Review Article
E Medicine and Public Health. 2025; Vol 03; 42- 51
eISSN 3023-3305

Emerging Medicine and Public Health EMPH

Molecular Aspects of Oral Pathological Lesions of Patients Infected with Corona Virus (Covid -19): A Narrative Review

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Abstract

The scientific community has been forced by the COVID-19 pandemic to create strong and trustworthy diagnostic techniques in order to efficiently and precisely detect the virus and stop the spread of diseases. A diverse family of enclosed single-stranded RNA viruses is represented by coronaviruses (CoVs). These infections cause illnesses that impact the neurological, gastrointestinal, hepatic, and respiratory systems in humans and other animal species. However, the exact processes by which it is transmitted to people are still unknown. As implied by the nomenclature, the Middle East has a comparatively greater frequency of this disease than other parts of the world. Although they are less likely to suffer from severe disease, children are just as likely as adults to get infected with the virus. ***Aim of review:*** In light of the COVID-19 epidemic, this narrative review highlighted the vital need of laboratory diagnoses. ***Materials:*** relevant articles which obtained from various sources, including electronic databases such as PubMed, PMICD, WILEY library, the Elsevier library, and Science Direct, as well as through manual searches of relevant articles. ***Conclusion:*** According to recent empirical studies, the mouth cavity may play a crucial role in the entrance and spread of the SARS-CoV-2 virus in addition to being a site for the disease's clinical manifestation.

Keywords: ***Coronaviruses (CoVs), laboratory diagnostic tests, clinical manifestation, diagnosis.***

Introduction

Coronaviruses infect humans and various mammalian species, resulting in respiratory, enteric, hepatic, and neurological disorders [1]. The β-CoV and α genera are known to exhibit infectivity in mammals, whereas δ- and γ-CoVs primarily target avian species. HCoV-HKU1, HCoV-OC43, SARS-CoV, MERS-CoV, and SARS-CoV-2, have been identified as Human Coronaviruses (HCoVs) [2].

The dissemination of Human Coronaviruses within the global population has been acknowledged for an extended period. The recently emerged SARS-CoV-2, are recognized as highly pathogenic variants [3]. It has been postulated that these strains have infiltrated the human population from wildlife through spillover incidents, leading to significant respiratory tract ailments. [2].

Severe acute respiratory syndrome coronavirus (SARS-CoV) was initially documented in China, subsequently proliferating across the globe and culminating in numerous fatalities, characterized by an 11% mortality rate [4,5]. The SARS pandemic was ultimately contained by July 2003 through the implementation of isolation protocols for individuals suspected of being infected and conducting screenings on all travelers arriving from affected nations for clinical manifestations of the disease [6]. Since 2004, there have been no recorded cases of SARS reported globally [7].

In Saudi Arabia MERS-CoV was first identified then subsequently disseminated [8]. MERS-CoV is classified as a zoonotic pathogen that is believed to have originated from camels; however, the precise mechanisms of transmission to humans remain elusive. This disease is notably more prevalent in the Middle East compared to other regions [9].

December 2019, SARS-CoV-2 was initially detected in Wuhan, China, presenting with atypical viral pneumonia that progressed into acute respiratory illness. This event precipitated a global pandemic of acute respiratory disease. Consequently, the ramifications of healthcare systems have been unparalleled, posing significant risks to healthcare professionals, with approximately one in seven contracting the virus [10].

From the year 2020 to 2023, it has been observed that children constituted around 18% of all reported COVID-19 cases within the United States. Furthermore, from 2020 until the conclusion of March 2024, individuals aged up to 17 years accounted for approximately 1.5% of those requiring hospitalization for COVID-19 treatment [11].

Demographic characteristics

With respect to the distribution of age, numerous scholarly articles have indicated in patients ranging from 55 to 65 and possessing various medical comorbidities, such as cardiovascular disease, obesity, chronic kidney disease, diabetes, lung disease, tobacco use, cancer, and individuals who have undergone solid organ or hematopoietic stem cell transplantation, exhibit an elevated susceptibility to severe manifestations of COVID-19 infection. This heightened risk is attributable to a compromised immune response, which has been associated with cytokine storm syndrome characterized by increased levels of circulating inflammatory cytokines, as well as hyper-inflammation syndrome, both of which are instigated by viral infection. In contrast, this phenomenon is notably less prevalent among pediatric populations aged less than 18 years. The reduced impact on children can be attributed to a higher presence of antibodies, a lower frequency of previous exposure to the virus, and comparatively diminished levels of inflammatory cytokines within their physiological systems. [12,13].

