J Oral Res
research in oral sciences

Article

Oral and Maxillofacial Lesions in COVID 19 Infection from Mosul Hospital in Iraq: Epidemiological Study and Approach to Classification and Treatment.

Lesiones orales y maxilofaciales en COVID 19 del Hospital de Mosul en Irak: estudio epidemiológico y enfoque de clasificación y tratamiento.

Alyaa Ismael Naser.[1]
Marwa Nazar Al-Sarraj.[2]
Ziad H. Deleme.[1]

Affiliations:
[1]Department of OMFS. College of Dentistry. University of Mosul, Mosul, Iraq.
[2]Nineveh Health Directorate. Al-Shiffa Hospital for Pyritic Diseases, Mosul, Iraq.

Corresponding author: Alyaa Ismael Naser. Department of OMFS. College of Dentistry. University of Mosul. Iraq, Mosul. E-mail: **alyaaismael@uomosul.edu.iq**

Receipt : 06/11/2021 Revised: 09/14/2021
Acceptance: 12/31/2021

Abstract: During the COVID-19 pandemic, many manifestations of the disease appear in the oral, perioral and maxillofacial regions, either related to the virus itself or to the drugs used in the treatment. **Aim:** This study aims to identify the most common oral and perioral lesions in hospitalized patients with COVID-19 in the city of Mosul and their management; and also to evaluate the incidence and prevalence of these lesions. **Material and Methods:** Prospective study included 338 patients (138 females, 200 males) who had positive PCR results for SARS-CoV-2, with oral manifestations. All data were analyzed taking the means, frequencies, and percentage. **Results:** The most common lesions were colored lesions (31%) and stomatalgia (27%). The most common oral disorder and prior comorbidity combination was stomatalgia in patients with a history of hypertension. The most common associated systemic diseases were diabetes mellitus (19%) followed by hypertension (17%). Macular lesions had a higher response to drugs (40%) followed by stomatalgia (28%), in comparison with necrotic lesions (0%). Treatment of oral lesions included surgical interventions (26%) as well as conventional medical treatment (74%). **Conclusion:** Oral and perioral disorders during COVID-19 are transitory and more evidence is warranted to efficiently address these comorbidities in the short term.

Keywords: *COVID-19; Oral Ulcer; incidence; Diabetes Mellitus; Hypertension; Prospective Studies.*

Resumen: Durante la pandemia de COVID-19, muchas manifestaciones de la enfermedad aparecen en las regiones oral, perioral y maxilofacial, ya sea relacionadas con el propio virus o con los fármacos utilizados en el tratamiento. **Objetivo:** Este estudio tiene como objetivo identificar las lesiones orales y periorales más comunes en pacientes hospitalizados con COVID-19 en la ciudad de Mosul y su manejo; y también evaluar la incidencia y prevalencia de estas lesiones. **Material y Métodos:** Estudio

Cite as: Naser AI, Al-Sarraj MN & Deleme ZH.
Oral and Maxillofacial Lesions in COVID 19 Infection from Mosul Hospital in Iraq: Epidemiological Study and Approach to Classification and Treatment.
J Oral Res 2021; 10(6):1-14.
Doi:10.17126/joralres.2021.069

prospectivo que incluyó a 338 pacientes (138 mujeres, 200 hombres) que tenían resultados positivos de PCR para SARS-CoV-2, con manifestaciones orales. Todos los datos se analizaron tomando las medias, frecuencias y porcentaje. **Resultados:** Las lesiones más frecuentes fueron las coloreadas (31%) y la estomatalgia (27%). La combinación de trastorno oral más común y comorbilidad previa fue la estomatalgia en pacientes con antecedentes de hipertensión. Las enfermedades sistémicas asociadas más comunes fueron la diabetes mellitus (19%) seguida de la hipertensión (17%). Las lesiones maculares tuvieron una mayor respuesta a los fármacos (40%) seguidas de la estomatalgia (28%), en comparación con las lesiones necróticas (0%). El tratamiento de las lesiones orales incluyó intervenciones quirúrgicas (26%) y tratamiento médico convencional (74%). **Conclusión:** Los trastornos bucales y periorales durante el COVID-19 son transitorios; se necesita más evidencia para abordar de manera eficiente estas comorbilidades a corto plazo.

Palabra Clave: *trastornos de la articulación temporomandibular; cóndilo mandibular; articulación temporomandibular; adulto joven; diagnóstico por imagen.*

INTRODUCTION.

Healthcare systems were challenged during this pandemic and patients with oral diseases were affected in the depriorization of dermatology and dental departments that were not receptive to non-seriously ill patients due to reconversion in the context of COVID-19.[1,2] Furthermore preventive strategies[3,4] mask mandates,[5-7] antibiotics misuse, lockdown and hand hygiene further increased the burden of oral and perioral of lesions. Telemedicine and teledermatology were unsuitable to assess oral disorders, so patients were disoriented and assessed in the emergency department only in case of severe manifestations. [8]

During the explosion of the COVID-19 pandemic, a myriad of disease manifestations and complications have emerged and are being reported. Humans are only infected by α and β family coronaviruses.[9] Exposure to coughing, sneezing, breathing drops, or airborne particles during close contact with an infected individual increases the risk of transmission of respiratory viruses between humans.[10,11]

Coronaviruses are a group of enveloped RNA viruses that have a typical structure with a spike protein in its membrane envelope.[12,13] The interaction between angiotensin-converting enzyme 2 (ACE2) receptors and this spike protein is considered the main route for entry into target cells, a crucial step before replication can occur intracellularly.[14] The ACE2 receptors are present in different tissues of the body, including mucosal tissues, gingiva, non-keratinizing squamous epithelium, and epithelial cells of the tongue and salivary glands.[15-17] In addition, saliva in periodontal pockets contains a high concentration of SARS-CoV-2 viruses.[18,19] Studies have shown virus transmission can occur via saliva droplets through coughing, sneezing, talking, and even during dental care making oral tissues a potential reservoir from which SARS-CoV-2 transmission may occur.[20-22] One of the first sites of viral infection is the oral cavity,[23-25] which may exhibit manifestations of underlying diseases such as oral ulcerations, gingival bleeding, glossitis, and oral pain.[26-28] Dry mouth was shown to be manifested in a relatively high proportion of COVID-19 patients.[29]

