Prevalence and Features of Oral Lesions in COVID-19

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Regardless of rapidly emerging findings on oral lesions described in adult SARS-CoV-2-positive subjects, the evidence level remains quite low and rather contrasting. It is well known that multiple viral pathogens, first of all, Herpes and human Papilloma viruses, are directly responsible for the genesis of benign, potentially malignant and malignant lesions of the oral mucosa, underlining the necessity to examine the potential causative role of SARS-CoV-2 in oral lesions.

COVID-19 coronavirus disease 2019 oral lesions

1. Introduction

The most common manifestations of COVID-19 comprise asthenia, headache, fever, hyposmia, oropharyngeal inflammation, dysgeusia, dry cough, dyspnea, vomiting, abdominal pain and diarrhea [1][2]. Further enriching the compound clinical presentation of the disease, muco-cutaneous manifestations, resembling varicella and measles rushes, as well as Erythema Multiforme lesions, urticaria and petechiae [3][4] have also been reported in SARS-CoV-2-positive subjects.

Such multi-system involvement characterizing COVID-19 may be attributable to the wide topographic distribution of the viral Angiotensin Converting Enzyme 2 (ACE2) binding receptor, mediating cell invasion, which has been detected in upper and lower respiratory apparatus; gastrointestinal tract, including oral epitheliocytes; exocrine glands, along with salivary ones; cardiovascular and genitourinary systems; skeletal muscles and skin [5][6][7]. Consistently, multiple case reports and series, as well as letters to the Editor and comments [8][9][10][11], have later described several lesions of the oral mucosa potentially ascribable to SARS-CoV-2 infection or observed in patients with COVID-19, clearly highlighting heterogeneous macroscopic features and uncertain prevalence.

2. Prevalence, Features and Degree of Association of Oral Lesions in COVID-19

A large body of evidence has described lesions of the oral mucosa, potentially ascribable to SARS-CoV-2 infection or observed in patients with COVID-19, clearly highlighting heterogeneous macroscopic features and uncertain prevalence [8][9][10][11].

Since data from studies included in research but not meeting eligibility criteria were not considered, findings concerning younger subjects were excluded from the current analysis. In addition, the average age of the cases diagnosed with oral lesions was only reported in six out of twelve research [12][13][14][15][16][17], revealing a mean age of 50.0 and not allowing a complete computation. Similarly, since appropriate data could only be extracted from six out of twelve research [12][14][15][16][18][19], showing a male–female ratio of 3156/1769, a precise estimate could not be carried out, not permitting a comparison with Nuno-Gonzalez et al.'s [20] results, pointing out a slightly higher prevalence of oral lesions in females potentially related to the influence of sex hormones on SARS-CoV-2 pathophysiology [21]. Severely incomplete data were also found concerning COVID-19 severity in the investigated populations, currently classified as mild/moderate or severe/hospitalized, as per Amorim Dos Santos et al. [18]. Consequently, the degree of association of oral lesions with SARS-CoV-2 infection [22] could not be determinately estimated, and the primary lesions, with related clinical presentations and microscopic features, could not be definitively graded in relation to COVID-19 forms [23]. Similarly, largely deficient data were acquired concerning ongoing COVID-19 treatments, potentially responsible of oral adverse reactions. Indeed, oral lesions, enriching the multi-systemic phenomenology of the illness, have been hypothesized to be potentially ascribable to the direct cytopathic effect of SARS-CoV-2, with the viral invasion of the oral epitheliocytes, mediated by ACE2 receptors [5][6] or attributable to the pathophysiology of SARS-CoV-2 infection; therefore, they could manifest as an indirect epiphenomenon of the immune–inflammatory reaction against viral antigens [24]. Moreover, the reported oral lesions were proposed to possibly represent the clinical expression of secondary immunity impairment and related co-infections, as well as adverse reactions to pharmacological therapies and iatrogenic injuries related to COVID-19 treatment [16][25][26].

