

Are the salivary glands the key players in spreading COVID-19 asymptomatic infection in dental practice?

Dear Editor,

We read with great interest the article by Song et al¹ on the assessment of the expression of angiotensin-converting enzyme 2 (ACE2) and transmembrane serine proteases 2 (TMPRSS2) in salivary glands using publicly available databases. Undiagnosed infections were reported to facilitate the rapid dissemination of the coronavirus disease 2019 (COVID-19)² caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The SARS-CoV-2 depends on ACE2 and TMPRSS2 for cell entry and priming.³ The salivary glands were suggested to act as reservoirs for COVID-19 asymptomatic infections and transmission since high expression of the ACE2 receptor was found in minor salivary glands.⁴ The Transcriptome data analysis by Song et al¹ showed that ACE2 and TMPRSS2 were expressed in salivary glands. Thus, the virus might enter into the salivary glands. Corroborating this, in other communication,⁵ ACE2 and TMPRSS2 were found to be expressed in the salivary glands.

The analysis carried out in available databases (Genotype-Tissue Expression portal and Human Protein Atlas repository) by Song et al,¹ Xu et al,⁴ and Pascolo et al⁵ are valid to reinforce the hypothesis of salivary gland infection by SARS-CoV-2.⁶ However, we cannot forget that several factors, such as gene regulatory networks, tissue pH, hormones, concentration of co-factors and metabolic events change the expression, concentration and activity of enzymes.⁷⁻⁹ To the best of our knowledge, besides the higher number of available publications, literature still lacks this information in the context of salivary glands infection by SARS-CoV-2.

Even though saliva is important biological fluid for SARS-CoV-2 detection, the source of virus in saliva has not been fully investigated in most studies. Chen et al⁶ collected saliva directly from the submandibular salivary glands ducts of 31 confirmed cases of patients with COVID-19. Interestingly, the expression of SARS-CoV-2 was found only in four patients (12.90%), being higher in severe cases (3/4). This suggested SARS-CoV-2 coming directly from the salivary gland might be due to high viral loads at the late stage of the disease⁶ and not from individuals with mild, limited, or lack of symptoms. It is encouraged, however, to carry on research on SARS-CoV-2 shedding from salivary glands to understand their contribution to viral load in saliva given literature on this topic is still scarce.

It has been widely reported that dental practice accounts for an increased risk of SARS-CoV-2 infection due to the close contact with the patient's airways and performance of aerosol-generating procedures.¹⁰⁻¹² Dental activities worldwide were profoundly

affected by the COVID-19 pandemic.^{13,14} Several dental care facilities closed or limited appointments to urgent and emergency care. In addition, several recommendations were issued to provide dental care while mitigating the disease spread.¹⁵⁻¹⁷ Mild, limited and asymptomatic infections, from individuals who never experience noticeable symptoms, have been widely reported for COVID-19.¹⁸⁻²⁰ However, even if asymptomatic infections are common, transmission from asymptomatic individuals was reported to be probably uncommon.²¹

Overall, even though the current literature shows that salivary glands can be infected, we cannot affirm that they act as reservoirs for COVID-19 asymptomatic infections. Despite the indication of mouthwashes might cause confusion among the practitioners, along with other biosafety practices they would be able to decrease the risk of SARS-CoV-2 transmission by limiting viral load in saliva droplets and aerosols produced during dental procedures.^{12,22}

The maintenance of oral healthcare is a serious problem that requires attention and appropriate measures.²³ The adoption of the preventive measures in dental setting to reduce viral load in mouth could be useful to provide elective care in asymptomatic patients in times of COVID-19. Studies are necessary to understand the real role of salivary glands in COVID-19 asymptomatic infections and transmission.

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CONFLICT OF INTEREST




The authors declare that there are no conflict of interest.

AUTHOR CONTRIBUTION

MS Pedrosa CR Sipert and FN Nogueira conceived the study and discussed the results. MS Pedrosa drafted the first manuscript. MS Pedrosa CR Sipert and FN Nogueira critically read and revised the manuscript, and gave final approval for publication.

