677
Hyporexia, n (%)	33(38)	29 (49)	4 (19)	**0.016**
Headache, n (%)	28 (35)	24 (41)	4 (19)	0.061
Arthralgia, n (%)	10(13)	8(14)	2 (10)	0.545
Chest Pain, n (%)	9 (11)	6 (10)	3 (14)	0.608
Odynophagia n, (%)	7 (9)	6 (10)	1 (5)	0.451
Vomiting, n (%)	7 (9)	6 (10)	1 (5)	0.451
Rash, n (%)	5 (6)	5 (9)	0	0.168
Rhinorrhea	2 (3)	1 (2)	1 (5)	-

IQR: interquartile range. GOD, Gustatory and olfactory dysfunction.

Table 2. Laboratory values according to the presence of gustatory and olfactory dysfunction in patients with COVID-19 pneumonia.

Variable	Cohort	GOD	Absence of GOD	p Value
N	80	59	21	
CRP mg/dL [< 1.0]	9 (3-14)	8 (3-16)	10 (5-13)	0.838
LDH mg/dL [< 234]	310 (268-386)	309 (250-367)	342 (260-453)	0.109
Ferritin mg/dL [< 200]	716 (256-1322)	592 (241-1255)	1066 (300-1552)	0-093
AST UI/L [5.0 - 40.0]	39 (25-61)	33 (22-50)	61 (39-94)	**0.003**
ALT UI/L [5.0 - 40.0]	29 (20-68)	28 (19-55)	49 (27-102)	**0.019**
BT mg/dL [0.20 - 1.20]	0.64 (0.8-0.4)	0.6 (0.4-0.75)	0.8 (0.55-1.05)	0.560
LYM cells/mm^3 [4.00 - 11.00]	0.9 (0.6-1.3)	0.9 (0.6- 1.3)	0.8 (0.6-1.5)	0.820
D-dimer ng/ml [< 500]	800 (400-1200)	700 (400-1100)	1000 (600-1800)	0.251
Platelets cells/mm^3 [130 - 400]	212 (168-266)	213(170-265)	209 (150-281)	0.735
Creatinine mg/dL [0.30 - 1.30]	0.6 (0.7-09)	0.78 (0.63-0.91)	0.86 (68-0.98)	0.630
Calcium meq/l[8.5 – 9.5]	8.2 (8-8.5)	8.2 (8-8.6)	8.1 (7.8 --8.3)	0.735
CD4 Cels/µL [530 - 1300]	356 (248-579)	358.5 (258.7-630)	328 (225-464)	0.414
CD8 Cels/µL [330 - 920]	225 (147-353)	241 (148 -256)	186 (140.7-396)	0.934
CD3 Cels/µL [1000 - 2200]	630 (404-1014)	676 (459.5-1035)	496 (386-792)	0.310

CRP, C-reactive protein; LDH, Lactate dehydrogenase; AST, Aspartate aminotransferase ; ALT, Alanine transferase; BT, total bilirubin; LYM, Lymphocyte; NEU, Neutrophil; CD4, CD4+ count; CD8, CD8+ count; GOD, Gustatory and olfactory dysfunction.

Table 3. Clinical outcomes according to the presence of gustatory and olfactory dysfunction in patients with COVID-19 pneumonia.

Variable	Cohort	GOD	Absence of GOD	p Value
N	80	59	21	
LOS (IQR)	8 (4-11.75)	8 (4.2-11)	7 (4-14)	0.836
SpO2/fiO2 ratio (IQR)	448 (245-247)	451 (257-471)	391 (197-471)	0.346
Lopinavir/ritonavir, n (%)	73 (94)	52 (91)	21 (100)	0.161
Interferon, n (%)	6 (8)	4 (7)	2 (10)	0.638
Corticosteroid, n (%)	24 (30)	15 (3)	9 (43)	0.147
Interleukin blocker, n (%)	33 (41)	22 (37)	11 (52)	0.228
ICU admission, n (%)	11 (14)	7 (12)	4 (19)	0.412
Complication n, (%)	32 (41)	20 (35)	12 (57)	0.07
Oxygen requirement, n (%)	55 (69)	40 (68)	15 (71)	0.758
Orotraqueal intubation, n (%)	8	5 (8.5)	3 (14)	0.867
Respiratory distress, n (%)	31	20 (34)	11 (52)	0.135
Pulmonary embolism, n (%)	5 (6)	0	5 (23)	0.0001
Organizing pneumonia, n (%)	10 (13)	5 (9)	5 (24)	0.068

LOS, length of stay; SpO2, peripheral capillary oxygen saturation; FiO2, Fraction of Inspired Oxygen; IQR, Interquartile range; GOD, Gustatory and olfactory dysfunction.