In a systematic review and meta-analysis by Lansbury et al., four fungal pathogens were recorded from three studies, which included *Candida albicans*, *Candida glabrata*, *Aspergillus flavus* and *Aspergillus fumigatus*.[30] *Candida albicans* is a normal colonizer in the oral cavity; for confirming the diagnosis of infection a successful response to antifungal treatment should be observed; additionally, culturing the pathogen, preparing a fungal wet smear, or even incisional biopsy can aid diagnosis.[31] Recent studies support that oral ulceration is a preliminary manifestation of COVID-19 infection which seemed to cause either ulceration in the palatal mucosa or localized erythema in the palate and marginal gingiva.[32]

Carreras-Presas et al.,[33] recorded pain and oral ulceration in COVID-19 in their study. Mucormycosis and orbital compartment syndrome are uncommon, time-sensitive diseases that must be diagnosed and treated properly to avert mortality and morbidity.[34] Mucormycosis, zygomycosis or phycomycosis is a rare opportunistic frequently fulminant fungal infection caused by saprobic organisms of the class Zygomycetes, such as Absidia, Mucor, Rhizomucor,

and Rhizopus. It is described by infarction and necrosis of host tissues that results from the invasion of the vasculature by fungal hyphae.[35,36] Medical literature is continuing to report new symptomatic manifestations and complications of COVID-19.

This study aims to describe the most common orodental and maxillofacial lesions and their management in patient with COVID-19; and also to assess if there is a relation with drugs used, particularly the effects of dexamethasone on the oral lesions and the relation of systemic diseases with its use. In addition, we aim to assess the incidence and prevalence of these lesions and conditions in Mosul-city hospitalized patients with COVID-19.

MATERIALS AND METHODS.

The present prospective study was approved by the scientific ethical committee of the College of Dentistry, University of Mosul, with reference No. UOM.Dent/H.13/21 and by the Ministry of Health and Environment, Nineveh Health Directorate, Training Center & Human Development with reference No. (21/1), 1224 in 12/1/2021. The location setting for the current study was Al-Shiffa hospital for pyritic diseases and coronavirus critical cases (Al-Salam teaching hospital) Nineveh health directorate, Mosul city, Nineveh governorate, Iraq. The study took place from August 2020 to March 2021.

Patients

This study included 338 patients (138 females, 200 males) who had PCR+ results for SARS-CoV-2 with oral manifestations, and were admitted to Al-Shiffa hospital for COVID-19 treatment, utilizing an additional appendix case sheet to the original one to record the data and treatment used, and whether oral manifestations worsened or improved.

Inclusion Criteria

All patients diagnosed with COVID-19 + by PCR. Patient's age ≥10 years, patients with acute oral or perioral lesions either during admission or which appeared later during treatment. Nonsmoker, and no alcohol consumption.

Exclusion Criteria: Patient's age ≤10 years. Lesions appeared or were well established before SARS-CoV-2 infection. Cannot tolerate follow-up or refuse to enroll in study.

Patient's case sheet with consent form

A consent form was signed by patients or their relatives to participate in this study. A specific case sheet for each patient recorded full personal information, past medical and dental history with thorough extra and intraoral examination. Any signs or symptoms of the face and oral cavity were recorded and photographed accordingly. The protocol of treatment of COVID-19 that was followed, and drugs given to the patients were also recorded.

Study design

A prospective study enrolled hospitalized patients who matched the inclusion criteria of the study, as mentioned previously. The first line of treatment was by teleconsultation between the specialist doctor and the oral surgeon. A photograph was sent to the surgeon with a history of the lesion. The final medical prescription was sent to the patient through e-mail with the signature of the surgeon. Complicated cases that needed surgical intervention in the hospital were treated after the patient was negative by PCR for SARS-CoV-2.

Diagnosis of oral manifestations

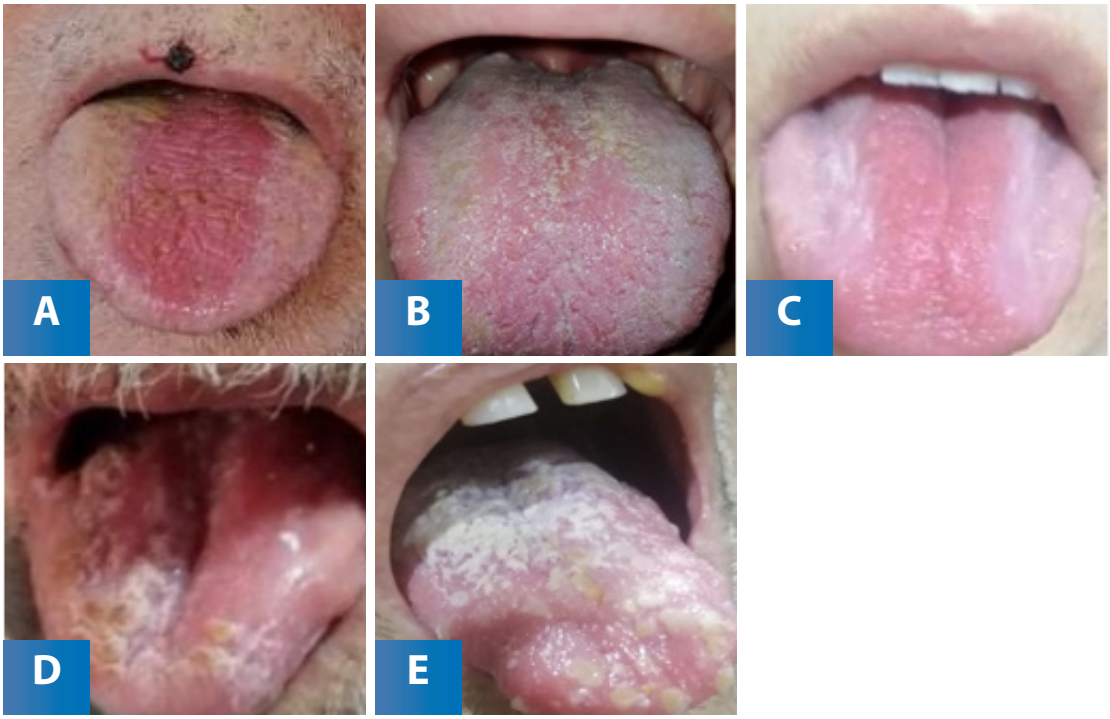
The diagnosis of oral lesions was achieved through clinical history, clinical examinations, and radiographic evaluation (if needed). All patients received preliminary management via teleconsultation and telemedicine, however, when there was a need for any surgical interventions, the patients were referred to the oral and maxillofacial emergency unit at the hospital.

