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Mikkola, Maria Kaarina

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# Triage and urgent dental care for COVID-19 patients in the Hospital District of Helsinki and Uusimaa

**Left running head:** M. K. MIKKOLA ET AL.

**Short title :**

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AQ1 Maria Kaarina Mikkola[a] Jenny Johanna Gästgifvars[a] Jaana Sisko Helenius-Hietala[a] Johanna Tuulikki Uittamo[a] Jussi Oskari Furuholm[a] Hannamari Välimaa[a b] Hellevi Merja A. Ruokonen[a] Karita Maaria Nylund[a]

[a]Department of Oral and Maxillofacial Diseases, University of Helsinki and Helsinki University Hospital, Helsinki, Finland;

[b]Department of Virology, University of Helsinki, Helsinki, Finland

*These authors contributed equally to this article.

CONTACT Jenny Gästgifvars jenny.gastgifvars@fimnet.fi Department of Oral and Maxillofacial Diseases, Helsinki University Hospital, Helsinki 00029, Finland

**Abstract**

## Objective

This paper describes and reports the patient-specific characteristics of an urgent dental care clinic for COVID-19 infected, suspected, exposed or quarantined patients from March to December 2020 in the Hospital District of Helsinki and Uusimaa, Finland.

## Material and methods

The triage and the treatment protocol were established based on the scientific data. Patient files were evaluated from the hospital district's electronic medical record system. IBM SPSS software was used for statistical analysis.

## Results

There were 1114 consultations and 257 visits at the clinic. Most of the patients were generally healthy with mean age of 35, had toothache and were suspected to be SARS-CoV-2 positive. Seventeen of the patients received positive tests for COVID-19 infection. The main treatment was tooth extraction, mostly due to caries. Statistically significant differences between COVID-19 infected and other patients occurred in age (45 vs 34 years-of-age, $p$ = .009) and number of teeth (25 vs 28, $p$ = .031). No SARS-CoV-2 infection transmission chains were traced to the clinic.

## Conclusion

During the challenging pandemic time, patients were carefully screened by specialists in clinical dentistry and treated safely and effectively. Patient-specific characteristics revealed no differences between COVID-19 infected and other patients in terms of symptoms or treatment needs.

**Keywords:** COVID-19; emergency dental care; SARS-CoV-2; treatment protocol; triage protocol

## Introduction

Coronavirus disease (COVID-19) caused by SARS-CoV-2 was first reported in Wuhan, China in December 2019 and the first COVID-19 infection in Finland was diagnosed on January 29th in 2020. The virus then spread rapidly all over the world. In August 2021, the total number of confirmed cases has been more than 200,000,000 globally [1] and more than 100,000 in Finland [2]. The Finnish government has guided the work against COVID-19 infection both locally and nationally together with the Ministry of Social Affairs and Health and the municipal authorities of each hospital district, University Hospitals and Finnish Institute for Health and Welfare (THL) [2].

SARS-CoV-2 is transmitted from person to person through respiratory droplets or aerosols produced by infected person through coughing and sneezing or by direct or indirect contact transmission by touching surfaces contaminated with the virus [3]. General worldwide instructions for protection from COVID-19 infection have been recommended for the general public i.e. good hand hygiene, physical distancing by keeping >2 metres interpersonal distance, adequate indoor ventilation, use of facemasks and coughing up the sleeve [4,5].

Dental staff have been reported to be a potential occupational risk group due to close contact with patients and frequent exposure to aerosols generated during treatment [6–10]. Aerosol generating procedures (AGP) include the use of high-speed handpieces, ultrasonic scalers, 3-in-1 spray and powder cleaning [11,12]. Dental settings are typically not designed to carry out all of the Transmission-Based Precautions recommended for hospitals, and facilities are not necessary appropriate to provide service for potentially infectious patients [13,14]. Standard measures may not be sufficient to prevent spread of COVID-19 in everyday clinical work settings [14].

