The fungus *Candida albicans* has become a major public health problem in recent years. The myriad of diseases caused by this species varies from vaginal infections, which affect up to 75% of women at least once in their lifetime, to serious infections in hospitalized patients that lead to high morbidity and mortality.¹

*Candida* is a commensal organism that can inhabit the normal flora of the oral cavity of 45% to 65% of healthy infants and 30% to 55% of healthy adults. A large spectrum of local and systemic factors can cause an overgrowth of *Candida* species in the mouth. *C. albicans* is the most common *Candida* species found in both healthy and diseased oral tissues because of its adherence properties and greater level of pathogenicity. *C. albicans* presents in both hyphal and yeast forms depending on the environment. Local factors such as dentures, corticosteroid inhalers, and xerostomia, and systemic causes such as immunocompromised states, HIV; leukemia; malnutrition; aging chemotherapy; radiation therapy; and the use of systemic corticosteroids, immunomodulatory drugs, xerogenic drugs, and broad-spectrum antimicrobials may cause the overgrowth.²

The recent global pandemic of COVID-19 has caused many patients to be affected by acute respiratory distress syndrome (ARDS), which poses a risk of super-infections.³ *Candida* strains are the main cause of invasive fungal infections, with a high mortality rate. Invasive yeast infections (IYIs) have become a...
significant complication in COVID-19. Despite the clear disruption of the immune system in COVID-19, no clear defects have been reported so far in the humeral and cellular immune cells that are required to form immunity against Candida. Therefore, it is assumed that IYIs may be caused by lengthy ICU stays, central venous catheters, and broad-spectrum antibiotic use.1 To date only a few studies have assessed the extent of association between COVID-19 and candidiasis. However, candidiasis is considered to be an immunosuppression marker and of prognostic value for HIV outcome in patients.4,5 In view of the potential role of Candida in the prediction and outcomes of viral infections including COVID-19, it is important for general dental professionals to be familiar with oral and general candidiasis as markers of immunosuppression, especially as they can be the first to diagnose the oral condition. The purpose of the present study was to investigate the frequency of the association between COVID-19 and C albicans, with focus on oral candidiasis and total candidiasis, in a large health center.

Method and materials

The study was pre-approved by the University of Florida (UF) Institutional Review Board (IRB), as no HIPPA (Health Insurance Portability and Accountability Act) identifiers were used. The UF Integrated Data i2b2 provided by the Repository (IDR and UF Health Office of the Chief Data Officer) for the period of June 2011 to September 2020 was used. Diagnoses of COVID-19, oral candidiasis, total candidiasis, and total hospital population by age and sex were searched by using the appropriate International Classification of Diseases (ICD)-9 and ICD-10. The diagnosis of COVID-19 was confirmed by a positive PCR test. The ICD-10 codes do not differentiate the different forms of oral candidiasis, therefore this information could not be provided.

Power analysis

With the assumptions of 24% of the population having total candidiasis and incidence of COVID-19 at 0.4%, a total sample of 16,540 (4,135 in the total candidiasis group and 12,405 in the no total candidiasis group) achieved 80% power to detect a difference between the group COVID-19 incidence of 0.4%. The test statistic used was the two-sided t test. The significance level of the test was .05.

The prevalence ratios were used to compare rates between groups. The Health Office of the Chief Data Officer provided the analytic data set for the project. MEDCLAC software was used to calculate odds ratio (OR) to compare the strength of the association. The 95% confidence interval (CI) and P value for