Oral and maxillofacial manifestations disease

Patients with COVID-19 showed different oral and maxillofacial manifestations gathered under the wide broad name including stomatalgia, which includes any pain related to the oral cavity; burning sensation, numbness or tingling of the tongue and dryness of the mouth; Any color changes in the oral mucosa includes a white coat of the tongue, gingiva, cheek and palate; Yellow coat of the lips; red or black discoloration in the oral cavity; blue discoloration of the tongue and lips; ulcerative lesion as single or multiple aphthous ulceration; skin ulceration, or necrotizing lesion including mucosal necrosis or skin necrosis or mucormycosis, and some cases appeared as an odd lesion with an unusual presentation like pemphigus vulgaris and parotitis. In addition, there might be loss

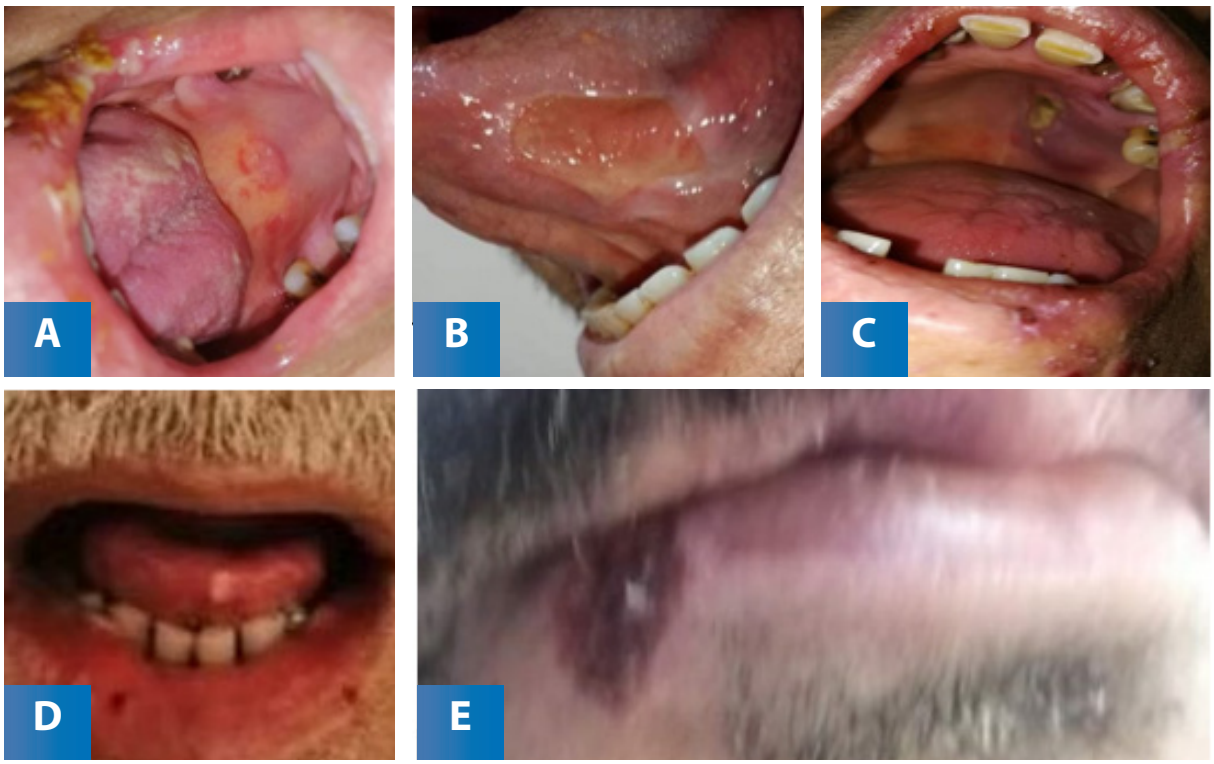
ISSN Print 0719-2460 - ISSN Online 0719-2479.

Figure 1. Colored lesions.



A. Red macules. **B.** White macules. **C.** White and red lesions. **D.** Yellow lesions. **E.** White, and yellow lesions.

Figure 2. Ulcerative and necrotic lesions.



A. Ulcerative lesions of palate and tongue and lips and perioral skin. **B.** Ulcerative lesion left side tongue. **C.** Ulcerative lesions oral and perioral region. **D.** Aphthous ulcer tip of the tongue. **E.** Ucerative lesion skin lower lip with localized necrosis.

of taste and loss of smell, orbital swelling or dysphagia.

All these lesions and conditions were recorded and treated with close monitoring and follow-up. The admitted cases were classified according to the presence of any systemic diseases or conditions present before COVID-19, which included: respiratory diseases (COPD, asthma or tuberculosis), diabetes of any type (DM), hypertension (HT), heart disease, mixed DM+HT, liver diseases, urogenital diseases, hematological diseases, and gastrointestinal diseases. In this study, we focused on the oral and maxillofacial signs and symptoms, their treatment and follow up, excluding the death rate cases.

Treatment

Coming to the management of oral diseases in COVID-19 patients, in this study, the treatment principles depends on three important factors: Age of patients (2); Severity of the disease (3); and underlying exacerbating factors like the presence of sharp fillings or dentures, as seen in the clinical examination or from

Table 1. Oral and perioral disorders recorded in COVID-19 patients in the study.

