CAROL DAVILA UNIVERSITY OF MEDICINE AND PHARMACY,
BUCHAREST
DOCTORAL SCHOOL
FIELD: DENTAL MEDICINE

ORAL LESIONS IN PATIENTS WITH COVID-19 – INITIAL SIGNS OR SECONDARY MANIFESTATIONS?

PhD Supervisor:
PROFESSOR LUMINOS MONICA, MD, PhD

Doctoral Student:
KOURIS CAMELIA

2025

Contents

Chapter/Section 1

List of abbreviations 4

List of articles 7

Introduction 8

I. General part-Current state of knowledge 11

1. SARS CoV-2 infection in the general population 11

1.1. Etiology of SARS CoV-2 virus 11

1.2. Structure of SARS CoV-2 virus 13

1.3. Mutations of SARS CoV- 2 virus 15

1.4. Mode of transmission 18

1.5. Contagiousness and incubation 19

1.6. Pathogenesis of SARS CoV-2 virus 20

1.7. Clinical manifestations in COVID 19 25

1.8. Clinical forms of the disease 28

1.9. Diagnosis of SARS CoV-2 infection 29

1.10. Paraclinical changes 30

1.11. Complication of SARS CoV-2 infection 32

1.12. Treatment of SARS CoV-2 infection 33

2. Oral cavity changes induced by SARS CoV-2 infection 35

2.1. Pathogenesis of oral lesion 36

2.2. Oral lesions caused by SARS CoV-2 40

2.2.1 Dysgeusia 40

2.2.2 Ulcerative lesions 42

2.2.3 Glossitis 44

2.2.4 Salivay gland lesions 45

2.2.5 Oral candidiasis 48
II. Personal contributions 51
3. Working hypothesis and general objectives 51
4. Researh methodology 54
5. Study 1. Dysgeusia as initial manifestation of SARS CoV-2 infection 58
5.1 Introduction 7
5.2 Materials and Methods 59
5.3 Results 59
5.4 Discussions and conclusions 112
6. Study 2. Oral candidiasis as secondary manifestation of SARS CoV-2 infection 118
6.1. Introduction 118
6.2 Materials and methods 119
6.3 Results 120
6.2. Discussions and conclusions 172
7. Final conclusions 177
List of tables 178
List of figfures 181
References 186
Appendix : published articles 202

Infection with the SARS-CoV-2 virus was one of the most publicized viral infections in history, posing a global challenge to healthcare systems through the pandemic it triggered, the first pandemic of the 21st century. [1, 2] The impact on national healthcare systems was substantial, simultaneously generating effects on social and economic life worldwide.

The clinical manifestations of COVID-19 are complex and range from asymptomatic forms to severe illness with symptoms such as acute respiratory distress syndrome (ARDS) and multi-organ failure. Many COVID-19 patients also exhibited clinical manifestations in the oral cavity.[3]

Working hyphotesis

We started from the hypothesis that SARS-CoV-2 has the potential to affect any organ, and we focused on potential alterations that might occur in the oral cavity. Since the onset of the pandemic, an association was observed between SARS-CoV-2 infection and taste perception disorders. This indication guided our assumption that the virus may act upon the oral mucosa, suggesting the presence of other associated manifestations. Based on this premise, our objectives focused on identifying and classifying the oral cavity changes that might occur.

Initially, we aimed to determine whether the oral lesions observed in the context of infection were early signs or secondary manifestations. As our research progressed and the number of cases increased, this idea began to take shape. By analyzing existing literature, we concluded that dysgeusia may represent an early manifestation of infection. In addition to dysgeusia, we identified a limited number of patients, 5 number presenting xerostomia, glossitis, and ulcerative lesions. The classification of these lesions remains controversial, and no current consensus exists. For this reason, these patients were excluded from our study. Moreover, due to the pandemic restrictions, we were unable to perform additional investigations such as sialometry, tongue biopsies, or lesion sampling. However, a significant advantage was the fact that hospitalized patients, due to the severity of illness and therapeutic complexity, required prolonged care, which allowed us to closely monitor them. Thus, we observed the onset of oral candidiasis in many cases, which allowed us to categorize it as a secondary manifestation. Unfortunately, due to limited access for non-COVID patients to our hospital, we were unable to follow these patients post-discharge to detect other potentially associated changes.

Our attention was focused on taste perception disorders at onset and the secondary development of oral candidiasis in COVID-19 patients. Over time, data analysis revealed that dysgeusia appears as an early manifestation, while oral candidiasis occurs as a secondary complication, particularly in patients with more severe disease. These conclusions were fundamental in guiding our research.

Starting from these simple but extremely valuable findings, the following hypotheses emerged:

- What are the factors that influence the occurrence of primary lesions (dysgeusia) or secondary lesions (candidiasis) in patients with SARS-CoV-2 virus infection? We propose to analyze a wide range of parameters grouped into six main domains: demographic indicators, paraclinical data, comorbidities, inflammatory markers, treatment options, and disease progression data.
- Can dysgeusia be considered a protective factor in preventing the progression to severe forms of the disease?
- Can a risk score be established based on which we can prevent the occurrence of secondary lesions such as candidiasis in SARS-CoV-2 virus infection?

Obiectivele generale

The main objective of the study was set separately for each cohort, as follows:

- For the dysgeusia-COVID19 cohort: Determining the incidence, clinical characteristics, and profile of patients with dysgeusia infected with the SARS-CoV-2 virus;
- For the candidiasis-COVID19 cohort: Determining the incidence, clinical characteristics, and profile of patients with oral candidiasis infected with the SARS-CoV-2 virus.