On 16th March 2020 the Finnish government declared an Emergency Powers Act. All elective health care was suspended at the Department of Oral and Maxillofacial diseases, Head and Neck centre, Helsinki University Hospital, Helsinki, Finland as it was gradually also done elsewhere in Finland in both the public and private sector. The Department of Oral and Maxillofacial Diseases provides highly specialized oral and dental care and emergency dental care for the residents of the Hospital District of Helsinki and Uusimaa (HUS). Some



dental professionals were assigned to work in COVID-19 testing and in epidemiological tracking when elective dental care was suspended. However, urgent dental care (UDC) had to be provided for COVID-19 infected, suspected, exposed and quarantined patients covering the Hospital District of Helsinki and Uusimaa (HUS) with 1.6 million inhabitants. Novel instructions and limitations regarding instrumentation and use of personal protective equipment (PPE) had to be followed.

The primary aim of this paper is to describe the HUS UDC clinic's patient-specific characteristics and reasons to seek for UDC and the treatments given from March to December. It was also assumed that well organized triage and treatment protocol would help to minimize the exposure of dental professionals to COVID-19. COVID-19 infected were not expected to suffer from different oral symptoms compared to other patients.

## Materials and methods

### Study design

This retrospective and descriptive study was performed to introduce the establishment and experiences of the COVID-19 UDC clinic at Helsinki University Hospital (HUH) during the year 2020. Altogether 250 patients who visited the clinic between March 19th and December 31st were analysed in this cross-sectional study.

The study was performed according to the World Medical Association Declaration of Helsinki, and it was approved by the Helsinki and Uusimaa Hospital research committee (license number §40 HUS/58/2020) and registered in the hospital database.

### Triage protocol

The triage protocol was established based on the existing scientific data for COVID-19 urgent dental care [7,10,13–20]. Patients first contacted their local municipal dentist who made the first assessment. Next, the municipal dentist contacted the COVID-19 UDC unit where a specialist in clinical dentistry acted as a gatekeeper to assess the treatment need more carefully by specific triage protocol (Figures 1 and 2). The aim was to identify COVID-19 infected, suspected based on symptoms, exposed, or quarantined patients with need of

UDC.

Figure 1. Assessment of urgent treatment need.

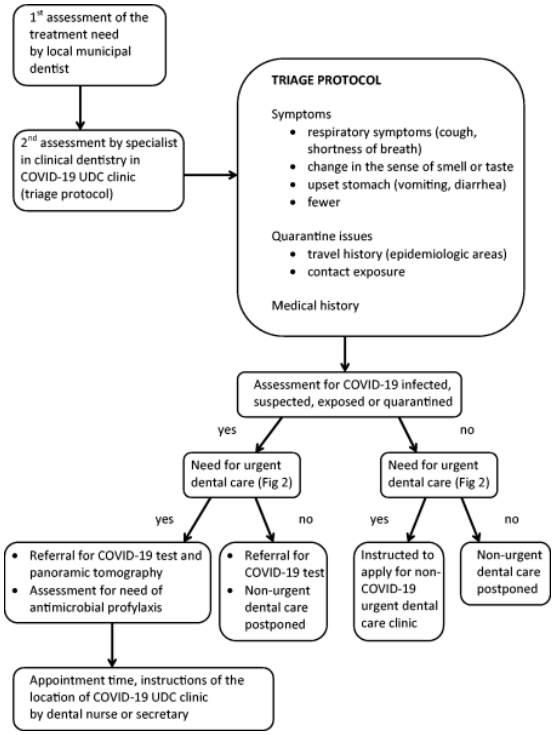
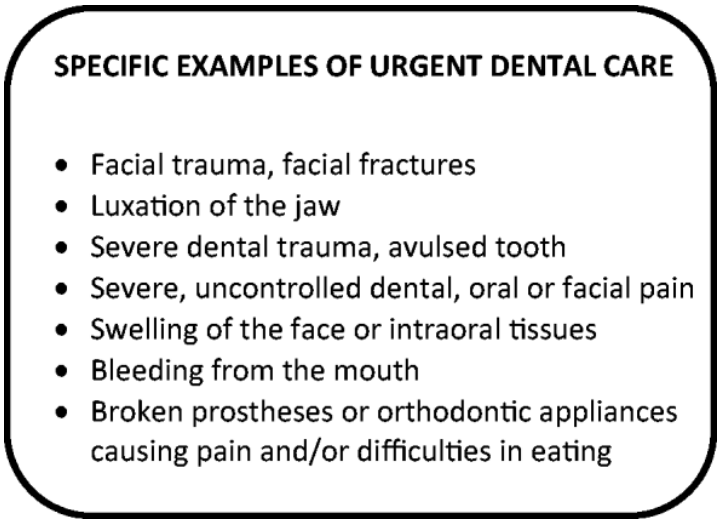