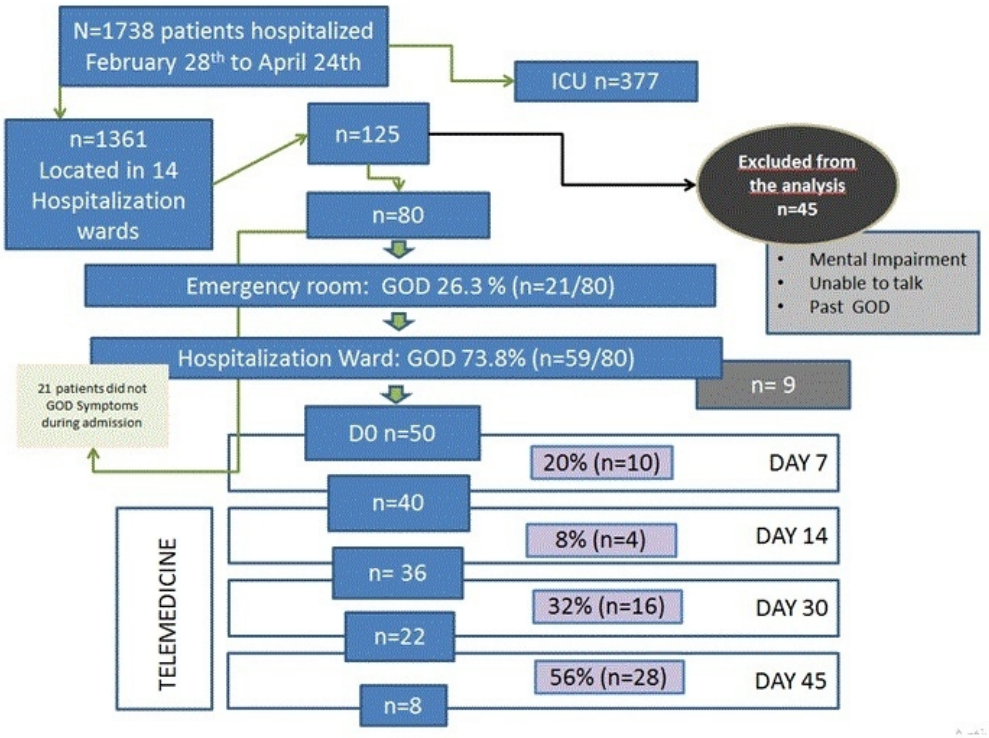
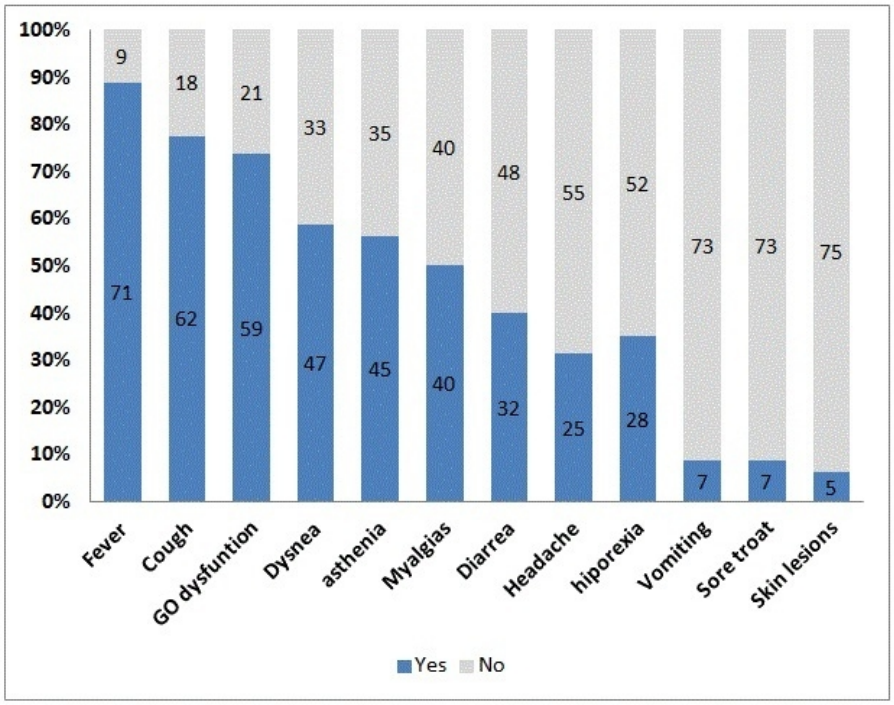


Figure 1. Study Flow Chart. Day 0: If the patient meets criteria is included in the study. Blue boxes represent individuals on follow-up with gustatory-olfactory dysfunction, lilac boxes represents individuals in which the recovery event develops. Gray boxes represent individuals lost to follow up. White boxes represent timelines and mode of follow-up.

58x45mm (300 x 300 DPI)

Figure 2. General symptoms in patients with COVID-19 pneumonia in absolute numbers (n=80)



GOD: gustatory and olfactory dysfunction

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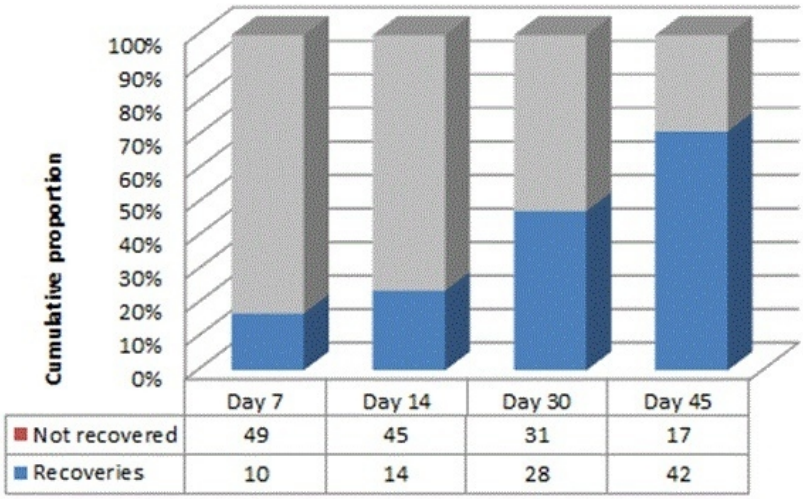
Figure 3. Recovery rates of gustatory-olfactory dysfunction trough time at follow up post – discharge n=50



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Section 1: What is already known on this topic?
• Self reported prevalence in Pneumonia population. • Prevalence in cross-sectional studies in mild disease forms in specific groups (health care workers) and specific consultation (ENT consultations) • One study retrospective study of recovery rates in pauci symptomatic patients.
Section 2: What this study adds?
• Prevalence of gustatory and olfactory symptoms in COVID-19 pneumonia population. • Prospective recovery rates in a more severe disease group (COVID-19 pneumonia patients) • Our study suggest there is no association between severity outcomes of patients with gustatory and olfactory dysfunction and those who don't
Implication: Support a more generalized consensus of gustatory and olfactory symptoms in case definition of COVID-19 in international organizations.