The analysis of gender differences reveals that male patients are more likely to have severe sickness and higher death rates than female patients. Results of a retrospective cohort study from March 1–November 21, 2020, evaluating mortality rates in 209 acute care hospitals in the United States with 42,604 patients with confirmed SARS-CoV-2 infection, showed that the mortality rate for male patients was significantly higher (12.5%) than that for female patients (9.6%) [14,15].

Moreover, pregnant individuals and neonates afflicted with SARS-CoV-2 exhibit an increased susceptibility to severe pneumonia [16].

Egypt reported its first verified case of COVID-19 on February 14, 2020, making it the first country in Africa to do so. Egypt then stepped up its precautionary measures, enforcing a partial shutdown that began on March 25. Nasopharyngeal swabs from symptomatic people and contacts of confirmed cases within the previous two weeks were subjected to reverse transcription polymerase chain reaction (RT-PCR) testing. After 48 hours, the testing process was repeated in cases where there was a strong suspicion of infection. Airport screening included clinical evaluations, body temperature measurements, and the use of a quick diagnostic test to identify IgM and IgG antibodies against the severe acute respiratory syndrome coronavirus 2 [17].

Mode of transmission of SARS-CoV-2

1. Respiratory transmission: respiratory droplets and aerosols

Exposure to respiratory droplets containing the infectious virus via close contact or droplet transmission from asymptomatic carriers or symptomatic persons harboring the virus is the main way that SARS-CoV-2 is spread [14].

Aerosol-generating processes and airborne transmission have also been linked to the spread of COVID-19. SARS-CoV-2 can proliferate in crowded, poorly ventilated indoor environments. Aerosols from the evaporation of waste toilet water [18].

2. Contact transmission

It has been shown that SARS-CoV-2 can survive on plastic and stainless-steel surfaces for up to 2-3 days, on cardboard surfaces for up to 1 day, and on copper surfaces for up to 4 hours. In addition, there is empirical evidence that contamination is much more common in intensive care units (ICUs) than in general wards. SARS-CoV-2 can be found on floors, computer mice, waste receptacles, and patient bed rails, as well as in the air up to 4 meters away from infected people, suggesting the possibility of nosocomial transmission [16-14].

3. Fecal-oral transmission

Epidemiological evidence derived from multiple case analyses has indicated that individuals infected with SARS-CoV-2 exhibit detectable levels of the live virus in their fecal matter, suggesting a potential for fecal-oral transmission [19].

4. Other

breast milk and vertical transmission from mother to offspring remains indeterminate [16]. A comprehensive meta-analysis encompassing 936 babies born to mothers diagnosed with it indicated that vertical transmission is feasible, albeit it is observed in a limited number of instances [20].

Incubation period

SARS-CoV-2 is thought to incubate for 3–7 days on average (range: 2-14 days) [21]. suggesting that SARS-CoV-2 has a lengthy transmission duration. The estimated SARS-CoV-2 latency (mean 3 days, range 2-5 days) is comparable to that of other known human CoVs, including non-SARS human CoVs [22].

Moreover, it has been shown that asymptomatic COVID-19-infected persons during their incubation stages are capable of effectively spreading SARS-CoV-2 [23,24].

Clinical presentations

A novel and extremely contagious illness, COVID-19 mostly manifests as respiratory symptoms. Nonetheless, it can appear in a wide range of ways that impact other bodily systems, and there have even been reports of several oral manifestations [25].

Respiratory tract involvement

The predominant clinical manifestations observed at the initiation of COVID-19 infection encompass fever, nonproductive cough, respiratory distress, rhinitis, thoracic discomfort, myalgia, and/or asthenia [26]. Conversely, additional symptoms such as sputum expectoration, cephalalgia, haemoptysis, diarrhea, dyspnoea, and lymphopenia have been documented subsequently [27].

In instances of exacerbated severity necessitating hospitalization, the onset of viral pneumonia is characterized by the emergence of opacities evident on chest computed tomography. This phenomenon is further compounded by cardiac dysfunction and secondary infections [28].

