Olfactory dysfunction quantified by olfactometry in patients with SARS-Cov-2 infection

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Research Article

Keywords: COVID-19, SARS-CoV-2, Loss, Olfactory, ENT, Quantitative, Olfactometry

Posted Date: June 24th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-35796/v1

Abstract

Objective: To quantify olfactory dysfunction by olfactometry in patients with laboratory confirmed SARS-Cov-2 infection.

Methods: Patients from a particular Spanish health area with SARS-Cov-2 infection were recruited to study the loss of smell. Olfactometry was performed using the Sniffin Sticks test. The following clinical symtoms were studied: ENT symptoms related to infection, duration of sensorineural loss, subjective and objective score of loss of smell, and its temporal relationship with other systemic symptoms.

Results: A total of 51 patients with SARS-Cov-2 infection completed the study. A total of 86.3% reported subjective loss of smell capacity. Objective loss of olfactory ability was quantified by olfactometry in 22% of patients. Statistical significance was demonstrated between the group of patients with anosmia/hyposmia and the Sniffin Sticks test (p-value: 0.013). The most frequent ENT symptoms in patients with quantified olfactory loss consisted of nasal obstruction, absence of rhinorrhea, sore throat, and ear pain. The subjective olfactory recovery rate prior to performing olfactometry was 64.3% of the sample. A total of 77% of patients in whom olfactory loss was quantified by olfactometry reported a subjective duration of more than 15 days.

Conclusion: Olfactory dysfunction is an objective clinical finding in patients with SARS- Cov-2 infection. Its persistence has been demonstrated beyond the first month after infection. Their quantitative study should be continued to determine the recovery rate and its possible long-term sequelae, as well as treatments to improve the quality of life of these patients.

Introduction

Anosmia has already been described as a symptom of SARS-Cov–21 in the scientific community by otorhinolaryngologists2 and other specialists3 to take this symptom into account early in the course of the infection.4

We consider it necessary to scientifically support the results obtained.5 Despite the fact that the relationship between SARS-Cov–2 infection and sensorineural deficits anosmia and ageusia has already been described, there are few quantitative studies that prove this possible causal relationship. We need to continue investigating and to quantify these subjective olfactory losses.6,7

It is worth noting that proposing a quantitative study involves performing olfactometry, exposing the researcher to possible infection.8 Perhaps this is one of the drawbacks why there are not yet sufficient quantitative studies.

The reduction of transmission is essential given the enormous social and medical impacts that this pandemic has had in recent months. Strengthening the scientific evidence9 that recommends, after a case of sudden anosmia, self-isolation and subsequent evaluation of the infection by PCR or serology, is

essential, since this strategy would aid the reduction in transmission of the virus and control new SARS-Cov–2 outbreaks.

Material And Methods

Participants

This study was conducted between the months of March and May 2020 in the outpatient clinics of the Hospital Universitario de Cáceres. A total of 51 patients (44 women, 7 men; mean age, 43.82 ± 10.7 years, range, 18–67 years) with SARS-Cov–2 infection were included in this study.

The inclusion criteria were: adult patients with SARS-Cov–2 detected by PCR or serology belonging to the Caceres health area. The exclusion criteria included patients with other possible causes of olfactory dysfunction such as a history of chronic rhinosinusitis, allergic rhinitis, previous anosmia, or situations that made medical history analysis difficult, such as intellectual dysfunction, as well as concomitant pathologies (nasal polyps, tumors in the ENT area, diseases neurodegenerative) or taking medication that could affect olfaction.

The nature of this study and its procedures were explained to all subjects. All of them provided their written informed consent to participate.

Telephone consultation

The anamnesis was conducted by telephone consultation. To meet the patients in person, they had to meet one of the following conditions: they must have passed a minimum of 14 days after the start of the asymptomatic period, have a negative PCR, or IgG + IgM- serology.

The subjective evaluation of olfactory dysfunction was performed as follows: patients were asked to answer a questionnaire that helped us obtain information about these symptoms. The questionnaire contained questions about runny nose, whether there was anterior or posterior runny nose, whether there was a sensation of plugging, whether there was subjective loss of smell ability, and, if any, that their olfactory ability should be graded on a scale of 0 to 4 (with 0 = I smell everything well; 1 = I have noticed some loss of smell; 2 = I smell practically everything; 3 = I smell less than usual; and 4 = I don’t smell anything).