The secondary objectives of the study were also established separately for each cohort and were represented by:

- *For the dysgeusia COVID19 cohort:*

- Identifying dysgeusia as a predictive factor for association with a lower incidence of progression to severe and critical forms of the disease;
- Identifying demographic factors and clinical characteristics associated with the occurrence of dysgeusia;
- Defining a risk stratification algorithm for unfavorable disease progression considering the association between dysgeusia and clinical characteristics.

➢ *For the candidiasis COVID19 cohort:*

- Identifying demographic factors and clinical characteristics associated with the occurrence of dysgeusia;
- Identifying the association between inflammatory markers, administered therapy, and the occurrence of oral candidiasis;
- Quantifying risk factors for the occurrence of oral candidiasis in patients hospitalized for SARS-CoV-2 infection, moderate and severe forms of the disease;
- Defining a risk score and its threshold value for initiating antifungal therapy to prevent the occurrence of oral candidiasis in patients hospitalized for SARS-CoV-2 infection, moderate and severe forms of the disease.

Research methodology

The protocol involved conducting a retrospective, non-randomized observational clinical study consisting of two cohorts of patients, the first associating dysgeusia as a primary lesion of SARS-CoV-2 infection (DIS-COVID19), and the second associating oral candidiasis as a secondary lesion of SARS-CoV-2 infection (CAN-COVID19).

The patient cohorts were selected from among patients hospitalized for confirmed SARS-CoV-2 virus infection in the 10th section of the National Institute of Infectious Diseases "Prof. Dr. Matei Balș" during the period March 2020 - December 2022.

Identification of eligible patients was carried out through a consecutive analysis of the medical records of all 1100 patients hospitalized for COVID-19 in the 10th section of the National Institute of Infectious Diseases "Matei Balș" during the study period. During this period, the institute functioned exclusively as a tertiary specialty center dedicated to the care of COVID-19

patients, so the medical records of all patients hospitalized during the study period were subjected to analysis and selection according to inclusion and exclusion criteria.

Inclusion criteria

- For the first study, DIS-COVID19, a number of 347 adult patients over the age of 18 diagnosed with COVID-19 based on RT-PCR Sars-CoV-2 tests who presented mild, moderate, and severe forms of the disease were included.
- For the second study, CAN-COVID19, a number of 294 adult patients over the age of 18 diagnosed based on RT-PCR Sars-CoV-2 tests with moderate or severe forms of COVID-19 at the time of admission, for whom tongue scraping culture was performed to identify Candida spp. were included.

Exclusion criteria

- For the first study, DIS-COVID19, pediatric patients, asymptomatic patients, patients with critical forms of the disease requiring hospitalization in intensive care units, and those whose medical records were incomplete or inconclusive were excluded from this study.
- For the second study, CAN-COVID19, pediatric patients, patients with mild forms of the disease (not associated with oral candidiasis), patients for whom tongue scraping culture was not performed, patients with critical forms of the disease requiring hospitalization in intensive care units, and those whose medical records contained incomplete or inconclusive data were excluded from the study. Patients with oral lesions with pre-existing Candida spp. infection were also excluded.

The study protocol is shown in figure 4.1.

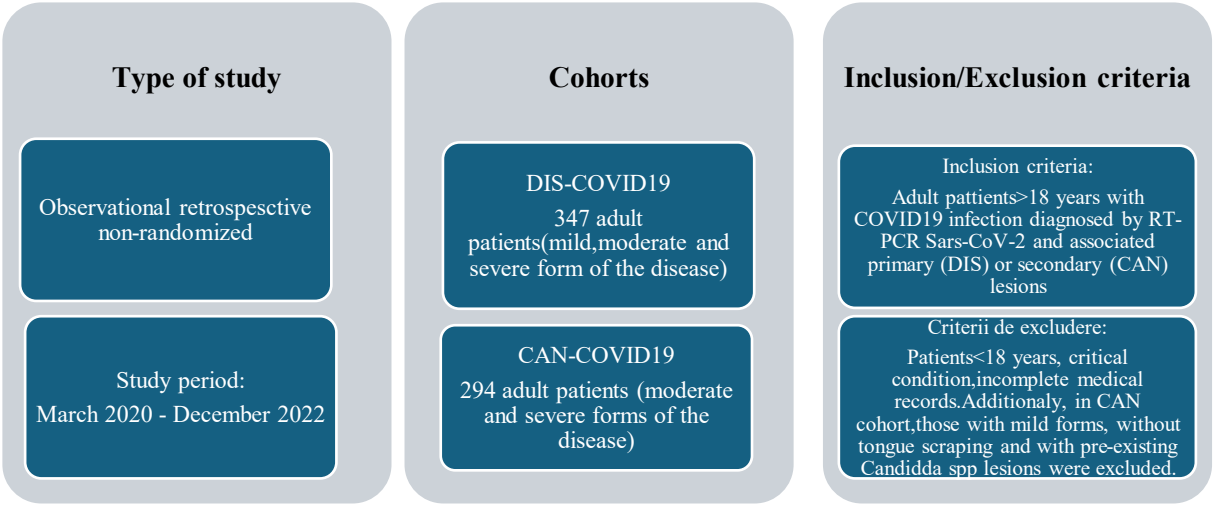

Figura.4.1 Protocol study

Source: Own, based on theoretical considerations of research methodology

We emphasize that the classification of clinical forms of COVID-19 was respected, corresponding to both national and international criteria, as follows:

- Mild forms associate clinical manifestations without presenting imaging changes on CT at the pulmonary level;
- Moderate forms present, in addition to clinical signs, imaging changes on CT at the pulmonary level, but with oxygen saturation maintained above 93% in atmospheric air;
- Severe forms are represented by symptomatic patients with pneumonia and oxygen saturations below 93%.

