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A COMPARATIVE STUDY FOR PROGNOSIS OF ANOSMIA IN COVID-19

Dr. Vishal Gupta[1], Dr. Sujata Agarwal[2]*, Dr. Govind Rankawat[3], Dr. Dileep Wadhwani[4], Dr. Lalit Wadhawan[5]

[1]Associate professor, Department of General medicine, SMS Medical college and attached group of Hospital, Jaipur, Rajasthan, India. Email: drvishalguptamd@rediffmail.com
[2]Associate professor, Department of General medicine, SMS Medical college and attached group of Hospital, Jaipur, Rajasthan, India. Email: sujataagrjp@gmail.com
[3]Senior Resident, Department of General Medicine, SMS medical college and attached group of Hospital, Jaipur, Rajasthan, India. Email: govindrankawat@gmail.com
[4]Principal Specialist, Department of General medicine, SMS Medical college and attached group of Hospital, Jaipur, Rajasthan, India. Email: drdileepwadhwani@gmail.com
[5]Resident, Department of General medicine, SMS Medical college and attached group of Hospital, Jaipur, Rajasthan, India. Email: Drlalitwadhwan@gmail.com
*Corresponding Author

ABSTRACT

Background: Anosmia is common in Coronavirus disease 2019, but its impact on prognosis is unknown. We aimed to analyze whether anosmia predicts in-hospital mortality or disease severity; and if patients with anosmia have a different clinical presentation or inflammatory response.

Methods: This retrospective observational case-control study included a total of 500 admitted patients of COVID-19 at SMS Medical College and attached hospital, Jaipur.190 patients had anosmia while 310 patients were without anosmia at the time of hospitalization. The patient's data concerning demography, clinical profile, underlying medical illness, severity of disease, inflammatory markers, radiological imaging, and outcome were extracted from their medical records. All collected data were tabulated, compiled, analyzed and compared among both groups.

Results: Patients of both groups had matched demographic and underlying chronic medical illness. Patients with anosmia had higher prevalence (35.79%) of mild disease as compared to patients without anosmia (27.42%) with P = 0.0488. Similarly, proportion of severe disease was significantly lower in patients with anosmia (9.47%) as compared to patients without anosmia (27.42%) with P<0.01. COVID-19 related inflammatory markers especially neutrophil-lymphocyte ratio (NLR), CRP, D-dimer, ferritin and IL-6 were found to be significantly lower in patients with anosmia as compared to patients of without anosmia (P<0.05).The average CTSS was found to be lower in patients with anosmia (10.54 ± 4.24) as compared to patients without anosmia (15.61 ± 6.08) with P<0.01.Average duration of hospital stay was found to be 10.18 days in patients with anosmia and it was 15.62 days in patients without anosmia (P<0.01). Patients with anosmia had lesser mortality (0.53%) as compared to the patients without anosmia which had higher mortality (3.23%) with P=0.0455.

Conclusion: The presence of anosmia was an independent predictor of good outcome as reflected by a lower in-hospital mortality rate and lesser duration of hospital stay. In COVID-19 patients with anosmia had early hospitalization, less severe form of disease, least raised

inflammatory markers, least lung involvement and least deterioration as compared to patients without anosmia.