On-site consultation

In this second contact, other anamnesis data was obtained, such as previous pathologies (hypertension, diabetes, cholesterol, autoimmune diseases, surgical interventions in the ENT area, history of rhinosinusitis, polyps, or other diseases that could influence the loss of olfaction, taking medication, etc.). Patients were also asked about the duration of the anosmia, whether they had suffered other symptoms, the temporal relationship of the anosmia to the other symptoms, whether they had been hospitalized, and

whether they had subjectively regained their olfactory ability. An examination of the ENT area was performed to rule out possible pathologies that could be affecting olfaction in the event that there was sensorineural dysfunction.

Olfactometry

The odor identification test was performed with a widely used in Europe and scientifically validated commercial test called “Sniffin Sticks.”10 One point was awarded for each correct answer, with a maximum of 12 if all of the answers were correct. If a score of 0 to 6 correct answers was obtained, the patient was diagnosed with anosmia; if a score of 7 to 9 correct answers was obtained, the patient was diagnosed with hyposmia; and if 10 to 12 correct answers were obtained, the patient was diagnosed with normosmia.

This test was conducted by taking into account the aspects that could influence the correct perception of odors: use of disposable gloves and mask by the examiner, the ventilated room, and abstaining form liquid and solid food as well as tobacco by the patient for 15 minutes prior to the test.

ENT exploration

For the physical examination, disposable gloves and a mask were used for the exploration of the oropharynx and cervical palpation. For the nasofibrolaryngoscopy, disposable flexible endoscopes were used. At the end of the day, a terminal cleaning of the room was carried out to avoid possible contamination.

Data analysis

To perform the statistical analyses, SPSS version 22.0 was used (IBM Corp, Armonk, NY, USA UU, Macintosh HD version). The olfactory dysfunction analysis was performed according to the value obtained in olfactometry using the Sniffin Sticks test (mean or median score) in each of the groups with objective anosmia at the time of examination: anosmia and hyposmia, using the Mann-Witney statistical test. Likewise, the analysis of olfactory dysfunction was performed according to the value obtained in olfactometry using the Sniffin Sticks test (mean or median score) in the group with subjective anosmia at the time of acute infection in each of the four groups, using the Kruskal-Wallis statistical test. A significance level of $p < 0.05$ was used to determine statistical significance.

Results

A total of 73 patients diagnosed with SARS-Cov–2 by PCR or serology were contacted by this service throughout the months of March and April. Of these, a total of 51 patients wanted to participate in the study and met the inclusion criteria. Of the 51 patients who met the inclusion criteria, 10 patients could not be explored before analyzing the data collected here, since they were still symptomatic or in preventive isolation, so that the total number of patients who went to the face-to-face consultation was 41 patients. The mean age of the patients was 43.82 +/- 10.76 years (range 18–67). There were 44

women and 7 men. The most prevalent patient comorbidities were hypertension (9.8%), diabetes (3.9%), and autoimmune diseases (11.8%). 15.7% of the patients had been adeno-tonsillectomized in childhood. Only 3.9% required hospitalization at the acute moment of infection.

Subjective olfactory results:

Of the total number of patients in the sample, 52.9% reported nasal obstruction, 23.5% reported anterior rhinorrhea, and 19.6% reported posterior rhinorrhea. Only 17.6% reported ear pain and 41.2% reported sore throat. Only 2 of the 51 patients (3.9%) required hospitalization at the acute moment of infection. (Figure 1).

Of the total number of included patients, 86.3% reported subjective anosmia at the acute moment of infection. 94.1% reported having had other systemic symptoms such as tiredness, headache, diarrhea, myalgia, cough, and fever. Regarding the temporal relationship between olfactory dysfunction and the rest of the systemic symptoms, 11.8% reported experiencing it before the rest of the symptoms, 23.5% at the same time, and 49% after the rest of the symptoms. (Figure 2).

Subjective olfactory dysfunction at the acute moment of infection was rated on a subjective scale ranging from 0 to 4 (with 0 = I smell everything well; 1 = I have noticed some loss of smell; 2 = I smell less than usual; 3 = I smell practically nothing; 4 = I don't smell anything). The results were 13.7% of patients reported no loss of smell, 9.8% noted some loss of smell, 9.8% smelled less than usual, 27.4% smelled practically nothing, and 39.2% did not smell anything. (Figure 3).

The duration of subjective olfactory dysfunction was classified as follows: non-dysfunction, duration from 1 to 4 days, from 5 to 8 days, from 9 to 14 days, and more than 15 days. The distribution of the sample was as follows: 19.5% of patients reported not having experienced olfactory dysfunction, 7.3% had dysfunction for 1 to 4 days, 7.3% for 5 to 8 days, 46.3% for 9 to 14 days, and 19.5% for more than 15 days. (Figure 4).