DISCLAIMER

The funding agencies had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

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REFERENCES

- Song J, Li Y, Huang X, et al. Systematic analysis of ACE2 and TMPRSS2 expression in salivary glands reveals underlying transmission mechanism caused by SARS-CoV-2. *J Med Virol.* 2020.
- Li R, Pei S, Chen B, et al. Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV-2). *Science.* 2020;368(6490):489-493.
- Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell.* 2020;181:271-280.
- Xu J, Li Y, Gan F, Du Y, Yao Y. Salivary glands: potential reservoirs for COVID-19 asymptomatic infection. *J Dent Res.* 2020;99:0022034-520918518.
- Pascolo L, Zupin L, Melato M, Tricarico P, Crovella S. TMPRSS2 and ACE2 coexpression in SARS-CoV-2 salivary glands infection. 2020.
- Chen L, Zhao J, Peng J, Li X, et al. Detection of 2019-nCoV in saliva and characterization of oral symptoms in COVID-19 patients. *SSRN Electron J.* <http://dx.doi.org/10.2139/ssrn.3557140>
- Atkinson DE. Regulation of enzyme activity. *Annu Rev Biochem.* 1966; 35(1):85-124.
- Wang Y. Gene regulatory networks. In: Dubitzky W, Wolkenhauer O, Cho K-H, Yokota H, eds. *Encyclopedia of Systems Biology.* New York, NY: Springer New York; 2013:801-805.
- Weake VM, Workman JL. Inducible gene expression: diverse regulatory mechanisms. *Nat Rev Genet.* 2010;11(6):426-437.
- 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):1-6.
- Jamal M, Shah M, Almarzooqi SH, et al. Overview of transnational recommendations for COVID-19 transmission control in dental care settings. *Oral Dis.* 2020.
- Ortega, KL, Camargo, et al. PHB. SARS-CoV-2 and dentistry. *Clin Oral Investig.* 2020:1-2.
- Meleti M, Cassi D, Bueno L, Bologna-Molina R. Covid-19 diffusion and its impact on dental practice in distant countries with similar ethnic background. *Oral Dis.* 2020.
- Yang Y, Zhou Y, Liu X, Tan J. Health services provision of 48 public tertiary dental hospitals during the COVID-19 epidemic in China. *Clin Oral Investig.* 2020;24(5):1861-1864.
- 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):481-487.
- Rupf S, Hannig M. Changes of the patient management in dentistry during the pandemic caused by the SARS-coronavirus 2—initial perspectives of a clinic of operative dentistry in Europe. *Clin Oral Investig.* 2020;24(7):2537-2539.
- Cirillo N. COVID-19 outbreak: succinct advice for dentists and oral healthcare professionals. *Clin Oral Investig.* 2020;24(7):2529-2535.
- Bai Y, Yao L, Wei T, et al. Presumed asymptomatic carrier transmission of COVID-19. *JAMA.* 2020;323(14):1406-1407.
- Tong ZD, Tang A, Li KF, et al. Potential presymptomatic transmission of SARS-CoV-2, Zhejiang Province, China, 2020. *Emerging Infectious Disease journal.* 2020;26(5):1052-1054.
- Wang Y, Kang H, Liu X, Tong Z. Asymptomatic cases with SARS-CoV-2 infection. *J Med Virol.* 2020. <http://dx.doi.org/10.1002/jmv.25990>
- Ferretti L, Wymant C, Kendall M, et al. Quantifying SARS-CoV-2 transmission suggests epidemic control with digital contact tracing. *Science.* 2020;368:6491.
- Herrera D, Serrano J, Roldán S, Sanz M. Is the oral cavity relevant in SARS-CoV-2 pandemic? *Clin Oral Investig.* 2020;24:2925-2930.
- Guo J, Xie H, Liang M, Wu H. COVID-19: a novel coronavirus and a novel challenge for oral healthcare. *Clin Oral Investig.* 2020;24(6):2137-2138.