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Original Article

Pathology Section

Analysis of COVID-19 and Mucormycosis Infection in Vaccinated and Unvaccinated Individuals: A Cross-sectional Study

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ABSTRACT

Introduction: Coronavirus Disease-2019 (COVID-19) pandemic unprecedentely led to health crisis in population across the globe. Even though the advent of vaccine has brought the spread of infection under control, shortage in vaccine supply, surge in breakthrough infections and associated mucormycosis in immunosuppressed individuals posed a potential threat.

Aim: To know the incidence and outcome of COVID-19 with superadded mucormycosis in vaccinated and unvaccinated people.

Materials and Methods: The present cross-sectional study undertaken for a period of four months. April to July 2021 in the Department of Respiratory Medicine at Tertiary Care Hospital, New Delhi, India. Hospitalised COVID-19 patients were enrolled in the study. Details of age, gender and co-morbidities were taken into account. In COVID-19 with mucormycosis, glycosylated haemoglobin value and steroid therapy were also noted. Clinical outcome for all the cases were analysed. Statistical analysis of the data collected was done with Statistical Package for the Social Sciences (SPSS) version 20.0 software.

Results: Out of 134 cases, 84 and 50 cases belonged to vaccinated and unvaccinated groups respectively. Isolated COVID-19 infection was noted in 102 cases and COVID-19 with mucormycosis in 32 cases. Diabetes mellitus and steroid therapy showed to be the predisposing factors for development of mucormycosis in COVID-19 cases. High proportion of unvaccinated individuals died due to isolated COVID-19 infection compared to vaccinated individuals and it was found to be statistically significant.

Conclusion: To combat serious threats caused by the COVID-19 pandemic, complete vaccination which offers maximum protection is mandatory.

Keywords: Coronavirus disease-2019, Outcome, Superadded infection, Vaccination

INTRODUCTION

The COVID-19 caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) became a pandemic resulting in loss of human life globally. First incident began at Wuhan city, Hubei province, China in the mid of December 2019 and since then it had rapidly spread across the world [1]. In India, COVID-19 infected millions of people following its first confirmed case on 30th January 2020 in Kerala [2]. World Health Organisation (WHO) imposed a lockdown worldwide in March 2020 with quarantine polices. To combat the pandemic, pharmaceutical companies started to develop vaccines in mid of 2020. In India, Central Drugs and Standard Committee approved Covishield and Covaxin vaccines which was prepared by Serum Institute of India and Bharat Biotect Limited respectively [3]. Vaccination program was initiated on 16th January 2021 targeting frontline healthcare workers and older civilians [4]. Indian government on 1st May 2021 announced vaccination for all people above 18 years of age. Due to vaccine shortage and negligence in social distancing, breakthrough COVID-19 infections began to flare up [5]. In midst of this crisis, accompanying co-morbidities and immunosuppression following steroid treatment for COVID-19, patients became susceptible to mucormycosis [6]. This study aims to know the incidence with the clinical outcome of COVID-19 and concomitant mucormycosis in vaccinated (partial and complete vaccination) and unvaccinated groups.

MATERIALS AND METHODS

This was a cross-sectional study carried out for a period of four months from April-July 2021 in the Department of Respiratory Medicine at Tertiary Care Hospital, New Delhi, India. The study obtained clearance from the Ethical Committee of the Institute with registration number ECR/5/Inst/DL/2013/RR-16. Sample size was accessible population which were 134 in number who were admitted in COVID-19 designated isolated wards of Respiratory Department. The sample size was taken from admission register used for writing down patients' details admitted in the wards.

Inclusion criteria: The study population comprised of 134 symptomatic COVID-19 patients who gave consent and were admitted in COVID-19 designated isolated wards of Respiratory Department and tested positive by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) of nasopharyngeal swab.

Exclusion criteria: Patients who required home isolation were excluded from the study.

Study Procedure

In addition to age and gender, clinical features, pre-existing illness and time interval between vaccination and the manifestations of COVID-19 symptoms were taken into account. People who received first dose of vaccine came under partial vaccination group. Two weeks following second dose of vaccine came under complete vaccination group. Breakthrough infection was infection occurring 14 days after receiving second dose of the vaccine [5]. High Resolution Computed Tomography (HRCT) chest findings was done in COVID-19 cases who presented with fever, cough and dyspnoea. The 25-point severity score was graded as mild (<8), moderate (9-15) and severe (>15). In dual infection of COVID-19 and mucormycosis, Glycated Haemoglobin (HbA1c) value and steroid treatment details was documented. Patients were followed for 30 days to know their clinical outcome.

