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# Prognostic Value of Anosmia in SARS-COV-2: A Case Control Study

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## ABSTRACT

Novel coronavirus disease 2019 (COVID-19) has rapidly evolved into a global pandemic and sudden onset of anosmia, has been recognized as a major clinical characteristic of the disease. Metanalysis of 107 studies suggested no objective parameter of severity of COVID-19 with anosmia is established. A study including age and gender matched 101 patients in each group was studied and patients with anosmia has strong association with D-Dimer, IL-6, Ferritin, LDH, Orf1ab gene, CT severity index. Also, better prognosis as compared to non-anosmic covid positive patients as compared to requirement of respiratory assistance. The present study is the first study to attempt to determine cut-offs of elevated levels of Inflammatory biomarkers in the prediction of requirement of respiratory assistance in SARS-CoV2 positive anosmia patients.

***Keywords:*** Anosmia, Covid-19, Inflammatory markers.

## INTRODUCTION

Novel coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an outbreak that emerged in China in December 2019, has rapidly evolved into a global pandemic and has become a persistent global health threat.

Sudden onset of anosmia, ageusia, or dysgeusia has now been recognized as a major clinical characteristic of the disease and has been included in the list of key clinical criteria for case definition of COVID-19 by the European Centre for Disease Prevention and Control as well as other public health surveillance organizations across the world, such as the CDC, the WHO[1] and Public Health England[2].

Recent self-report questionnaire data from many countries highlights an association between sudden onset smell and taste loss and COVID-19 infection, with reported incidences of changes in sensory acuity ranging from 5%-98%[3,4,5] with one study in central India reporting 6.6%[6], potentially suggesting variable geographic presentations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Widespread downregulation of olfactory receptors (ORs) is a key component of their signaling pathway for abrupt sensory deficit[7].

Increased recognition of these olfactory/gustatory symptoms is important for patient management and for timely initiation of isolation precautions to curb the spread of infection. Additionally, earlier detection of the disease may improve the

overall prognosis of the patient by earlier utilization of diagnostic procedures and timely initiation of treatment.

Meta-analysis[8] of 107 studies including 32,142 patients of covid reported various aspects of severity of covid 19 infection. However, presence of anosmia and its correlation with severity and mortality has not been observed in previous studies. Hence, we set out to characterize patients reporting new onset smell disturbance during the COVID-19 pandemic and report on severity and mortality taking into account and integrating multiple clinical laboratory and radiological features.

**Aim:**

To study Prognostic value of Anosmia in SARS-CoV-2.

**Objectives:**

1. To study clinical, pathological and radiological parameters a in COVID 19 patients with and without Anosmia.
2. To study outcome variable in COVID 19 patients with and without Anosmia.

## METHODOLOGY

This prospective case control study was conducted at Sri Aurobindo Medical College and Post Graduate Institute from 1st April 2021 to 31st June 2021. The hospital was the largest designated COVID-19 care center in central India.

Patients with suspected hospitalized covid (n = 5266) were screened in the three months of the study period. During this period, a total of 2396 nasopharyngeal SARS-CoV2 RT-PCR positive patients were recruited in our study. Of them, 101 (4.21%) had anosmia, self-reported symptom of with (cases) and without altered Smell (control) were included in the study. The Participants not willing to participate in the study, Head Injury in past 6 months and history of Neurological Symptom pertaining to Smell/Taste in past were excluded from the study population.

A detailed history of symptoms and pre-existing risk factors was obtained from the patients/ attendants/ previous medical records. The risk factors enquired for included diabetes mellitus, hypertension, prior cerebrovascular events, prior or current cardiovascular events or peripheral arterial disease (PAD), habits like smoking and alcohol consumption. All these patients were evaluated physically by the investigator and were subjected to study population. The patients who were not found to have age and gender matched population with anosmia ($n$ = 2295) were excluded from further analysis (Fig.1).

The study was approved by the institutional ethical committee. The data of the included patients was filled in research-approved proforma with informed consent.

A set of laboratory tests were done in all the patients. The values for all laboratory variables were measured within 24 h of the admission and the cut-off of laboratory variables were according to institutional reference values.

All patients were given similar treatment for SARS-CoV2, as per the governmental advisories and institutional guidelines.

The outcome of all patients in both groups was noted in the form of requirement of respiratory assistance and further death or discharge.

**Definitions used in the study:**

According to protocol for Covid-management: updated version 2.1 – Aiims 3rd may 2021 and Institutional laboratory values –

A) Anosmia was defined as temporary or permanent loss of the ability to detect one or more smells.

B). Clinical criteria for Covid – 19 cases –

| Mild disease | Moderate disease | Severe disease |
|---|---|---|
| upper respiratory tract infections & or fever | any one of: respiratory rate >24/min | any one of: respiratory rate >30/min |
| without shortness of breath or hypoxia | spo2 <93% on room air | spo2 <90% on room air |

C). RT PCR report CT (Cycle threshold) –

| SCORE | VIRAL LOAD |
|---|---|
| 17-24 | High Viral Load |
| 24-35 | Moderate Viral Load |
| >35 | Mild Viral Load |

D) HRCT chest - CT Severity score

Scoring the percentages of each of the five lobes that is involved:
1: <5% involvement
2: 5%-25% involvement
3: 26% - 49% involvement
4: 50% - 75% involvement
5: >75% - involvement

