Title: Smell loss is a prognostic factor for lower severity of COVID-19

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Coronavirus disease 2019 (COVID-19) can present with a myriad of symptoms. Guidelines from China, the United Kingdom and Italy had focused screening efforts on patients with fever and cough, excluding anosmia from similar scrutiny. However, screening of individuals with reported anosmia and dysgeusia has been associated with a greater likelihood of a positive COVID-19 result than other indicator of an upper respiratory infection. The relative predictive value of presenting COVID-19 symptoms is under current investigation. This study seeks to ascertain the role of smell loss in risk stratification and predicting COVID-19 patients’ prognosis.

Adult COVID-19 positive patients evaluated at a university medical center between February 1 and April 3, 2020 were identified by an electronic medical records query and included in our initial series. Complete data on demographic variables, clinical characteristics, COVID-19 symptoms, COVID-19 treatments, and clinical evaluations was retrieved. Through a pre-designed screening questionnaire for COVID-19, patients evaluated by telemedicine, in-person, or at the emergency room were asked about their symptoms during the history taking, including whether they had acute smell loss. Patients with incomplete clinical data, or those for whom smell loss was not recorded, were excluded.

The retrieved information included demographics, BMI, comorbid conditions (asthma, allergic rhinitis, chronic rhinosinusitis, eczema, food allergy), pre-existing smell dysfunction, COVID-19 related inflammatory laboratory values (complete blood counts, c-reactive protein, albumin, creatinine, ferritin and erythrocyte subdimension rate), COVID-19 outcomes (need for hospitalization, ICU admission, intubation) and development of acute respiratory disease syndrome. To identify and confirm comorbidities and other clinical variables, all charts were
reviewed by two independent trained researchers and 20% of the charts were randomly checked by the principal investigator. Data points with lack of concordant information were reviewed again by an independent investigator, and if needed excluded from analysis.

SPSS v23 (SPSS, Inc., Chicago, IL, USA) was used for all analyses. Continuous variables’ results are presented in the text as mean ± SD, unless otherwise specified, and were compared using parametric if normally distributed (Student’s t test). The χ² test was performed to analyze the correlation between categorical parameters. Logistic regression was conducted to calculate the odds ratio (OR) of smell loss in association with nominal dependent variables such as pre-existing comorbidities as well as COVID-19 outcome adjusted for possible confounders (demographics and BMI). The adjusted ORs are presented with their 95% confidence intervals (CIs). Analysis of covariance (ANCOVA) was conducted to compare the adjusted means of continuous variables such as laboratory values in association with smell loss, adjusting for demographics and BMI. This research study was approved by the Institutional Review Board.

The initial series consisted of 1013 patients who were evaluated and tested positive for COVID-19. Sufficient data on smell loss, demographic variables, comorbidities, and outcomes was available in 949 patients (93.7%) who were included for analysis. The cohort consisted of 55.2% female patients, with a mean age ± standard deviation (SD) of 48.42±15.67 years. In this series, 54.3% of patients were African-American or Black, 25.0% were non-Latino White, 22.9% were Latino, and 14.3% were identified as other race/ethnicity.

Overall, 198 (20.9%) patients reported smell loss during their initial evaluation for COVID-19. Smell loss was significantly associated with younger age, female gender, and higher BMI. The mean age was 46 versus 49 years in those with and without smell loss, respectively (p=0.02); 64.7% of subjects with smell loss vs 52.8% of those without smell loss were females (p= 0.003);
and mean BMI was 33.6 vs 31.5 in those with and without anosmia, respectively (p=0.001).

There was a significant association between smell loss and history of pre-existing smell dysfunction (OR, 4.66; 95% CI, 2.07-10.46), allergic rhinitis (OR, 1.79; 95% CI, 1.12-2.87), and chronic rhinosinusitis (CRS) (OR, 3.70; 95% CI, 1.29-10.67) compared to patients without smell loss.

Sufficient data on laboratory markers was available for 419 (41.8%) patients. Compared to patients without smell loss, patients with smell loss demonstrated less lymphopenia (the mean ± SD of lymphocyte count was 1.84 ± 3.69 vs 1.11 ± 0.81 in those with and without smell loss, p = 0.001) and higher albumin counts (3.02 ± 0.83 vs 2.77 ± 0.83, p = 0.02). Other laboratory values and inflammatory markers were not associated with smell loss among COVID-19 positive patients. These results did not change after adjusting for demographics and BMI.