However, regardless of the proposed pathogenesis of oral lesions occurring in COVID-19, which goes beyond the scope of the studies, the overall prevalence of cases diagnosed with oral lesions in SARS-CoV-2-positive subjects ≥ 18 years of age is still debated. Such prevalence may be very difficult to be determined and, conceivably, under-evaluated as a result of life-threatening conditions and supplementary breathing bias use in severe and critical COVID-19 patients, as well as domiciliary care in mild illness, beyond the particularly defensive personal protective equipment limiting photographic documentation. The total cases diagnosed with oral lesions accounted for 13.54% of the population analyzed in the twelve systematic research. Noteworthy, it may be hypothesized that the presently computed prevalence could be affected by the high number of case reports and series considered in the systematic research, thus potentially resulting overestimated, although Fidan et al.'s [27] and Elamrousi et al.'s [28] studies reported prevalence values as high as 65.5% and 90.3%. Such discrepancies may be explained by the exclusion from the present analysis of oral lesions self-diagnosed by means of questionnaires, which were included, instead, in Qui et al.'s review [29], of normal variations, such as fissured and geographic tongue, and of likely pre-existing conditions and diseases, principally represented by Oral Lichen Planus, which were also recorded.

The retrieved findings revealed extremely heterogeneous denominations of primary oral lesions, probably referable to the fact that the cases were mainly diagnosed by internists, anesthesiologists and dermatologists, rather than oral medicine consultants and dentists, especially during the first peak of the pandemic and the related suspension of non-urgent care. Given these considerations, the researchers categorized the reported primary oral lesions as

aphthous-like and/or erythema multiforme-like and/or herpetiform erosions and ulcers, white and/or red plaques, and vesicles and bullae, attempting to reduce heterogeneity in reporting forms and suggesting the use of such common denominations in future research. In addition, a high frequency of cases with polymorphous and complex intra- and peri-oral macroscopic pictures clearly emerged, making extremely complex the identification of the underlying primary lesions. However, the most frequently reported primary oral lesions resulted to be erosion and ulcers, found in 48.96% of diagnosed cases; in more detail, no specific characteristics were delineated for 38.24% of such lesions, while aphthous-like, herpetiform and erythema multiforme-like appearances were described in 16.76%, 1.89% and 1.07% of the overall erosions and ulcers recorded, respectively. Similarly, Fidan et al. [27] described erosions and ulcers as the most frequent primary oral lesions in SARS-CoV-2-positive subjects and estimated a prevalence of 39.7% of aphthous-like ones. Second for reported frequency were maculae (12.47%), mostly depicted as erythema, and petechiae (3.96%), representing 16.44% of the primary oral lesions, followed by vesicles and bullae, mainly diffuse, and plaques, exclusively white, accounting for 4.97% and 0.25% of the reported oral lesions. Such primary oral lesions could not be analyzed in relation to the most frequently affected intra-oral site due to the incompleteness of findings, although tongue, buccal and palatal mucosa, gingiva and lip resulted to be involved in a descending order, also in accordance with Iranmanesh et al. [25], representing the tongue and labial mucosa as the most common affected locations. Particularly relevant would have also been identifying the timing of the appearance of the described oral lesions, reported only by Orilisi et al. [15]; this has been previously proposed to be a potential indicator both of COVID-19 onset, as established for taste and smell alterations, and illness worsening [1][2][8][9][10][11]. Moreover, broadening the knowledge of the natural history of the disease, also including the expected timing of the appearance of oral lesions in COVID-19, may bring a two-fold effect: on one hand, it may aid in categorizing lesions into early ones, potentially attributable to the viral cytopathic effect, and late ones, detected after the start of therapy and potentially associated with it [30], while, on the other hand, it may improve oral and dental care provision planning, as part of the interdisciplinary management of patients with COVID-19.

At the current state of knowledge, since the histopathological features of oral mucosal lesions were only reported in few cases [16][30][31] diagnosed with oral erosions or ulcers by mostly describing similar non-specific pictures, no definitive evidence on the microscopic appearance of the oral lesions most frequently observed in adult SARS-Cov-2-positive subjects has been achieved. However, the most commonly reported histopathological feature for such erosive and ulcerative oral lesions is the vacuolization of oral epithelial cells, which, similarly to the microscopic alterations observed in other infections by epitheliotropic viruses, including those belonging to the *Herpesviridae* family, could constitute the epiphenomenon of the direct cytopathic effect operated by SARS-CoV-2. The latter hypothesis would be validated by the contextual detection of the virus within oral epithelial layers by in situ hybridization or immunohistochemistry, which was conducted, at the current state of evidence, only by Soares et al. [32]. Necrotic phenomena, leukocytosis and Langerhans cell activation were also described within the oral epithelium [16][18][30]. In the underlying connective tissue, similar to cutaneous and pulmonary biopsies, multiple micro-thrombi with consequent partial or total occlusion of small-and medium-caliber vesselswere also described, along with massive inflammatory cell infiltration at peri-vascular and peri-glandular sites, as well as with a band-like lichenoid distribution, and reactive vascular hyperplasia and peri-vascular fibrosis [16][18][30].