Figure 2. Need for urgent dental care.




Questions about COVID-19 symptoms, contact exposure and travel history were asked. The need for UDC was evaluated and non-urgent dental care was postponed. Patient selection was made carefully, and admission criteria were constantly updated as the knowledge of the virus increased. Patients were referred to receive a COVID-19 test if they had not been tested before UDC. Please see Figures 1

and 2 for details.

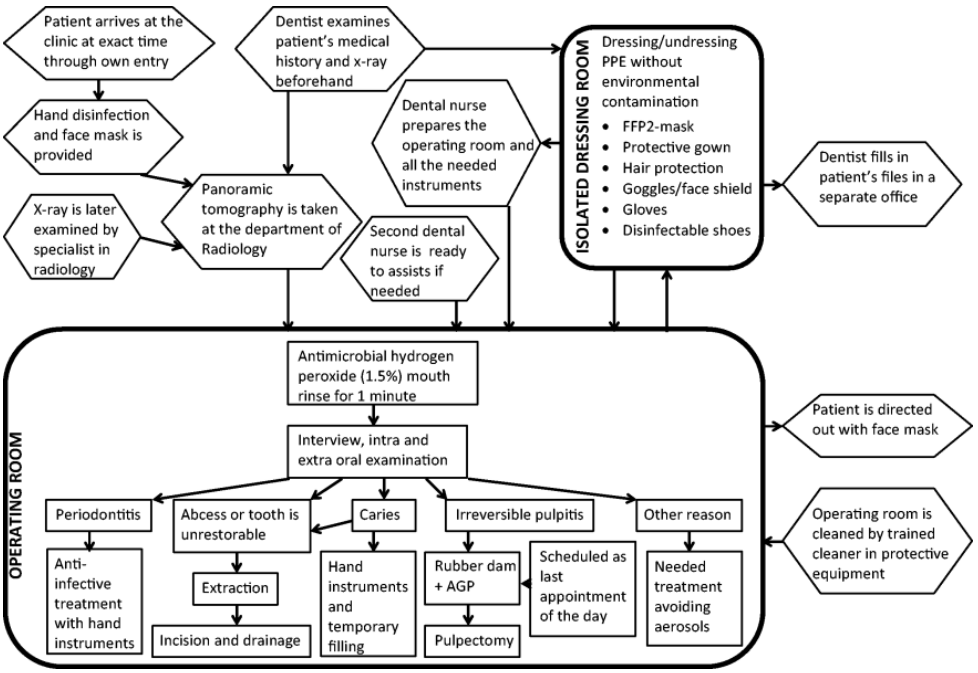
## Treatment protocol

The aim of the protocol was to provide safe treatment, avoid aerosol production and stop the spreading of the virus. The treatment protocol guidelines were based on the existing scientific data [3,6,7,10,11,14–16,18–22] and the consultation of several professionals from oral medicine, infectious diseases, and oral microbiology. Guidelines were continuously updated during the clinic's operating months. Staff including doctors, nurses, and secretaries were educated by simulation exercises and by a video tutorial [14].