The analysis of the medical records of the patients was completed by extracting the following data: age, sex, origin, pre-existing chronic diseases, circulating virus variants (Alpha, Beta, Delta), clinical form and symptoms, time interval from disease onset to hospitalization, paraclinical investigations performed at the time of admission and during hospitalization (total leukocyte count, neutrophil count, lymphocyte count, alanine aminotransferase-ALT, aspartate aminotransferase-AST, lactate dehydrogenase-LDH, amylase, lipase, D-dimers, fibrinogen, C-reactive protein-PCR, ferritin, interleukin 1-IL 1, interleukin 6-IL 6), pulmonary CT, treatment administered during hospitalization (oxygen therapy, antiviral medication, corticosteroid therapy, anticoagulant, biological therapy, antibiotic therapy) as well as the evolution and duration of hospitalization.

In the next step, the extracted data were clustered into six domains for statistical analysis and processing, which we present in Table 4.1.

Table l 4.1. Clustering of data extracted from the analysis of patient records

Domain I **Demographic data**	***DomainII*** **Phenotype**	***Domain III*** **Associated chronic diseases**	***Domain IV*** **Paraclinic investigations**	***Domain V*** **Treatment**	***Domain VI*** **Evolution**
Sex	Viral phenotype	At least one chronic disease	HLG	Antibiotic	Duration from onset to presentation
Age	Alpha	Obesity	Neutrophils	Antiviral	Duration of hospitalization

Domain I Demographic data	*DomainII* Phenotype	*Domain III* Associated chronic diseases	*Domain IV* Paraclinic investigations	*Domain V* Treatment	*Domain VI* Evolution
Origin	Beta	HTA	Lymphocytes	Biological	Evolution towards acute respiratory failure
	Delta	Diabetes mellitus	Inflammatory markers	Glucocorticoid	
	Clinical phenotype	CVdiseases	Fibrinogen	Anticoagulant	
	Mild	Chronic pulmonary disease	C reactive protein		
	Moderate	Chronic pulmonary disease	IL 1		
	Severe	Neurological diseases	IL 6		
			D-dimers		
			LDH		
			Ferritin		
			Biochemistry		
			TGO		
			TGP		
			Lipase		
			Amylase		

Source: Own, based on data extracted from the analysis of patient records

The data were analyzed using SPSS for Windows version 25.

For Cluster I variables - Age, sex, origin, we used descriptive statistics to calculate the median and interquartile range (IQR, percentiles 25 - 75).

For the other variables, we proceeded to construct contingency tables and calculate chi-square, p-value, df, OR or RR, 95% CI, and CV where possible. Below we present the significance of each of the calculated parameters.

Comparative analysis of categorical variables was performed using the chi-square test. The Chi-square test indicates whether there is a significant association between DIS and CAN and categorical variables (TGO, TGP, etc.)

Formula for χ^2:

$\chi 2 = \sum \frac{(O - P)^2}{P}$

Where:

• O = Observed Frequency

• E = Expected Frequency

We calculated frequencies, percentages, and odds ratio (OR) or relative risk (RR) values, as appropriate, along with the confidence interval (CI 95%). For CI 95% values that include the value 1, statistical significance is not achieved.

Relative risk calculation was performed for variables where there is a degree of certainty based on previous clinical studies and which would influence the parameters under investigation. In our study, we performed RR calculation for biological therapy, glucocorticoid therapy, and antibiotic therapy in relation to their secondary development of Candida spp. infections. For the rest of the variables, we used OR calculation. Relative Risk (RR) compares the risk of an event occurring in the exposed group versus the unexposed group. Odds Ratio compares the likelihood of an event occurring (indirect risk) in the exposed group versus the unexposed group.

Comparative analysis of continuous variables was performed using the Mann-Whitney-U test as all our data were not normally distributed.

Statistical significance was established for p-value values below 0.05. Values of $p<0.001$ imply a high degree of statistical significance.

For the DIS-COVID-19 cohort, we developed a risk stratification algorithm for unfavorable disease progression considering the association between dysgeusia and clinical characteristics.

In the case of the CAN-COVID-19 cohort, we proceeded to establish a risk score based on odds ratio and relative risk obtained from the analysis of categorical variables. Each variable was assigned an absolute score based on the values (OR or RR) and the degree of statistical significance obtained. The cut-off value was established to reach a threshold of 75%.

Study 1. Dysgeusia, initial manifestation of SARS-CoV-2 virus infection

Introduction

Dysgeusia was considered from the onset of the pandemic to be pathognomonic for SARS-CoV-2 virus infection. Most cases were reported in the following variants: initial, alpha, beta, delta.

With the emergence of the omicron variant, the incidence of dysgeusia as a clinical manifestation has sharply decreased. We all know that the manifestations of SARS-CoV-2 virus infection can be complex and can vary from asymptomatic forms to severe forms with multi-organ involvement.

Dysgeusia along with anosmia were in many cases among the few early signs of the disease.

We discussed in the theoretical part that the mechanism of dysgeusia is not yet known, with several theories being proposed, namely:

- Direct involvement of the olfactory, glossopharyngeal, and facial nerves;[4]
- Direct action on the central nervous system, in cases with dysgeusia persisting for several weeks[5];
- Direct involvement of taste buds at the lingual level where ACE2 receptors are very well represented [6];
- Increase in IL 6 levels, following the massive release of pro-inflammatory factors, alters taste pathways[7];
- Quantitative and qualitative changes in salivary gland secretion[8,9];
- Advanced age, chronic medication, pre-existing diseases (anemia, diabetes mellitus, anxiety, depression, cardiovascular and pulmonary diseases), zinc deficiency, poor oral hygiene [4,8,10].