<table>
<thead>
<tr>
<th>Parameter</th>
<th>COVID-19 and oral candidiasis</th>
<th>Oral candidiasis</th>
<th>COVID-19</th>
<th>Hospital</th>
<th>COVID-19 and total candidiasis</th>
<th>Total candidiasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population (n)</td>
<td>14</td>
<td>10,535</td>
<td>889</td>
<td>1,385,102</td>
<td>106</td>
<td>42,555</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Female</td>
<td>7</td>
<td>5,761</td>
<td>509</td>
<td>742,072</td>
<td>90</td>
<td>32,502</td>
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<tr>
<td>Male</td>
<td>7</td>
<td>4,774</td>
<td>380</td>
<td>643,080</td>
<td>16</td>
<td>10,053</td>
</tr>
<tr>
<td>Female/male ratio</td>
<td>1.00</td>
<td>1.20</td>
<td>1.32</td>
<td>1.15</td>
<td>5.63</td>
<td>3.23</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>6 (42%)</td>
<td>3,390 (32%)</td>
<td>26%</td>
<td>143,350 (10%)</td>
<td>46 (43%)</td>
<td>11,991 (28%)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0%)</td>
<td>1,046 (10%)</td>
<td>3%</td>
<td>564,522 (40%)</td>
<td>12 (11%)</td>
<td>5,486 (13%)</td>
</tr>
<tr>
<td>White</td>
<td>8 (58%)</td>
<td>6,099 (58%)</td>
<td>45%</td>
<td>677,230 (49%)</td>
<td>48 (45%)</td>
<td>25,078 (59%)</td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–9</td>
<td>0 (0%)</td>
<td>3,823 (36%)</td>
<td>5%</td>
<td>115,919 (8%)</td>
<td>0 (0%)</td>
<td>7,559 (18%)</td>
</tr>
<tr>
<td>10–17</td>
<td>0 (0%)</td>
<td>182 (2%)</td>
<td>3%</td>
<td>91,902 (7%)</td>
<td>0 (0%)</td>
<td>911 (2%)</td>
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<tr>
<td>18–34</td>
<td>0 (0%)</td>
<td>790 (7%)</td>
<td>40%</td>
<td>304,262 (22%)</td>
<td>39 (37%)</td>
<td>12,529 (30%)</td>
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<tr>
<td>35–44</td>
<td>3 (21%)</td>
<td>608 (6%)</td>
<td>11%</td>
<td>136,738 (10%)</td>
<td>17 (16%)</td>
<td>4,883 (11%)</td>
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<td>45–54</td>
<td>3 (21%)</td>
<td>747 (7%)</td>
<td>1%</td>
<td>145,462 (11%)</td>
<td>13 (12%)</td>
<td>3,837 (9%)</td>
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<tr>
<td>55–64</td>
<td>3 (21%)</td>
<td>1,330 (13%)</td>
<td>11%</td>
<td>209,016 (15%)</td>
<td>8 (8%)</td>
<td>4,414 (10%)</td>
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<tr>
<td>65–74</td>
<td>5 (36%)</td>
<td>1,475 (14%)</td>
<td>12%</td>
<td>291,754 (21%)</td>
<td>11 (10%)</td>
<td>4,374 (10%)</td>
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<tr>
<td>74–85</td>
<td>0 (0%)</td>
<td>1,580 (15%)</td>
<td>17%</td>
<td>90,049 (7%)</td>
<td>18 (17%)</td>
<td>4,048 (10%)</td>
</tr>
</tbody>
</table>
each OR were tabulated. $P < .05$ was deemed significant. The $P$ value was calculated according to Sheskin. A standard normal deviation (z-value) was calculated as $\ln(\text{OR})/\text{SE}(\ln(\text{OR}))$, where the $P$ value was the area of the normal distribution that fell out side $\pm z$. The age groups were a standard age classification provided by the i2b2 platform based on the WHO classification of eight age groups: 0 to 9, 10 to 17, 18 to 34, 35 to 44, 45 to 54, 55 to 64, 65 to 74, and 75 to 84 years.

### Results

From a total population of 1,385,102, a total of 889 patients were identified with diagnosis of COVID-19; 42,555 were diagnosed with total candidiasis of which 10,535 had oral candidiasis. From the COVID-19 patients, 106 (12%) were diagnosed with total candidiasis and 14 (1.6%) had oral candidiasis. The female/male ratio in the COVID-19 group was 1.32 (1.00 in the COVID-19 and oral candidiasis group, 1.20 in the oral candidiasis group, 3.23 in the total candidiasis group, 5.62 in the COVID-19/candidiasis group, and 1.15 in the general hospital population).

Regarding ethnicity, African American comprised 10% of the hospital population, 43% of the COVID-19/candidiasis group, 42% of the COVID-19/oral candidiasis group, 32% of the oral candidiasis group, 28% of the total candidiasis group, and 25.6% of the COVID-19 group. For age, 36% of the oral candidiasis groups were in the age group 0 to 9 years, compared to 17% of the candidiasis group (Table 1).

The OR for COVID-19 in the presence of oral candidiasis was 2.01 (95% CI 1.1870 to 3.4143, $P = .0094$) (Table 2) and the OR for COVID-19 in the presence of total candidiasis was 3.73 (95% CI 3.0419 to 4.5847, $P < .0001$) (Table 2).