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	7,8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	9-10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	11
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	13

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11 12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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GUSTATORY AND OLFACTORY DYSFUNCTION IN HOSPITALIZED PATIENTS WITH COVID-19 PNEUMONIA: A PROSPECTIVE STUDY

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GUSTATORY AND OLFACTORY DYSFUNCTION IN HOSPITALIZED PATIENTS WITH COVID-19 PNEUMONIA: A PROSPECTIVE STUDY

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Running title: Olfactory and gustatory dysfunction in COVID-19 pneumonia.

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ABSTRACT

Importance: Identifying undetected clinical signs is imperative in the prevention of SARS-CoV-2.

Objective: To establish the prevalence of clinical gustatory and olfactory dysfunction in patients with COVID-19 pneumonia. Clinical outcomes and recovery rates associated with gustatory and olfactory dysfunction were also assessed.

Design: A prospective study was performed in 80 patients admitted to Hospital Clínic of Barcelona (Spain) for COVID-19 pneumonia. Patients were reevaluated in the ward daily until discharge. Gustatory and olfactory dysfunction symptoms were retrospectively collected from emergency room (ER) charts after first assessments. Follow-up was performed in telemedicine consultation.

Setting: The single-center study was performed in a hospitalization ward at a university hospital.

Participants: Consecutive patients meeting hospitalization criteria for COVID-19 pneumonia were eligible. Study exclusion criteria were patients who could not speak, had previous gustatory and olfactory dysfunction or whose PCR tests for SARS-CoV-19 were negative.

Interventions: Systematic assessment of gustatory and olfactory symptoms with standardized questions.

Outcome(s): Prevalence of gustatory and olfactory dysfunction in patients with COVID-19 pneumonia.

Results: Of the 80 study subjects, 62.5% were male and the median age was 57 years. Half of the cohort (n=40) presented with comorbidities. The prevalence of chemosensitive disorder was 73.8%(n=59) [CI-95%,(63.8-83.8)], although self-reported symptoms were recorded in only 26.3%(n=21) of patients in the ER. Gustatory and olfactory dysfunction were observed in 58.8%(n=47) and 55%(n=44) of cases, respectively. They were also the first symptoms in 25%(n=20) of patients. Anosmia was associated with ageusia, OR:7(CI-95%,2.3-21.8 p=0.001). No differences in

clinical outcomes were observed when patients with and without gustatory and olfactory dysfunction were compared. Recovery rates were 20%(n=10) and 85%(n=42) at day 7 and 45, respectively.

Conclusion: The prevalence of gustatory and olfactory dysfunction in COVID-19 pneumonia was much higher than in self-report. Presence of gustatory and olfactory dysfunction was not a predictor of clinical outcomes.

Article Summary

- Prospective study design in consecutive patients with COVID-19 pneumonia.
- Prospective recovery rates of gustatory and olfactory function in patients with COVID-19 pneumonia.
- Lack of validated questionnaires of olfactory and gustatory function.
- Lack of quantitative assessments of olfactory and gustatory function.
- The selected population primarily represents hospitalized patients, excluding milder cases.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in a pandemic with more than 26 million reported cases and, as last reported in September 2020, 800000 deaths **(1)**. With no effective vaccine available, basic preventive strategies against transmission of the highly contagious virus include the early recognition of potential clinical signs. Such a strategy could minimize the possibility of early transmission, as has been described in several studies **(2-4).** Similarly, per the latest recommendations of the World Health Organization, establishing contact tracing of suspected cases could provide key clinical findings related to SARS-CoV-2 and mitigate risk of transmission **(5)**. Lastly, prompt diagnosis and treatment of possibly severe viral infection could improve clinical outcomes.

Within this context, gustatory and olfactory dysfunction is an unrecognized and poorly defined condition, for which establishing strong causal relationships is challenging. Viruses, however, are the most frequent pathogens with respect to etiology. For example, *Coronavirus, Influenza* and *Picornavirus* have been detected in nasal secretions in smell studies, with various degrees of severity and an even permanent loss of smell and taste **(6)**. Consequently, gustatory and olfactory dysfunction leads to a decrease in the quality of life and mood state **(7)**.

When initial reports of the SARS-CoV-2 outbreak in Wuhan area were published, gustatory and olfactory dysfunction were not described **(8-10).** However, a small retrospective study performed in Milan estimated a prevalence of gustatory and olfactory dysfunction of around 34% of hospitalized patients with coronavirus disease 2019 (COVID-19) infection **(11)**. Similarly, several other reports of isolated sudden onset anosmia have recently been described in patients with COVID-19 **(12,13)**. Finally, a multicenter, cross-sectional study

performed in France and Belgium reported a prevalence of gustatory and olfactory dysfunction of 85% in mild cases of COVID-19 **(14).**

However, incidence of gustatory and olfactory dysfunction has yet to be defined in severe cases of COVID-19 requiring hospital admission. Since the onset of the pandemic in Barcelona, a great number of gustatory and olfactory symptoms have been self-reported by patients admitted to our health care center for confirmed COVID-19 pneumonia. The present study aims to estimate the prevalence, clinical traits and evolution of gustatory and olfactory dysfunction in patients hospitalized for COVID-19 pneumonia.

Materials and methods

Study design

We performed a prospective assessment on patients consecutively admitted to a dedicated ward where attending physicians evaluated gustatory and olfactory dysfunction. After initial evaluations, a retrospective review of ER charts prior to admission was also performed to determine self-report. Negative findings were determined by the absence of the studied symptoms on ER charts, whereas positive findings were determined by the presence of studied symptoms on ER charts. The study was conducted at Hospital Clínic of Barcelona, a tertiary university reference center. The study population comprised patients with COVID-19 pneumonia admitted to a hospitalization ward between February 28th and April 24th, 2020. Data collection was performed on April 30th, 2020.