In addition to primary oral lesions, desquamative gingivitis (0.63%), lichenoid (4.2%) and hemorrhagic (2.3%) lesions were also reported, as well as oral candidiasis (5.4%) and necrotizing periodontal disease (1.27%), probably attributable to immune impairment. Besides the periodontal necrotizing lesions, also those from chronic periodontitis were related to the COVID-19, and the most severe stages of periodontitis were associated with higher rates of hospitalization, need of ventilation and mortality [33]. Researchers conclude that a periodontal state assessment could help identify those at risk, recognizing as statistically significant and common risk factors both COVID-19 and periodontitis in diabetes mellitus and cardiovascular diseases [33][34]. Indeed, it has been hypothesized that periodontitis, poor oral hygiene and periodontal microbiome may themselves constitute risk factors for complications from COVID-19 and the worsening of illness forms [19][35]. It may be consequently proposed that instructions and motivation for oral hygiene and, above all, active periodontal treatment should be systematically integrated into inter-disciplinary management in subjects with mild and moderate COVID-19, and where possible, in severe cases, especially in those with diabetes and cardiovascular disease. Furthermore, considering periodontal pockets as possible reservoirs of SARS-CoV-2, as already amply demonstrated for herpesviruses, including herpes simplex, Epstein-Barr virus andhuman cytomegalovirus [36], it may be hypothesized that periodontal treatment and oral antisepsis with chlorhexidine and hydrogen peroxide, by controlling suspected periodontal pathogens and viral microbial load, may reduce the risk of re-infection in COVID-19 healed subjects [11][37].

Despite the very inclusive eligibility criteria applied, only few and poor-quality systematic research could be retrieved. Moreover, high heterogeneous and incomplete data were extracted, precluding the possibility of conducting a meta-analysis and achieving definitive results, which may represent the main limitation of studies. However, current study may be the first to synthesize findings from available systematic research and aim to grade, based on the reported frequency, the oral primary lesions, with clinical presentations and microscopic features, and to estimate their degree of association with SARS-CoV-2 infection [22] and with COVID-19 severity [23].

Further studies with a higher evidence level should be conducted to accurately describe and assess the prevalence of cases diagnosed with oral lesions among adult SARS-CoV-2-positive subjects, especially considering novel variants and occurring following vaccine administration. Additional investigations may also aid in grading the frequency of primary oral lesions with related clinical presentations and microscopic features and in determining their degree of association with SARS-CoV-2 infection [22] and with COVID-19 forms [23]. Furthermore, the putative role of SARS-CoV-2 in oral lesion genesis, on the one hand, and the supposed contribution of periodontitis and periodontal microbiome, seemingly interconnected with the gut–lung axis [35], in COVID-19 worsening and re-activations, on the other hand, should be evaluated.

Deeper insights into oral lesions in adult SARS-CoV-2-positive subjects, which may behypothetically attributable to the direct cytopathic effect of SARS-CoV-2 or to the indirect effect of the immune–inflammatory reactions occurring in the course of the disease or may be somehow related to COVID-19 pharmacological therapy and treatment procedures, could enhance the comprehension of illness pathogenesis, thus improving the preparedness of health professionals, including oral healthcare workers [4][38][39][40][41][42][43][44], in the inter-disciplinary management of COVID-19 [45][46][47].