E) CT SEVERITY SCORE

| SCORE | CT SEVERITY |
|---|---|
| <8 | Mild |
| 9 - 15 | Moderate |
| >15 | Severe |

**Data analysis**

The responses obtained were sorted out in the form of an excel sheet, analyzed, and evaluated for fulfilling the objectives. Statistical software, SPSS Trial version 2017 was used for analysis. Both, descriptive and inferential statistics were used. Descriptive statistics were used to depict the main features and characteristics of the collected data. Results on categorical measurements were presented in numbers/percentages. For continuous data, a statistical test for normality – Kolmogorov-Smirnov was applied using SPSS. Results of normally distributed continuous measurements are presented as mean ± standard deviation and that of non-normal data as a median, inter-quartile range (IQR). As and when required, a comparison of proportions (chi-square test) and a comparison of means (independent sample t-test) were performed for data following a normal distribution. The level of significance was set at $p<0.05$.

Cut-off values were determined for the study population and anosmia for laboratory parameters- CRP, D-Dimer, ESR, serum Ferritin, serum LDH, serum IL-6, ORF1 gene from nasal swab, Ct severity and percentage lung involvement. For each of these parameters, the receiver operating characteristic (ROC) curve was drawn to find a possible cut-off to predict the requirement of respiratory assistance by using values of cases and controls. Cut-offs with optimal sensitivity and specificity were chosen as per the optimal criterion, Youden's J statistic, and area under the curve (AUC).

Limits of normative laboratory values were not used as cut-offs in the binary multivariate logistic regression analysis (LRA), as the absolute values of all patients included in both groups (anosmia and control) were significantly deranged in the same direction. This may be explained by the fact that both groups were selected from a cohort of SARS-CoV2 positive hospitalized patients and are known to have abnormalities in the above-mentioned laboratory parameters. Hence, there was a need to determine a cut-off in the deranged range, for the possible requirement of respiratory assistance in both groups. These cut-offs and ROCs are depicted in Fig 2 and table 3.

## RESULTS

Anosmia was found in 101 (4.21%) patients out of total COVID-19 RTPCR positive patients. The percentage of RT-PCR positive confirmed COVID-19 cases was 45.49% (n=2396) out of the total screened (n=5266) suspected COVID-19 patients.

The profile of the study population (Anosmia and Controls) is provided in table 1. The mean age was 48.08 ±12.59 years which was matched in both the groups. The genders were also matched in both groups of which there were 70 males and 31 females in each group. The number of diabetic and hypertensive patients did not differ significantly in both the groups. The mean BMI was 25.22 and 26.76 in anosmia and control group. There was 1 death in anosmia and 8 in control group.