Oral and Perioral Conditions Recorded	(N=338) * The total number including mixed cases (%)	Cases that responded to treatment, with follow up (%)	Mean age (years)	Mean dexame-thasone use (days)
Pain related to the oral cavity	27.8	88 (26)	26	12
Burning sensation in the oral cavity	6	23 (6)	30	7
Numbness or tingling of the tongue	2	7 (2)	23	9
Dryness of the oral cavity	24.5	77 (22.7)	60	7
White coat of the tongue	31.6	93 (27.5)	65	10
White coat of the gingiva and cheek	22.4	71 (21)	40	10
White coat of the palate	15.6	51 (15)	33	11
Yellow coat of the lips	5.3	17 (5)	25	6
Red discoloration in the oral cavity	4.7	13 (3.8)	25	8
Blue discoloration of the tongue and lips	6.8	23 (6.8)	65	9
Black discoloration of the oral cavity	4.7	11 (3.2)	55	14
Single Aphthous ulceration anywhere in the oral cavity	9.1	30 (8.8)	20	3
Multiple Aphthous ulceration in the oral cavity	24.8	79 (23.3)	40	8
Skin ulceration	7.9	21 (6.2)	50	13
Mucosal necrosis	2.6	2 (0.5)	56	16
Skin necrosis	0.5	1 (0.2)	60	18
Loss of taste	79.5	177(52.3)	38	5
Loss of smell	81.9	151(44.6)	50	4
Orbital swelling	1.1	4 (1.1)	28	5
Dysphagia	23	78 (23)	38	9
Parotitis	0.5	2 (0.5)	41	7

*: Total number of percentage not equal to 100 due to presence of mixed lesions in the same case.

ISSN Print 0719-2460 - **ISSN Online** 0719-2479.

Table 1. Oral and perioral disorders recorded in COVID-19 patients in the study.

Oral and Perioral Conditions Recorded	(N=338)* The total number including mixed cases (%)	Cases that responded to treatment, with follow up (%)	Mean age (years)	Mean dexame-thasone use (days)
Pain related to the oral cavity	27.8	88 (26)	26	12
Burning sensation in the oral cavity	6	23 (6)	30	7
Numbness or tingling of the tongue	2	7 (2)	23	9
Dryness of the oral cavity	24.5	77 (22.7)	60	7
White coat of the tongue	31.6	93 (27.5)	65	10
White coat of the gingiva and cheek	22.4	71 (21)	40	10
White coat of the palate	15.6	51 (15)	33	11
Yellow coat of the lips	5.3	17 (5)	25	6
Red discoloration in the oral cavity	4.7	13 (3.8)	25	8
Blue discoloration of the tongue and lips	6.8	23 (6.8)	65	9
Black discoloration of the oral cavity	4.7	11 (3.2)	55	14
Single Aphthous ulceration anywhere in the oral cavity	9.1	30 (8.8)	20	3
Multiple Aphthous ulceration in the oral cavity	24.8	79 (23.3)	40	8
Skin ulceration	7.9	21 (6.2)	50	13
Mucosal necrosis	2.6	2 (0.5)	56	16
Skin necrosis	0.5	1 (0.2)	60	18
Loss of taste	79.5	177(52.3)	38	5
Loss of smell	81.9	151(44.6)	50	4
Orbital swelling	1.1	4 (1.1)	28	5
Dysphagia	23	78 (23)	38	9
Parotitis	0.5	2 (0.5)	41	7

*: Total number of percentage not equal to 100 due to presence of mixed lesions in the same case.

Table 2. Frequencies of oral and facial lesions associated with systemic diseases.

Medical disorder	Stomatalgia	Ulcerative lesions	Macular lesions	Necrotic lesions (including mucormycosis)	Parotitis or Pemphigus Vulgaris
Respiratory disorders	9	8	1	0	0
Diabetes mellitus	10	20	5	1	0
Hypertension	23	11	7	0	0
Heart diseases	19	6	7	0	0
DM+HT	13	9	5	1	0
Liver diseases	4	2	1	0	0
Renal diseases	12	5	4	0	0
Blood diseases	4	4	3	0	0
GIT diseases	4	3	1	0	0
No systemic disorder	12	3	3	0	1

DM+HT: Diabetes melitus and hypertension. **GIT:** Gastrointestinal.

Table 3. Oral and perioral disorders and their resolution, in relation to dexamethasone usage, according to pre-existing systemic diseases. (Total N=338)

Systemic pre-existing conditions	Number of cases (%)	With oral & perioral lesions	With cases resolution of oral & perioral lesions	Dexamethasone use (mean number of days)
Respiratory disorders	32 (9.5)	32	18	4
Diabetes mellitus	122 (36)	122	106	4
Hypertension	139 (41)	105	100	5
Heart diseases	108 (32)	86	85	8
DM+HT	96 (28.5)	88	70	4
Liver diseases	26 (7.7)	21	21	6
Renal diseases	69 (20)	57	55	7
Blood diseases	37 (11)	26	25	10
GIT diseases	27 (8)	24	23	8
No systemic disorders	99 (29)	66	66	14

DM+HT: Diabetes melitus and hypertension. **GIT:** Gastrointestinal.

Table 4. Drugs used in the treatment of oral and perioral lesions in COVID-19 patients.

	Drug used	Percentage of cases (%)
1	Chlorhexidine 0.2% mouthwash	35
2	Nystatin	15
3	Mycoheal	8
4	Anginovag spray	22
5	Fluconazole	13
6	Kenalog spray	6
7	Amphotericin B	1

Table 5. Percentage of oral disorders that appear in COVID-19 patients and their response to treatment.

Conditions	N=743 (%)	Respond to treatment (%)
Stomatalgia	28	28
Mucosa Color change	40	40
Oral Ulcer	19	19
Necrosis	2	0
Others	11	11
Total	**100**	**98**

ISSN Print 0719-2460 - **ISSN Online** 0719-2479.

Table 6. Appearance of oral lesions according to period of dexamethasone used in patients during study.

Number of patients (n=338)	Period in days
15	2
17	3
19	4
29	5
37	6
38	7
36	8
31	9
28	10
28	11
28	12
19	13
13	14
Total	**338**

the diagnostic aids.

After a thorough examination of the lesion, the treatment was started by using medicines as chlorhexidine 0.2% mouthwash, nystatin oral drops, Anginovag mouth spray, fluconazole tablets, Kenalog oral gel, and amphotericin B, according to the type of lesion, in order to eliminate or reduce patient complaints. The treatment and follow-up were continued until oral lesions improved and subsided completely.

Dexamethasone was used in COVID-19 patients, but there was a wide range of doses even on the same patient at different times. It was used at higher doses at admission according to presenting clinical signs, and the time of use varied according to appearance or decrease of the conditions or lesions, as it is used for prolonged periods and with dose tapering.