The main objective of this study was to determine the proportion of gustatory and olfactory dysfunction in hospitalized patients with confirmed COVID-19 pneumonia. Secondary endpoints were to define clinical traits, describe laboratory values, identify factors associated with gustatory and olfactory dysfunction, explore potential differential outcomes between patients with and without gustatory and olfactory dysfunction, and examine time to recovery rates from gustatory and olfactory dysfunction.

Patients

SARS-CoV-2 infection was confirmed by either real-time polymerase chain reaction (PCR) viral detection in a nasopharyngeal swab or by clinical and radiological characteristics set forth by ECDC criteria **(15)**, including: 1) acute respiratory tract infection (sudden onset of cough, fever and shortness of breath) and 2) severe acute respiratory infection [fever and at least one sign/symptom of respiratory disease (e.g., cough, fever or shortness breath)]

requiring hospitalization with unilateral or bilateral interstitial infiltrate in the chest X-ray. This clinical definition was set on March 15th, 2020, when the percentage of microbiologically-confirmed cases of COVID-19 from all collected samples was higher than 70%. Patients with prior dysfunction, unable to speak, with mental impairment or who tested negative for SARS-CoV-2 were excluded from the analysis. Additionally, to avoid memory bias, patients with direct admission to the intensive care unit (ICU) or posterior discharge to the ward were excluded. Inclusion of consecutive patients from the same ward was established to avoid selection bias.

Data Collection

Directed anamnesis was performed in each patient upon arrival to the ward, including baseline characteristics, demographics and classic pneumonia signs. Patients were asked about gustatory and olfactory dysfunction symptoms, such as ageusia, dysgeusia, anosmia and hyposmia on a daily basis until discharge. The following questions were asked systematically to all patients: 1) have you noticed any sudden and recent changes in smell and taste?; 2) If the response was affirmative, was this the first symptom?; 3) is there a total loss of taste and smell; 4) is there a partial loss of taste and smell?; 5) have the symptoms disappeared?; and, 6) when did the symptoms disappear? Gustatory and olfactory dysfunction were reevaluated during telemedicine consultations on a weekly basis after discharge. The following questions were then asked systematically to all discharged patients: 1) was there resolution of symptoms?; 2) was there partial or total recovery?; and, 3) when did symptoms resolve? Additional laboratory tests (liver enzymes, creatinine, C-reactive protein, leukocyte count, CD4, CD8 and CD3 count, ferritin and D-dimer levels, and procalcitonin) were performed in all patients. The last follow-up date was April 24th, 2020.

For data collection, variables were extracted from electronic health records in the SAP 740 Hospital Information System© (Societas Europaea, Walldorf, Germany). The results obtained were included in a database created with MICROSOFT EXCEL© for later analysis with statistical package SPSS v18.0© (IBM corporation, Armonk, New York, USA).

Statistical analysis

The primary endpoint of the study was to determine the proportion of patients with gustatory and olfactory dysfunction, reflected in percentages with a confidence level of 95%. The Fisher's exact test was performed to analyze categorical variables between groups; significant p values were shown in odds ratios and confidence intervals. The significance level was set at a p-value <0.05. Inferential analysis of continuous variables, such as laboratory values, was performed using parametric tests (Student's t-test); Pearson test was performed to correlate the duration of symptoms and inflammatory markers. Missing data was reduced by the use of an operator manual at the start of the study and careful data collection. Missing data was managed with the listwise approach.

Sample size calculation

An estimated sample size of 80 patients would allow for an expected prevalence of 33% at a 10.5% accuracy rate and 95% confidence interval, as has been shown in a prior study by Giacomelli *et al.* **(11)**

Ethics

The hospital's research ethics committee and competent Spanish authorities approved the protocol describing the project proposed by the researcher (approval number HCB/2020/0458). Processing, reporting and transfer of personal data for all participating subjects complied with provisions in Organic Act 15/1999 of December 13th (Spanish Royal Decree 1720/2007 of December 21st) and in current Regulation EU 2016/679 of the European Parliament and the European Council on April 27th, 2016, being mandatory after May 25th, 2018, on the Protection of Personal Data and guarantee of digital rights. The patients either signed written consent or when not possible, due to the pandemic and isolation measures in place, provided oral consent. In such cases, oral consent was recorded in Electronic Clinical Documentation.

Patient and public involvement: The patients were not involved in the study described.

Results

Baseline characteristics

Of the 1738 patients with COVID-19 admitted to the hospital between February 28th and April 24th, 1371 were placed in several hospitalization wards and 337 in the intensive care unit (ICU). Analysis of gustatory and olfactory dysfunction was prospectively performed in 80 patients [Figure 1 flow chart]. The median (IQR) age was 57 (43-70) years and 62.5 % were males. Eleven (14%) patients were health care workers. Continent origin of patients comprised 71% (n=57) European primarily, and 25% (n=20) Latin American. Comorbidities were present in 50% (n=40) of patients. The median (IQR) time from symptom onset to hospital admission was 8 (5-10) days, and the median (IQR) length of stay (LOS) was 8 (5-12.5) days [Table 1].