STATISTICAL ANALYSIS

Data was collected with the help of a proforma and managed in Microsoft Excel. Statistical analysis was done with SPSS version 20.0 software.

RESULTS

In a total of 134 cases, 84 (63%) were vaccinated in which 72 (54%) and 12 (9%) cases came under partial and complete vaccinated groups, respectively. The rest 50 (37%) cases belonged to unvaccinated group. From the total, dual infection of COVID-19 and mucormycosis was

noted in 32 (24%) cases and isolated COVID-19 infection in 102 (76%) cases. The patient's age varied between 20-80 years with a median age of 48 years. Females were 48 (36%) and males were 86 (64%).

In vaccinated group, dual infection was seen in 12 (14.3%) cases in which 10 and two cases received partial and complete vaccination respectively. While only COVID-19 infection was seen in 72/84 (86%) cases in which 62 and 10 cases had partial and complete vaccination respectively. In unvaccinated group, dual infection and only COVID-19 infection was noted in 20/50 (40%) and 30/50 (60%) cases, respectively.

In dual infection category, in vaccinated group [Table/Fig-1] the mean time interval between COVID-19 symptoms and onset of mucormycosis was 19 days while in unvaccinated group [Table/Fig-2] it was 15 days. Clinical severity of COVID-19 patients prior to the occurrence of mucormycosis was mild in 8/32 (25%) cases and moderate in 24/32 (75%) cases. In moderate clinical severity cases a cumulative dose of 520 mg of intravenous methylprednisolone was given. Average duration of steroid therapy was 15 days along with nasal oxygen support. Co-morbidities were seen in 28/32 (87.5%) cases and not present in 4/32 (12.5%) cases. Diabetes mellitus was present in all 28 cases. It was associated with hypertension, coronary artery disease and cirrhosis in 10, four and two cases respectively. Common site for mucormycosis was nose and sinus 30/32 (94%) followed by rhino-sino-orbit 16/32 (50%) and maxillary sinus 2/32 (6.25%). Glycosylated haemoglobin value in all the 32 cases was above 7% [Table/Fig-1,2]. Recovery from dual infection was seen in 26/32 (81.25%) cases. In six cases (6/32,18.75%) who were above 60 years with underlying pre-existing illness and moderate clinical severity died due to COVID-19 pneumonia and multi-organ failure.Of the six cases, two and four belonged to partial vaccinated and unvaccinated groups, respectively.

In COVID-19 infection category, mean time interval between partial and complete vaccination with that of COVID-19 symptoms was found to be 18 days and 32 days, respectively. Common clinical presentation was triad of fever, cough and dyspnoea present in 84 cases. In all these cases HRCT chest showed mild, moderate and severe severity score in 40/84 (48%), 30/84 (36%) and 14/84 (16%) cases, respectively. Combination of fever and sore throat was seen in 16 cases followed by fever and loose stools in two cases.

S. No.	Age (years)	Sex	Vaccine doses	Co-morbidities	It b/w vaccine and C-19 (days)	I b/w C-19 and MU (days)	Site of MU	HbA1c (%)	Outcome
1	48	Male	I	DM	11	22	Left RS	7.8	Re
2	38	Male	I	DM	13	18	Left RSO	11.2	Re
3	61	Male	I	DM,HTN	10	16	Right RSO	11.3	E
4	53	Female	II	DM, HTN	26	21	Right RSO	8.3	Re
5	66	Male	I	DM	10	18	Right RS	10.9	Re
6	26	Female	I	Nil	12	19	Right RSO	7.2	Re
7	64	Male	I	DM,HTN	11	16	Right RSO	11.3	E
8	39	Male	I	DM	19	17	Left RSO	11.2	Re
9	56	Female	II	DM, HTN	28	23	Right RSO	8.3	Re
10	62	Male	I	DM	16	19	Right RS	10.9	Re
11	28	Female	I	Nil	12	22	Right RSO	7.2	Re
12	45	Male	I	DM	14	19	Left RS	7.8	Re

[Table/Fig-1]: Details of dual infection in vaccinated (partial and complete) group.
First: I; Second: II; It: Interval; b/w: Between; COVID: 19: C: 19; MU: Mucormycosis; R: Rhino; S: Sino; O: Orbital; Re: Recovered; E: Expired; DM: Diabetes mellitus; HTN: Hypertension