Some patients needed surgical interventions so they were referred to the oral and maxillofacial emergency unit for biopsy under local anesthesia, and one week later the sutures were removed. In some cases, complicated by more than one systemic disease, their treatment was challenging and took longer until improvements of oral lesions were achieved.

Statistical analysis

All data were translated into a computerized database structure, and all statistical analysis was performed using commercially available statistical software SPSS version 23, calculating the means, frequencies and percentage.

RESULTS.

Demographic characteristics

Three hundred thirty-eight patients positive for COVID-19 who had intraoral and extraoral lesions in the head and neck region participated in this study, 59% males and 41% females. The mean age of patients was 42.1 years old.

Incidence and prevalence

According to the documented data from the central statistical organization –Ministry of Planning– Iraq at the end of 2020, the total number of people living in the Nineveh governorate was 3,879,198 persons, of which 1,998,599 people live in Mosul city according to general public health data.

The total number of recorded cases of patients positive for SARS-CoV-2 by laboratory tests were 25,635 cases according to Nineveh health directorate data, out of which 1,004 critical cases need were admitted to Al-Shiffa hospital for coronavirus management; out of these, 338 patients (138 females and 200 males) according to Al-Shiffa hospital data,

who had COVID-19 confirmed by PCR, had oral and maxillofacial manifestations of the disease. This percentage represents about 38.6% from all critical admitted cases and 1.5% from total SARS-CoV-2 recorded cases, as well as 0.02% from the total Mosul city population, and 0.01% from the Nineveh governorate population.

The most common incidence of oral and perioral lesions that appeared in COVID-19 patients in this study was colored lesions (white coated tongue) (31%), followed by stomatalgia (27%), ulcerative lesions (multiple aphthous ulceration) (2%) and dryness in the oral cavity. (Table 1). The least common oral and perioral lesions that appeared in this study was skin necrosis and parotitis (0.5%), followed by orbital swelling (1.1%) and numbness or tingling of the tongue (2%). (Table 1).

Table 2 shows the frequencies of oral and facial lesions associated with systemic diseases, stomatalgia being the most common condition recorded, while Table 3 shows the oral and perioral disorder in their resolution and relationship of the use of dexamethasone, according to systemic diseases.

The percentage of medical diseases concerning oral disorders in relation to other comorbidities included diabetes mellitus (19%) with healed cases (19%), followed by hypertension (17%) with healed cases (18%), compared with liver disease (3%), blood disease and gastrointestinal disease (4%) and respiratory disease (5%), which showed the lowest percentage of healed cases: respiratory disease (3%), liver disease, blood disease, gastrointestinal disease (4%). (Table 3).

Several modalities of treatment were used in this study to ease the severity of disease and inhibit secondary infections that may occur that affect the patient, as listed in the Table 4. Regarding the percentage of response of oral lesions to the medications used, the macular lesions had a higher percentage in response to drugs (40%) followed by stomatalgia (28%), in comparison with necrotic lesions (0%), as shown in Table 5. Dexamethasone was used in a wide range in COVID-19 patients; the average period of use of dexamethasone until the appearance of oral lesions was 7.7 days. (Table 6).

Surgical interventions were required in 26% of cases, while conventional non-surgical medical treatment was implemented in 74% of cases.

DISCUSSION.

The presence of SARS-CoV-2 in an aggressive form worldwide, in addition to the limitations and controversies regarding the effectiveness of the present vaccines[37-40] has made a high incidence of infection unavoidable. The documentation of oral and perioral lesions that are present and need attention for their registration and early management with adequate and precise treatment in COVID-19 patients is necessary, especially considering the use of steroids as part of the medical management of infection. Therefore, this study aimed to determine the most common oral and maxillofacial lesions and their relationship with drug management, and to find a relationship with the drugs used and the effects of dexamethasone on the lesions, as well as their relationship with systemic diseases. In this study, the oral and maxillofacial lesions were classified according to clinical observations into five categories; the less clinical concerning lesions are not given immediate care, whereas more threatening or severe conditions were preferred to give an immediate dental treatment through oral surgery care following SARS-CoV-2 PCR negative results.

The first category considered rare lesions like orbital swelling, dysphagia and parotitis. The second category included skin or mucosal necrosis. The third category was the incidence of ulceration of the oral mucosa or skin either single or multiple. The fourth category was macular lesions, recorded as any alteration of the color of tissue into white, yellow, red, or blue-black. The fifth category was the stomatological cases which included pain, intraoral and extraoral neurological symptoms like numbness and burning sensation, in addition to the dryness due to infection itself or due to drugs taken during treatment in the hospital; Loss of smell and taste were added as additional data and documented.

Systemic diseases that were already present in some patients *prior* to receiving COVID-19 were classified according to the affected system. The usage of dexamethasone (*per* number of days) was also recorded in order to assess an association between the use of this steroid according to valid protocol and

ISSN Print 0719-2460 - ISSN Online 0719-2479.

its effect in the appearance of oral lesions.

Concerning demographic data, the percentage of COVID-19 in Mosul city is similar to what is reported worldwide: 1.3 % infection. Our finding is in agreement with many published studies that showed sex differences in the prevalence and outcomes of infectious diseases, with a higher burden of bacterial, viral, fungal, and parasitic infections in human males than females.[41-43] The innate and adaptive immune systems have sex dissimilarities, with females faring better in COVID-19. For the adaptive immune system, females have higher numbers of $CD4^+$ T cells cytotoxic activity with increased B cell formation of immunoglobulin leading to more antigen-specific IgG in response to trivalent inactivated seasonal influenza vaccination (TIV), which has important implications for the development of vaccination strategies for COVID-19. Concerning sex hormones concentration and the number of X chromosomes, females form higher levels of type 1 interferon (IFN) which is a potent antiviral cytokine, upon toll-like receptor 7 sensing of viral RNA, which is important for the early response in COVID-19.[44-50]

For stomatological cases the intraoral and extraoral pain was the highest due to long periods of dexamethasone use, most of it due to ulceration; other neurological symptoms like numbness, burning and dryness may be related to the infection itself or due to the drugs administered. Xerostomia is one of the stomatological manifestations in COVID-19 patients that appeared after infection, this finding is in keeping with several studies that stated xerostomia might increase the severity of infection as the amount of antiviral proteins in saliva could be reduced.[51-53]