Objective olfactory results

Olfactometry was performed using the 'Sniffin Stiks' test, which was administered to the 41 patients who were able to attend the face-to-face consultation. The following results were obtained.

After a month had passed from the acute moment of the infection to the face-to-face consultation, 9 patients, or 22% of the sample, still presented with olfactory dysfunction that was observed in olfactometry. Of these 9 patients, 5 obtained a score of 7 to 9 in the test, so they were diagnosed with hyposmia, and 4 obtained a score from 0 to 6, so they were diagnosed with anosmia.

Regarding the characteristics of the patients to whom the olfactory dysfunction could be determined, there were 7 women and 2 men. Only 22.22% were smokers, 11.11% were hypertensive, and 33.33% had

been adeno-tonsillectomized. There was no diabetics or dyslipidemics among them, and none suffered from autoimmune diseases, or from previous pathologies in the ENT area. None of the patients had required hospitalization.

Regarding symptoms in the ENT area, 77.77% reported not having suffered from either anterior or posterior rhinorrhea, 66.6% reported having had nasal obstruction, 66.6% reported not having sore throat, and 88.88% reported not having had ear pain. (Figure 1).

Regarding objective dysfunction and the relationship of this symptom with the rest of the systemic symptoms, 11.11% had suffered from olfactory dysfunction as the only symptom of SARS-Cov–2 infection, 11.11% had suffered loss of olfaction before the rest of the symptoms, 33.33% suffered the loss of olfaction at the same time as the rest of the symptoms, and 44.44% suffered the loss of olfaction after the rest of the symptoms. (Figure 2).

Regarding subjective olfactory loss grading on a scale of 0 to 4, the patients who were finally diagnosed with olfactory dysfunction defined their loss as follows: 11.11% rated their loss as “I have noticed some loss of smell,” 22.22% as “I don’t smell practically nothing,” and 66.66% as “I don’t smell anything.” (Figure 3).

Regarding objective olfactory dysfunction and subjective duration of dysfunction, 11% reported having experienced a duration of 5 to 8 days, 11% reported having had a duration of 9 to 14 days, and 77% reported having had a duration more than 15 days. (Figure 4).

Subjective vs. objective olfactory association

Statistical significance could be demonstrated between the group of patients with anosmia/hyposmia and the Sniffin Sticks test (p-value: 0.013). However, statistical significance could not be demonstrated between the group of patients with subjective anosmia and the actual anosmia evaluated using the Sniffin Sticks test (p-value: 0.235).

Discussion

Anosmia has already been identified in the scientific literature as a common symptom after a viral upper respiratory infection (URTI). The viruses that most frequently cause this symptom are influenza viruses and respiratory syncytial virus;11 however Suzuki et al. already defined coronaviruses (CoVs) as one of the viruses causing post-URTI anosmia.

The first to define the symptom picture of SARS-Cov–2 were our colleaues in Asia;12 however, it was not until the arrival of the virus in Europe that olfactory dysfunction began to take center stage as a symptom to consider.2 Regarding this difference, Leichen et al. raises two possible causes: the first cause would be the lack of data collection at the ENT level, either for having overlooked these symptoms due to their contrast with other more serious ones, or for lack of complaint about them by the Asian population, while

the second would be a difference in the genetic characteristics that could influence the transcription of the virus and therefore its biological behavior, which may result in a greater affinity for the cells of the olfactory bulb by SARS-Cov–2 strains that have affected the European population compared to those that have affected the Asian population.

Although several hypotheses have been described that could explain the cause of chemosensory dysfunction caused by SARS-Cov–2, a consensus has not yet been reached. What the scientific community does agree on is that the most probable cause of transitory olfactory dysfunction in patients infected with SARS-CoV2 is direct contact and interaction of the virus with taste receptors or olfactory receptor cells.13

The prevalence of subjective olfactory dysfunction obtained in this study (86.3%) is very similar to that obtained in other studies that used validated instruments: 86.6% (95% CI, 72.95%–95.95%).9 However, the olfactory dysfunction observed by olfactometry one month after the onset of symptoms drops to 22% in our sample. This prevalence is more similar to the results in the retrospective study by Bénézit et al (20%), in which this symptom was documented incidentally rather than systematically.14 The fact of finding such a low percentage of olfactory dysfunction compared to the percentage that patients reported having at the acute moment could be due to the fact that the recovery of smell in most cases occurs during the first month after infection.9 These results would support the hypothesis presented by Wu et al. of the neurotropic invasion capacity of SARS-Cov–2 manifested clinically in the form of anosmia and dysgeusia.15 However, as Vavougious et al. has indicated, more studies in this line of research would be needed to document the scope of this neuroinvasive capacity as well as its duration and possible sequelae.16