References

1. Orozco, M.S.; Niño-Martínez, N.; Martínez-Castañón, G.-A.; Marín, N.P.; Valencia, C.S.; Velázquez, F.D.; Munguía, P.S.; Santana, M.C. Presence of SARS-CoV-2 and Its Entry Factors in Oral Tissues and Cells: A Systematic Review. Medicina 2021, 57, 523.
2. Wan, S.; Li, M.; Ye, Z.; Yang, C.; Cai, Q.; Duan, S.; Song, B. CT Manifestations and Clinical Characteristics of 1115 Patients with Coronavirus Disease 2019 (COVID-19): A Systematic Review and Meta-analysis. Acad. Radiol. 2020, 27, 910–921.
3. Recalcati, S. Cutaneous manifestations in COVID-19: A first perspective. J. Eur. Acad. Dermatol. Venereol. 2020, 34, e212–e213.
4. Rocha, B.A.; Souto, G.R.; Grossmann, S.D.M.C.; de Aguiar, M.C.F.; de Andrade, B.A.B.; Romañach, M.J.; Horta, M.C.R. Viral enanthema in oral mucosa: A possible diagnostic challenge in the COVID-19 pandemic. Oral Dis. 2021, 27, 776–778.
5. Xu, J.; Li, Y.; Gan, F.; Du, Y.; Yao, Y. Salivary Glands: Potential Reservoirs for COVID-19 Asymptomatic Infection. J. Dent. Res. 2020, 99, 989.
6. Xu, H.; Zhong, L.; Deng, J.; Peng, J.; Dan, H.; Zeng, X.; Li, T.; Chen, Q. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int. J. Oral Sci. 2020, 12, 8.
7. Mazur, M.; Duś-Ilnicka, I.; Jedliński, M.; Ndokaj, A.; Janiszewska-Olszowska, J.; Ardan, R.; Radwan-Oczko, M.; Guerra, F.; Luzzi, V.; Vozza, I.; et al. Facial and Oral Manifestations Following COVID-19 Vaccination: A Survey-Based Study and a First Perspective. Int. J. Environ. Res. Public Health 2021, 18, 4965.
8. Martín Carreras-Presas, C.; Amaro Sánchez, J.; López-Sánchez, A.F.; Jané-Salas, E.; Somacarrera Pérez, M.L. Oral vesiculobullous lesions associated with SARS-CoV-2 infection. Oral Dis. 2021, 27, 710–712.
9. Petrescu, N.; Lucaciu, O.; Roman, A. Oral mucosa lesions in COVID-19. Oral Dis. 2022, 28, 935–936.
10. Vieira, A.R. Oral manifestations in coronavirus disease 2019 (COVID-19). Oral Dis. 2020, 27, 770.
11. Di Spirito, F.; Pelella, S.; Argentino, S.; Sisalli, L.; Sbordone, L. Oral manifestations and the role of the oral healthcare workers in COVID-19. Oral Dis. 2022, 28, 1003–1004.
12. Bhujel, N.; Zaheer, K.; Singh, R.P. Oral mucosal lesions in patients with COVID-19: A systematic review. Br. J. Oral Maxillofac. Surg. 2021, 59, 1024–1030.
13. Cuevas-Gonzalez, M.V.; Espinosa-Cristóbal, L.F.; Donohue-Cornejo, A.; Tovar-Carrillo, K.L.; Saucedo-Acuña, R.A.; García-Calderón, A.G.; Guzmán-Gastelum, D.A.; Cuevas-Gonzalez, J.C.

COVID-19 and its manifestations in the oral cavity: A systematic review. Medicine 2021, 100, e28327.