S. No.	Age (years)	Sex	Co-morbidities	It b/w C-19 and MU (days)	Site of MU	HbA1c (%)	Outcome
1	45	Female	DM	12	Bilateral RSO	7.6	Re
2	48	Male	DM	16	Right M	7.8	Re
3	48	Male	DM, HTN, C	14	Right RSO	10.8	Re
4	21	Male	Nil	15	Bilateral RS	7.1	Re
5	62	Female	DM, HTN	11	Left RS	8.8	Re
6	42	Male	DM	21	Left RS	8.2	Re
7	61	Male	DM, CAD	13	Right RSO	10.2	E
8	72	Female	DM, CAD	12	Bilateral RS	11.8	E
9	58	Male	DM, HTN	17	Left RS	11.3	Re
10	62	Male	DM	17	Right RSO	9.6	Re
11	44	Male	DM	19	Right M	7.8	Re
12	65	Female	DM, HTN	14	Left RS	8.8	Re
13	73	Female	DM, CAD	11	Bilateral RS	11.8	E
14	22	Male	Nil	22	Bilateral RS	7.1	Re
15	47	Female	DM	15	Bilateral RSO	7.6	Re
16	64	Male	DM	18	Right RSO	9.6	Re
17	40	Male	DM	21	Left RS	8.2	Re
18	48	Male	DM, HTN, C	14	Right RSO	10.8	Re
19	55	Male	DM, HTN	12	Left RS	11.3	Re
20	63	Male	DM, CAD	11	Right RSO	10.2	E

[Table/Fig-2]: Details of dual infection in unvaccinated group.
It: Interval; b/w: Between; COVID-19-C-19; MU-Mucormycosis, R-Rhino, S: Sino; O: Orbital; M:Maxillary sinus; Re: Recovered; E: Expired; DM: Diabetes mellitus; HTN: Hypertension; CAD: Coronary artery diseases; C: Cirrhosis

Co-morbidities such as hypertension, diabetes mellitus, pulmonary tuberculosis, bronchial asthma, malignancy and hypothyroidism were present in 76 cases and not seen in 26 cases. Hypertension was present in all 76 cases. It was associated with diabetes mellitus (88 cases), pulmonary tuberculosis (10 cases), bronchial asthma (eight cases), malignancy (six cases) and hypothyroidism (four cases) respectively. Two cases each of chronic kidney and coronary artery diseases were noted. Recovery from COVID-19 was seen in 72/102 (71%) cases. In 30/102 (29%) cases patients died due to pneumonia and multi-organ failure. From this, 12/30 (40%) and 18/30 (60%) cases belonged to partial vaccinated and unvaccinated group respectively.

Complete vaccinated group showed no mortality. In partial vaccinated group, recovery cases were 58/72 (81%) and mortality cases were 14/72 (19%). In unvaccinated group, recovery and mortality cases were 28/50 (56%) and 22/50 (44%), respectively [Table/Fig-3].

Group	Dual infection (Number of cases)		COVID-19 infection (Number of cases)		Total
Outcome	Recovery	Death	Recovery	Death	
Partial Vaccinated	08 (30.8%)	02 (33.3%)	50 (69.4%)	12 (40%)	72 (53.7%)
Complete Vaccinated	02 (7.7)	0	10 (13.9%)	0	12 (9.0%)
Unvaccinated	16 (61.5%)	04 (66.7%)	12 (16.7%)	18 (60%)	50 (37.3%)
Total	26 (100%)	06 (100%)	72 (100%)	30 (100%)	134 (100%)

[Table/Fig-3]: Clinical outcome in vaccinated (partial and complete) and unvaccinated group.

Association between dual infection and outcome was not statistically significant with p-value of 0.815 while that between COVID-19 infection and outcome was statistically significant with p-value of 0.001 [Table/Fig-4,5].

Group	Death	Recovery	Total
Unvaccinated	04 (20%)	16 (80%)	20 (100%)
Vaccinated (partial and complete)	02 (16.7%)	10 (83.3%)	12 (100%)
Total	06 (18.75%)	26 (81.25%)	32 (100%)

[Table/Fig-4]: Association between dual infection and outcome for p-value=0.815.