Gustatory and olfactory dysfunction

The main clinical symptoms reported by patients are depicted in Table 1. The prevalence of gustatory and olfactory dysfunction was found to be 73.8 % (n=59) [95 % (CI 63.8% to 83.8 %] in this sample. Separately, gustatory and olfactory dysfunction was present in 58.8% (n=47) and 55% (n=44) of cases, respectively. Anosmia was the most frequent symptom present in 46.3% (n=37) of cases, followed by dysgeusia in 41.3 % (n=33), ageusia in 28.3% (n=23) and hyposmia in 15% (n=12). In 21% (n=7) of cases of dysgeusia, patients reported a salty taste. There was an association between ageusia and anosmia, OR: 7 [IC: 95 2.26 to 21.8 p= 0.001]. Gustatory and olfactory dysfunction was the first symptom to appear in 25% (n=20) of cases. Only one case presented with gustatory and olfactory dysfunction a7 days after admission; the remaining patients presented with gustatory and olfactory symptoms prior to hospital admission. In the ER, only 26.3 % (n=21) of patients reported olfactory-gustatory dysfunction. ER physicians were more likely to report positive than negative

clinical findings (90.5% vs. 9.5%, respectively), OR: 4.6 [0.97-21.95 IC: 95 p= 0.039]. Among classic pneumonia symptoms, fever was present in 89% (n=71) of patients. It was also the most frequent consulted symptom in 53.8% (n=43) of patients who visited the ER. The second most common symptom was coughing, being present in 77.5% (n=62) of cases, followed by dyspnea in 58.8% (47%), asthenia in 56.3% (n=45), myalgia in 50% (n=40), hyporexia in 38% (n=33), vomiting in 8.8 % (n=7) and skin lesions in 6.3% (n=5) [Figure 2]. Vomiting and skin lesions were uncommon. Furthermore, hyporexia was associated with gustative dysfunction, OR: 4.1 [1.23 to 13.67 IC: 95 p= 0.016]. An association between cough and the presence of gustatory and olfactory dysfunction was also observed, OR: 1.2 [0.12 to12.86 IC: 95, p= 0.046] [Table 1].

Per laboratory abnormalities, C-reactive protein (CRP) values were elevated upon admission in 91.8% of cases; lymphopenia was present in 98.8% of cases. Other common findings included elevated levels of lactate dehydrogenase (76.2% of cases), D-dimer (66.2%) and serum ferritin (63.2%) [Table 2].

Differences between AST and ALT values were observed between patients with gustatory-olfactory dysfunction and those without symptoms [(33 vs. 61 UI/l) p=0.019 and (28 vs. 49) p= 0.003, respectively]. No differences in other laboratory findings were found between the studied groups [Table 2].

Treatment prescribed

All patients received hydroxychloroquine and azithromycin. In approximately 91.3 % (n=73) of patients, lopinavir boosted with ritonavir was administered; 38.8% (n=31), interleukin blockers; and 30.4% (n=24), corticosteroids. In 18.8% (n=15) of patients, teicoplanin was

administered, whereas in 7.6% (n=6) of patients, interferon was administered. Oxygen supplementation and intubation were required in 69.8% (n=55) and 10% (5%) of patients, respectively. No differences were observed between study groups [Table 3].

Clinical outcomes

A total of 90% (n=73) of patients were discharged upon completion of the study period and 13.8% (n=11) required ICU admission during hospitalization, of whom none died. After discharge, 87% (n=67) of patients were followed up via a telemedicine consultation for any possible changes in status. No readmission episodes were recorded.

In terms of ICU admission, LOS, SpO2/FiO2 ratio, oxygen supplementation, respiratory distress or organizing pneumonia. No association was observed in outcomes between patients with gustatory and olfactory dysfunction and patients without gustatory and olfactory dysfunction. Pulmonary embolism was associated with the absence of gustatory and olfactory dysfunction (21% vs 0) p=0.0001 [Table 3].

Gustatory and olfactory outcomes

Of the 59 patients with gustatory and olfactory dysfunction, 50 were reassessed for follow-up. At day 7 after discharge, 20% (n=10) of these patients had recovered gustatory and olfactory function. Recovery rates at day 14, 30 and 45 were 28% (n=14), 56% (n=28) and 84% (n=42), respectively. The median time of olfactory-gustatory recovery was 14 (7-30) days [Figure 3].

Time of olfactory-gustatory recovery was positively correlated with age (r: 0.48 p= 0.03) and ferritin levels (r: 0.353 p=0.037). No correlations with severity of respiratory function or any other abnormal laboratory values were found.

Discussion

This is a prospective study evaluating the prevalence of gustatory and olfactory dysfunction in hospitalized patients. We found a prevalence of 74% in all patients admitted to a hospital ward with COVID-19 pneumonia who could be questioned. In a previous study in hospitalized patients, overall prevalence was reported at 33% **(11).** The main reasons for this discrepancy could be attributed to the retrospective design of that study and an unidentified prevalence of gustatory and olfactory dysfunction of 53% in this prospective cohort due to reassessment of ER electronic health records in hospitalization wards. In fact, brief communication reports in Italy have already acknowledged a self-reported prevalence of gustatory and olfactory dysfunction of 19 % in retrospective charts **(16).**

In our cohort, gustatory and olfactory dysfunction syndrome was almost as prevalent as fever and cough, two classic symptoms of viral pneumonia. Within the context of flu-like symptoms and gustatory-olfactory dysfunction syndrome, the possibility of COVID-19 infection is worth considering. In a recent case-control study, gustatory and olfactory dysfunction were 10 times more common in patients with positive PCR testing results than in those who tested negative for the COVID-19 infection **(17).**

Our study reported anosmia in 55% of cases, whereas investigators Lechein *et al.* reported anosmia in 86% of cases within the setting of a symptom-oriented, otorhinolaryngology-specialized consultation. Patients in that study were younger, without comorbidities and primarily health care providers, contrasting our older cohort of hospitalized patients who presented with more comorbidities. Similarly, with results being obtained by quantitative testing of sense of smell, an Iranian case-control study reported olfactory changes in nearly 98% of patients with COVID-19 and a median age of 46 years. This study suggests that

quantitative testing of hyposmia might serve as a rapid, alternative diagnostic approach for SARS-CoV-2 screening **(18)**. However, the role of this test in older patients remains unclear given age-related changes that occur in olfactory function **(19).**

Similar clinical signs and symptoms were observed between patients with and without gustatory and olfactory dysfunction. Coughing was observed more frequently in patients with gustatory and olfactory dysfunction, whereas a more severe respiratory syndrome was not. Gustatory dysfunction was associated with hyporexia, which could affect a patient's quality of life and daily activities especially in cases of persistence (**20-21**).