There are significant limitations in the study of this disease due to the high infection rate of this virus, and its high viral load in oropharyngeal samples at the acute moment of infection,17 since it prevents us from performing olfactometry at the acute moment that allows one to quantitatively verify the loss of olfaction. Even so, having obtained 22% a result of olfactory dysfunction, we can affirm that this percentage of patients did have olfactory loss and that the majority (77%) experienced a dysfunction of more than 15 days, for this reason we were able to objectify it at the time of face-to-face consultation. This does not mean that the remaining 64.3% who could not quantitatively objectify the loss, would not have had it at the acute moment. These patients probably experienced it and regained their ability to smell. What is interesting and encourages the study to continue is to finally quantify the total percentage of patients who fully recover their sensorineural capacity.

In this sample, if the 86.3% who reported subjective loss had actually had it, the recovery percentage would have been 74.5% in the first month. At the present time, we continue to study patients with olfactometry-targeted loss to document their full recovery date.

The most repeated pattern in patients with hyposmia or targeted anosmia was patients with a mean age of 43.7 years who had not required hospitalization, who had suffered from olfactory dysfunction of more than 15 days, and that this dysfunction had appeared after the rest of the systemic symptoms. Regarding

symptoms related to the ENT area, the majority did not report rhinorrhea, either anterior or posterior, odynophagia, or otalgia, although they mostly reported nasal obstruction.

Regarding treatment, given that the otorhinolaryngological community does not recommend any treatment that has shown improvement,2 we did not make pharmacological recommendations to our patients. Some of them decided to do nasal washes with very slight subjective improvement. What they did mostly refer to was a recovery that, was very progressive and occurred characteristically with smells to which patients were exposed repeatedly and daily, such as their usual perfume, the aroma of coffee, and other elements with this feature. This leads us to believe that repeated exposure to certain smells stimulates the recovery of the nerve cells that recognize those particular aromas to which they have been exposed the most.

Strengths and weaknesses

The main limitation of our study is that olfactometry was not performed on patients at the acute moment of infection. Our examinations were conducted one month after olfactory loss, and many of the patients had reported a complete improvement in olfactory dysfunction. The conducting of physical examinations of patients who are in home isolation at the acute moment of infection is an important logistical limitation. In addition, we agree with Leichen et al. that it seems unethical to investigate anosmia in patients who are in intensive care units. All these weaknesses should be considered in future studies.

The most significant advantage of our study is that we have assessed the loss of smell that had already been described in several recent studies,4 but this time in a quantitative manner. We have accomplished this with a widely used and scientifically validated olfaction test.10

For future studies in this line of research, we suggest that the issues still to be clarified are finding reproducible means to perform olfactometry at the acute moment of infection without risk to the physician, defining more broadly the neurotropic character of the virus and its long-term sequelae, and lastly, investigating treatments that could accelerate the recovery of olfactory dysfunction.

Conclusions

Anosmia is an objective clinical finding in the symptoms of SARS-Cov–2. Its persistence over time has been objectively verified in 22% of the analyzed sample. Although much progress has been made in a short time in the study of this disease, important aspects remain to be elucidated, such as the etiopathological mechanisms that lead to the sensorineural involvement of this virus. We consider it necessary to conduct more quantitative studies of the sensorineural loss caused by SARS-Cov–2 to verify the results obtained so far. Our intention is to continue investigating in this way to expand knowledge about long-term sequelae in the ENT area and to study treatments that improve the quality of life of these patients.

Declarations

ACKNOWLEDGMENTS

We would like to thank Scribendi for the proofreading, the head and staff of the Otorhinolaryngology and head and neck Surgery service at the Caceres University Hospital Complex, and the following researchers:

J. M. Cervilla, J. Zamorano, P. Fernandez del Valle, and their collaborators.

Statement of ethics approval: We declare that this study was conducted between the months of March and May 2020 in the outptient clinics of the Hospital Universitario de Cáceres, after approval by the Research Ethics Comittee of this hospital.

Statement on participant consent: We declare that the nature of this study and its procedures were explained to all subjects. All of them provided their written informed consent to participate.

Statement regarding potential competing interests: The authors declare no competing interests.