Patients were referred to the COVID-19 UDC clinic at an exact time and place. Passage to the UDC clinic was separated from the other parts of the Hospital by tight plywood and plastic walls, which were specifically set up for this purpose. Hand disinfection and facemasks were provided at the entry to the clinic and the patient was directed to the Radiology department if needed. Intraoral X-rays were avoided in order to prevent coughing [23].

If dental staff had any COVID-19 symptoms, they were instructed to stay home and referred to COVID-19 testing. One asymptomatic day was required before returning to work. All dental staff were protected by a FFP2–mask, disposable liquid impermeable protective gown, a cap, goggles/face shield, nitrile or latex gloves, and disinfectable shoes. PPE was put on in an isolated, separate space that was specifically prepared for this purpose. In the operating room, the patient was given antimicrobial hydrogen peroxide (1.5%) mouth rinse to rinse for 1 min as recommended earlier [3]. The dentist checked the medical and dental history and oral symptoms, examined the patient and possible X-ray image, assessed the diagnosis and gave the necessary dental treatment in agreement with the patient. Dental nurses prepared for the upcoming procedure and only the necessary instruments were provided to avoid contamination. There was one dental nurse in the operating room and another outside ready to assist with necessary instruments if needed. Using rubber dam was recommended whenever possible based on its efficacy to significantly reduce airborne particles [24]. Between patients longer breaks than usual were taken, which allowed better ventilation in operating rooms [8]. Staff was instructed not to enter operating room without FFP2-mask at least for 30 min after AGP. The treatment protocol is shown in Figure 3.

Figure 3. Treatment protocol.




## Patients

Of the 250 patients that visited the COVID-19 UDC clinic between 19th March and 31st December 2020, 7 had two appointments, which has been taken into consideration while analysing the data; 27 (10.8%) were children (<18 years old).

Patients' medical and dental records and radiological data were evaluated in this study. ICD10 classification was used to determine their general health. The hospital laboratory database was inspected for results of COVID-19 laboratory tests taken at earliest one month before and latest one month after the visit.

Modified Total Dental Index (mTDI; Table 1) [25], and the number of teeth were used to determine the overall oral health of the patients. These parameters were assessed from the panoramic tomography. Panoramic tomography was



available for 222 patients, of which 207 were adults. The number of teeth was determined only for adults. Unerupted and supernumerary teeth were also included in the number of teeth.

**Table 1. Modified Total Dental Index (mTDI). Modified from Mattila et al. 1989 [25].**

| | |
|---|---|
| Caries | |
| No caries lesions | 0 |
| 1 − 3 caries lesions | 1 |
| 4 − 7 caries lesions or no teeth in maxilla or mandible | 2 |
| ≥8 caries or radix or no teeth | 3 |
| Periodontitis | |
| No alveolar bone loss | 0 |
| Alveolar bone loss in cervical third | 1 |
| Alveolar bone loss in middle third | 2 |
| Alveolar bone loss in apical third | 3 |
| Periapical lesions | |
| 1 periapical lesion or vertical bone pocket or both | 1 |
| 2 periapical lesions | 2 |
| ≥3 periapical lesions | 3 |
| Pericoronitis | |
| Absent | 0 |
| Present | 1 |
| Maximum score | 10 |

### Data analysis

We used the SPSS for statistical software package IBM (SPSS for Macintosh, version 27.0, IBM Corp., Armonk, NY, USA) for data analysis. For categorical variables, we evaluated differences in association between the study groups with Pearson's Chi-square test. We used Student's t-test to analyse differences between groups for continuous variables. Effect sizes were evaluated with Phi and Cramer's V tests for categorical variables, and Cohen's *d* test for continuous variables. Throughout the study, we considered *p*-values below .05 to be statistically significant.

## Results

### Outcome of the triage

Altogether 1114 telephone contacts were made between March 19th and December 31st 2020 ranging from 0 to 13

per day. The total number of visits was 257 ranging from 0 to 4 per day. Seven patients visited the clinic twice hence the total number of patients was 250.