Additionally, no major alterations in laboratory values were observed. A mild-to-moderate elevation of liver enzymes were common in the absence of gustatory and olfactory dysfunction symptoms; no case of acute liver failure was reported. Although an explanation for these findings is difficult to provide, this observation may be due to inflammatory changes in the liver or in relation to a different tissue expression of receptors and entry molecules. ACE2 and TMPRSS2 are expressed in cells from multiple tissues, including olfactory cells and liver; the degree to which tropism might affect different tissues has not been well established **(22).**

Clinical outcomes were similar in both groups, however pulmonary embolism occurs in 20% of patients without gustatory and olfactory dysfunction symptoms. Confounding factors associated with pulmonary embolism such as thromboprophylaxis could not be excluded **(23),** and 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 **(24)**. 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 **(25)**. Disparity of these findings might be explained by bias, e.g., severe and critically ill patients who are vulnerable to self-neglect and by consequence, do not recognize chemosensory loss and older patients failing to recognize an acute chemosensory loss due to a prior, unidentified olfactory impairment related to senescence. Investigators Lechein *et al.* reported recovery rates of olfactory function at 72% on day 8. Since our study represented olfactory and gustatory outcomes together, performing comparisons might be difficult; nonetheless, we found recovery rates of 20% on day 7 and 84% on day 45. Lastly, another possibility for this discrepancy is the older age and more severe clinical manifestations of COVID-19 infection in our cohort.

Although no correlation between etiopathogenic factors and the length of gustatory and olfactory function recovery has been made thus far, the inflammatory response might play a role. Our data supports that higher levels of ferritin and older age are associated with longer recovery rates. Ferritin levels have been reported to be markedly higher in severe cases than in moderate cases of COVID-19 with longer recovery rates; older age was associated with higher disease severity (**26-28**).

Strengths and weaknesses of the study

The main limitation of this study was the lack of validated olfactory and gustatory questionnaires based on smell and taste components, which could have provided an even more standardized approach. Another limitation was the impossibility to perform olfactory-gustatory testing using quantitative measurements and to include accepted retronasal olfaction test methods. In spite of this, a standardized, non-validated questionnaire was

implemented and used systematically in all patients. Consecutive patients were included in this study to minimize selection bias, although selection could be a cause of bias in our data.

The study population selected is limited to a single center, representing hospitalized patients mostly and excluding milder cases without pulmonary involvement and the most critical cases with direct ICU admission. Moreover, not all of the patients had microbiologically-confirmed cases of infection or underwent complete follow-up after hospital discharge.

Conclusions and policy implications

There is high prevalence of gustatory and olfactory dysfunction in hospitalized patients with COVID-19 pneumonia. Self-reporting rates are low in our population. Clinical outcomes were not related with presence or the absence of gustatory and olfactory dysfunction in hospitalized patients.

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Contributorship statement : AI, CC, MC, PA,BT, AGC, VR, DA, NGP, MHM, LA, JR, FM, LDL, LL, PPA, IM, ML, JA, AR, LM, MB, EMG, AM, MS , performed clinical assessments. AI and FG designed the study, contributed to data analysis and wrote the first draft of the manuscript. AI, CC, MC, LL, MT were responsible for data entry. AI, CGV, JAM, IA, AS, LM, EG, VDB, CL, JGP, FG, critically reviewed the manuscript and agreed on its final version.

Transparency statement: All the information displayed in the present manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Data sharing statement: Extra data will be available by emailing ajinciar@clinic.cat

Patient and public involvement: Patients were not involved in the study described; there will be an enlisting of patients to disseminate the research findings to the general population in primary care settings.

Table 1. Baseline characteristics according to the presence of gustatory and olfactory dysfunction in patients with COVID-19 pneumonia.

Variable	Cohort	GOD	Absence of GOD	p Value
N	80	59	21	
Median (IQR) Age	57 (42-70)	58 (44-69)	55 (38-72)	0.782
Male, n (%)	50 (63)	34 (59)	15 (71)	0.325
RT-PCR (+) nasopharyngeal swab, n (%)	73 (91.2)	55 (93)	19 (86)	0.985
European, n (%)	57 (71)	37 (64)	14 (67)	0.940
Co-existing illness, n (%)	40 (50)	27 (47)	12 (57)	0.370
Hypertension, n (%)	22 (29)	17 (29)	5 (23)	0.738
Diabetes, n (%)	8 (10)	6 (10)	2 (10)	0.932
Pulmonary disease, n (%)	8 (10)	7 (14)	1 (5)	0.168
Oncological disease, n (%)	5 (6)	2 (3)	3 (14)	0.76
Heart disease, n (%)	5(6)	3 (5)	2 (11)	0.453
Health care worker, n (%)	11(14)	3 (14)	3 (14)	0,934
Median (IQR) days from onset to ER	8 (5.25-10)	8 (5-11)	7 (5.5-9)	0.135
Fever, n (%)	71 (89)	52 (88)	19 (91)	0.771
Cough, n (%)	62 (78)	49 (83)	13(62)	**0.046**
Shortness of breath, n (%)	52 (65)	35 (59)	17 (81)	0.074
Asthenia, n (%)	45 (56)	33 (56)	12 (57)	0.934
Myalgia, n (%)	40 (50)	34 (53)	9 (43)	0.147
Diarrhea, n (%)	35 (44)	25 (42)	10 (48)	0.677
Hyporexia, n (%)	33(38)	29 (49)	4 (19)	**0.016**
Headache, n (%)	28 (35)	24 (41)	4 (19)	0.061
Arthralgia, n (%)	10(13)	8(14)	2 (10)	0.545
Chest Pain, n (%)	9 (11)	6 (10)	3 (14)	0.608
Odynophagia n, (%)	7 (9)	6 (10)	1 (5)	0.451
Vomiting, n (%)	7 (9)	6 (10)	1 (5)	0.451
Rash, n (%)	5 (6)	5 (9)	0	0.168
Rhinorrhea	2 (3)	1 (2)	1 (5)	-

IQR, interquartile range; GOD, Gustatory and olfactory dysfunction.