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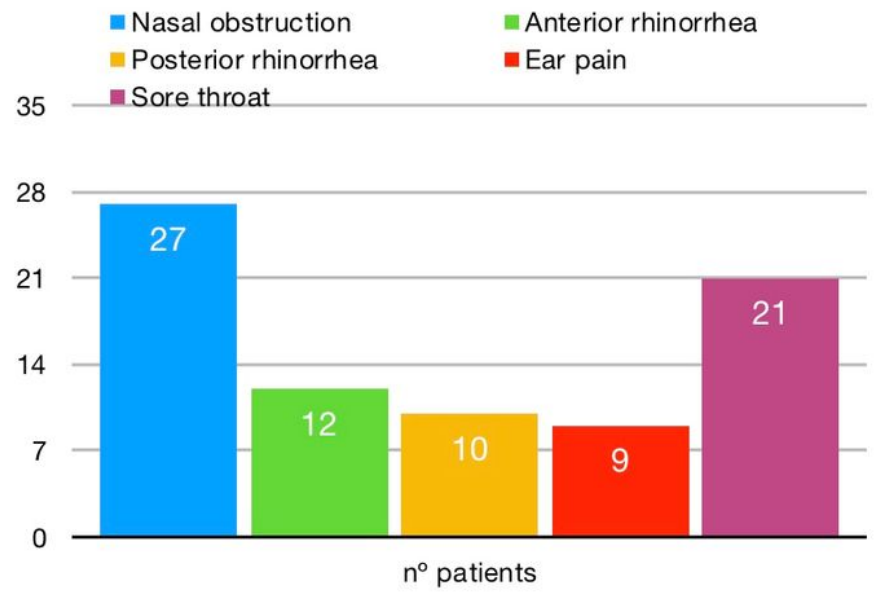
Figures

A



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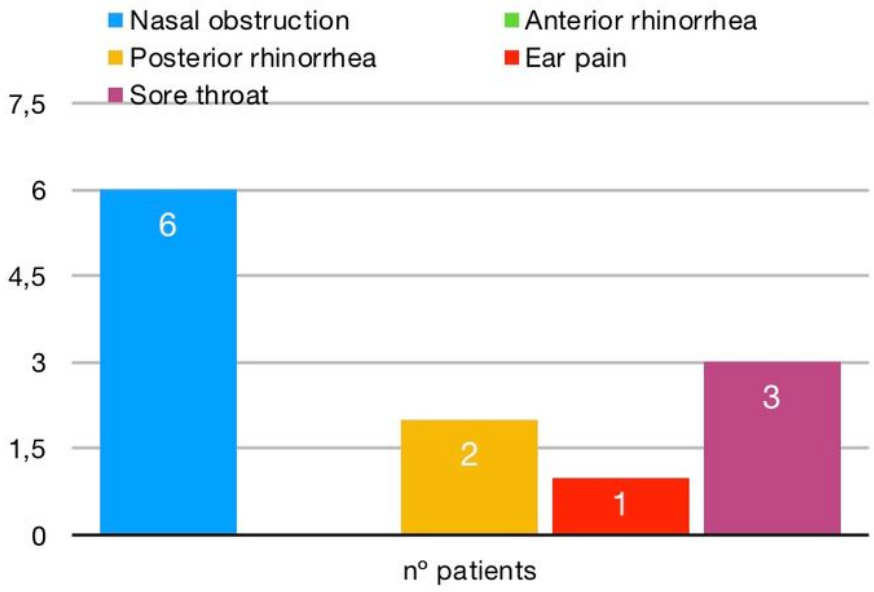

Figure 1

ENT symptoms related to SARS-Cov-2 infection. The ordinate axis consists of the number of patients with these symptoms. Graph A. Patients with subjective dysfunction: Nasal obstruction 27 (52.9%), posterior rhinorrhea 10 (23.5%), sore throat 21 (41.12%), anterior rhinorrhea 12 (23.53%), and ear pain 9 (17.64%). Graph B. Patients with quantified olfactory dysfunction: Nasal obstruction 6 (66.66%), posterior rhinorrhea 2 (22.22%), sore throat 3 (33.33%), anterior rhinorrhea 0 (0%), and ear pain 1 (11.11%).