Multiple aphthous ulceration in the oral cavity was noted, this may be due to weak immunity and bad psychological condition of the patient as a result of isolation, but may also be due to trauma during mastication. Our study showed that the painful oral ulceration and Candida infection appeared in COVID-19 patients, especially those medically compromised otherwise,[33-54] who needed counseling about the importance of their diet in order to improve their general condition and keep good oral hygiene to prevent secondary infections. The macular lesions present as a white coat of the tongue, mostly due to dexamethasone use and fungal infection, respond dramatically to antifungal agents.[55]

Skin necrosis is usually due to pressure from a high-pressure mask and in some cases endotracheal tube, CPAP or BIPAP ventilator used for extended periods and lack of paramedical staff to change or relieve pressure, or use tissue conditioner to alleviate pressure. Infection with SARS-CoV-2 is considered as a true cause of severe immunosuppression that might increase the risk of developing opportunistic infections. Furthermore, when patients are medically compromised and are neutropenic there is a likelihood of increasing the chance for developing mucormycosis.[35, 56-58]

These results were in line with the data obtained from our study. Invasive mucormycosis has appeared in several forms, such as nasal obstruction, facial pain or swelling, and visual disturbances with proptosis or cranial nerve involvement with progression of the disease to the cranium and loss of vision, followed by death. If the maxillary sinus is involved there is intraoral swelling and black palatal ulceration and massive tissue destruction. So the course of the disease is a rhino-orbital-cerebral infection, which may be secondary to inhalation of spores into the paranasal sinuses of a vulnerable host. Surgical intervention of mucormycosis, besides systemic antifungal, is recommended for this case. Oral lesions presented by our patients are either a consequence of systemic deterioration, increasing the possibility of opportunistic secondary infections, or from side effects of drugs used for the treatment of COVID-19.

Regarding rare lesions like orbital swelling, dysphagia and parotitis, linked to COVID-19, in this study only a single case of vesiculobullous disease (pemphigus vulgaris) was reported in a healthy patient three months after infection. As pemphigus vulgaris is related to a high level of fatigue and emotional stress, the tapering of the dose of immunosuppressive drugs may be considered as exacerbating factors or triggers for *pemphigus vulgaris*.[50,60] Parotitis was reported in our study in a single case in a patient with a history of COVID-19 infection; the patient had a fever, dry cough, and bilateral swelling of the parotid gland.

This observation was also reported in the study of Fisher *et al*.,[61] that presents parotitis as one of the

complications of COVID-19 infection. One of the outcomes of this study is that COVID-19 is associated with loss of taste and smell, which was also recorded to a degree similar to global percentages.[62-64] SARS-CoV-2 infection, as well as vaccines are capable of triggering a flare-up of autoimmune diseases[65-67] and these patients may decrease their compliance to prescribed therapies during pandemics.[68]

CONCLUSION.

Most of the intraoral and extraoral lesions are temporary and disappear with appropriate treatment in COVID-19 patients, so early treatment is quite important to decrease complications. Dexamethasone is a double-edged sword, so precaution should be taken when used in high doses especially in patients with systemic diseases.

Topical use of chlorhexidine 0.2% as mouthwash may aid in decreasing oral complications and opportunistic infections. The presence of a bedside patient companion is very important in relieving the pressure on the skin and hence decreasing incidence of tissue necrosis.

Conflict of interests: The authors declare no conflicts of interest.

Ethics approval: Study approved by the scientific ethical committee of the College of Dentistry, University of Mosul, with reference No. UOM. Dent/H.13/21 and by the Ministry of Health and Environment, Nineveh Health Directorate, Training Center & Human Development with reference No. (21/1), 1224 in 12/1/2021.

Funding: Selfunded.

Authors' contributions: All authors contributed to the execution of this study and writing of the manuscript.

Acknowledgements: Great thanks to the University of Mosul, College of Dentistry, Ministry of Health and Environment. Nineveh Health Directorate, Al-Shiffa hospital for pyritic diseases, for providing full support for the completion of the research.

REFERENCES.