Table 2. Laboratory values according to the presence of gustatory and olfactory dysfunction in patients with COVID-19 pneumonia.

Variable	Cohort	GOD	Absence of GOD	p Value
N	80	59	21	
CRP mg/dL [< 1.0]	9 (3-14)	8 (3-16)	10 (5-13)	0.838
LDH mg/dL [< 234]	310 (268-386)	309 (250-367)	342 (260-453)	0.109
Ferritin mg/dL [< 200]	716 (256-1322)	592 (241-1255)	1066 (300-1552)	0-093
AST UI/L [5.0 - 40.0]	39 (25-61)	33 (22-50)	61 (39-94)	**0.003**
ALT UI/L [5.0 - 40.0]	29 (20-68)	28 (19-55)	49 (27-102)	**0.019**
BT mg/dL [0.20 - 1.20]	0.64 (0.8-0.4)	0.6 (0.4-0.75)	0.8 (0.55-1.05)	0.560
LYM cells/mm^3 [4.00 - 11.00]	0.9 (0.6-1.3)	0.9 (0.6- 1.3)	0.8 (0.6-1.5)	0.820
D-dimer ng/ml [< 500]	800 (400-1200)	700 (400-1100)	1000 (600-1800)	0.251
Platelets cells/mm^3 [130 - 400]	212 (168-266)	213(170-265)	209 (150-281)	0.735
Creatinine mg/dL [0.30 - 1.30]	0.6 (0.7-09)	0.78 (0.63-0.91)	0.86 (68-0.98)	0.630
Calcium meq/l[8.5 – 9.5]	8.2 (8-8.5)	8.2 (8-8.6)	8.1 (7.8 --8.3)	0.735
CD4 Cels/µL [530 - 1300]	356 (248-579)	358.5 (258.7-630)	328 (225-464)	0.414
CD8 Cels/µL [330 - 920]	225 (147-353)	241 (148 -256)	186 (140.7-396)	0.934
CD3 Cels/µL [1000 - 2200]	630 (404-1014)	676 (459.5-1035)	496 (386-792)	0.310

CRP, C-reactive protein; LDH, Lactate dehydrogenase; AST, Aspartate aminotransferase ; ALT, Alanine transferase; BT, total bilirubin; LYM, Lymphocyte; NEU, Neutrophil; CD4, CD4+ count; CD8, CD8+ count; GOD, Gustatory and olfactory dysfunction.

Table 3. Clinical outcomes according to the presence of gustatory and olfactory dysfunction in patients with COVID-19 pneumonia.

Variable	Cohort	GOD	Absence of GOD	p Value
N	80	59	21	
LOS (IQR)	8 (4-11.75)	8 (4.2-11)	7 (4-14)	0.836
SpO2/fiO2 ratio (IQR)	448 (245-247)	451 (257-471)	391 (197-471)	0.346
Lopinavir/ritonavir, n (%)	73 (94)	52 (91)	21 (100)	0.161
Interferon, n (%)	6 (8)	4 (7)	2 (10)	0.638
Corticosteroid, n (%)	24 (30)	15 (3)	9 (43)	0.147
Interleukin blocker, n (%)	33 (41)	22 (37)	11 (52)	0.228
ICU admission, n (%)	11 (14)	7 (12)	4 (19)	0.412
Complication n, (%)	32 (41)	20 (35)	12 (57)	0.07
Oxygen requirement, n (%)	55 (69)	40 (68)	15 (71)	0.758
Orotraqueal intubation, n (%)	8	5 (8.5)	3 (14)	0.867
Respiratory distress, n (%)	31	20 (34)	11 (52)	0.135
Pulmonary embolism, n (%)	5 (6)	0	5 (23)	0.0001
Organizing pneumonia, n (%)	10 (13)	5 (9)	5 (24)	0.068

LOS, length of stay; SpO2, peripheral capillary oxygen saturation; FiO2, Fraction of Inspired Oxygen; IQR, Interquartile range; GOD, Gustatory and olfactory dysfunction.

Figure 1. Study Flow Chart. Day 0: If the patient meets criteria is included in the study. Blue boxes represent individuals on follow-up with gustatory-olfactory dysfunction, lilac boxes represents individuals in which the recovery event develops. Gray boxes represent individuals lost to follow up. White boxes represent timelines and mode of follow-up.

Figure 2. General symptoms in patients with COVID-19 pneumonia in absolute numbers (n=80), GOD; gustatory and olfactory dysfunction.

Figure 3. Recovery rates of gustatory and olfactory dysfunction trough time at follow up post discharge (n=50)