On most ($n$ = 189, 73.5%) of the 257 visits patients were suspected to be SARS-CoV-2 positive based on symptoms, 19.8% ($n$ = 51) were exposed or quarantined, and 6.3% ($n$ = 16) were tested positive beforehand. Respiratory symptoms including fewer were the most common ($n$ = 163, 63.4%) symptoms to indicate possible COVID-19 infection. No COVID-19 related symptoms were detected for 17.9% ($n$ = 46) of the patient visits.

The leading acute dental symptoms were pain and tooth ache ($n$ = 202, 78.6%), swelling and abscess ($n$ = 38, 14.8%). A minority ($n$ = 17, 6.6%) of the oral symptoms were orthodontic, prosthetic and TMD problems, bleeding and trauma. Patients' need for treatment is presented in Table 2.

**Table 2. Descriptive statistics of patient contacts and visits.**

| | All visits ($N$ = 257) | Visits of COVID-19 infected ($N$ = 18) |
|---|---|---|
| Consultations/Phone calls | 1114 | |
| Range (per day) | 0–13 | |
| Visits at the clinic | 257 | 18 |
| Range (per day) | 0–4 | 0–2 |
| | $n$ (%) | $n$ (%) |
| COVID-19 symptoms | | |
| Respiratory | 163 (63.4) | 8 (44.4) |
| No symptoms | 46 (17.9) | 2 (11.1) |
| Various symptoms | 40 (15.6) | 3 (16.7) |
| Intestinal/Upset stomach | 2 (0.8) | 1 (5.6) |
| Unknown | 6 (2.3) | 4 (22.2) |
| COVID-19 status beforehand | | |
| Positive | 16 (6.3) | 16 (88.9) |
| Suspected | 189 (73.5) | 0 (0.0) |
| Quarantined or exposed | 51 (19.8) | 2 (11.1) |
| Unknown | 1 (0.4) | 0 (0.0) |
| Oral symptoms/Assessment of treatment need | | |
| Pain, toothache | 202 (78.6) | 12 (66.6) |
| Swelling/Abscess | 38 (14.8) | 2 (11.1) |
| TMD problems | 6 (2.3) | 1 (5.6) |
| Dentures/orthodontic related problems | 6 (2.3) | 1 (5.6) |
| Others | 5 (2.0) | 2 (11.1) |
| Need of analgesic | | |
| Yes | 180 (70.0) | 13 (72.2) |
| No | 2 (0.8) | 0 (0.0) |
| Unknown | 75 (29.2) | 5 (27.8) |
| Aetiology of oral symptoms | | |
| Caries | 171 (66.5) | 10 (55.6) |
| Pericoronitis | 28 (10.9) | 0 (0.0) |
| Unknown | 13 (5.1) | 4 (22.2) |
| Periodontitis | 12 (4.7) | 1 (5.5) |
| Other infections, not teeth related | 10 (3.9) | 0 (0.0) |
| Others | 23 (8.9) | 3 (16.7) |

| | All visits ($N$ = 257) | Visits of COVID-19 infected ($N$ = 18) |
|---|---|---|
| Antibiotic prophylaxis | | |
| No | 164 (63.8) | 15 (83.3) |
| Yes | 61 (23.7) | 2 (11.1) |
| Course of antibiotics started beforehand | 30 (11.7) | 1 (5.6) |
| Unknown | 2 (0.8) | 0 (0.0) |
| Treatment | | |
| Surgical | 177 (68.9) | 11 (61.1) |
| Examination and instructions | 25 (9.7) | 3 (16.7) |
| Antibiotics as main treatment | 13 (5.1) | 2 (11.0) |
| Endodontic | 11 (4.3) | 0 (0.0) |
| Restorative | 10 (3.9) | 0 (0.0) |
| Periodontal | 6 (2.2) | 0 (0.0) |
| Treatment of TMD | 4 (1.6) | 1 (5.6) |
| Treatment of pericoronitis (excluding extraction) | 4 (1.6) | 0 (0.0) |
| Others | 7 (2.7) | 1 (5.6) |

TMD: Temporomandibular disorders.