**Figure 1 -**

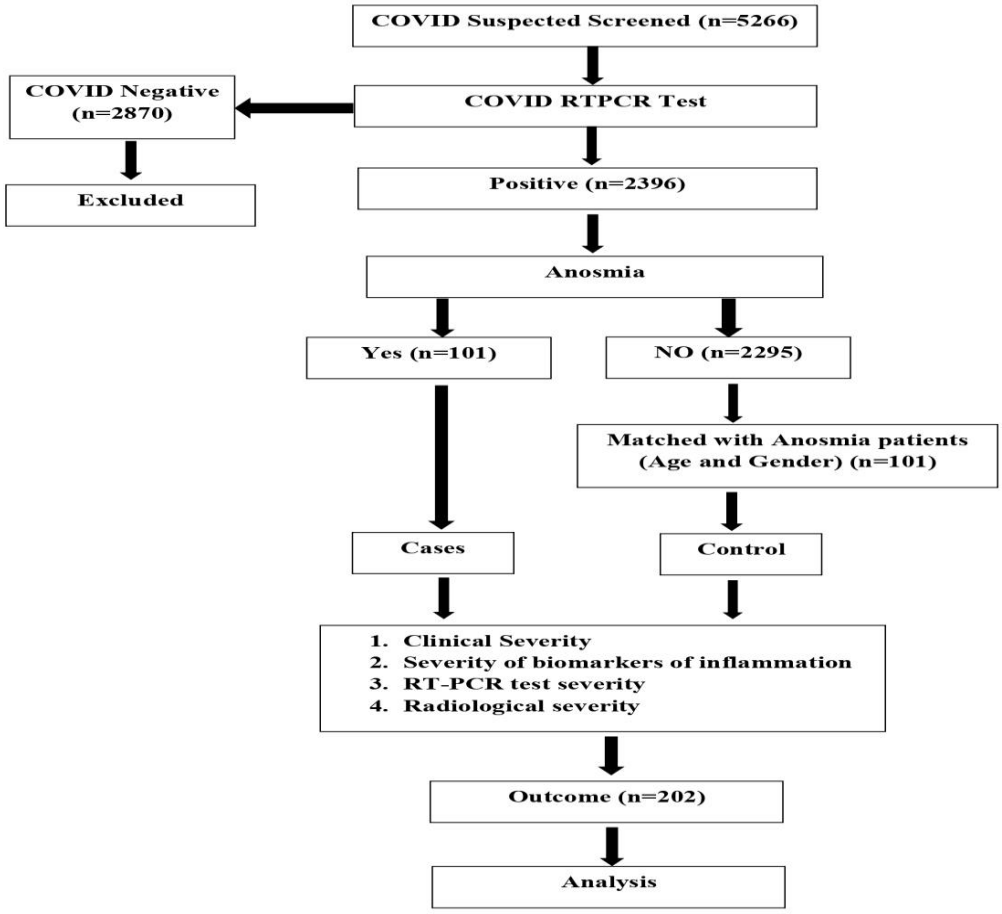


**Table 1: Profile of the study population**

| **Parameter** | | **Anosmia Group (n=101)** | | | **Control Group (n=101)** | | **p-value** |
|---|---|---|---|---|---|---|---|
| Gender | Males | 70 | | | 70 | | Matched |
| | Females | 31 | | | 31 | | |
| Age (in years) | | 48.08±12.59 | | | 48.08±12.59 | | Matched |
| Diabetes Mellitus | | 12 (11.88%) | | | 15 (14.85%) | | >0.05 |
| Hypertension | | 18 (17.82%) | | | 16 (15.84%) | | |
| Clinical Severity | Mild | 19 (18.81%) | | | 17 (16.83%) | | >0.05 |
| | Moderate | 52 (51.48%) | | | 51 (50.49%) | | |
| | Severe | 30 (29.70%) | | | 32 (31.68%) | | >0.05 |
| Outcome | Death | 1 | | | 8 | | <0.05 |
| | Discharge | 100 | | | 93 | | |
| Group | | N | Mean | Std. Deviation | p-value | 95% Confidence Interval of the Difference | 95% Confidence Interval of the Difference |
| Parameter | Sub-Group | | | | | Lower | Upper |
| BMI | case | 101 | 25.22 | 2.512 | .000 | -2.251 | -.838 |
| | control | 101 | 26.76 | 2.577 | | -2.251 | -.838 |
| ESR | case | 101 | 22.30 | 13.450 | .000 | -18.059 | -10.496 |
| | control | 101 | 36.57 | 13.805 | | -18.059 | -10.496 |
| CRP | case | 101 | .9810 | 1.29863 | .088 | -.81638 | .05757 |
| | control | 101 | 1.3604 | 1.80926 | | -.81666 | .05784 |
| IL-6 | case | 101 | 29.16 | 97.933 | .093 | -38.853 | 3.034 |
| | control | 101 | 47.07 | 42.457 | | -38.913 | 3.094 |
| LDH | case | 101 | 321.14 | 135.543 | .000 | -211.003 | -108.799 |
| | control | 101 | 481.04 | 222.395 | | -211.068 | -108.733 |
| Ferritin | case | 101 | 606.69 | 450.625 | .001 | -453.073 | -124.327 |
| | control | 101 | 895.39 | 706.216 | | -453.251 | -124.149 |
| TLC | case | 101 | 8439.21 | 3950.519 | .004 | -3098.043 | -604.333 |
| | control | 101 | 10290.40 | 4977.466 | | -3098.435 | -603.942 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| D-Dimer | case | 101 | 345.17 | 373.212 | .000 | -664.152 | -291.294 |
| | control | 101 | 822.89 | 873.777 | | -664.696 | -290.750 |
| % Lung Involvement | case | 101 | 27.03 | 18.032 | .000 | -35.298 | -24.247 |
| | control | 101 | 56.80 | 21.631 | | -35.299 | -24.246 |
| CT Score | case | 101 | 8.96 | 4.494 | .000 | -8.668 | -6.065 |
| | control | 101 | 16.33 | 4.881 | | -8.668 | -6.064 |
| N Gene | case | 101 | 34.17 | 4.416 | .000 | 5.977 | 8.538 |
| | control | 101 | 26.91 | 4.804 | | 5.977 | 8.538 |
| ORF1-ab Gene | case | 101 | 34.15 | 4.222 | .000 | 5.195 | 7.597 |
| | control | 101 | 27.75 | 4.430 | | 5.195 | 7.597 |

All the suspected covid-19 patients presenting to hospital were tested for RT-PCR on admission and were within 3 days of symptoms onset. On clinical severity (table 1) anosmia and controls were nearly same in both the groups. With mild, moderate and severe anosmia patients were 18.81%, 51.48%, 29.70% and in controls were 16.83%, 50.49%, 31.68% respectively. The results of various laboratory and radiological parameters as summarized in table 2. The average values of inflammatory markers were significantly deranged in both the groups. Compared to controls mean ESR, LDH, Ferritin, TLC, D-Dimer, CT score and percentage lung involvement with N gene and orf1-ab gene had statistically significant difference. The values were less severe in anosmia group as compared to controls.