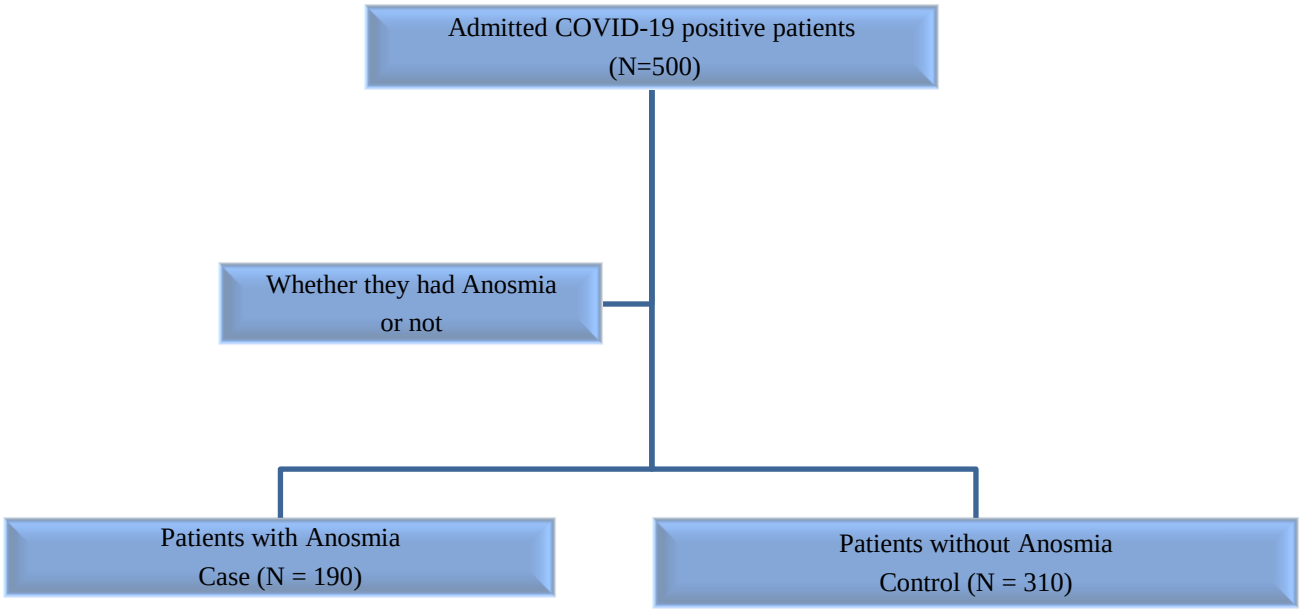
Keywords: Anosmia, COVID-19, Inflammatory markers, disease severity

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a communicable disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). In COVID-19 infection, clinical symptoms of patients are diverse. Patient can be asymptomatic or have severe pneumonia with respiratory distress that requires mechanical ventilation or severe pneumonia that leads to death [1,2]. COVID-19 positive patients mostly presented with fever, cough, shortness of breath, anosmia, ageusia, headache pain abdomen and other systemic symptoms. Anosmia is one of the most characteristic symptoms of Coronavirus disease 2019 (Covid-19) [3], however the pathophysiology of the loss of smell remains unclear [4,5]. In general change in odor is due to inflammatory responses against viral infection, but COVID-19 related anosmia is present without conventional inflammatory or coryzal symptoms [6,7]. The prevalence of anosmia in COVID -19 disease varies greatly from5.1% to 98.3% [8]. It is suggested that anosmia might be related to a milder course, implying a less symptomatic course.[9,10]. The affected population is usually younger and more frequently female.[11]. SARS-CoV-2 virus affects the olfactory system and thus represents neurotropic and neuro-invasive nature of the virus [12,13]. However, the role of anosmia on COVID-19 severity and mortality in hospitalized patients has not been elucidated yet. Therefore, our aim was to evaluate whether the anosmia have favorable prognosis in COVID-19 and to know distinct clinical and laboratory features in patients presented with anosmia.

METHODS

Study Design: The present retrospective observational case-control study was conducted on 500 admitted *COVID-19* positive patients at S.M.S. Medical College and Attached Hospitals, Jaipur, India from 1st April 2021 to 30th June 2021. This study was approved by the Institutional Ethics Committee of our institute. In this study, we include 190 COVID-19 positive patients who had clinical feature of anosmia on admission while 310 COVID-19 positive patients who didn't had clinical feature of anosmia on admission. These patients underwent serial observation to collect data till discharge from hospital.