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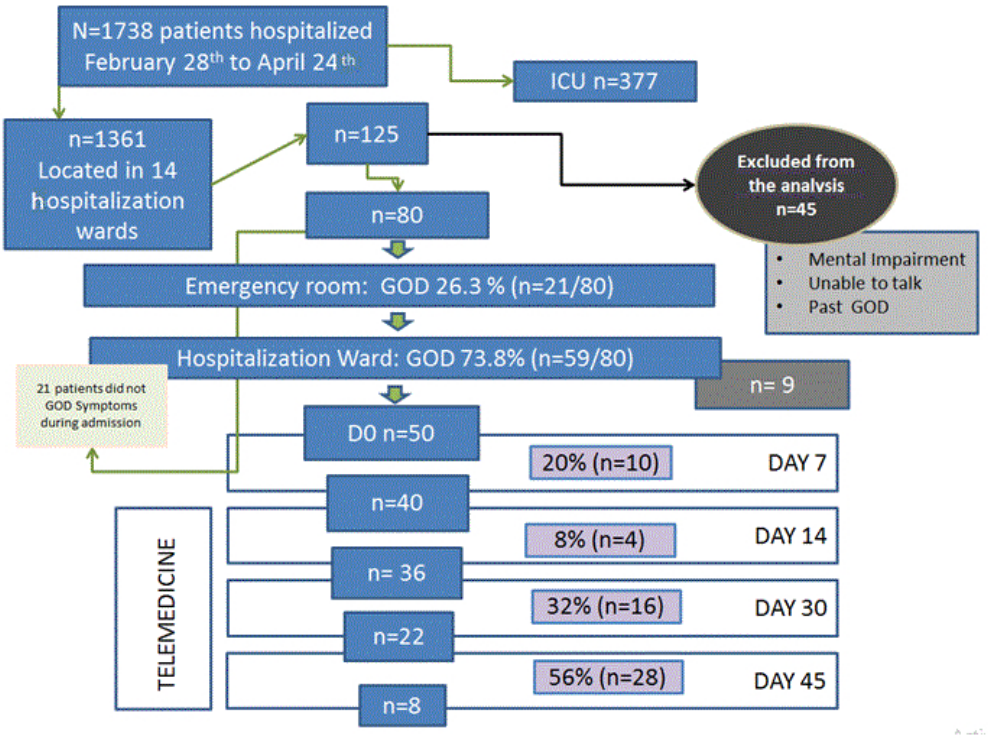

Caption : Figure 1. Study Flow Chart. Day 0: If the patient meets criteria is included in the study. Blue boxes represent individuals on follow-up with gustatory-olfactory dysfunction, lilac boxes represents individuals in which the recovery event develops. Gray boxes represent individuals lost to follow up. White boxes represent timelines and mode of follow-up.

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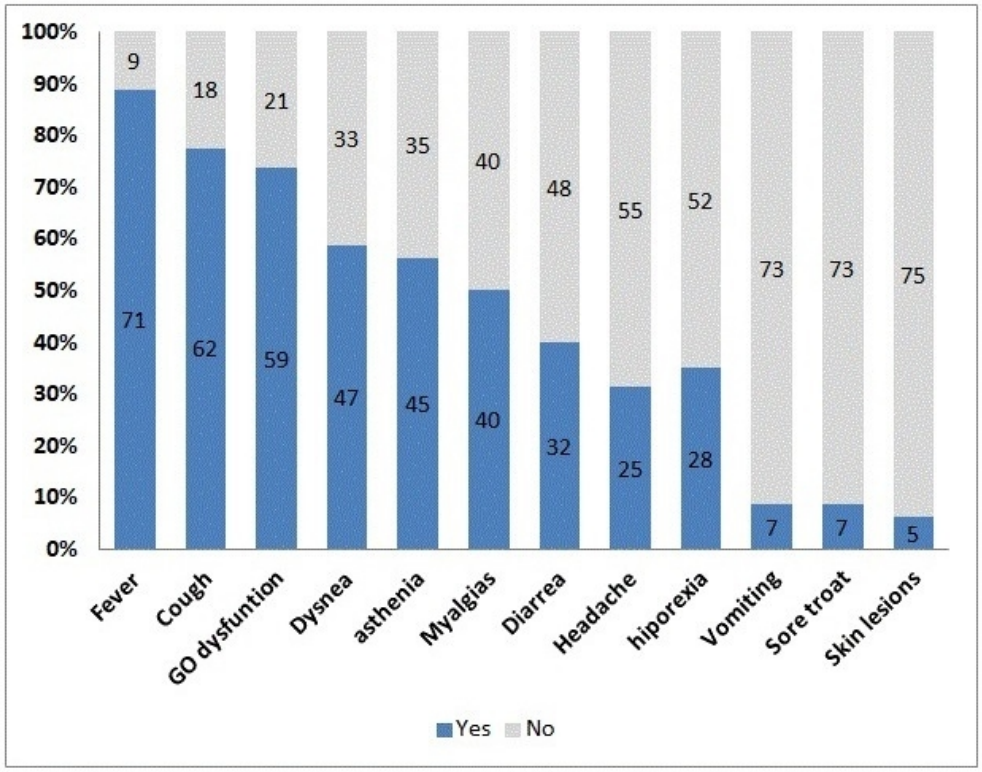

Figure 2. General symptoms in patients with COVID-19 pneumonia in absolute numbers (n=80), GOD; gustatory and olfactory dysfunction

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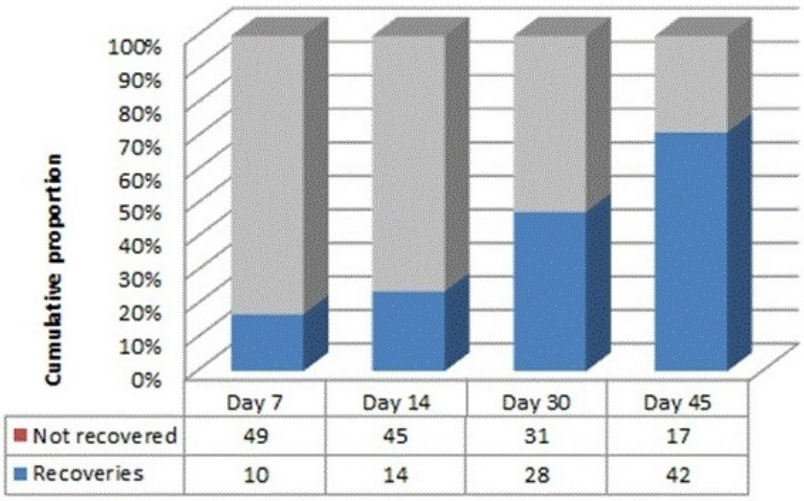

Figure 3. Recovery rates of gustatory and olfactory dysfunction trough time at follow up post discharge (n=50)

59x37mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	7,8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	9-10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	11
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	13

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11 12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.