14. Nijakowski, K.; Wyzga, S.; Singh, N.; Podgórski, F.; Surdacka, A. Oral Manifestations in SARS-CoV-2 Positive Patients: A Systematic Review. J. Clin. Med. 2022, 11, 2202.
15. Orilisi, G.; Mascitti, M.; Togni, L.; Monterubbianesi, R.; Tosco, V.; Vitiello, F.; Santarelli, A.; Putignano, A.; Orsini, G. Oral Manifestations of COVID-19 in Hospitalized Patients: A Systematic Review. Int. J. Environ. Res. Public Health 2021, 18, 12511.
16. Silveira, F.M.; Mello, A.L.R.; Fonseca, L.D.S.; Ferreira, L.D.S.; Kirschnick, L.B.; Martins, M.D.; Schuch, L.F.; de Arruda, J.A.A.; Soares, C.D.; Sales, A.D.O.; et al. Morphological and tissue-based molecular characterization of oral lesions in patients with COVID-19: A living systematic review. Arch. Oral Biol. 2022, 136, 105374.
17. Uzêda-E-Silva, V.D.; de Sá, I.B.; Martins, J.; Pedreira, N.; Vieira, V.; Silva, B. Oral lesions associated with COVID-19: A systematic review. Stomatologija 2021, 23, 3–8.
18. dos Santos, J.A.; Normando, A.; da Silva, R.C.; Acevedo, A.; Canto, G.D.L.; Sugaya, N.; Santos-Silva, A.; Guerra, E. Oral Manifestations in Patients with COVID-19: A 6-Month Update. J. Dent. Res. 2021, 100, 1321–1329.
19. Doceda, M.V.; Gavriiloglou, M.; Petit, C.; Huck, O. Oral Health Implications of SARS-CoV-2/COVID-19: A Systematic Review. Oral Health Prev. Dent. 2022, 20, 207–218.
20. Nuno-Gonzalez, A.; Martin-Carrillo, P.; Magaletsky, K.; Rios, M.M.; Mañas, C.H.; Almazan, J.A.; Casasola, G.G.; Castro, E.P.; Arenas, A.G.; Ibarguren, A.M.; et al. Prevalence of mucocutaneous manifestations in 666 patients with COVID-19 in a field hospital in Spain: Oral and palmoplantar findings. Br. J. Dermatol. 2021, 184, 184–185.
21. Gebhard, C.; Regitz-Zagrosek, V.; Neuhauser, H.K.; Morgan, R.; Klein, S.L. Impact of sex and gender on COVID-19 outcomes in Europe. Biol. Sex Differ. 2020, 11, 29.
22. Classification and diagnostic criteria for oral lesions in HIV infection. EC-Clearinghouse on Oral Problems Related to HIV Infection and WHO Collaborating Centre on Oral Manifestations of the Immunodeficiency Virus. J. Oral Pathol. Med. Off. Publ. Int. Assoc. Oral Pathol. Am. Acad. Oral Pathol. 1993, 22, 289–291.
23. World Health Organization (WHO). Living Guidance for Clinical Management of COVID-19: Living Guidance. Available online: WHO-2019-nCoV-clinical-2021.2-eng.pdf (accessed on 7 May 2022).
24. Tay, M.Z.; Poh, C.M.; Rénia, L.; Macary, P.A.; Ng, L.F.P. The trinity of COVID-19: Immunity, inflammation and intervention. Nat. Rev. Immunol. 2020, 20, 363–374.
25. Iranmanesh, B.; Khalili, M.; Amiri, R.; Zartab, H.; Aflatoonian, M. Oral manifestations of COVID-19 disease: A review article. Dermatol. Ther. 2021, 34, e14578.