DATA COLLECTION

COVID-19 were diagnosed based upon World Health Organization interim guidance [14]. The patient information about demographic data, medical history, clinical presentation, laboratory investigations, high-resolution computed tomography (HRCT) scans of the chest, duration of hospital stay, and final outcome was extracted from the medical records for data analysis. We defined anosmia as the partial or complete loss of the sense of smell [15]. We included both hyposmia and anosmia altogether. We categorize these selected patients into two groups based on clinical symptoms of anosmia. Group A have patients presented with anosmia and Group B had patients presented without anosmia. In this study, the severity of COVID-19 patients was decided as per the Indian Council of Medical Research (ICMR) guidelines. Selected patients categorized for severity of disease on admission according to ICMR guidelines. Laboratory tests includes Neutrophil-Lymphocyte ratio (NLR), D-dimer, C-reactive protein (CRP), ferritin and interleukin-6 (IL-6). HRCT chest evaluated for CT severity score. HRCT chest evaluated for CT severity score (*CT Severity Score was assigned out of 25 based on the percentage area involved in each of the 5 lobes*)[16]. Progression of disease after 3 days was determined on the behalf of clinical status of patients and percentage change in oxygen saturation at room air. On the basis of progression of disease all patients were categorized into three groups viz clinical deterioration, same status and clinical improvement. Duration of hospital stays and final outcome were extracted, compiled, and compared among both groups. All Patients were treated according to the national Covid-19 management protocol standard of care (SOC) [17]. Patients who had incomplete medical records, critical at admission and previous nasal pathology were excluded from the study. The data was compiled, tabulated, interpreted, and compared among patients presented with anosmia and without anosmia to detect progression of disease in COVID-19 infection.

STATISTICAL ANALYSIS

Quantitative data was expressed as mean and standard deviation. Qualitative data was expressed as proportions. The parameters were compared among different groups using chi-square test and z-score for significant differences. The level of significance was assigned at p-value less than 0.05. Statistical Package for the Social Sciences (SPSS) was used for statistical analysis.

RESULTS (TABLE 1)

A total of 500 COVID-19 patients were included in this study out of which 190 patients presented with anosmia and 310 patients presented without anosmia. In this study, we try to evaluate prognosis of anosmia in progression of COVID-19 infection. Hence, we select matched control group of COVID-19 infected patients without anosmia, to avoid the influence of variable demographic parameters and other confounding factors. COVID-19 infected patients, selected for the study groups was in the range of 30 to 65 years of age. The mean age of SARS-CoV-2 infected patients with anosmia was 45.34 years (45.34 ± 8.56) while in the control group it was 45.05 years (45.05 ± 8.14) without any statistically significant difference (p=0.7047). Male patients were affected more in both cases as well as the control group (p=0.3575). However, proportion of female was higher in patients with anosmia (48.42%) as compared to without anosmia (42.22%) but difference was not statistically significant. All patients had COVID-19 related clinical symptoms at hospitalization. Duration of illness at hospitalization was found to be higher in patients without anosmia (7.11 ± 1.92 days) while it was lower in patients with anosmia (6.68 ± 1.84 days). All selected patients categorized into mild, moderate and severe COVID-19 disease at the time of admission. Proportion of mild disease was significantly higher in patients with anosmia (35.79%) as compared to patients without anosmia (27.42%) with P = 0.0488. Proportion of severe disease was significantly lower in patients with anosmia (9.47%) as compared to patients without anosmia (27.42%) with

P<0.01.There was no any significant difference observed in underlying chronic medical illness among both groups. As underlying comorbidities like hypertension, diabetes mellitus, cardiac disease and respiratory disease are major confounders for progression and outcome of COVID-19 infection. In this study, there was no any significant difference was observed in underlying comorbidities among both groups.

COVID-19 related inflammatory markersespecially neutrophil-lymphocyte ratio (NLR), CRP, D-dimer, ferritin and IL-6 were found to be significantly lower in patients with anosmia as compared to patients of without anosmia viz. NLR 6.45 ± 1.70 v/s 7.49 ± 1.68 with P<0.01; CRP (mg/L) 28.61 ± 15.50 v/s 40.15 ± 17.91 with P<0.01; D-dimer (µg/mL) 1535.4 ± 918.18 v/s 2081.65 ± 1015.12 with P<0.01; IL-6 (pg/mL) 42.15 ± 31.21 v/s 51.88 ± 37.56 with P=0.0019; Ferritin (ng/mL)415.52 ± 321.54 v/s 568 ± 387.65 with P<0.01for with anosmia and without anosmia respectively. Lung involvement in COVID-19 detected by CT severity score in HRCT chest. The average CTSS was found to be lower in patients with anosmia (10.54 ± 4.24) as compared to patients without anosmia (15.61 ± 6.08) with P<0.01.