There currently exists a lack of distinctive clinical characteristics that can consistently differentiate COVID-19 from other viral respiratory infections. Furthermore, other, less prevalent symptoms have been noted, including cephalalgia, pharyngitis, and rhinorrhea. Moreover, alongside respiratory manifestations, gastrointestinal symptoms (for instance, nausea and diarrhea) have also been observed; in certain patients, these may constitute the primary presenting complaint [29,30].

Extrapulmonary manifestation of COVID-19

Neurologic deficits, gastrointestinal (GI) symptoms, liver function impairment, hyperglycemia and diabetic ketosis, thromboembolic complications, cardiac injury and arrhythmia, acute coronary syndromes, acute renal injury, and dermatologic complications are some of these additional manifestations [31].

Cutaneous manifestations

Patients with COVID-19 were most frequently affected with pseudo-chilblain, other vesicular eruptions, urticarial lesions, maculopapular eruptions, livedo or necrotic exanthematous rashes, and petechiae [31,33]. Additionally, the red half-moon nail sign has been discovered as a marker of nail alterations [34,35].

Liver dysfunction and other GI manifestation

COVID-19 patients have also been found to exhibit liver symptoms. Increased CRP, LDH, and hyperferritinaemia, which may be indicative of acute-phase inflammation, higher liver function tests (AST, ALT, γ-GT, and ALP), hypoalbuminemia, delayed prothrombin time, and other biochemical indicators of mild-to-moderate liver damage are commonly seen. [36]. Anorexia, diarrhea, vomiting, and abdominal discomfort are common gastrointestinal symptoms [37]. Samples of feces have been shown to contain viral RNA on many occasions. [38,39].

Oral manifestations

Health care professionals must be aware of the possible link between COVID-19 and oral mucosal lesions in order to treat oral symptoms [25]. The tongue, palate, lips, gingiva, and buccal mucosa have been found to be the oral areas most commonly impacted [40,41]. According to recent research, the oral cavity may be a key entry point and route of transmission for the SARS-CoV-2 virus in addition to being the location of the disease's clinical symptoms. There is growing evidence that the virus may directly infiltrate and multiply in oral tissues, particularly the salivary glands and mucosa. Several thorough studies have lately provided a clinical overview of the pathological disorders affecting the oral cavity in the context of COVID-19 [42,43].

According to the study by Martín Carreras-Presas et al. (2020), there were several excruciating ulcers with different sizes and uneven borders on a red, non-hemorrhagic background. The whole hard palate was mostly damaged by these ulcers [44,45]. Other related oral symptoms include xerostomia, hypogeusia, and changes in chemosensory perception [46]. With a reported prevalence of 45%, the acute loss or alteration of taste and smell has been identified as one of the most common symptoms. The UK National Health Service has formally recognized this as a critical indicator for the suspicion of COVID-19 infection [40].

Buhjel et al. (2021) conducted a comprehensive review that delineated potential oral manifestations in COVID-19 patients, as evidenced by preceding scholarly investigations, which are enumerated as follows [25].

Herpetic stomatitis, erythema multiforme, non-specific ulcers, and aphthous-like ulceration are examples of ulcerative lesions [44,48-50]. Geographic tongue, red or swollen tongue, strawberry tongue, fissured tongue, macroglossia, and coated tongue are examples of tongue changes [51,52]. Angina bullosa, mucosal vasculitis, thrombosis, petechiae, hemorrhagic ulcer, localized erythema, and spontaneous oral bleeding are examples of hemorrhagic lesions [49,50,52]. Desquamative gingivitis, necrotizing ulcerative gingivitis, and papillary hyperplasia are examples of gingival lesions [44,49,52]. Oral lichenoid lesions and Candidal lesions, particularly oral pseudomembranous candidiasis and nonspecific candidiasis [50-52]. Oral enanthema [53] Blisters that are not specific [52,53] Mucositis [48,52].