Discussion

Our study was conducted during the period March 2020-December 2021, in the 10th section of the National Institute of Infectious Diseases "Prof. Dr. Matei Balș" and included patients hospitalized with SARS-CoV-2 infection.

I would like to mention that these discussions were published in the article "Unraveling dysgeusia in SARS-CoV-2 infection: clinical and laboratory insights from hospitalized COVID-19 patients in Romania" of which I am the author, in March 2025, during the research period.[11]

The results obtained, as observed below, are extremely interesting and help us better understand the impact of dysgeusia in SARS-CoV-2 virus infection. Out of the total of 347 hospitalized patients included in this study, 111 associated taste changes, the incidence being 32%. Similar results were obtained in the meta-analysis by Mutiawati et al [12], where 30901 patients from 101 studies in the international literature were included to calculate the incidence of dysgeusia, the results obtained being similar to those of our study, namely 36.6%. The study conducted by Ali FA et al [13], carried out during the same period as our study and which included

405 COVID-19 positive patients, identified a percentage of 48.1% incidence of dysgeusia, higher than in our case. This result can be explained by the increased number of enrolled patients who presented mild forms of the disease 87.4% compared to our study, where only 8.5% were diagnosed with mild forms.

Regarding sex distribution, our study highlighted a predominance of dysgeusia among the female population 65.8%, with a median age of 42 years. The association of dysgeusia with the female sex was also highlighted in the study by Ali FA et al [13], 60.2% of women manifesting taste perception disorders. However, a difference was observed in the median age, 36 years versus 42 years in our study, explained by the inclusion in our study of a much larger number of older patients. (the median age of patients enrolled in the study was 52 years versus 36 years in the study by Ali FA et al [13]). Both Vaira L et al[14] and Paderno A et al [15] concluded that the female population, with younger ages, most frequently associates taste perception disorders.

The hypothesis was proposed that ACE receptors essential for SARS-CoV-2 virus adhesion are better represented on the X chromosome, hence the association of taste perception changes with the female population.[16]

What we found in this study is a balanced distribution of dysgeusia in the three forms of the disease: mild, moderate, and severe. However, those who did not associate dysgeusia had a 4.5 times higher risk of progressing to severe forms of the disease. Many studies associate dysgeusia with mild forms of the disease and younger ages, see Paderno A et al [15] and Quasim H et al [17]. This conclusion is very pertinent, considering that these studies took place in the general population, not focusing on hospitalized patients. However, in the study by Sheng W et al [18], on a cohort of 217 hospitalized patients, a high incidence of dysgeusia was identified among patients with mild and moderate forms of the disease, similar to our study.

It is known that patients infected with SARS-CoV-2 associate at least one chronic disease: hypertension, diabetes mellitus, cardiovascular diseases, obesity. Following statistical analyses, we found that dysgeusia is significantly less common in patient groups with comorbidities such as obesity, hypertension, diabetes mellitus, cardiovascular diseases. The statistically significant information is related to obesity and hypertension, so patients with dysgeusia have a 2 times lower probability of risk of suffering from obesity than those without dysgeusia and a 2.5 times lower risk of associating hypertension. A study from Indonesia supports our findings, obtaining similar

results. Siswanto JLJ et al [19] concluded that in the group of patients with dysgeusia, the percentage of those with obesity, hypertension, and diabetes mellitus was reduced.

Regarding paraclinical changes, we found that patients with dysgeusia had a hematological profile suggestive of a mild-moderate stage of the disease, with a competent immune status, without associating a high degree of lymphopenia, compared to those without taste perception changes, who had a 2 times higher risk of presenting lymphopenia and obviously an unfavorable clinical evolution. The analysis of biochemical markers shows higher median values in the group of patients without dysgeusia, in the case of all analyzed parameters (TGO, TGP, amylase, lipase), significantly higher extreme values and more frequent, compared to the group of patients with dysgeusia. The results support the idea that dysgeusia can represent a biological marker signaling a less severe clinical phenotype. Studying inflammatory markers, a significant association of increased values of ferritin, fibrinogen, and C-reactive protein was found in the group of patients with non-dysgeusia. Increased values of inflammatory markers are associated with a high potential for developing complications and reflect an increased incidence of progression to moderate and severe forms of the disease. The high risk of unfavorable evolution in this category was described from the beginning of the pandemic. The fact that patients with dysgeusia or other taste perception disorders did not have significant changes in inflammatory markers was also noted by Thippeswamy SN et al [20], in a group of 160 participants with mild, moderate, and severe forms. Before obtaining the results of this study, I documented myself in the specialized literature and observed that dysgeusia was associated with increased values of IL 6 and LDH [21,22,23]. In our study, an increased value of IL 6 was found in both groups of patients with and without dysgeusia, without statistical significance, while the increased value of LDH was statistically significant for the group of patients without dysgeusia. One explanation could be that our study included a smaller number of patients and a high percentage of moderate and severe forms, which generally associate with inflammatory phenomena, thus clarifying the presence of increased values of IL6, IL1, and LDH. I would like to mention that the number of studies that aimed to identify a specific biological profile among patients with taste perception disorders is quite limited, so the information obtained in our research can be considered valuable, bringing additional information.

Regarding the medication used, both groups with and without dysgeusia used anticoagulant therapy, without statistically significant differences from this point of view. However, biological therapy and corticosteroid therapy were administered 2.6 and 1.6 times more frequently among

patients without dysgeusia, which strengthens the hypothesis that patients with dysgeusia associated milder forms of the disease and the medication used among them was less complex. Indeed, in the case of enrolled patients without taste perception changes, we found statistically significant changes in the use of antibiotic therapy, antiviral medication, biological therapy, and corticosteroid therapy, with p-values <0.001, which supports the theory that dysgeusia can be considered to have a protective role in unfavorable evolution.