### Discussion

The OR for COVID-19 in the presence of oral candidiasis was 2.00 ($P = .0094$), compared to 3.73 associated with total candidiasis, which was statistically significant ($P < .0001$). Although 11% of the COVID-19 patients had a diagnosis of total candidiasis, only 1.5% were diagnosed with oral candidiasis. These results are reasonable considering that the total candidiasis group includes, in addition to oral, also vaginal, pulmonary, and other mucocutaneous forms of candidiasis. The OR of oral candidiasis in COVID-19 would probably increase with a larger study population. The female to male ratio was much higher in the total candidiasis and COVID-19/candidiasis groups because of the vaginal candidiasis, which is easier to diagnose than oral candidiasis that can be missed by medical professionals not familiar with the different forms of oral presentation of candidiasis.

It is suggested that candidiasis, and oral candidiasis in particular, is an important feature of COVID-19 that is characterized by both T-cell and humoral immunosuppression. However, the present medical database is entered by physicians who use ICD-9 and ICD-10 medical codes and are not always familiar with oral examination and oral diagnosis, often resulting in underestimation of oral diagnoses. These features of candidiasis as a marker of immunosuppression should be brought to the attention of the general dental practitioner, who may be the first to perform a thorough oral examination.
When searching for pertinent literature, only a handful of case reports on oral candidiasis in COVID-19 were found. A case of white plaques on the dorsum of the tongue with pseudo-membranous structures and glossitis in a COVID-19 patient was described. A case was reported of a persistent white plaque on the tongue dorsum that was treated by a physician with intravenous fluconazole and oral nystatin without resolution; however, the presence of Candida was not confirmed.

In 53 COVID-19 patients with oropharyngeal candidiasis with underlying cardiovascular diseases and diabetes, 65 Candida isolates were recovered, with C. albicans being the most common species.

Some investigators argue that since the lymphocytes have a major role in maintaining immune response against microbial invasion, depleted lymphocyte count may be a contributing factor for oral candidiasis in COVID-19 patients. Isolated case reports such as thrush on attached gingiva successfully treated with chlorhexidine and nystatin rinses, and three neonate patients with COVID-19 diagnosis that presented with oral candidiasis were reported. In the latter, the authors claim that this is relevant as no other author has associated these two clinical entities of neonatal COVID-19 infection and candidiasis.

Acute systemic dissemination of Candida species can cause significant morbidity and mortality most notably in immunocompromised hosts. C. albicans-associated candidemias may cause mortality rates higher than 30%. When host defenses are diminished, the biphasic nature of C. albicans allows the organism to switch from a commensal nonpathogenic to pathogenic state by the formation of biofilms. The 3D structures are resistant to high concentrations of antifungal drugs and the fungus may disseminate systemically. In severely immunocompromised patients, oral candidiasis causes candidemia associated with a high mortality rate.

Fungal infections may originate from complications of viral pneumonia, especially in immunocompromised patients, and this may necessitate intensive care and increased mortality. Data regarding bacterial and fungal infections in viral pneumonia led by coronavirus are limited.

Candidemia is responsible for between 30% and 47% of mortality cases in the intensive care unit (ICU). Candida infection was linked to the use of medical devices such as central venous lines, cardiovascular devices, and urinary catheters. Candidemia was shown to be seeding organs, such as the liver, spleen, bones, joints, eyes, and brain.

In COVID-19 critically ill patients in the ICU, mechanical ventilation, parenteral nutrition, broad-spectrum anti-bacterial treatment, indwelling central venous or bladder catheters, older age, morbidities, lymphopenia, corticosteroids, and anticytokine medications are common risk factors that increase mortality from candidemia. However, in a recent study, for patients with candidemia the mortality rate in COVID-19 was lower (12%) than in other at-risk groups of patients.

Finally, the present findings that approximately 40% of the COVID-19/candidiasis groups were of African American ethnicity are compatible with other reports about the high prevalence of COVID-19 in this population.

Conclusion
In conclusion, the present study and others have indicated that both oral candidiasis and total candidiasis are associated with COVID-19 infection. It is not yet clear whether COVID-19 patients have a specific immunologic impairment or if the acute medical setup in ICUs and the wide spectrum of medication and devices used are responsible for the association.

The general dental practitioner should be educated about candidiasis as a surrogate for general health and infectious diseases such as HIV and COVID-19.

Acknowledgment
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Disclosure
The author declares there are no conflicts of interest associated with this manuscript.
References


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