Table 1: Demographic, clinical, laboratory and outcome data of COVID-19 infected patients with and without anosmia

Prognosis of Anosmia in COVID-19			
Parameters	**With Anosmia (N=190)**	**Without Anosmia (N=310)**	**P-value**
Age (Years)	45.34 ± 8.56	45.05 ± 8.14	P = 0.7047
Gender			
Male	98 (51.58)	183 (57.78)	Z = 0.9209, P=0.3575
Female	92 (48.42)	137 (42.22)	
Duration of illness (Days)	6.68 ± 1.84	7.11 ± 1.92	0.0139
Severity of disease			
Mild	68 (35.79)	85 (27.42)	Z = 1.9714, P = 0.0488
Moderate	104 (54.74)	140 (45.21)	Z = 2.0792, P = 0.0375
Severe	18 (9.47)	85 (27.42)	Z = 4.816, P < 0.01
Comorbidities	72 (37.89)	135 (43.55)	Z = 1.245, P = 0.2113
Hypertension	42 (22.11)	80 (25.81)	Z = 0.9353, P = 0.3472
Diabetes mellitus	44 (23.16)	92 (29.68)	Z = 1.590, P = 0.1118
Cardiac disease	29 (15.26)	60 (19.35)	Z = 1.161, P = 0.2460
Respiratory disease	31 (16.32)	66 (21.29)	Z = 1.365, P = 0.1706
Laboratory Investigation			
NLR	6.45 ± 1.70	7.49 ± 1.68	P < 0.01
CRP (mg/L)	28.61 ± 15.50	40.15 ± 17.91	P < 0.01
D-DIMER (µg/mL)	1535.4 ± 918.18	2081.65 ± 1015.12	P < 0.01
IL-6 (pg/mL)	42.15 ± 31.21	51.88 ± 37.56	P = 0.0019
Ferritin (ng/mL)	415.52 ± 321.54	568 ± 387.65	P < 0.01
CTSS (out of 25)	10.54 ± 4.24	15.61 ± 6.08	P<0.01
Progression after 3 days			
Deteriorate	18 (9.47)	52 (16.77)	Z = 2.283, P = 0.0226
Same status	70 (36.84)	128 (41.29)	Z = 0.9872, P = 0.3221
Improved	102 (53.68)	130 (41.94)	Z = 2.556, P = 0.0104
Outcome			
Hospital Stay (Days)	10.18 ± 8.75	15.62 ± 9.74	P < 0.01
Live	187 (99.47)	301 (96.77)	Z = 1.9974, P = 0.0455
Death	1 (0.53)	10 (3.23)	

After Hospitalization, patients are treated as per standard of protocol and reassessed on daily basis. Data collected for reassessment on 3rd day of hospitalization to see progression of disease. In follow-up progression on 3rd day, higher proportion of COVID-19 infected patients improved clinically and vitally among groups of patients presented with anosmia (53.68%) as compared to patients presented without anosmia (41.94%) with P=0.0104.Small fraction of patients did not improve and they deteriorated clinically and vitally. Proportion of deterioration was found to be lower in patients presented with anosmia (9.47%) compared to patients presented without anosmia (16.77%) with P=0.0226.Patients presented with anosmia had lesser hospital stay and discharged early with average duration of hospital stay was found to be 10.18 days as compared to 15.62 days in patients without anosmia with P<0.01.Patients with anosmia had lesser mortality (0.53%) as compared to the patients without anosmia which had higher mortality (3.23%) with P=0.0455.

DISCUSSION

Anosmia has been described as one of the characteristic symptoms of COVID-19 infection. It is even considered as a key marker for diagnosis of COVID-19 for the United States Center for Disease Control and Prevention [18]. Despite of having an estimated frequency of up to 52.7% [8], and being a clinical marker of COVID-19, little has been studied about its relationship with COVID-19 prognosis [11]. Some studies have related anosmia to a milder course of COVID-19, describing a relationship between anosmia and an inverse probability of being admitted to hospital [9]. Contrary, other studies have shown no relationship between the presence of olfactory alteration and severity of COVID-19.This study was conducted to know the relationship between anosmia and severity of COVID-19 infection. Based on the progressive follow-up of COVID-19 patients, from the COVID ward and intensive care unit (ICU), our results implicate that anosmia is inversely related with severity of disease.