1. Gironi LC, Boggio P, Giorgione R, Esposto E, Tarantino V, Damiani G, Savoia P. The impact of COVID-19 pandemics on dermatologic surgery: real-life data from the Italian Red-Zone. J Dermatolog Treat. 2020:1-7.
2. Pacifico A, Ardigò M, Frascione P, Damiani G, Morrone A. Phototherapeutic approach to dermatology patients during the 2019 coronavirus pandemic: real-life data from the Italian red zone. Br J Dermatol. 2020;183(2):375-6.
3. Cinelli E, Fabbrocini G, Fattore D, Marasca C, Damiani G, Annunziata MC. Safe distance, safe patients! Therapeutic management of oncological patients affected by cutaneous and mucosal adverse events during the COVID-19 pandemic: an Italian experience. Support Care Cancer. 2020;28(9):3991-3993.
4. Cristaudo A, Pigliacelli F, Pacifico A, Damiani G, Iacovelli P, Morrone A. Teledermatology and hygiene practices during the COVID-19 pandemic. Contact Dermatitis. 2020;83(6):536.
5. Damiani G, Gironi LC, Kridin K, Pacifico A, Buja A, Bragazzi NL, Spalkowska M, Pigatto PDM, Santus P; Young Dermatologists Italian Network, Savoia P. Mask-induced Koebner phenomenon and its clinical phenotypes: A multicenter, real-life study focusing on 873 dermatological consultations during COVID-19 pandemics. Dermatol Ther. 2021;34(2):e14823.
6. Giovanni Damiani, Laura C. Gironi, Ayman Grada, Khalaf Kridin, Renata Finelli, Alessandra Buja, Nicola L. Bragazzi, Paolo D. M. Pigatto, Paola Savoia, COVID-19 related masks increase severity of both acne (maskne) and rosacea (mask rosacea): Multi-center, real-life, telemedical, and observational prospective study First published: 03 February 2021 ,
7. Damiani G Gironi LC , Pacifico A , Cristaudo A , Malagoli P , Allocco F , Bragazzi NL , Linder DM , Santus P , Buja A , Savoia P , Pigatto PD , COVID-19 Dermatologic Italian Task Force, Young Dermatologists Italian Network , Italian Journal of Dermatology and Venereology, 01 Apr 2021, 156(2):220-225
8. Laura Cristina Gironi, Giovanni Damiani, Elisa Zavattaro, Alessia Pacifico, Pierachille Santus, Paolo Daniele Maria Pigatto, Ottavio Cremona, Paola Savoia Tetracyclines in COVID-19 patients quarantined at home: Literature evidence supporting real-world data from a multicenter observational study targeting inflammatory and infectious dermatoses, first published: 22 December 2020
9. Macha MJ, Boonyang U, Cazalbou S, Ben-Nissan B, Charvillat C, Oktar FN, David Grossin D. Comparative study of Coral Conversion, Part 2: Microstructural evolution of calcium phosphate. J Aust Ceram Soc 2015; 51:149–59.
10. Zhong NS, Zheng BJ, Li YM, Poon, Xie ZH, Chan KH, Li PH, Tan SY, Chang Q, Xie JP, Liu XQ, Xu J, Li DX, Yuen KY, Peiris, Guan Y. Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People's Republic of China, in February, 2003. Lancet. 2003 ;362(9393):1353-8.
11. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KSM, Lau EHY, Wong JY, Xing X, Xiang N, Wu Y, Li C, Chen Q, Li D, Liu T, Zhao J, Liu M, Tu W, Chen C, Jin L, Yang R, Wang Q, Zhou S, Wang R, Liu H, Luo Y, Liu Y, Shao G, Li H, Tao Z, Yang Y, Deng Z, Liu B, Ma Z, Zhang Y, Shi G, Lam TTY, Wu JT, Gao GF, Cowling BJ, Yang B, Leung GM, Feng Z. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med. 2020;382(13):1199-1207.
12. Peng X, Xu X, Li Y, Cheng L, Zhou X, Ren B. Transmission routes of 2019-nCoV and controls in dental practice. Int J Oral Sci. 2020;12(1):9.
13. Yoon JG, Yoon J, Song JY, Yoon SY, Lim CS, Seong H, Noh JY, Cheong HJ, Kim WJ. Clinical Significance of a High SARS-CoV-2 Viral Load in the Saliva. J Korean Med Sci. 2020;35(20):e195.
14. Li F. Structure, Function, and Evolution of Coronavirus Spike Proteins. Annu Rev Virol. 2016;3(1):237-61.
15. Chen Y, Guo Y, Pan Y, Zhao ZJ. Structure analysis of the receptor binding of 2019-nCoV. Biochem Biophys Res Commun. 2020.
16. Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci. 2020;12(1):8.
17. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor Recognition by the Novel Coronavirus from Wuhan: An Analysis Based on Decade-Long Structural Studies of SARS Coronavirus. J Virol. 2020;94(7).
19. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203(2):631-7.
19. Badran Z, Gaudin A, Struillou X, Amador G, Soueidan A. Periodontal pockets: A potential reservoir for SARS-CoV-2? Med Hypotheses. 2020; 143:109907.
20. Li Y, Ren B, Peng X, Hu T, Li J, Gong T, et al. Saliva is a non-negligible factor in the spread of COVID-19. Mol Oral Microbiol. 2020;35(4):141-5.
21. Baghizadeh Fini M. Oral saliva and COVID-19. Oral Oncol. 2020; 108:104821.
22. Anschau V, Sanjuan R. Fibrinogen Gamma Chain Promotes Aggregation of Vesicular Stomatitis Virus in Saliva. Viruses. 2020;12(3).
23. Siqueira WL, Moffa EB, Mussi MC, Machado MA. Zika virus infection spread through saliva--a truth or myth? Braz Oral Res. 2016;30.
24. Meng L, Hua F, Bian Z. Coronavirus Disease 2019 (COVID-19): Emerging and Future Challenges for Dental and Oral Medicine. J Dent Res. 2020;99(5):481-7.
25. To KK, Tsang OT, Yip CC, Chan KH, Wu TC, Chan JM, et al. Consistent Detection of 2019 Novel Coronavirus in Saliva. Clin Infect Dis. 2020;71(15):841-3.
26. Sabino-Silva R, Jardim ACG, Siqueira WL. Coronavirus COVID-19 impacts to dentistry and potential salivary diagnosis. Clin Oral Investig. 2020;24(4):1619-21.
27. HL. G. Oral manifestations of systemic disease. Gen Dent 2017;65(6):23-9.
28. Galvan Casas C, Catala A, Carretero Hernandez G, Rodriguez-Jimenez P, Fernandez-Nieto D, Rodriguez-Villa Lario A, et al. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. Br J Dermatol. 2020;183(1):71-7.
29. Vieira AR. Oral manifestations in coronavirus disease 2019 (COVID-19). Oral Diseases. 2020; 00:1:1.
30. Chen L ZJ, Peng J, Li X, Deng X, Geng Z, et al. Detection of 2019-nCoV in Saliva and Characterization of Oral Symptoms in COVID-19 Patients. Available at SSRN 3556665. 2020.

31. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. J Infect. 2020;81(2):266-75.
32. Corchuelo J, Ulloa FC. Oral manifestations in a patient with a history of asymptomatic COVID-19: Case report. Int J Infect Dis. 2020; 100:154-7.
33. Santosh ABR, Muddana K. Viral infections of oral cavity. J Family Med Prim Care. 2020;9(1):36-42.
34. Martín Carreras-Presas C, Amaro Sánchez J, López-Sánchez AF, Jané-Salas E, Somacarrera Pérez ML. Oral vesiculobullous lesions associated with SARS-CoV-2 infection. Oral Dis. 2021;27 Suppl 3:710-712.
35. Werthman-Ehrenreich A. Mucormycosis with orbital compartment syndrome in a patient with COVID-19. Am J Emerg Med. 2020.
36. Mehta S, Pandey A. Rhino-Orbital Mucormycosis Associated with COVID-19. Cureus. 2020;12(9): e10726.
37. Interim Clinical Considerations for Use of mRNA COVID-19 Vaccines Currently Authorized in the United States. Available at: https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html.
38. United States Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19). Help stop the spread of COVID-19 in children. Ways to protect children from getting and spreading COVID-19. Available at: www.cdc.gov/coronavirus/2019-ncov/daily-life-coping/children/protect-children.html.
39. FDA. Emergency Use Authorization (EUA). Pfizer-BioNTech COVID-19 Vaccine/BNT162b2. Available at: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/pfizer-biontech-covid-19-vaccine.
40. Emergency Use Authorization (EUA). Moderna COVID-19 Vaccine/mRNA-1273. Available at: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/moderna-covid-19-vaccine.
41. Peckham H, de Gruijter NM, Raine C, Radziszewska A, Ciurtin C, Wedderburn LR, et al. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. Nat Commun. 2020;11(1):6317.
42. Jose RJM, A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. Lancet Respiratory Med 2020; 8, e46–e7.
43. Ding Tea. A Multi-Hospital Study in Wuhan, China: Protective Effects of Non-menopause and Female Hormones on SARS-CoV-2 infection. medrxiv202.
44. Flanagan KL, Fink AL, Plebanski, M, Klein SL. Sex and Gender Differences in the Outcomes of Vaccination over the Life Course. Annu Rev Cell Dev Biol 2017; 33:577–99
45. Klein SLF, K L. Sex differences in immune responses. Nat Rev Immunol 2016; 16:626–38.
46. Abdullah Mea. Gender effect on in vitro lymphocyte subset levels of healthy individuals. Cell Immunol 2012; 272:214–9.
47. Mori Mea. Sex Differences in Antiretroviral Therapy Initiation in Pediatric HIV Infection. PLoS One. 2015;10: e0131591.
48. Voigt EAea. Sex differences in older adults' immune responses to seasonal influenza vaccination. Front Immunol. 2019; 10:180.
49. Webb Kea. Sex and pubertal differences in the type 1 interferon pathway associate with both X chromosome number and serum sex hormone concentration. Front Immunol 2019; 10:3167.
50. Ziegler SMA. Human Immunodeficiency Virus 1 and Type I Interferons—Where Sex Makes a Difference. Front Immunol 2017; 8:1224.
51. Farshidfar N, Hamedani S. Hyposalivation as a potential risk for SARS-CoV-2 infection: Inhibitory role of saliva. Oral Dis. 2020.
52. Marlus da Silva Pedrosa CRS, Fernando Neves Nogueira. Salivary Glands, Saliva and Oral Presentations in COVID-19 infection. short communication. 2020.
53. Dziedzic A WR. The impact of coronavirus infectious disease 19 (COVID-19) on oral health. Oral Dis 2020;
54. Putra BE, Adiarto S, Dewayanti SR, Juzar DA. Viral exanthem with "Spins and needles sensation" on extremities of a COVID-19 patient: A self-reported case from an Indonesian medical frontliner. Int J Infect Dis. 2020;96:355-8.
55. Picciani BLS, Santos LR, Teixeira-Souza T, Dick TNA, Carneiro S, Pinto JMN, Avelleira JCR, Azulay DR, Luiz RR, de Sousa Gonzaga HF. Geographic tongue severity index: A new and clinical scoring system. Oral Surg Oral Med Oral Pathol Oral Radiol. 2020;129(4):330-8.
56. Garg D, Muthu V, Sehgal IS, Ramachandran R, Kaur H, Bhalla A, Puri GD, Chakrabarti A, Agarwal R. Coronavirus Disease (Covid-19) Associated Mucormycosis (CAM): Case Report and Systematic Review of Literature. Mycopathologia. 2021;186(2):289-98.
57. Pasero D, Sanna S, Liperi C, Piredda D, Branca GP, Casadio L, Simeo R, Buselli A, Rizzo D, Bussu F, Rubino S, Terragni P. A challenging complication following SARS-CoV-2 infection: a case of pulmonary mucormycosis. Infection. 2020:1–6.
58. Singh AK, Singh R, Joshi SR, Misra A. Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India. Diabetes Metab Syndr. 2021;15(4):102146.
59. Elmas OF, Demirbas A, Tursen U, Atasoy M, Lotti T. Pemphigus and COVID-19: Critical overview of management with a focus on treatment choice. Dermatol Ther. 2020;33(6): e14265.
60. Ghalamkarpour F, Pourani MR. Aggressive course of pemphigus vulgaris following COVID-19 infection. Dermatol Ther. 2020;33(6): e14398.
61. Fisher J, Monette DL, Patel KR, Kelley BP, Kennedy M. COVID-19 associated parotitis. Am J Emerg Med. 2021; 39:254 e1- e3.
62. Bénézit F, Le Turnier P, Declerck C, Paillé C, Revest M, Dubée V, Tattevin P; RAN COVID Study Group. Utility of hyposmia and hypogeusia for the diagnosis of COVID-19. Lancet Infect Dis. 2020;20(9):1014-1015.
63. Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, Dequanter D, Blecic S, El Afia F, Distinguin L, Chekkoury-Idrissi Y, Hans S, Delgado IL, Calvo-Henriquez C, Lavigne P, Falanga C, Barillari MR, Cammaroto G, Khalife M, Leich P, Souchay C, Rossi C, Journe F, Hsieh J, Edjlali M, Carlier R, Ris L, Lovato A, De Filippis C, Coppee F, Fakhry N, Ayad T, Saussez S. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Otorhinolaryngol. 2020;277(8):2251-61.
64. Stern R AA, Sugahara KN. 2006; Hyaluronan fragments: an information-rich system. Eur J Cell Biol 2006; 85:699–715.
65. Damiani G, Pacifico A, Pelloni F, Iorizzo M. The first dose of COVID-19 vaccine may trigger pemphigus and bullous pemphigoid flares: is the second dose therefore contraindicated? J Eur Acad Dermatol Venereol. 2021;35(10):e645-e647

ISSN Print 0719-2460 - **ISSN Online** 0719-2479.

66. Kridin K, Schonmann Y, Tzur Bitan D, Damiani G, Peretz A, Weinstein O, Cohen AD. Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization and Mortality in Patients with Psoriasis: A Population-Based Study. Am J Clin Dermatol. 2021;22(5):709-718.
67. Pacifico A, d'Arino A, Pigatto PDM, Malagoli P, Young Dermatologists Italian Network, Damiani G. COVID-19 vaccines do not trigger psoriasis flares in patients with psoriasis treated with apremilast. Clin Exp Dermatol. 2021;46(7):1344-6.
68. Bragazzi NL, Riccò M, Pacifico A, Malagoli P, Kridin K, Pigatto P, Damiani G. COVID-19 knowledge prevents biologics discontinuation: Data from an Italian multicenter survey during RED-ZONE declaration. Dermatol Ther. 2020;33(4):e13508.