It is unclear how the oral cavity contributes to the pathophysiology and spread of COVID-19. This is crucial because the glands or mucosa may be key players in the virus's "inter-mucosal" transmission to the lungs or gastrointestinal tract if they are the locations of an early infection. However, in situations that are asymptomatic, pre-symptomatic, or symptomatic, saliva may also be a major factor in the extra-oral transmission of the virus. The mouth cavity of humans is a heterogeneous group of tissue niches that may be particularly susceptible to viral infection. The terminally developed secretory epithelia of the minor saliva glands (distributed in the buccal and labial mucosa, hard and soft palate, ventral and dorsal tongue) and oral mucosae (hard palate, buccal mucosa, dorsal and ventral tongue) are among these locations. Diverse oropharyngeal niches (soft palate, palatine and lingual tonsils) are located nearby. The saliva glands are largely responsible for producing saliva, which is a combination of fluids, electrolytes, proteins, and cells (immune and sloughed mucosal epithelial cells). It then empties into the oral cavity, where it combines with other fluids (crevicular fluid) and cells [47,54].

Structure of SARS-CoV-2

The RNA that is single-stranded the lipid bilayer makes up the SARS-CoV-2 viral envelope. Along with membrane (M) and envelop (E) proteins, extensively glycosylated type I glycoproteins (S protein) form the petal-shaped spikes that are attached to the envelope. The RNA genome and one species of nucleocapsid (N) protein make up the ribonucleoprotein (RNP) core, which is located inside the envelope. Ten genes in the 29.8 kb SARS-CoV-2 genome code for 27 proteins [26,55]. Both structural and nonstructural proteins are expressed by gene fragments. While the ORF area encodes nonstructural proteins such RNA-dependent RNA polymerase, papain-like protease, and 3chymotrypsin-like protease, the S, E, M, and N genes encode structural proteins [56].

Structures formed by protein S protrude from the viral membrane. It is the protein that establishes the virus's tropism since it has the domain needed to attach to the receptor of the cells it infects (RBD). It is made up of two distinct domains: domain S1 is in charge of binding to the receptor, while domain S2 is in charge of fusing with the cell membrane [57]. The angiotensin converting enzyme 2 (ACE2) serves as a receptor for SARS-CoV-2 protein S to enter the host cell. Numerous cells in the intestines, arteries, lungs, mucous membranes, etc. have ACE2 on their surface. It increases the vasoconstrictive impact of angiotensin I by converting it to angiotensin II. Viral RNA is used as messenger RNA by the cellular ribosomes to generate virus proteins when the virus enters the cell via this molecule. This facilitates the production of many copies of the virus, which promotes its spread, in conjunction with the viral replicase [58].

Diagnosis

The significance of assessments, for the management of populations has become increasingly evident in light of the ongoing COVID-19 pandemic. Numerous diagnostic approaches have received approval from regulatory bodies globally; nevertheless, ambiguity persists concerning the appropriate tests to be utilized [60].

Three main tests: according to [61]

i. Molecular RT-PCR swab tests;
ii. serological tests;
iii. rapid antigen or antibody tests.

Molecular tests

Since the symptoms of COVID-19 (such as fever, exhaustion, dry cough, and breathing problems) can be confused with those of the common cold and influenza, molecular testing is essential for diagnosing the illness. There are several molecular targets accessible, much as in other viral testing.

Acute infection can be diagnosed by detecting the presence of viruses in patients using viral proteins or nucleic acids [62,63]. The development of novel molecular techniques depends on a thorough knowledge of the virus's proteome and genomic composition, as well as changes in the host's protein expression patterns before and after infection. For scientists to create primers and probes for polymerase chain reaction (PCR) and other molecular diagnostic tests, genome sequencing is an essential procedure [69].

Nucleic acid tests (NATs)

In order to detect SARS-CoV-2 infections, nucleic acid tests (NATs) are used, and they are usually carried out after clinical symptoms appear. It is still unclear what the features and sensitivity of testing procedures are in asymptomatic groups. Recovery from moderate COVID-19 is thought to take around two weeks, whereas recovery from severe instances takes about six weeks. In the worst cases, it might take anywhere from two to eight weeks from the start of symptoms until death [6].

Reverse transcription of viral RNA produces DNA, which is then amplified using the polymerase chain reaction (PCR) technique in nucleic acid testing. NATs are the main diagnostic method used to find SARS-CoV-2, the virus that causes COVID-19 and need several hours to complete, and are increasingly carried out utilizing automated technologies [6,70,71]. The use of particular RNA sequences specific to SARS-CoV-2 for diagnostic testing, such as the human RNase P gene and the viral nucleocapsid N1 and N2 genes, along with the proper primers and reagents, has been approved by the Centers for Disease Control and Prevention (CDC) and the U.S. Food and Drug Administration (FDA) [6,70,71]. This testing approach differs from the World Health Organization's (WHO) recommended technique, which prioritizes the detection of CoV-2's envelope (E) and RNA-dependent RNA polymerase (RdRP) genes [64].