## Demographic data of the patients

A majority ($n$ = 169, 67.6%) of the 250 patients were tested for COVID-19 infection by PCR from nasopharyngeal swap sample by the Helsinki University Hospital laboratory (HUSLAB). Of these patients, only 17 (6.8%) were found to be SARS-CoV-2 positive. Positive tests were taken at the latest on the same day the patient visited the clinic.

Most of the 250 patients ($n$ = 158, 63.2%) were generally healthy, their mean age was 35 years, and they were slightly more often female ($n$ = 132, 52.8%). Demographic and oral health data were compared between SARS-CoV-2 infected ($n$ = 17) and other patients ($n$ = 233). SARS-CoV-2 infected patients were statistically significantly older compared to other patients (45 vs 34 years-of-age, $p$ = .009). Demographic data is provided in Table 3.

**Table 3. Demographics and oral health data.**

| Demographics | All patients ($N$ = 250) | COVID-19 infected ($N$ = 17) |
|---|---|---|
| Age | | |
| Range | 2–81 | 12–81 |
| Mean | 34.97 | 44.7 |
| Median | 31 | 41 |
| | $n$ (%) | $n$ (%) |
| Gender | | |
| Female | 132 (52.8) | 7 (41.2) |
| Male | 118 (47.2) | 10 (58.8) |
| Medical history | | |
| No systemic diseases | 158 (63.2) | 11 (64.7) |
| Respiratory diseases | 28 (11.2) | 2 (11.8) |
| Endocrinological diseases | 28 (11.2) | 2 (11.8) |
| Including DM type I and II | 11(4.4) | 1 (5.9) |
| Cardiovascular diseases | 21 (8.4) | 3 (17.6) |
| Neurological diseases | 19 (7.6) | 2 (11.8) |
| Mental and behavioural disorders | 17 (6.8) | 1 (5.9) |

| Demographics | All patients ($N = 250$) | COVID-19 infected ($N = 17$) |
|---|---|---|
| Other | 37 (14.8) | 2 (11.8) |
| Number of drugs in use | | |
| 0 | 162 (64.8) | 10 (58.8) |
| 1–2 | 43 (17.2) | 1 (5.9) |
| 3–4 | 20 (8.0) | 0 (0.0) |
| 5 or more | 16 (6.4) | 4 (23.5) |
| Unknown | 9 (3.6) | 2 (11.8) |
| Smoking | | |
| Yes | 36 (14.4) | 1 (5.8) |
| No | 34 (13.6) | 2 (11.8) |
| Not known | 180 (72.0) | 14 (82.4) |
| Tested for COVID-19 | | |
| Positive | 17 (6.8) | 17 (100.0) |
| Negative | 152 (60.8) | 0 (0.0) |
| Not tested/Unknown | 81 (32.4) | 0 (0.0) |
| **Oral health** | | |
| mTDI | | |
| 0 | 34 (13.6) | 0 (0.0) |
| 1–3 | 119 (47.6) | 14 (82.4) |
| 4–6 | 47 (18.8) | 2 (11.8) |
| 7–10 | 22 (8.8) | 0 (0.0) |
| Unknown | 28 (11.2) | 1 (5.8) |
| Number of teeth in X-ray (only adults) | ($n = 207$) | ($n = 15$) |
| Range | 4 – 34 | 9 – 31 |
| Mean | 27.7 | 25.3 |
| Median | 29 | 26 |

DM: Diabetes mellitus; mTDI: Modified Total Dental Index (see Table 1).

Two patients died during our research period, and both were infected with SARS-CoV-2 and medically compromised.

## Oral and dental health of the patients

The leading aetiologies behind the need for treatment were cariological ($n = 171$, 66.5%) and pericoronitis ($n = 28$, 10.9%).