The presence of dysgeusia in COVID-19 correlates with a less severe disease course, with early presentation to medical consultation, reduced hospitalization duration, and a lower risk of associating respiratory failure. Regarding the duration of hospitalization, patients with dysgeusia showed a faster clinical recovery, and thus the costs were lower.

Conclusions and Proposals

The additional information provided in this study is considerable, given the fact that there are few clinical and laboratory data regarding hospitalized patients with dysgeusia who presented moderate and severe forms, most studies focusing on the association of dysgeusia with mild forms of the disease. The records of these patients are quite complex and help us better understand certain particularities and associations.

Our study identified an incidence of 32% of dysgeusia among hospitalized patients with SARS-CoV-2 infection, mild, moderate, and severe forms during the circulation of the Alpha, Beta, and Delta variants. A predisposition of the female sex was observed, with a predominance of younger ages and an equal distribution of dysgeusia cases across the forms of the disease.

We identified that patients with taste perception disorders had fewer comorbidities and fewer changes in biological variables. These patients had a low percentage of systemic inflammatory response and did not experience the well-known stage of the "cytokine storm," which is associated with an increased risk of ARDS.

The necessary treatment was less complex, and the risk of associating respiratory failure was much reduced. In this context, the hospitalization time and associated costs were reduced, so dysgeusia can be considered a protective factor during SARS-CoV-2 infection.

From the perspective of public health systems and triage, the presence of dysgeusia can help stratify patient risk in relation to the clinical phenotype, guide therapeutic decisions, the intensity of therapy administration, and not least, the allocation of public health system resources in pandemic conditions.

Study 2. Oral candidiasis, secondary manifestation of SARS-CoV-2 infection

Introduction

Oral candidiasis is a fungal infection caused by various species of Candida and is considered an opportunistic infection, meaning it is favored by the occurrence of an imbalance within the immune system. During the pandemic, numerous cases of oral candidiasis were described in patients infected with the SARS-CoV-2 virus, being a secondary complication not at all coincidental, given the multitude of changes caused by the virus at the oral cavity level.

In the general part, we discussed the characteristics observed in COVID-19 patients who associated oral candidiasis. Regarding our study, I will briefly highlight some particularities that help us better understand the pattern of these patients and the importance of monitoring them to prevent the occurrence of fungal infections.

- Poor oral hygiene, secondary to the immobilization of these patients due to the use of oxygen therapy and altered general condition;
- The most affected were those who associated severe and critical forms of the disease;[24]
- Frequent use of antibiotics, with secondary modification of the oral microbiota, thus favoring the occurrence of fungal infections;[25]
- Pre-existing chronic conditions, especially diabetes mellitus, neoplastic diseases;
- Quantitative and qualitative changes produced by the virus at the salivary level;[26]
- Associated severe lymphopenia, decreased the body's defense capacity against opportunistic germs;
- Significant inflammatory reaction, with massive release of cytokines and increased ferritin levels, favoring fungal infections;
- Use of corticosteroid therapy and biological medication;
- Administration of zinc supplements during the pandemic increased the incidence of candidiasis.

Considering all these aspects, it can be concluded that COVID-19 patients, especially those with severe and critical forms of the disease, are predisposed to developing oral candidiasis as a secondary complication. It is essential to closely monitor these patients to promptly prevent and treat fungal infections.

Discussions and Conclusions

In this study, we conducted a retrospective analysis among 294 hospitalized patients diagnosed with SARS-CoV-2 virus infection and who associated oral candidiasis, infection proven by culture performed from tongue scraping. I mention that the results obtained were published in the article "The Incidence and Characteristics of Oral Candidiasis in Patients Hospitalized for SARS-CoV-2 Infection During the Circulation of Alpha, Beta, and Delta Variants," of which I am the author, published in 2024 .[27]

The incidence of oral candidiasis in the study group was 17%, the result obtained being different compared to data published in other studies. Thus, the incidence of candidiasis in the study by Di Spirito et al [28] was 10.74%, from a group of 4925 enrolled patients, Babamahmoodi et al [29] identified 2.9% patients with oral candidiasis from 4133 patients enrolled in the study, and Salehi et al [30] a percentage of 5% of oral candidiasis. These observed variations can be attributed to several factors, such as patient selection criteria, inclusion in their groups of all forms of the disease, medication used, associated comorbidities.

As it appears from domain I, demographic data, the presence of candidiasis seems to be more frequent among the female population, without having a statistically significant association. In addition, the group of patients diagnosed with candidiasis has a median age higher by over 4 years (55.5 years vs. 51.5 years, $p = 0.0052$), compared to those without candidiasis. Riad et al [31] identified in an analysis of 63 cases of oral candidiasis an average age of 59.5 years and a predominance of the female sex 56.7%, results similar to those obtained in our case.

Regarding the distribution of oral candidiasis according to the form of the disease, the incidence was higher among patients with severe form (86%), therefore, patients with COVID-19 with a severe form of the disease were 4.2 times more likely to develop oral candidiasis, a result that was highly statistically significant. This aspect has often been emphasized in the literature and is logical, considering that severe forms of COVID-19 required high-flow oxygen, which led to a decrease in saliva quantity, had poor oral hygiene due to limited physical activity secondary to associated respiratory insufficiency, and benefited from complex and aggressive therapy, which involved the association of antibiotic therapy, corticosteroid therapy, and biological medication. In addition, most patients with oral candidiasis had at least one chronic disease (80%). In our study, no statistically significant association was found, but it was observed that type 2 diabetes mellitus was more frequent among patients with candidiasis, and patients with hypertension and obesity

were 1.9 and 1.7 times more likely to develop oral candidiasis. Similar results were obtained in the studies by Salehi et al [32] and Negm et al [33], who reported that diabetes mellitus and hypertension are more frequent among patients with oral candidiasis.