**Table 2 Profile of patients with and without anosmia**

| **Parameter** | **Cut off values** | **Anosmia** | | | | **Control** | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | **N** | **Required Respiratory Assistance** | **Not Required Respiratory Assistance** | **P-Value** | **N** | **Required Respiratory Assistance** | **Not Required Respiratory Assistance** | **P-Value** |
| BMI | <25 | 61 | 29 | 32 | 0.327 | 18 | 17 | 01 | 0.030 |
| | ≥25 | 40 | 23 | 17 | | 83 | 83 | 00 | |
| CRP | ≤1 | 77 | 36 | 41 | 0.088 | 42 | 41 | 01 | 0.233 |
| | >1 | 24 | 16 | 8 | | 59 | 59 | 00 | |
| D-Dimer | ≤200 | 78 | 35 | 43 | 0.014 | 48 | 47 | 01 | 0.290 |
| | >200 | 23 | 17 | 06 | | 53 | 53 | 00 | |
| ESR | ≤20 | 53 | 26 | 27 | 0.608 | 13 | 12 | 01 | 0.008 |
| | >20 | 48 | 26 | 22 | | 88 | 88 | 00 | |
| Ferritin | ≤291 | 27 | 06 | 21 | 0.000 | 18 | 17 | 01 | 0.030 |
| | >291 | 74 | 46 | 28 | | 83 | 83 | 00 | |
| IL6 | ≤7 | 39 | 10 | 29 | 0.000 | 10 | 09 | 01 | 0.002 |
| | >7 | 62 | 42 | 20 | | 91 | 91 | 00 | |
| LDH | ≤618 | 98 | 49 | 49 | 0.087 | 82 | 81 | 01 | 0.628 |
| | >618 | 03 | 03 | 00 | | 19 | 19 | 00 | |
| TLC | ≤11000 | 85 | 40 | 45 | 0.040 | 64 | 63 | 01 | 0.444 |
| | >11000 | 16 | 12 | 04 | | 37 | 37 | 00 | |
| Lymphocyte | ≤40 | 99 | 52 | 47 | 0.141 | 100 | 99 | 01 | 0.920 |
| | >40 | 02 | 00 | 02 | | 01 | 01 | 00 | |
| Neutrophil | ≤80 | 50 | 21 | 29 | 0.058 | 27 | 26 | 01 | 0.096 |
| | >80 | 51 | 31 | 20 | | 74 | 74 | 00 | |
| RDW | ≤14 | 39 | 18 | 21 | 0.395 | 42 | 41 | 01 | 0.233 |
| | >14 | 62 | 34 | 28 | | 59 | 59 | 00 | |
| ORF1abGene | ≤35 | 71 | 36 | 35 | 0.244 | 67 | 66 | 00 | 0.167 |
| | >35 | 30 | 19 | 11 | | 34 | 34 | 01 | |
| CT_Score | ≤8 | 49 | 02 | 47 | <0.000 | 04 | 03 | 01 | 7.5e-7 |
| | >8 | 52 | 50 | 02 | | 97 | 97 | 00 | |
| Lung_Involvement | ≤5 | 13 | 00 | 13 | 0.000 | 02 | 01 | 01 | 0 |
| | >5 | 88 | 52 | 36 | | 99 | 99 | 00 | |
| O2 requirement | >93 | 54 | 05 | 49 | 0.000 | 05 | 04 | 01 | 0.000 |
| | ≤93 | 47 | 47 | 00 | | 96 | 96 | 00 | |

On comparing both groups with requirement of respiratory assistance with individual parameters within the group, D-dimer, Ferritin, IL-6, CT score, Percentage lung involvement and oxygen requirement was statistically significant in anosmia while ESR, Ferritin, IL-6, CT score, Percentage lung involvement and oxygen requirement had statistically significant values in controls.

As per ROCs, values of CRP >0.6 (AUC 0.663), D-Dimer >200 (AUC 0.680), ESR >19 (AUC 0.695), Ferritin >384 (AUC 0.697), IL-6 >10 (AUC 0.848), LDH >307 (AUC 0.799), ORF1 gene <34 (AUC 0.902), CT severity >8 (AUC 0.991) and percentage lung involvement >26 (AUC 0.975) were found to be strong predictors of requirement of respiratory assistance in both the groups.