a. PCR

It constitute a sophisticated molecular methodology aimed at the identification of viral RNA, which encompass bronchial aspirate, nasopharyngeal swab, nasopharyngeal aspirate, throat swab, blood, saliva, sputum, urine, stool, and rectal swabs [72]. A variety of RT-PCR kits meticulously developed for the specific detection of SARS-CoV-2, demonstrating proficiency to amplify trace amounts of viral genetic material contained within a given sample. RT-PCR necessitates the reverse transcription of viral RNA into complementary DNA strands, succeeded by amplification of regions designated within these strands [69].

The two-step technique: this methodological framework fundamentally comprises two essential phases: which is particularly mandated by the necessity for multiple temperature variations throughout each cycle utilizing thermocycling apparatus[69].

One step technique: it is currently implemented through one-step quantitative RT-PCR (qRT-PCR) specifically aimed at SARS-CoV-2, whereby primers and probes advocated [62,63].

Two target systems: assays designed to incorporate a primer that recognizes various coronaviruses including SARS-CoV-2, in addition to secondary primers meticulously tailored specifically for it [64].

Automated system: Pfefferle et al. (2020) presented a molecular diagnostics automated solution that includes processing a large number of samples. All aspects of nucleic acid extraction, purification, amplification, and detection are entirely automated by the Cobas 6800 System used in this investigation. Purified RNA, the control in automated systems, is incorporated into the samples and moves through the full apparatus's workflow, including extraction and purification [65].

Using a variety of diagnostic procedures, including target primer sequences from the World Health Organization's public database, the real-time RT-PCR assay offers a sensitive (the assay can accurately identify people with the disease) and specific (the assay can accurately identify people without the disease) framework for the detection of SARS-CoV-2 [66].

The conventional RT-PCR method for detecting SARS-CoV-2 in saliva samples (and upper respiratory specimens) can be substituted with RT-PCR/MALDI-TOF mass spectrometry-based assays for the identification of targeted amplicons. This detection platform showed improved diagnostic sensitivity and specificity and has the potential to supplement traditional nucleic acid amplification testing technologies and increase diagnostic capabilities [67].

The polymerase gene, which includes two overlapping open reading frames (ORFs), 1a and 1b, makes up around two-thirds of the total RNA. Through the recognition of the peptidase domain of ACE2 by the S1 subunit [68] and the subsequent fusing of viral and cellular membranes by the S2 subunit, the S protein facilitates the entrance of the virus into host cells. The SARS-CoV-2 S protein has shown to have a greater affinity for ACE2 than SARS-CoV itself [68].

In both cell culture and clinical specimens, the analysis of the RdRp/Hel gene revealed no cross-reactivity with other harmful coronaviruses and human respiratory infections. On the other hand, in cell culture conditions, the particular SARS-CoV-2 (RdRp) gene showed reactivity with it. Avoiding genes use that could unintentionally result in false-negative results is essential [73].

Protein tests rapid antigenic and rapid antibody tests (immunoglobulins, viral antigens)

Rapid antigen and antibody assays are characterized by their swift execution times, typically ranging from 15 to 30 minutes, diminished financial implications, and uncomplicated methodologies that not require the engagement of trained personnel [6]. Diagnostic tools primarily leverage platform the lateral flow immunoassay (LFIA) technique, thereby facilitating direct viral proteins detection in rapid antigen tests or human antibodies [61].

Concerning rapid antigen testing, these methodologies permit the identification of positive individuals by detecting virus nucleocapsid or spike proteins in nasopharyngeal swabs obtained from individuals displaying symptoms. Applications of serological testing include determining immunological surrogates to direct vaccine development, analyzing an individual's immune state, and determining past exposure within populations for the retrospective assessment of the efficacy of control measures. Diagnostic approaches are subject to certain restrictions in each of these applications [6,70,71,74].