Regarding laboratory investigations, we observed a significant association of increased values of ferritin, LDH, and fibrinogen with the presence of oral candidiasis in COVID-19 patients. The presence of a significant inflammatory response is associated with severe forms of the disease, with the need for more complex treatment, which can in turn favor the occurrence of candidiasis. Similar results were obtained in a study conducted in Turkey [34] . It is known that severe lymphopenia is closely related to a more reserved prognosis and the development of candidiasis, in our case we observed that patients in the candidiasis group have a 1.3 times higher risk of associating lymphopenia, a fact also found by Ortega et al [35] in his study.

In our study, the treatment administered to patients with oral candidiasis infected with the SARS-CoV-2 virus was complex and long-lasting. Antibiotic therapy and glucocorticoids recorded the most significant differences between patient groups, the associations between these and the occurrence of oral candidiasis being statistically significant, patients having a relative risk of developing oral candidiasis of 13% and 19%, respectively. Therefore, both antibiotic therapy and corticosteroid therapy can be considered risk factors for the occurrence of oral candidiasis. In a study conducted in Iran during the pandemic, patients who developed secondary oral candidiasis received antibiotic therapy and corticosteroid therapy .[36] The same results regarding the association between corticosteroid therapy and fungal infections were published in the pre-pandemic period in China .[37]

The presence of candidiasis in patients with SARS-CoV-2 infection correlates with a more severe, unfavorable evolution, including an increase in hospitalization duration, and a higher risk of associating respiratory insufficiency. The average hospitalization duration for patients with candidiasis was 15-16 days, longer compared to the median corresponding to the group without candidiasis, which was between 10-12 days. A statistically significant association that emerges from our study is related to the risk of progression to respiratory insufficiency, this being approximately 3.6 times higher in the group of patients with oral candidiasis.

Conclusions

The results of this study are relevant for understanding the clinical context and for the effective management of oral candidiasis cases in patients with COVID-19.

The incidence of oral candidiasis was 17% among hospitalized patients with moderate and severe forms of COVID-19 during the circulation of the Alpha, Beta, and Delta variants. We identified that severe forms of the disease are associated with a higher risk of developing secondary fungal infections. The administration of antibiotic therapy and corticosteroid therapy proved to be positive predictive factors for oral candidiasis. The results obtained are encouraging, helping us to create an algorithm to support the prevention of fungal infections.

It is important to emphasize that we managed to include a significant number of patients, generating an extensive data set. This allowed us to identify relevant characteristics and risk factors for the development of oral candidiasis among Romanian patients hospitalized in the largest infectious disease hospital in the country and the main coordination center for the COVID-19 pandemic. Thus, although the study has its limitations, its contributions are essential for understanding and managing oral candidiasis in the context of SARS-CoV-2 infection.

Given the size of our cohort and the fact that certain variables did not reach the threshold of statistical significance, we will integrate our results with literature data for known variables that could favor Candida spp. infections. Based on the corroboration of all these data, we propose a risk score that will consider the statistical significance of the association between the analyzed variable and the occurrence of oral candidiasis reached during our research.

Final Conclusions

- We identified the incidence of dysgeusia among hospitalized patients with SARS-CoV-2 infection, based on clinical forms during the circulation of the Alpha, Beta, and Delta variants.
- A predisposition of the female sex was observed, with a predominance of younger ages and an equal distribution of dysgeusia cases across the clinical forms of the disease.
- We found that patients with taste perception disorders had fewer comorbidities.
- Biological variables in patients with dysgeusia did not undergo significant changes, mostly falling within laboratory limits.
- The necessary treatment for these patients was less complex and did not require the use of associated therapies: antibiotic therapy, biological therapy, and corticosteroid therapy.
- The risk of respiratory failure among patients with dysgeusia was much lower.
- The hospitalization period in these cases was shorter, thus reducing hospitalization costs.

- Dysgeusia can be considered a protective factor during SARS-CoV-2 infection, as these patients had a much lower risk of unfavorable outcomes.
- We identified the incidence of candidiasis among hospitalized COVID-19 patients, based on clinical forms and circulating virus variants.
- Severe forms of COVID-19 are associated with a higher risk of developing fungal infections.
- The incidence was higher among the female population, with older ages.
- Patients with candidiasis had changes in laboratory parameters, associating a significant inflammatory syndrome and marked lymphopenia.
- The administration of antibiotic therapy and corticosteroid therapy are positive predictive factors for oral candidiasis.
- Therapeutic management in cases of candidiasis is much more complex, requiring rigorous evaluation of patient records and a multidisciplinary approach.
- The clinical evolution of patients with candidiasis involves a more frequent association of respiratory failure and a longer hospitalization duration.
- Limitations were largely due to the epidemiological situation imposed during the pandemic, which restricted access for both doctors and patients to interdisciplinary consultations and certain investigations.
- Some of the oral cavity lesions described in the literature could not be scientifically argued in our case, as we did not have access to all medical resources during that period.
- Although the studies were conducted on smaller cohorts, the results are consistent with other research published to date.

Personal Contributions

Our research guides clinicians towards an appropriate approach to future epidemic situations, offering solutions for public health management. It is essential that future research focuses on identifying risk factors and developing effective clinical guidelines. Additionally, multidisciplinary collaboration and access to comprehensive medical resources are paramount for optimal management of these cases, especially in restrictive epidemiological situations.