**Figure 2 -**

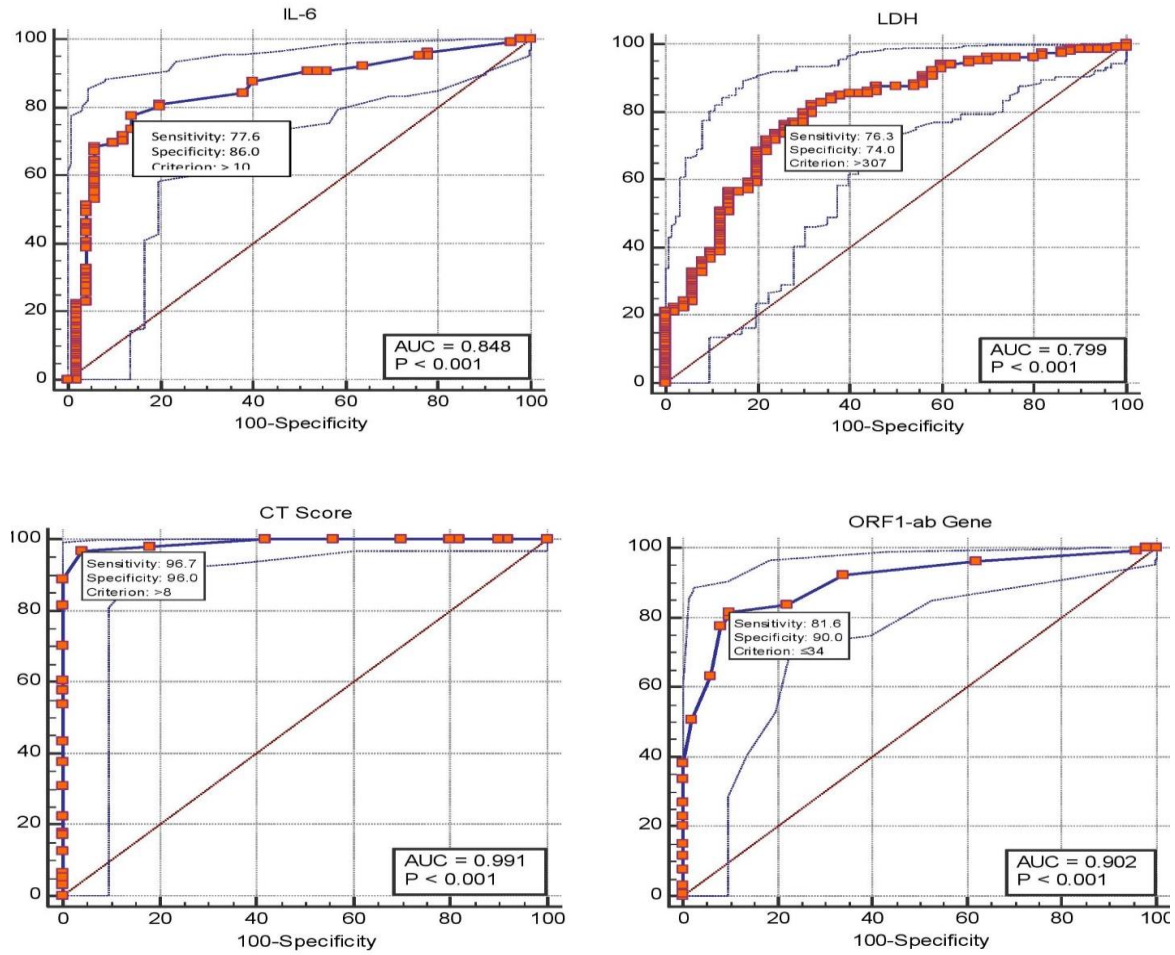


**Table 3: Possible cut-offs for requirement of Respiratory assistance for various parameters (ROC Values)**

| Parameter | Normal Values | Optimal Criteria | Sensitivity | Specificity | Area Under Curve | P - Value | Youden' J Statistic |
|---|---|---|---|---|---|---|---|
| CRP | <1 | >0.6 | 49.3 | 84 | 0.663 | <0.0001 | 0.3334 |
| D-Dimer | <200 | >200 | 46.05 | 88 | 0.680 | <0.0001 | 0.3405 |
| ESR | <20 | >19 | 78.9 | 54 | 0.695 | <0.0001 | 0.3295 |
| Ferritin | <291 | >384 | 76.3 | 58 | 0.697 | <0.0001 | 0.3432 |
| IL-6 | <7 | >10 | 77.63 | 86 | 0.848 | <0.0001 | 0.6363 |
| LDH | <618 | >307 | 76.3 | 74 | 0.799 | <0.0001 | 0.5032 |
| ORF 1 Gene | >35 | <34 | 81.6 | 90 | 0.902 | <0.0001 | 0.7158 |
| CT Severity | <8 | >8 | 96.7 | 96 | 0.991 | <0.0001 | 0.9271 |
| % Lung involvement | <5% | >26 | 88.2 | 98 | 0.975 | <0.0001 | 0.8616 |

A binary multivariate logistic regression model (summarized in Table 4) was used to determine the predictors for the requirement of respiratory assistance in SARS-CoV2 patients. As per the model, the Log Odds Ratio for Prediction of respiratory assistance in a SARS-CoV2 patient was formed (Table 4).

**Table 4: Predictors of Respiratory assistance in SARS-CoV2-a binary logistic regression analysis**

| Parameter | β | S.E. | Wald | df | Sig. | Odds ratio | 95% C.I.for EXP(B) | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Upper | Lower |
| BMI (>26) | 1.587 | 1.022 | 2.413 | 1 | .120 | 4.889 | .660 | 36.207 |
| CRP (>0.6) | -.158 | 1.063 | .022 | 1 | .882 | .854 | .106 | 6.857 |
| ESR (>19) | 2.096 | 1.231 | 2.900 | 1 | .089 | 8.133 | .729 | 90.733 |
| D- dimer (>200) | 1.156 | .553 | 4.364 | 1 | .037 | 3.176 | 1.074 | 9.393 |
| IL6 (>10) | 2.827 | .515 | 30.166 | 1 | .000 | 16.898 | 6.161 | 46.344 |
| Ferritin (>384) | 1.246 | .534 | 5.456 | 1 | .019 | 3.477 | 1.222 | 9.894 |
| LDH (307) | .803 | .507 | 2.502 | 1 | .114 | 2.231 | .825 | 6.032 |
| TLC (>10700) | 1.127 | .666 | 2.860 | 1 | .091 | 3.086 | .836 | 11.395 |
| ORF1abGene (<34) | 3.575 | .544 | 43.152 | 1 | .000 | 35.710 | 12.288 | 103.774 |
| CT Score (>8) | 5.769 | 1.465 | 15.508 | 1 | .000 | 320.298 | 18.135 | 5656.951 |
| Lung Involvement (>26%) | 3.985 | 1.512 | 6.948 | 1 | .008 | 53.773 | 2.778 | 1040.749 |
| Constant | -154.941 | 11431.391 | 0.999 | 1 | 0.989 | | | |