This is a retrospective case-control observational study that includes an age-matched, gender-matched and underlying chronic medical illness matched control group in order to avoid these confounding factors for severity of COVID-19 infection. However, proportion of female population was found to be higher in patients presented with anosmia as compared to patients without anosmia but this was not statistically significant. The prevalence of anosmia in our inpatient study is 38%, lower than the 52.7% prevalence reported in a recent meta-analysis[8]. However, we include only hospitalized patients of COVID-19 but if severity of COVID-19 is lower in patients of anosmia then hospitalization might be lower and patient may be isolated at home or quarantine center. Other studies done in-hospital population report a 34% frequency, similar to the rate observed in our study [19].In COVID-19 disease anosmia and ageusia gives a major attention to patient for seek to hospitalization, so in this study patients with anosmia had early hospitalization while patients without anosmia had comparatively late hospitalization. Early hospitalization also improves further outcome in patients with anosmia. In this study, we found that more than 90% patients with anosmia had mild or moderate disease while in patients without anosmia more than one fourth of patients had severe disease and only 72% patients had mild or moderate disease. Katharine J. Foster et al. [20] studied that anosmia is an independent positive prognostic factor of less severe COVID-19 infection. Their study proved that anosmia was related with decreased hospitalization, ICU admission, and mechanical ventilation rates compared with the lack of anosmia. Our study also supports that there is less incidence of anosmia in severe form of COVID-19 infection.

In our sample, patients with anosmia had higher level of COVID-19 related inflammatory markers especially neutrophil-lymphocyte ratio (NLR), CRP, D-dimer, ferritin and IL-6 as compared to patients without anosmia. The alteration from most of these parameters has been associated with a worse prognosis and as an indirect measure of systemic inflammatory

response [11,21]. In fact, some authors recommend monitoring these parameters in the management of COVID-19 patients [22]. Consequently, patients with anosmia seem more likely to have a better analytical profile, suggesting that the inflammatory or immune response might be different and probably more benign. Similarly, patients with anosmia were less likely to be admitted to ICU, even though there was no significant difference in the received treatment between the two groups [23]. This finding is in line with other authors results, that described a milder disease course in patients with anosmia [11,22]. We encourage other authors to analyze if the clinical presentation of COVID-19 out-patients with anosmia also differs from those without it. Lung involvement detected by CT severity score in HRCT chest also showed lesser lung infiltrations in patients presented with anosmia.

After Hospitalization, patients are treated as per standard of protocol and reassessed on daily basis. Data collected for reassessment on 3rd day of hospitalization to see progression of disease. In follow-up progression on 3rd day, higher proportion of patients with anosmia was improved clinically and vitally as compared to patients presented without anosmia. Small fraction of patients did not improve and they deteriorated clinically and vitally. Proportion of deterioration was found to be lower in patients presented with anosmia compared to patients presented without anosmia. Patients presented with anosmia had lesser hospital stay and discharged early with average duration of hospital stay was found to be 10.18 days as compared to 15.62 days in patients without anosmia.Similarly, mortality in patients with anosmia is lesser as compared to patients without anosmia. Our study suggests that patients with anosmia had tendencies for early hospitalization, early clinical improvement and early discharge from hospital with high survival rate.

CONCLUSION

In our study, the presence of anosmia was an independent predictor of good outcome as reflected by a lower in-hospital mortality rate and lesser duration of hospital stay. In COVID-19 patients with anosmia had early hospitalization, less severe form of disease, least raised inflammatory markers, least lung involvement and least deterioration as compared to patients without anosmia. COVID-19 infection is associated with chemo-sensitive dysfunction and anosmia may be the only symptom that presents the disease. This could be related to a different clinical presentation that may be associated with a more benign immune and inflammatory response to SARS-COV-2.

Limitation: There are several limitations to this study. Firstly, it is a study conducted in an inpatient population. Likewise, the sample was drawn from a single center in which, the protocols and management may differ from the rest. Secondly, this is a retrospective study in which all the data have been carefully collected and analysed, although some might be incomplete. Thirdly, despite the acute and spontaneous onset of anosmia within the context of the diagnosis of COVID-19, neuroimaging studies were not performed in all the patients with anosmia. Thus, other causes, although infrequent, produced by anosmia could not be excluded, nor could their possible relationship be explained [24]. Fourthly, we did not evaluate the severity of anosmia, nor its duration or characteristics that could play a role in the endpoints.

Ethical approval: This study approved by ethical and research committee of SMS medical college and Hospital, Jaipur, India.

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Availability of data and materials: Available from the corresponding author upon reasonable request.

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