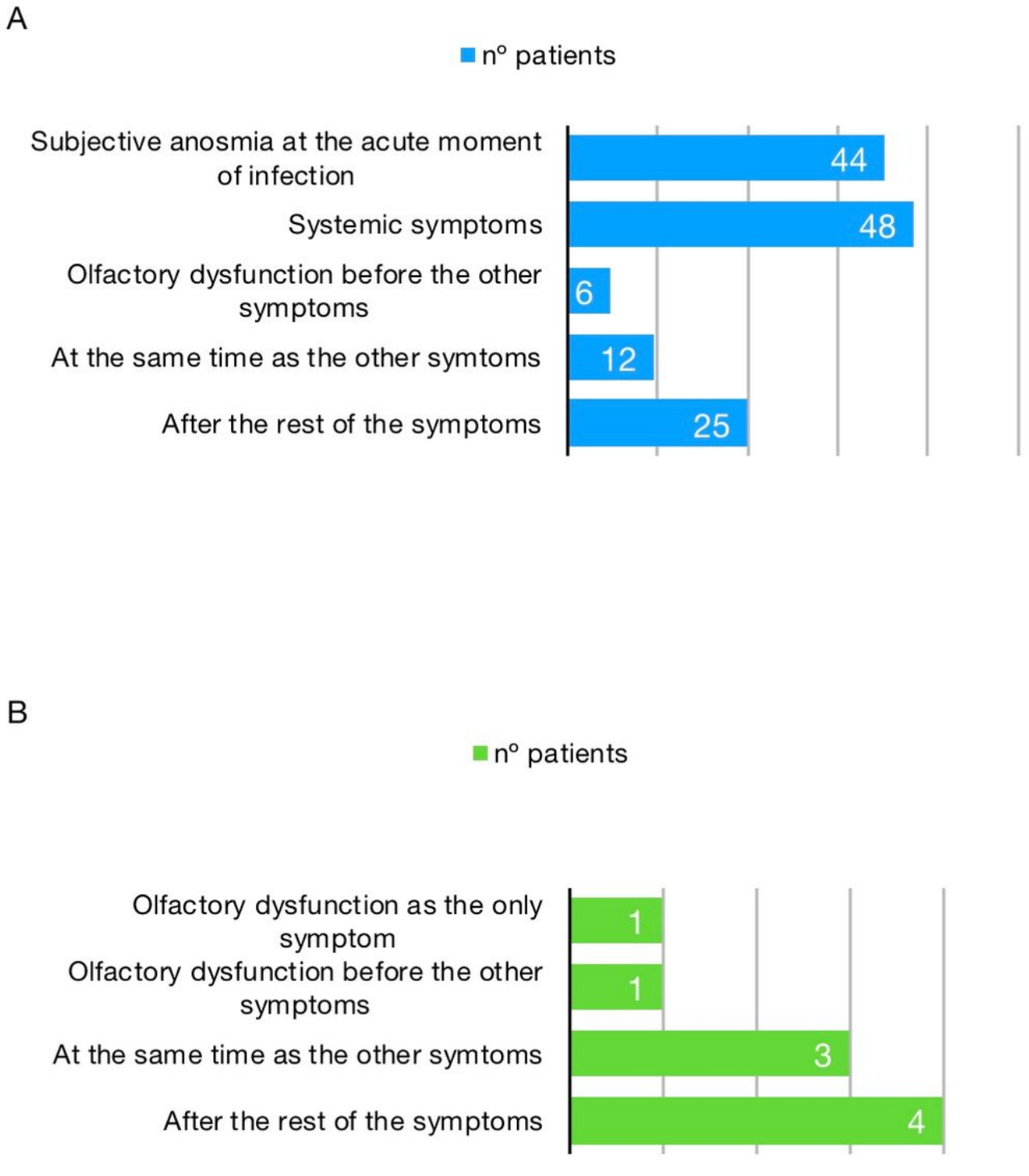

Figure 2

Temporal relationship of olfactory dysfunction with respect to systemic symptoms. The axis of the abscissa consists of the number of patients. Graph A. Patients with subjective dysfunction: The total number of patients with subjective dysfunction 44 (86.3% of the total), the total number of patients with systemic symptoms 48 (94.1% of the total), and the temporal relationship It was: 6, (11.8%) before the rest of the symptoms, 12 (23.5%) at the same time as the rest of the symptoms and 25 (49%) after the

rest of the symptoms. Graph B. Patients with quantified olfactory dysfunction: The total number of patients with olfactory dysfunction as the only symptom is shown, and the temporal relationship was: 1, (11.11%) before the rest of the symptoms, 3 (33.33%) at the same time as the rest of the symptoms and 4 (44.44%) after the rest of the symptoms.