As per the model, the Log Odds Ratio for Prediction of requirement of Ventilatory assistance in SARS-CoV2 patients = -154.941 + (1.587) x BMI {1, if >26 and 0, if ≤26} + (-.158) x CRP {1, if >0.6 and 0, if ≤0.6} + (2.096) x ESR {1, if >19 and 0, if ≤19} + (1.156) x D - dimer {1, if >200 and 0, if ≤200} + (2.827) x IL-6 {1, if >10 and 0, if ≤10} + (1.246) x Ferritin {1, if > 384 and 0, if ≤384} + (.803) x LDH {1, if > 307 and 0, if ≤307} + (1.127) x TLC {1, if >10700 and 0, if ≤10700} + (3.575) x ORF1abGene {1, if <34 and 0, if ≥34} + (5.769) x CT Score {1, if >8 and 0, if ≤8} + (3.985) x Lung Involvement {1, if >26 and 0, if ≤26}

In multivariate analysis (table 4), D-Dimer >200 (Odds ratio = 3.176, 95% CI 1.074 to 9.393) Ferritin >384 (Odds ratio = 3.477, 95% CI 1.222 to 9.894), IL-6 >10 (Odds ratio = 16.898, 95% CI 6.161 to 46.344), ORF1 gene <34 (Odds ratio = 35.170, 95% CI 12.288 to 103.774), CT severity >8 (Odds ratio = 320.298, 95% CI 18.135 to 5656.951) and percentage lung involvement >26 (Odds ratio = 53.773, 95% CI 2.778 to 1040.749).

As per the model (table 4), the Log Odds Ratio for Prediction of requirement of Ventilatory assistance in SARS-CoV2 patients is calculated. This model has an excellent probability of prediction of requirement of ventilatory assistance in SARS – COVID RT-PCR positive patients of 94% (McFadden test).

A binary multivariate logistic regression model (summarized in Table 4) was used to determine the predictors for the requirement of respiratory assistance in Anosmia - SARS-CoV2 patients. As per the model, the Log Odds Ratio for Prediction of respiratory assistance in a SARS-CoV2 patient was formed (Table 5).

**Table 5 Predictors of Respiratory assistance in Anosmia in sars-CoV2-a binary logistic regression analysis**

| Parameter | β | S.E. | Wald | df | Sig. | Odds ratio | 95% C.I.for EXP(B) | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Upper | Lower |
| BMI (>26) | .856 | .470 | 3.312 | 1 | .069 | 2.353 | .936 | 5.913 |
| CRP (>0.6) | .823 | .490 | 2.827 | 1 | .093 | 2.278 | .873 | 5.946 |
| ESR (>19) | .354 | .400 | .786 | 1 | .375 | 1.425 | .651 | 3.121 |
| D- dimer (>200) | 1.247 | .527 | 5.610 | 1 | .018 | 3.481 | 1.240 | 9.771 |
| IL6 (>10) | 2.514 | .504 | 24.875 | 1 | .000 | 12.353 | 4.600 | 33.175 |
| Ferritin (>384) | 1.386 | .431 | 10.338 | 1 | .001 | 4.000 | 1.718 | 9.312 |
| LDH (307) | 1.515 | .436 | 12.073 | 1 | .001 | 4.552 | 1.936 | 10.701 |
| TLC (>10700) | 1.216 | .617 | 3.888 | 1 | .049 | 3.375 | 1.007 | 11.308 |
| ORF1abGene (<34) | 2.890 | .595 | 23.635 | 1 | .000 | 18.000 | 5.613 | 57.722 |
| CT Score (>8) | 6.376 | 1.020 | 39.040 | 1 | .000 | 587.500 | 79.509 | 4341.093 |
| Lung Involvement (>26%) | 5.187 | 1.066 | 23.680 | 1 | .000 | 178.909 | 22.148 | 1445.187 |
| Constant | 138.917 | 27745.885 | 0.999 | 1 | .996 | | | |

As per the model, the Log Odds Ratio for Prediction of requirement of Ventilatory assistance in anosmia - SARS-CoV2 patients = 138.917 + (.856) x BMI {1, if >26 and 0, if ≤26} + (.823) x CRP {1, if >0.6 and 0, if ≤0.6} + (.354) x ESR {1, if >19 and 0, if ≤19} + (1.247) x D - dimer {1, if >200 and 0, if ≤200} + (2.514) x IL-6 {1, if >10 and 0, if ≤10} + (1.386) x Ferritin {1, if > 384 and 0, if ≤384} + (1.515) x LDH {1, if > 307 and 0, if ≤307} + (1.216) x TLC {1, if >10700 and 0, if ≤10700} + (2.890) x ORF1abGene {1, if <34 and 0, if ≥34} + (6.376) x CT Score {1, if >8 and 0, if ≤8} + (5.187) x Lung Involvement {1, if >26 and 0, if ≤26}

In multivariate analysis (table 5), D-Dimer >200 (Odds ratio = 3.481, 95% CI 1.240 to 9.771), Ferritin >384 (Odds ratio = 4.000, 95% CI 1.718 to 9.312), IL-6 (Odds ratio = 12.353, 95% CI 4.600 to 33.175), LDH >307 (Odds ratio = 4.552, 95% CI 1.936 to 10.701), TLC >10700 (Odds ratio = 3.375, 95% CI 1.007 to 11.308), >10, ORF1 gene <34 (Odds ratio = 18.000, 95% CI 5.613 to 57.722), CT severity >8 (Odds ratio = 587.500, 95% CI 79.509 to 4341.093) and percentage lung involvement >26 (Odds ratio =178.909, 95% CI 22.148 to 1445.187).