In situ hybridization

The research undertaken by Massoth et al. (2021) demonstrated significantly enhanced specificity, enables more straightforward analytical processes, and is correlated with improved interobserver concordance compared to immunohistochemistry when utilized with human tissues, thereby positioning it as a potentially optimal assay for the identification of the virus [75]. ISH is instrumental in the assessment of viral distribution, cellular tropism, and cytopathological changes within tissues, thereby serving as a complementary technique to conventional histopathological methods, a range of molecular approaches, and serological tests [76]. A plethora of methodologies exists for the execution of RNA ISH, among which the RNA scope® technology is particularly recognized for its robustness, specificity, and sensitivity in ISH applications [77].

The RNA scope assays are designed to specifically target the ORF1ab, spike, and nucleocapsid genes of SARS-CoV-2 within both cellular and tissue environments [76]. This specific methodology enables a semi-quantitative evaluation of target nucleic acids while maintaining the spatial organization of expression within cellular and tissue architectures, particularly regarding distinct cellular and tissue structures. This critically important information is, in fact, compromised when alternative detection methods such as western blotting, PCR/RT-qPCR, or RNA sequencing are employed, as these methods necessitate the disaggregation of cells and tissues. In situ hybridization (ISH) and immunohistochemistry (IHC) represent well-established methodologies that are extensively utilized in both research contexts and routine laboratory diagnostics [78].

Because saliva is a simple and non-invasive way to collect specimens, it is well recognized as a reliable specimen for the detection of SARS-CoV-2. The Food and Drug Administration (FDA) has developed and approved saliva-based tests for SARS-CoV-2 under an Emergency Use Authorization. The use of standardized saliva collecting equipment can further increase the sensitivity for identifying symptomatic and pre-symptomatic illnesses, hence increasing the reliability of saliva specimens for SARS-CoV-2 detection [79].

As a screening tool for evaluating antibody profiles in large populations, serological assays that examine the generation of IgM and IgG antibodies in response to viral infections can significantly increase the sensitivity and precision of molecular diagnostic tests [80]. Serum, plasma, fingerstick blood, and whole blood specimens were used to assess the quantification of antibodies. When both IgM and IgG antibodies were examined simultaneously, the sensitivity and specificity metrics were often better [82,83]. When IgM and IgG antibodies were evaluated simultaneously with RT-PCR tests, rectal swabs/stools, urine, and plasma, the sensitivity was comparatively lower; however, sputum samples (97.2% [90.3%-99.7%]) demonstrated increased sensitivity in the viral detection [74,80].

Single-cell RNA sequencing analyses facilitate profiling 28 receptors levels and associated SARS-CoV-2 factors. These host factors are postulated to play a role in the entry of it into healthy tissues. Basal expression levels of these factors significantly influence, at least in part, the viral tropism, rendering this information essential for predicting which tissues are predisposed to infection. Furthermore, these data are pivotal for directing and prioritizing clinical interventions and pathological investigations, including biopsy procedures. Ultimately, this analytical approach possesses the potential to elucidate potential pathways of infection both within and among individuals [81].

Illustration of different molecular tests that can be used in Covid 19 diagnosis according to Weissleder, et.al. 2020 science translate supported by csb.mgh.harvard.edu [6].

3 Groups of Tests

a) Nucleic acid tests (NATs)
b) Protein tests (immunoglobulins, viral antigens)
c) Ancillary tests

Nucleic acid tests (NATs) as

1. Real time RT-PCR
2. Isothermal amplification
3. CRISPR
4. Next generation sequencing (NGS)
5. Micro NMR (μNMR)

Protein tests (immunoglobulins, viral antigens)

1. Serological rapid diagnostic test (RDT)
2. Serological ELISA
3. Viral antigen tests (VAT)
4. Microarrays
5. Other methods: Virus neutralization test (VNT)

Western blots (WB) Ancillary other tests

Additional tests include: 1. coagulation tests; 2. blood gas analysis; and 3. cytokine storm markers such ferritin, granulocyte colony-stimulating factor (G-CSF), interleukin-6 (IL-6), macrophage inflammatory protein-1α (MIP-1α), and tumor necrosis factor-α (TNFα).

Imaging

Computed tomography (CT) and chest X-rays are common in clinical practice. CT equipment is widely available around the world, and the scanning process is often simple and quick. Chest CT scans of patients with it usually show multifocal bilateral patchy ground-glass opacities or consolidation, along with vascular thickening and interlobular septal thickening in the peripheral lung areas. However, as the disease progresses, the CT radiological results may change, and similar symptoms might also be suggestive of other pneumonias [84,85].