Smell loss was also significantly associated with decreased hospitalization (OR, 0.69; 95% CI, 0.47-0.99), ICU admission (OR, 0.38; 95% CI 0.20-0.70), intubation (OR, 0.43; 95% CI, 0.21-0.89), and ARDS (OR, 0.45; 95% CI, 0.23-0.89) after adjustment for demographics and BMI (see Table 1). These results remained significant after further adjustment for allergic rhinitis and CRS.

Our data implicates smell loss as an independent positive prognostic factor of a less severe COVID-19 infection. It was significantly associated with decreased hospitalization, ICU admission, intubation, and ARDS rates compared to the absence of smell loss. In further support, a smaller studies of 169 and 34 COVID-19 positive patients showed an association between anosmia with outpatient care as opposed to hospitalization. Our data aligns with these findings.

Additionally, smell loss was associated with less lymphopenia and higher levels of albumin,
suggesting a less severe reaction to COVID-19 in patients with smell loss compared to those with intact smell.

A history of pre-existing smell dysfunction, allergic rhinitis, or chronic rhinosinusitis (CRS) was associated with greater chance of acute smell loss in patients with COVID-19. However since most patients who experience smell loss in the setting of COVID-19 report return of smell with clinical resolution of illness\(^8\) and an initial neuroimaging study appears to show an absence of acute visible size changes to the neural olfactory system\(^9\), COVID-19 is not associated with permanent anosmia. Positive and negative predictive values could not be calculated because the basal rates of hyposmia and anosmia and the prevalence of COVID infection and each infected subject individual phase of illness are not established for the studied population, but have been examined in further detail elsewhere\(^6\). Female gender, lower age, higher BMI, history of previous smell loss, and pre-existing allergic rhinitis and chronic rhinosinusitis appeared as important predictors of smell loss in the setting of COVID-19 infection. The main limitations of our study were its retrospective nature, subjective nature of smell loss, and focused nature of the data collection, which did not include subjects’ current medications.
References:


Table 1: Preexisting conditions and COVID-19 related outcomes in 949 COVID-19 patients in association with smell loss

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Number of cases with condition among the series</th>
<th>Odds ratio (95% confidence interval) of having smell loss in patients with condition compared to those without the condition</th>
<th>Adjusted p.value ¥</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of past smell dysfunction</td>
<td>27</td>
<td>4.66 (2.07-10.46)</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>101</td>
<td>1.79 (1.12-2.87)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Food allergy</td>
<td>71</td>
<td>1.64 (0.95-2.83)</td>
<td>0.08</td>
</tr>
<tr>
<td>Atopic dermatitis (eczema)</td>
<td>42</td>
<td>1.22 (0.59-2.50)</td>
<td>0.60</td>
</tr>
<tr>
<td>Asthma</td>
<td>243</td>
<td>1.18 (0.82-1.70)</td>
<td>0.36</td>
</tr>
<tr>
<td>Chronic rhinosinusitis</td>
<td>15</td>
<td>3.70 (1.29-10.67)</td>
<td>0.02*</td>
</tr>
<tr>
<td>GERD</td>
<td>60</td>
<td>0.67 (0.29-1.58)</td>
<td>0.36</td>
</tr>
<tr>
<td>Diabetes</td>
<td>243</td>
<td>0.86 (0.57-1.29)</td>
<td>0.46</td>
</tr>
<tr>
<td>Hypertension</td>
<td>391</td>
<td>1.14 (0.77-1.68)</td>
<td>0.52</td>
</tr>
<tr>
<td>Emergency room visit for COVID-19</td>
<td>520</td>
<td>0.83 (0.59-1.16)</td>
<td>0.28</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>311</td>
<td>0.69 (0.47-0.99)</td>
<td>0.04*</td>
</tr>
<tr>
<td>ICU admitted</td>
<td>131</td>
<td>0.38 (0.20-0.70)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Intubated</td>
<td>86</td>
<td>0.43 (0.21-0.89)</td>
<td>0.02*</td>
</tr>
<tr>
<td>ARDS</td>
<td>93</td>
<td>0.45 (0.23-0.89)</td>
<td>0.02*</td>
</tr>
</tbody>
</table>

¥ = Odds ratios and adjusted p.values are calculated by logistic regression adjusting for age, gender and BMI.
*: p.value<0.05
***: p.value<0.001