The clinical data obtained and presented throughout our research support the use of dysgeusia as a phenotypic marker in stratifying the risk of COVID-19 patients towards a severe form of the disease and an unfavorable evolution. In combination with comorbidity status, inflammatory

markers, and multi-organ involvement, it provides an accurate and stratified picture of the severity of COVID-19 evolution, thus guiding therapeutic decisions, case prioritization, and resource allocation, especially in pandemic conditions. Based on the results obtained, we propose an integrated risk stratification algorithm, taking into account the analyzed variables and the statistical significance achieved during our research. The risk score matrix that underpins our algorithm is presented in Table 5.29 of the thesis.

Another proposal aims at creating a risk score for patients infected with the SARS-CoV-2 virus regarding the association of infections with opportunistic germs, particularly Candida spp. Even if certain variables did not reach the threshold of statistical significance, we integrated our results with those from the literature. Based on the corroboration of all these data, we proposed a risk score that considers the statistical significance of the association between the analyzed variables and the occurrence of oral candidiasis achieved during our research. This is found in Figure 6.48 of the doctoral thesis.

We also propose, based on the identified risk categories, the use of a preventive cut-off score in clinical practice, from which antifungal therapy should be instituted, as presented in Figure 6.49 of the thesis.

References

1. Hasöksüz M, Kiliç S, Saraç F (2020) Coronaviruses and SARS-COV-2. Turk J Med Sci 50: 549-556.

2. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Napoli RD (2020) Features, evaluation and treatment coronavirus (COVID-19). StatPearls .

3. "Healthcare Professionals: Frequently Asked Questions and Answers". United States Centers for Disease Control and Prevention (CDC). 11 February 2020. Archived from the original on 14 February 2020. Retrieved 15 February 2020.

4. Risso D, Drayna D, Morini G. Alteration, reduction and taste loss: main causes and potential implications on dietary habits. Nutrients 2020; 12: 3284.

5. Finsterer J, Stollberger C. Causes of hypogeu sia/hyposmia in SARS-CoV2 infected patients. J Med Virol 2020.

6. Vilela-Estrada MA, Benites-Flores IR, García-Saave dra MB, Mejia CR. Clinical manifestations and course of the first six reported cases of COVID-19 in the medical doctors of Peru. Medwave. Chile 2020; 20: e7994.

7. Khan AS, Hichami A, Khan NA. Obesity and COVID-19: oro-naso-sensory perception. J Clin Med 2020; 9: 2158.

8. Lozada-Nur F, Chainani-Wu N, Fortuna G, Sroussi H. Dysgeusia in COVID-19: possible mechanisms and implications. Oral Surg Oral Med Oral Pathol Oral Radiol 2020; 130: 344-346.

9. Lechien JR, Hsieh JW, Ayad T, Fakhry N, Hans S, Chiesa-Estomba CM, Saussez S. Gustatory dysfunctions in COVID-19. Eur Arch Otorhinolaryngol 2020: 2397-2398

10. Almeria M, Cejudo JC, Sotoca J, Deus J, Krupinski J. Cognitive profile following COVID-19 infection: Clinical predictors leading to neuropsychological impairment. Brain Behav Immun Health 2020; 9: 100163

11. Kouris, E.C.; Mirea, S.I.; Covaci, S.; Luminos, M.L.; Miron, V.D. Unraveling Dysgeusia in SARS-CoV-2 Infection: Clinical and Laboratory Insights from Hospitalized COVID-19 Patients in Romania. *Pathogens* **2025**, *14*, 300. https://doi.org/10.3390/pathogens14040300

12. Ali FA, Jassim G, Khalaf Z, Yusuf M, Ali S, Husain N, Ebrahim F. Transient Anosmia and Dysgeusia in COVID-19 Disease: A Cross Sectional Study. Int J Gen Med. 2023;16:2393-2403 https://doi.org/10.2147/IJGM.S408706]

13. Objective evaluation of anosmia and ageusia in COVID-19 patients: Single-center experience on 72 cases Luigi Angelo Vaira 1,✉, Giovanna Deiana 2, Alessandro Giuseppe Fois 3, Pietro Pirina 3, Giordano Madeddu 4, Andrea De Vito 4, Sergio Babudieri 4, Marzia Petrocelli 5, Antonello Serra 6, Francesco Bussu 7, Enrica Ligas 1, Giovanni Salzano 8, Giacomo De Riu 1

14. Objective evaluation of anosmia and ageusia in COVID-19 patients: Single-center experience on 72 cases Luigi Angelo Vaira 1,✉, Giovanna Deiana 2, Alessandro Giuseppe Fois 3, Pietro Pirina 3, Giordano Madeddu 4, Andrea De Vito 4, Sergio Babudieri 4, Marzia Petrocelli 5, Antonello Serra 6, Francesco Bussu 7, Enrica Ligas 1, Giovanni Salzano 8, Giacomo De Riu 1

15. Paderno A, Schreiber A, Grammatica A, Raf fetti E, Tomasoni M, Gualtieri T, Taboni S, Zorzi S, Lombardi D, Deganello A, Redaelli De Zinis LO, Maroldi R, Mattavelli D. Smell and taste al terations in COVID-19: a cross-sectional analy sis of different cohorts. Int Forum Allergy Rhinol 2020; 10: 955-962.