The main treatment approach taken was surgical, including extractions ($n = 169$, 65.8%), abscess incision and drainage ($n = 3$, 1.2%), treatment of dry socket ($n = 4$, 1.6%) and trauma splinting ($n = 1$, 0.4%). The second most frequent treatment was oral examination only and follow-up care instructions ($n = 25$, 9.7%), including treatment of mucosal problems and other non-tooth related infections, and the third was antibiotics as a main given treatment ($n = 13$, 5.1%).

Prophylactic antibiotics were given at the clinic in 23.7% of visits ($n = 61$) and in 11.7% ($n = 30$) antibiotics were already prescribed elsewhere before the patient entered the clinic. The aetiology of symptoms and the treatment provided are presented in Table 2.

The mean mTDI for all the patients with panoramic tomography ($n = 222$) was 2.8. Men had more caries and periapical lesions according to mTDI (3.6 vs. 2.2, $p < .001$). The mean number of teeth among all the adults with panoramic tomography ($n = 207$) was 27.7. SARS-CoV-2 infected patients ($n = 15$) had less teeth compared to the other 192 patients (25 vs. 28, $p = .031$). Patients' oral health is presented in Table 3.

## Discussion

The UDC clinic was set up quickly with the help of several professionals from oral medicine, infectious diseases, and oral microbiology. The working instructions evolved when new information about the virus was available. The purpose was to provide optimal UDC whilst minimising the possible exposure of dental professionals and patients to COVID-19. The treatment protocol seemed to be effective in controlling the spread of the SARS-CoV-2 virus: as far as we know no infection chains have been traced to the clinic. According to patient medical histories, no UDC clinic patients gotcarried COVID-19 infection within the month following their visit.



This suggests that SARS-CoV-2 was not transmitted to the patients from the clinic.

Cagetti et al. [26] and Negucioiu et al. [14] both describe a lack of data and certainty regarding the real risk of SARS-CoV-2 transmission by dental procedures, and they discuss the ideal protective measures that could prevent SARS-CoV-2 contamination in dental settings. Although Cagetti et al. [26] reported that there might be greater SARS-CoV-2 infection diffusion among dentists. Nonetheless, previous studies as well as ours have suggested that triage and treatment protocols seemed to have been relatively effective in avoiding SARS-CoV-2 transmission [10,14,27].

The role of UDC is significant. If dental care is delayed, the risk for more notable infection is increased [28]. Therefore, it was remarkable that we were able to take care of these patients even during the challenging epidemic situation. The number of patients per day varied between 0 and 4, which was surprisingly few because the clinic was prepared to take care of 24 patients per day. The treatment provided at the first visit was also effective, there were only 7 patients who returned. From the beginning we thought the triage to be extremely important. Out of the 1114 consultations, there were only 257 appointments, and these were the patients who fulfilled the criteria for UDC. The role of specialists in clinical dentistry as a gatekeeper and the specific triage protocol as well as close collaboration with infectious disease specialists and oral microbiologists were probably crucial. Though these numbers speak not only about the success of triage but also the overall management of the pandemic in Finland.

Patients were more often female, generally healthy and their mean age was 35. Oral health was generally good according to mTDI (mean mTDI under 3). There were no significant differences in dental symptoms, treatment needs, or the cause of the dental symptoms in SARS-CoV-2 positive patients in comparison with the rest of the patients (COVID-19 suspected, exposed or quarantined patients). Patients with COVID-19 infection were, however, older and had less teeth compared to the rest of the patients.

Less teeth might reflect long-lasting low-level oral inflammation predisposing to systemic diseases and even to death. Research from Ruokonen et al. [29] showed that among chronic kidney disease patients, missing teeth, higher age, and diabetic nephropathy diagnoses were statistically significant independent risk factors for death. Even a few missing teeth may predict cardiovascular events, diabetes and death according to a Finnish population-based survey [30]. Only two patients died during our research period. Both were SARS-CoV-2 infected and medically compromised predisposing them to a more critical situation. Our study is in line with other studies where older age and the existence of underlying comorbidities (e.g. diabetes, hypertension and, cardiovascular disease) were associated with poorer prognosis of COVID-19 [31].