As per the model (table 5), the Log Odds Ratio for Prediction of requirement of Ventilatory assistance in SARS-CoV2 patients was calculated. This model has an excellent probability of prediction of requirement of ventilatory assistance in anosmia - SARS – COVID RT-PCR positive patients of 100% (McFadden test).

In anosmia group, the outcome was significantly better as compared to controls. In anosmia group there was single death while in controls had 8 deaths (table 1). Also the requirement of respiratory assistance in the anosmia group was significantly less as compared to controls.

## DISCUSSION

Among 202 patients in this study, mean age was 48.08 years and males were 69.30%. While other studies[6,9,10] had the mean age being 50.40 years, Garg et al (49.07±07 years), Wang et al (56.0 years), Chen et al (55.5 years) and Huang et al (49.0 years). Most of the patients having COVID-19 were male (61.54%, 73.10%, 54.3%) which was like that reported by Huang et al and Chen et al and Wang et al. Another study[10] had an average sex ratio being 0.69 in study group.

Number of patients with diabetes was 12 (11.88%) and hypertension 18 (17.82%) in anosmia group while in control was 15 (14.85%) and 16 (15.84%) respectively. The most prevalent co morbidity observed in present study was Diabetes mellitus and Hypertension. While in other study[11] comorbidities was present in 38 per cent (n = 21) of patients in the anosmia group and 29 percent (n = 16) in the comparison group (p = .06). Hypertension and hypothyroidism were the commonest comorbidity in the anosmia group (13% each) where as diabetes mellitus was the commonest in the control group (7%). 49.5% hypertension[12], 19.4% suffer diabetes[12] in covid group. Although pronounced olfactory dysfunction was demonstrated, no meaningful relationships between olfactory function test scores and sex, disease severity, or comorbidities could be demonstrated.

In our study the clinical disease severity of patients enrolled was similar in both the groups. In symptomatic patients, fever and cough were the most common presenting features, followed by shortness of breath, sore throat and headache which is in accordance with other studies[9,10,12].

In our study, Anosmia group had significant differences in inflammatory markers and CT grading with lower mean values of ESR, CRP, Ferritin, LDH, D-Dimer, IL-6 and CT SS, ORF1ab Gene as compared to controls. Previous studies[13,14] laboratory values and inflammatory markers were not associated with smell loss among patients with COVID-19 other then lymphopenia. CRP was significantly raised as compared to D-Dimer, Ferritin in anosmia group in another study.

All the studies[15] highlighted the frequency of dry cough, Respiratory distress, Hypertension, diabetes, anti-inflammatory drugs, lymphopenia and elevated C-reactive protein are incriminated as risk factors for severe disease. In a study[10] CT severity score of asymptomatic radiologically positive patients was found to be correlated with the CT severity score, with mild cases showing score 15/25 in 87.50% patients. K Li et al.[15] have noted a strong correlation between the degree of radiological severity and the clinical severity of symptoms in patients infected with SARS COV-2.

As CT severity index raised, clinical status of patients deteriorated hence this show poor prognostic indicator for COVID-19 patients. Chest CT is useful for triaging

symptomatic patients who may or may not require hospitalization in isolation in the absence of or while awaiting the results of RT-PCR; it is also useful for differential diagnosis, evaluation of severity and search for complications.

Among all the studied patients 152/202 (75.24%) required oxygen, of which 100/152 (65.78%) were cases and 52/152 (34.21%) were anosmia group. Findings suggestive of severity and requirement of oxygen is significantly higher in controls then in anosmia group. In a study[13] Smell loss was also significantly associated with decreased hospitalization (OR, 0.69), intensive care unit admission (OR, 0.38), intubation (OR, 0.43) and acute respiratory distress syndrome (OR, 0.45). In further support, smaller studies[12,13,16] of 169 and 34 patients who received a positive COVID-19 diagnosis found an association between anosmia with outpatient care as opposed to hospitalization. Our data aligns with these findings.

It seems clear that the presence of anosmia would imply a more benign prognosis of the disease. The olfactory system is a unique neuroimmune interface where interaction between nervous and immune systems occurs. This inflammation can induce olfactory sensitive neurons degenerations and apoptosis as a protective mechanism. Because the health of the central nervous system (CNS) is likely to be heavily influence by the immune status of the olfactory system, the reactions should be harmonic, because new olfactory sensory neurons (OSN) may help in the repair of nasal damaged tissue[17]. On the other hand, immune cells in the olfactory mucosa regulate the depletion of old OSN and generation of new OSN, because there could be a lower immune reaction and therefore less epithelial and olfactory cells degeneration. This situation could explain our results that patients with an immune dysfunction could have less olfactory dysfunction and anosmia.

Patients possessing inborn errors in type I IFN-related signaling or neutralizing autoantibodies against type I IFNs are highly susceptible to severe COVID-19 pneumonia. the timing of an all-or-none type I IFN response appears to dictate the severity of disease. the dramatic stimulation of PRRs, especially TLR2, NLRP3, and cGAS-STING, early in infection is sufficient to drive COVID-19 immunopathology in the lungs. The inhibition of these PRRs seems to prevent severe disease in SARS-CoV-2-infected animals[17].