16. Tong JY, Wong A, Zhu D, et al. The prevalence of olfactory and gustatory dysfunction in COVID-19 patients: a systematic review and meta-analysis. Otolaryngol Head Neck Surg. 2020;163(1):3–11. doi:10.1177/0194599820926473

17. Characteristics of COVID-19 smell and taste dysfunction in hospitalized patients Qasim Husain, Konstandina Kokinakos, Yen-Hong Kuo, Faiha Zaidi, Sean Houston, Josef Shargorodsky

18. Dysosmia and dysgeusia in patients with COVID-19 in northern Taiwan;Wang-Huei Sheng ,Wang-Da Liu,Jann-Tay Wang ,Su-Yuan Chang ,Shan-Chwen Chang

19. Anosmia, Dysgeusia, and Comorbidity in COVID-19 Patients with Respiratory Tract Manifestations, Jason Lefranda Jocelino Siswanto 1, Viskasari Pintoko Kalanjati 2 , Soetjipto Soetjipto3, Azlin Muhammad Mohd Yasin4

20. Taste Dysfunction In COVID-19 Patients; A Cross-Sectional Observational Study Sreedevi Nunkappa Thippeswamy, Keerthi kumar Kabbyar Chidananda, Kamalesh Tagadur Nataraju https://doi.org/10.47210/bjohns.2023.v31i2.898

21. Cazzolla AP, Lovero R, Lo Muzio L, Testa NF, Schirinzi A, Palmieri G, Pozzessere P, Procacci V, Di Comite M, Ciavarella D, Pepe M, De Ruvo C, Crincoli V, Di Serio F, Santacroce L. Taste and

smell disorders in COVID-19 patients: role of interleukin-6. ACS Chem Neurosci 2020; 11: 2774-2781

22. Mahmoud M, et al. Pathogenesis of dysgeusia in COVID-19 patients: a scoping review. Eur Rev Med Pharmacol Sci. 2021;25(2):1114–34

23. Eshraghi AA, Mirsaeidi M, Davies C, Telischi FF, Chaudhari N, Mittal R. Potential mechanisms for COVID-19 induced anosmia and dysgeusia. Front Physiol 2020; 11: 1039.

24. COVID-19-Associated Candidiasis: Possible Patho-Mechanism, Predisposing Factors, and Prevention Strategies Nafisa Ahmed, Maiesha Samiha Mahmood, Abu Tayab Moin, · Mohammad Jakir Hosen. Received: 24 October 2021 / Accepted: 23 February 2022

25. Segrelles-Calvo G, de S Araújo GR, Frases S. Systemic mycoses: a potential alert for complications in COVID-19 patients. Future Microbiology. 2020;15(14):1405–13.

26. Torres S.R., Peixoto C.B., Caldas D.M., Silva E.B., Akiti T., Nucci M., de Uzeda M. Relationship between salivary flow rates and Candida counts in subjects with xerostomia. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endodontology. 2002;93:149–154. doi: 10.1067/moe.2002.119738. [DOI] [PubMed] [Google Scholar]

27. Kouris EC, Mirea SI, Luminos ML, Miron VD. The Incidence and Characteristics of Oral Candidiasis in Patients Hospitalized for SARS-CoV-2 Infection During the Circulation of Alpha, Beta, and Delta Variants. Microorganisms. 2024 Oct 18;12(10):2090. doi: 10.3390/microorganisms12102090. PMID: 39458399; PMCID: PMC11509929.

28. Di Spirito F, Iandolo A, Amato A, Caggiano M, Raimondo A, Lembo S, et al. Prevalence, Features and Degree of Association of Oral Lesions in COVID-19: A Systematic Review of Systematic Reviews. Int J Environ Res Public Health. 2022;19(12).

29. Babamahmoodi F, Rezai MS, Ahangarkani F, Mohammadi Kali A, Alizadeh-Navaei R, Alishahi A, et al. Multiple Candida strains causing oral infection in COVID-19 patients under corticosteroids and antibiotic therapy: An observational study. Front Cell Infect Microbiol. 2022;12:1103226.

30. Salehi M, Ahmadikia K, Mahmoudi S, Kalantari S, Jamalimoghadamsiahkali S, Izadi A, et al. Oropharyngeal candidiasis in hospitalised COVID-19 patients from Iran: Species identification and antifungal susceptibility pattern. Mycoses. 2020;63(8):771-8.

31. Riad A, Gomaa E, Hockova B, Klugar M. Oral candidiasis of COVID-19 patients: Case report and review of evidence. J Cosmet Dermatol. 2021;20(6):1580-4.

32. Salehi M, Khajavirad N, Alavi Darazam I, Hashemi SJ, Ansari S, Ghiasvand F, et al. Risk Factors of Oropharyngeal Candidiasis in COVID-19 Patients: A Case-control Study. Arch Clin Infect Dis. 2021;16(5):e114631.

33. Negm EM, Mohamed MS, Rabie RA, Fouad WS, Beniamen A, Mosallem A, et al. Fungal infection profile in critically ill COVID-19 patients: a prospective study at a large teaching hospital in a middle-income country. BMC Infect Dis. 2023;23(1):246.

34. Kazancioglu S, Bodur H, Mumcuoglu I, Bastug A, Ozbay BO, Aydos O, et al. Candidemia in critically ill COVID-19 patients: Risk factors and impact on mortality. Heliyon. 2024;10(6):e28033.

35. Babamahmoodi F, Rezai MS, Ahangarkani F, Mohammadi Kali A, Alizadeh-Navaei R, Alishahi A, et al. Multiple Candida strains causing oral infection in COVID-19 patients under corticosteroids and antibiotic therapy: An observational study. Front Cell Infect Microbiol. 2022;12:1103226.

36. Ortega-Loubon C, Cano-Hernandez B, Poves-Alvarez R, Munoz-Moreno MF, Roman-Garcia P, Balbas-Alvarez S, et al. The Overlooked Immune State in Candidemia: A Risk Factor for Mortality. J Clin Med. 2019;8(10).

37. Xiao JL, Xu GC, de Hoog S, Qiao JJ, Fang H, Li YL. Oral Prevalence of Candida Species in Patients Undergoing Systemic Glucocorticoid Therapy and the Antifungal Sensitivity of the Isolates. Infect Drug Resist. 2020;13:2601-7.