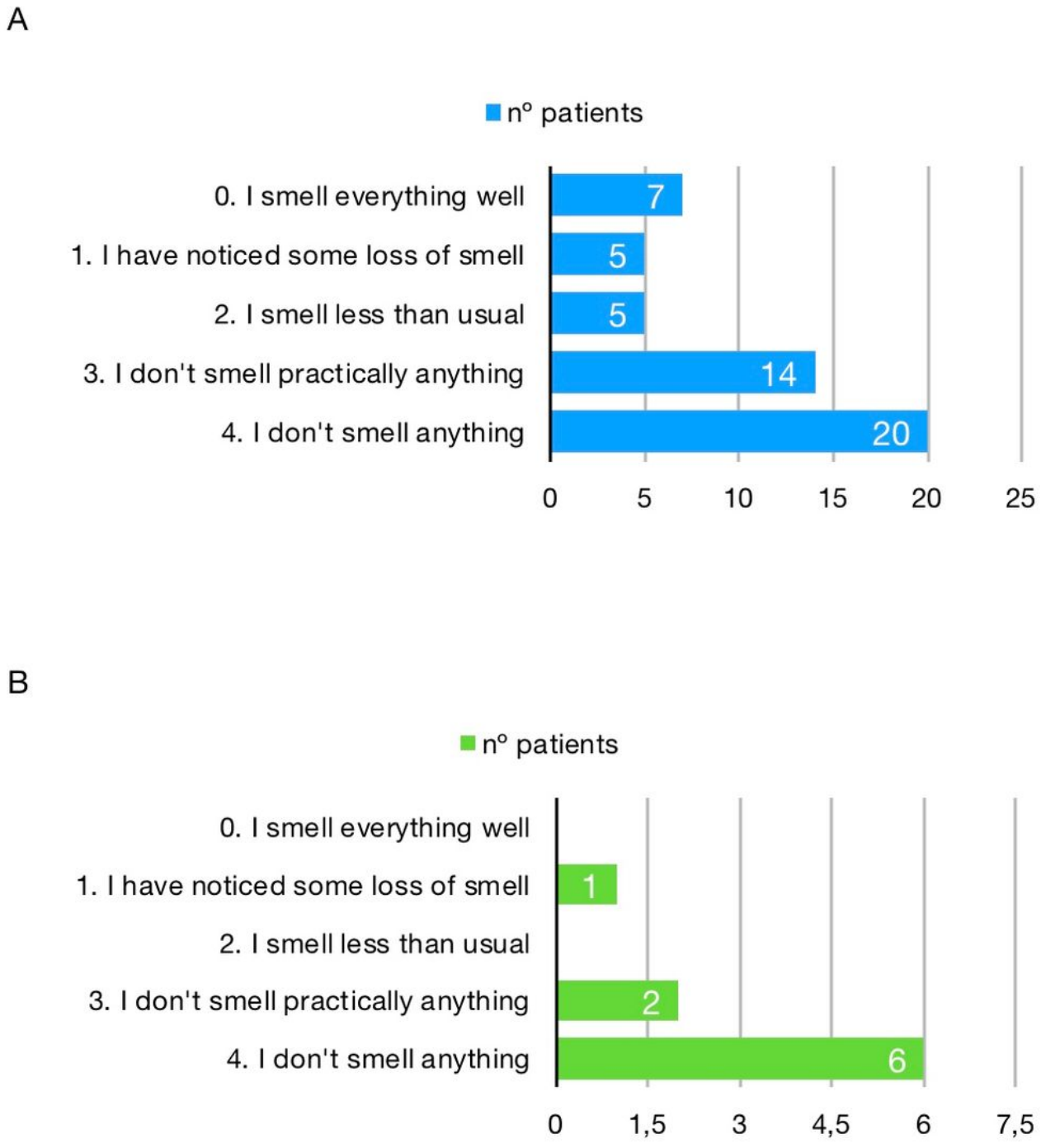

Figure 3

Gradual distribution of subjective olfactory dysfunction on a scale of 0 to 4. The axis of the abscissa consists of the number of patients. The ordinate axis consists of 5 groups distributed by subjective score from 0 to 4. Being 0 'I smell everything well', 1 'I have noticed some loss of smell', 2 'I smell less than usual', 3 'I don't smell practically nothing ', 4' I don't smell anything '. Graph A. Patients with subjective olfactory dysfunction: Group 0 had 7 patients (13.7%), group 1 had 5 patients (9.8%), group 2 had 5 patients (9.8%), group 3 had 14 patients (27.4%) and group 4 had 20 patients (39.2%). Graph B. Patients with quantified olfactory dysfunction: Group 0 had 0 patients (0%), Group 1 had 1 patients (11.11%), Group 2 had 0 patients (0%), Group 3 had 2 patients (22.22%) and group 4 had 6 patients (66.66%).