We observed that the main symptom for seeking UDC was pain/toothache followed by swelling or abscess. Tooth extraction was the most common treatment, which was performed when a tooth was non-restorable, and the patient suffered from severe dental infection and/or pain. Irreversible pulpitis was treated with pulpectomy when the tooth was restorable and periodontally sound. Alharbi et al. [16] describes urgent conditions that can be managed with minimally invasive procedures and without aerosol generation. Our treatment protocols followed their suggested guidelines and a rubber dam was used with restorative and endodontic procedures.

In case of an abscess, antibiotics were prescribed beforehand, and thus the use of prophylactic antibiotics is explained by the severity of the infections rather than patients' medical conditions. Prescribing antibiotics as the only given treatment is not the protocol recommended by the Finnish Medical Society Duodecim current care guidelines [32] and there is also a global concern about overuse of antibiotics leading to antibiotic resistance. For example, a significant increase in dental antibiotic prescribing has been reported in England [33]. In our study, the reasons for prescribing antibiotics as a main treatment ($n$ = 13, 5.1%) were that some patients were refused the recommended dental treatment, the procedure could not be performed at the urgent dental care clinic (e.g. advanced surgical extraction) or the patient was referred to another specialist.

The main oral manifestations observed in COVID-19 patients are aphthous like lesions, ulcers, necrotising gingivitis, fungi or other virus infection, erythema multiforme–like lesions, and loss of smell and/or taste [17,34]. We found no relationship between COVID-19 infection and oral symptoms, nor possible oral manifestations of COVID-19. This might be explained by the fact that none of our patients had severe COVID-19 infection at the time they visited the clinic. Nonetheless, we can conclude that poor oral health of our study participants was unlikely to predispose to COVID-19 infection.

SARS-CoV-2 can be transmitted from an asymptomatic person to another and this is still one of the challenges that patient screening and triage are facing [35,36]. Dental offices could be potential places for testing and thus identifying infectious patients early [37–39]. As Ren et al. [19] suggest, an ideal solution is to provide a rapid point-of-care testing in the UDC clinic that gives the result in minutes. This protocol and tests still need to be developed further, but already there are good studies on this subject [40]. Also using SARS-CoV-2 saliva tests might be one way of detecting infected individuals in the future [9].

There are some limitations to this study that need to be addressed. At the end of our study period there had been over 37,000 SARS-CoV-2 infected in Finland, 24,000 of them at HUS district with 1.6 million inhabitants [41]. Despite these numbers only a small cohort of SARS-CoV-2 positive patients attended the UDC clinic ($n$ = 17), therefore we cannot reliably compare positive and negative groups. Patients who visited the clinic in March 2020 were not systematically tested because the national testing capacity for COVID-19 infection was insufficient at the beginning of the pandemic. This might affect the number of positive patients recorded in this study. From the end of April, most patients ($n$ = 169, 67.3%) were tested before or after visiting the clinic.



In our study patient-specific characteristics revealed no new data on COVID-19 and visits were typical for urgent dental care. We can conclude that the triage protocol and the treatment protocol described in this study have both fulfilled their objectives during the challenging COVID-19 pandemic. Still, both protocols should be developed further when knowledge about the virus increases, and testing evolves. In the future, dental offices could play an essential role in screening infectious patients and preventing disease spread.

Since the commencement of the COVID-19 pandemic, standard dental care services in Finland are still not running at full capacity and elective dentistry has been postponed. This will present a great challenge in the future, as we play catch up treating patients that have delayed care.

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## Author contributions

M.M. and J.G. contributed equally to collecting data and drafting the manuscript.

J.F. assisted in the analysis of data.

J.H-H., J.U., J.F., H.V., H.R., and K.N. participated in study design, interpretation of data, writing and editing the manuscript.

All authors agreed on the final version of the review to be published and are responsible for all aspects of the work.

## Disclosure statement

Authors declare no conflicts of interest with respect to authorship and/or publication of article.

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