Histopathological examination:

There exists a notable deficit of conclusive microscopic features correlated with oral lesions in patients affected by COVID-19 (OLICs) that would elucidate an underlying etiopathogenetic mechanism. As a result, a relatively small number of histopathological studies concerning OLIC have been reported in the existing literature. These investigations have typically shown nonspecific histological features including perivascular lymphocytic infiltration and vascular ectasia. Additionally, it has been shown by immunohistochemistry that the SARS-CoV-2 spike protein is positive in keratinocytes, inflammatory endothelium cells, and both acinar and ductal cells of the minor salivary glands [86,87]. Histopathological examination of early oral lesions exhibiting peripheral thrombosis has been proposed as a potential early indicator of the development of severe illness [44,45,52].

The electron microscope represents a sophisticated instrument for substantiating infection by that virus; however, careful scrutiny essential when interpreting cytoplasmic structures to accurately discern viral particles. Conventional cytoplasmic structures found within a cell have been mistakenly recognized as

viral particles [88]. Clusters of virus particles are generally located within membrane-bound regions of the cisternae of the rough endoplasmic reticulum–Golgi complex, where the spikes are oriented toward the interior of the cisternal space [89].

Immunohistochemical reactions (IHC)

Although SARS-CoV-2 can be visualized utilizing electron microscopy techniques, there is an increasing demand for methodologies that are widely applicable for viral components detection within histological specimens. The identification can be achieved through IHC within formalin-fixed paraffin-embedded (FFPE) tissues and ISH, respectively. In this investigation, we evaluate the staining efficacy of IHC targeting nucleocapsid protein using three distinct antibodies specific the nucleocapsid (N) and one antibody specific to the spike (S) protein [75].

Thrombi, which were mostly made of fibrin and endothelial cells, obstructed prominent tiny arteries. Within these vessels, the endothelial cells showed CD34 positivity. In the basal epithelium layer, nearby salivary glands showed significant infiltration lymphocytes, mostly CD3 and CD8 positive [44,45].

The epithelial tissues of keratinized and non-keratinized mucosa of the oral cavity, as well as those of the salivary glands, express essential factors that facilitate the entry and dissemination of SARS-CoV-2, particularly angiotensin-converting enzyme Type 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2). Numerous studies have validated ACE2 as the functional host receptor for SARS-CoV-2 [42,90].

Conclusions

- The oral pathological features observed in individuals afflicted with that virus remain largely nonspecific. Huang et al. (2021) determined that it serves as a significant infection site by virus, suggesting that saliva may act as a potential vector for the transmission of this virus.
- This pandemic has shown how important laboratory diagnoses are to managing a public health emergency that has had a significant impact on the world's social, economic, and medical infrastructures.
- For the detection of virus in sputum samples, RT-PCR is still considered the best standard diagnostic technique. Even while RT-PCR has a high sensitivity, it frequently misdiagnoses individuals who have a lower viral load.
- The mechanisms underlying SARS-CoV-2 infection remain inadequately elucidated. It is still ambiguous whether the pathologies observed are attributable to direct infection of the affected organs or to indirect effects arising from systemic inflammatory responses or existing comorbidities [81].
- To guarantee the best sensitivity and specificity, a comprehensive strategy combining serological diagnostic clinical, and molecular testing highly recommended. Molecular diagnostic employing a dual-target system for its detection are being developed.
- Enhanced molecular techniques, such as droplet digital PCR (ddPCR) and biosensors, are progressively receiving approval from international regulatory bodies for the diagnosis of COVID-19 infections. Rapid antigen, rapid antibody, and immune-enzymatic assays constitute the predominant methodologies employed for the surveillance of COVID-19 infection dissemination.
- Accurate characterisation of new genomic variations of the virus requires next-generation sequencing (NGS) approaches and detailed analysis; yet, their use in clinical settings is limited by their high costs.

Recommendations

- Morphological and molecular characterizations remain inadequately delineated; hence, additional investigations are required.
- The oral cavity role in COVID-19 remains inadequately elucidated, necessitating further investigation. Study virus variants that are emerging and why some are more transmissible.
- The interactions between host genetic determinants and the virus, as well as their influence on the trajectory of infection, remain inadequately elucidated and warrant additional investigation.

Declarations

Ethical Approval

Not Applicable

Conflict of Interest

There is no conflict

Funding/ financial support

Not funded

Contributors

Both author equal contribution.

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