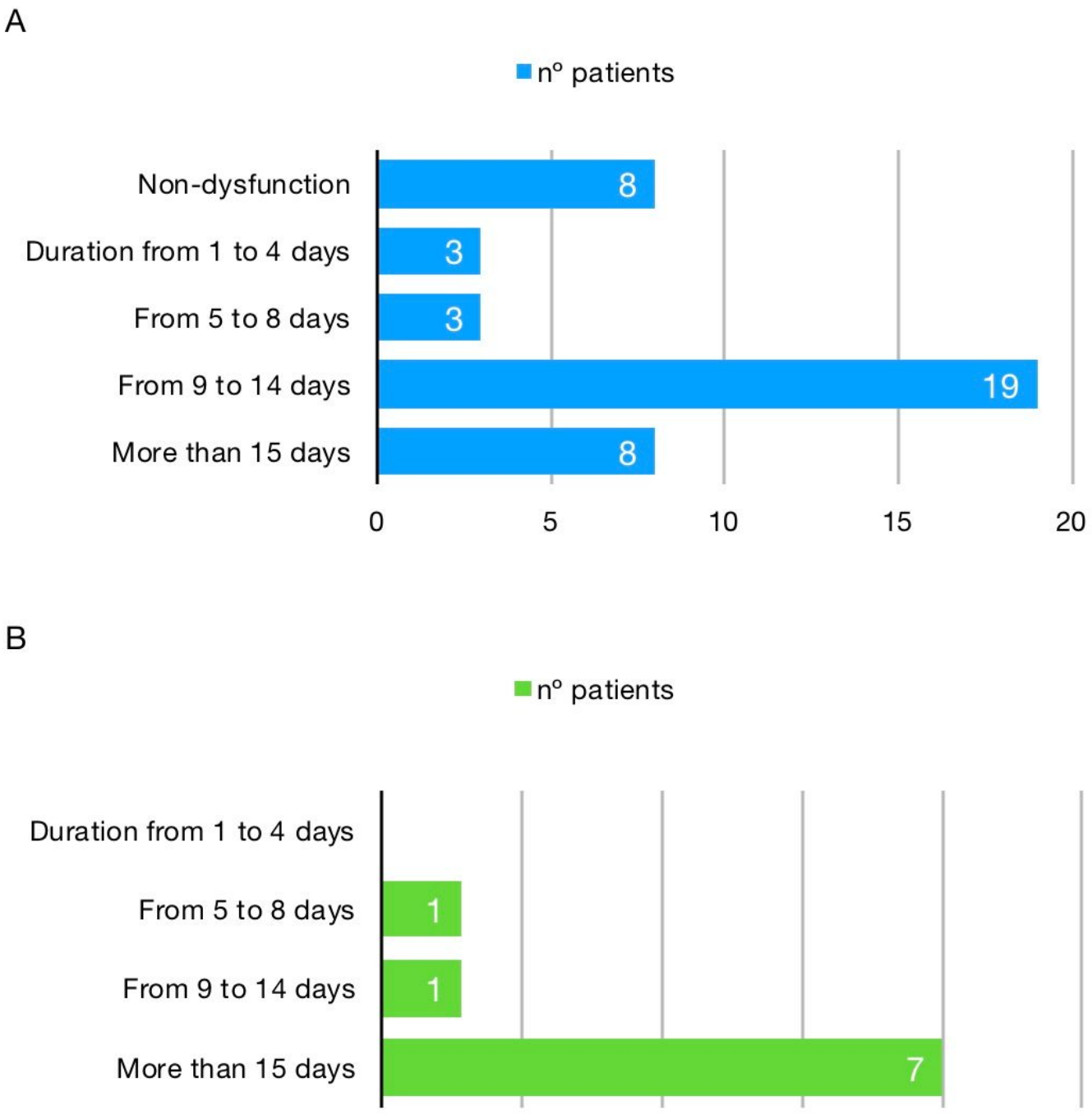

Figure 4

ENT symptoms related to SARS-Cov-2 infection. The ordinate axis consists of number of patients. Graph A. Patients with subjective dysfunction had the following duration times: non- dysfunction 8 (19.5%), 1-4 days 3 (7.3%), 5-8 days (7.3%), 9- 14 days 19 (46.3%), more than 15 days 8 (19.5%). Graph B. Patients with quantified olfactory dysfunction had the following recovery times: dysfunction 1- 4 days 0 (0%), 5-8 days 1 (11.11%), 9-14 days 1 (11.11%), more than 15 days 7 (77.77%).