The presence of anosmia is useful in the diagnosis of SARS-CoV-2 infection, but also could be important when in categorize patients and also in therapeutic decision making. The present study is the first study to attempt to determine cut-offs of elevated levels of Inflammatory biomarkers in the prediction of requirement of respiratory assistance in SARS-CoV2 positive anosmia patients.

## CONCLUSION

Anosmia has better prognosis as compared to non-anosmic covid positive patients and has strong association with D-Dimer, IL-6, Ferritin, LDH, Orf1ab gene, CT severity index.

### *Declaration by Authors*

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## REFERENCES

1. Cirillo N. Taste alteration in COVID-19: a rapid review with data synthesis reveals significant geographical differences. Sep. 2020.
2. Public Health England. COVID-19: investigation and initial clinical management of possible cases. Updated October 2,2020.
3. Haehner et al.: Olfactory Loss in the Diagnosis of COVID-19. ORL 2020;82:175–180.
4. Mao L, Wang M, Chen S, Hu Y, Chen S, He Q, et al. Neurological manifestations of

hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 2020 Apr.
5. Hannum M, Ramirez V, Lipson S, Herriman RD, Toskala AK, Lin C, et al. Objective Sensory Testing Methods Reveal a Higher Prevalence of Olfactory Loss in COVID-19-Positive Patients Compared to Subjective Methods: A Systematic Review and Meta-Analysis. Chem Senses 2020 Dec 05;45(9):865-874.
6. Garg et.al. Neurological symptoms as initial manifestation of Covid-19.Ann Indian Acad Neurol.2020. Jul-Aug;23(4):482-486.
7. Zazhytska M, Kodra A, Hoagland DA, Fullard JF, Shayya H, Omer A, Firestein S, Gong Q, Canoll PD, Goldman JE, Roussos P, tenOever BR, Overdevest JB, Lomvardas S. Disruption of nuclear architecture as a cause of COVID-19 induced anosmia. bioRxiv [Preprint]. 2021 Feb 9:2021.02.09.430314.
8. Mutiawati E, Fahriani M, Mamada SS et al. Anosmia and dysgeusia in SARS-CoV-2 infection: incidence and effects on COVID-19 severity and mortality, and the possible pathobiology mechanisms - a systematic review and meta-analysis [version 1; peer review: 2 approved, 1 approved with reservations] F1000Research 2021, 10:40.
9. Gaur A, Meena SK, Bairwa R, Meena D, Nanda R, Sharma SR, Rajawat GS. Clinico-radiological Presentation of COVID-19 Patients at a Tertiary Care Center at Bhilwara Rajasthan, India. J Assoc Physicians India. 2020 Jul;68(7):29-33. PMID: 32602678.
10. Bhandari S, Rankawat G, Bagarhatta M, Singh A, Singh A, Gupta V, Sharma S, Sharma R. Clinico-Radiological Evaluation and Correlation of CT Chest Images with Progress of Disease in COVID-19 Patients. J Assoc Physicians India. 2020 Jul;68(7):34-42. PMID: 32602679.
11. Dev N, Sankar J, Gupta N, et al. COVID-19 with and without anosmia or dysgeusia: A case-control study. J Med Virol. 2021; 93:2499-2504.
12. Porta-Etessam J, Núñez-Gil IJ, González García N, Fernandez-Perez C, Viana-Llamas MC, Eid CM, Romero R, Molina M, Uribarri A, Becerra-Muñoz VM, Aguado MG, Huang J, Rondano E, Cerrato E, Alfonso E, Mejía AFC, Marin F, Roubin SR, Pepe M, Feltes G, Maté P, Cortese B, Buzón L, Mendez JJ, Estrada V. COVID-19 anosmia and gustatory symptoms as a prognosis factor: a subanalysis of the HOPE COVID-19 (Health Outcome Predictive Evaluation for COVID-19) registry. Infection. 2021 Aug;49(4):677-684. doi: 10.1007/s15010-021-01587-9. Epub 2021 Mar 1. PMID: 33646505; PMCID: PMC7917537.
13. Foster KJ, Jauregui E, Tajudeen B, Bishehsari F, Mahdavinia M. Smell loss is a prognostic factor for lower severity of coronavirus disease 2019. Ann Allergy Asthma Immunol. 2020 Oct;125(4):481-483. doi: 10.1016/j.anai.2020.07.023. Epub 2020 Jul 24.
14. Algarf, T.M., Youssef, M.A., Elshazly, M. et al. Radio-laboratory findings in COVID-19 anosmia patients: a single-center experience. Egypt J Otolaryngol 37, 80 (2021). https://doi.org/10.1186/s43163-021-00133-6.
15. Diallo ID, Sekkat A, Traore WM, Bouardi N, Haloua M, Lamrani MY, et al. Clinico-Radiological Correlation in COVID-19 Disease: Experience of the Hassan II University Hospital of Fez. Austin J Radiol. 2022; 9(1): 1184.
16. Saluja M, Pillai D, Jeliya S, Bauddh N, Chandel R. COVID 19- Clinical Profile, Radiological Presentation, Prognostic Predictors, Complications and Outcome: A Perspective from the Indian Subcontinent. J Assoc Physicians India. 2020 Jul;68(7):13-18. PMID: 32602675.
17. Natale, NR, Lukens, JR, Petri, WA. The nervous system during COVID-19: Caught in the crossfire. *Immunol Rev*. 2022; 311: 90-111.

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