26. Di Spirito, F.; Iacono, V.J.; Alfredo, I.; Alessandra, A.; Sbordone, L.; Lanza, A. Evidence-based Recommendations on Periodontal Practice and the Management of Periodontal Patients during and after the COVID-19 Era: Challenging Infectious Diseases Spread by Air-borne Transmission. Open Dent. 2021, 15, 325–336.
27. Fidan, V.; Koyuncu, H.; Akin, O. Oral lesions in COVID-19 positive patients. Am. J. Otolaryngol. 2021, 42, 102905.
28. Elamrousy, W.A.H.; Nassar, M.; Issa, D.R. Prevalence of Oral Lesions in COVID-19 Egyptian Patients. J. Int. Soc. Prev. Community Dent. 2021, 11, 712–720.
29. Qi, X.; Northridge, M.E.; Hu, M.; Wu, B. Oral health conditions and COVID-19: A systematic review and meta-analysis of the current evidence. Aging Health Res. 2022, 2, 100064.
30. Favia, G.; Tempesta, A.; Barile, G.; Brienza, N.; Capodiferro, S.; Vestito, M.C.; Crudele, L.; Procacci, V.; Ingravallo, G.; Maiorano, E.; et al. COVID-19 Symptomatic Patients with Oral Lesions: Clinical and Histopathological Study on 123 Cases of the University Hospital Policlinic of Bari with a Purpose of a New Classification. J. Clin. Med. 2021, 10, 757.
31. dos Santos, J.A.; Normando, A.G.; Da Silva, R.C.; Acevedo, A.; Canto, G.D.L.; Sugaya, N.; Santos-Silva, A.; Guerra, E. Oral Manifestations in Patients with COVID-19: A Living Systematic Review. J. Dent. Res. 2021, 100, 141–154.
32. Soares, C.; Carvalho, R.; Carvalho, M.; Almeida, O. Letter to Editor: Oral lesions in a patient with COVID-19. Med. Oral Patol. Oral Y Cir. Bucal 2020, 25, e563–e564.
33. Gupta, S.; Mohindra, R.; Singla, M.; Khera, S.; Sahni, V.; Kanta, P.; Soni, R.K.; Kumar, A.; Gauba, K.; Goyal, K.; et al. The clinical association between Periodontitis and COVID-19. Clin. Oral Investig. 2022, 26, 1361–1374.
34. Di Spirito, F.; Schiavo, L.; Pilone, V.; Lanza, A.; Sbordone, L.; D'Ambrosio, F. Periodontal and Peri-Implant Diseases and Systemically Administered Statins: A Systematic Review. Dent. J. 2021, 9, 100.
35. Pitones-Rubio, V.; Chávez-Cortez, E.G.; Hurtado-Camarena, A.; González-Rascón, A.; Serafín-Higuera, N. Is periodontal disease a risk factor for severe COVID-19 illness? Med. Hypotheses 2020, 144, 109969.
36. Sampson, V.; Kamona, N.; Sampson, A. Could there be a link between oral hygiene and the severity of SARS-CoV-2 infections? Br. Dent. J. 2020, 228, 971–975.
37. Vergara-Buenaventura, A.; Castro-Ruiz, C. Use of mouthwashes against COVID-19 in dentistry. Br. J. Oral Maxillofac. Surg. 2020, 58, 924–927.
38. Scully, C.; Samaranayake, L.P. Emerging and changing viral diseases in the new millennium. Oral Dis. 2016, 22, 171–179.

39. Lo Giudice, R.; Famà, F. Health care and health service digital revolution. Int. J. Environ. Res. Public Health 2020, 17, 4913.
40. Zannella, C.; Shinde, S.; Vitiello, M.; Falanga, A.; Galdiero, E.; Fahmi, A.; Santella, B.; Nucci, L.; Gasparro, R.; Galdiero, M.; et al. Antibacterial activity of indolicidin-coated silver nanoparticles in oral disease. Appl. Sci. 2020, 10, 1837.
41. Amato, A.; Ciacci, C.; Martina, S.; Caggiano, M.; Amato, M. COVID-19: The Dentists' Perceived Impact on the Dental Practice. Eur. J. Dent. 2021, 15, 469–474.
42. Gasparro, R.; Scandurra, C.; Maldonato, N.M.; Dolce, P.; Bochicchio, V.; Valletta, A.; Sammartino, G.; Sammartino, P.; Mariniello, M.; Di Lauro, A.E.; et al. Perceived job insecurity and depressive symptoms among italian dentists: The moderating role of fear of COVID-19. Int. J. Environ. Res. Public Health 2020, 17, 5338.
43. Martina, S.; Amato, A.; Faccioni, P.; Iandolo, A.; Amato, M.; Rongo, R. The perception of COVID-19 among Italian dental patients: An orthodontic point of view. Prog. Orthod. 2021, 22, 11.
44. Lo Giudice, R. The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS CoV-2) in Dentistry. Management of Biological Risk in Dental Practice. Int. J. Environ. Res. Public Health 2020, 17, 3067.
45. Schiavo, L.; Calabrese, P.; Aliberti, S.M.; Tramontano, S.; Iannelli, A.; Pilone, V. Impact of SARS-CoV-2 Lockdown on the Preoperative Care Program of Patients Scheduled for Bariatric Surgery. Nutrients 2022, 14, 1488.
46. Marinaci, T.; Carpinelli, L.; Venuleo, C.; Savarese, G.; Cavallo, P. Emotional distress, psychosomatic symptoms and their relationship with institutional responses: A survey of Italian frontline medical staff during the COVID-19 pandemic. Heliyon 2020, 6, e05766.
47. Sica, A.; Casale, D.; Rossi, G.; Casale, B.; Ciccozzi, M.; Fasano, M.; Ciotti, M.; Sagnelli, E.; Papa, A.; Sagnelli, C. The impact of the SARS-CoV-2 infection, with special reference to the hematological setting. J. Med. Virol. 2020, 93, 223–233.