Group	Death	Recovery	Total
Unvaccinated	18 (60%)	12 (40%)	30 (100%)
Vaccinated (partial and complete)	12 (16.7%)	60 (83.3%)	72 (100%)
Total	30 (29.4%)	72 (70.6%)	102 (100%)

[Table/Fig-5]: Association between COVID-19 infection and outcome for p-value=0.001.

DISCUSSION

The COVID-19 infection had an enormous impact on health of people but also caused social and economic disruption. On 11th March 2020, WHO proclaimed this communicable disease as a pandemic across the world [1]. COVID-19 and SARS-CoV-2 were officially coined by WHO and International Committee on Taxonomy of Viruses respectively on 11th February 2020 [7].

Vaccination campaigns in India commenced on 16th January 2020 and to vaccinate a population of 1.39 billion was a challenge for the government. As stated by the Delhi government on 31st July 2021, Delhi with a population of 1.5 crore above 18 years of age, people who received complete vaccination were less compared to those who were partially vaccinated [8]. In this study, too similar observations were noted. The reason for not being completely vaccinated was due to vaccine shortage [9]. It was also due to COVID-19 infection in people who had taken their first dose and did not follow social distancing norms as observed in present study. There were 50 patients in present study who did not choose to get vaccinated and were scared of the side-effects and complications encountered following vaccination [10]. There is no vaccine which offers 100% protection from any disease leading to breakthrough infections as seen in this study. According to the statement released by Indian Council of Medical Research (ICMR) on 21st April 2021, 2 to 4 per 10,000 got infected with COVID-19 after vaccinations in India [5]. The breakthrough infections may be due to COVID-19 variants bypassing the immunity, lack of social distancing norms and also ability of the vaccinated population to spread the diseases [11]. Symptomatic breakthrough infections seen in present study was 12/84 (14.3%)which was comparable with the study done by Kanika T et al., where it was 15/113 (13.3%) [5]. In another study done by Moriah B et al., breakthrough infection documented was 2.6% which was low compared to present study [12].

In COVID-19 infection category the common clinical symptom was fever followed by cough and dyspnoea in present study which was consistent with Macera M et al., [13]. Sore throat and loose motion seen in present cases were documented in a study done by Kanika T et al., [5]. Mean interval between complete vaccination and onset of COVID-19 symptoms in present study was 32 days which was consistent with the studies done by Kanika T et al., and Moriah B et al., where the mean were 34.8 days and 39 days, respectively [5,12]. Co-morbidities seen in this study were also observed in the study done by Macera M et al., with hypertension being the most common one in both the studies [13]. HRCT chest severity score was mild in most of the cases which correlated with Ghufran AS et al., study [14].

Recently the prevalence of mucormycosis in India was 0.14 per 1000 and was found out to be higher when compared globally which was 0.005 to 1.7 per million population [15]. The use of high dose of steroids with pre-existing illness has increased the susceptibility of opportunistic fungal infection in COVID-19 patients. Singh AK et al., stated 82 cases of mucormycosis in COVID-19 patients were reported from India and present study reported 32 cases [15]. Cases of dual infection were documented in studies done by Patel DJ et al., Sen M et al., and Ravani SA et al., as with this study [6,16,17]. Diabetes mellitus was the common pre-existing illness in dual infection cases along with high HbA1c levels which was consistent with the studies done by Singh AK et al., Sen M et al.,and Ravani SA et al., [15-17]. In unvaccinated group the mean time interval between the COVID-19 symptoms and onset of mucormycosis noted in this study was comparable with that of the Sen M et al., study [16]. High dose of steroids for COVID-19 was a risk factor for the development of mucormycosis which was compatible with the study done by Singh AK et al., [15]. Commonest site was rhino-sinus region which was consistent with Singh AK et al., study [15].

Median age of present study population was 48 years with men being affected more than women. This correlated with the study done by Kanika T et al., Brown CM et al., and Ghufran AS et al., [5,11,14]. In another study, the incidence of COVID-19 infection following first dose of vaccine was comparatively more than following complete vaccination [18]. Similar observation was noted in this study.

In another study, 0 and 0.4% mortality were reported respectively following breakthrough infection which was comparable with the present study in complete vaccination group [19,20]. According to another study, mortality rate was more in unvaccinated group than in those who were partially vaccinated [21].Similar finding was observed in present study also.

Limitation(s)

The limitation in the present study was only hospitalised COVID-19 patients were taken into account because of easy accessibility.

CONCLUSION(S)

The COVID-19 pandemic had shown high mortality rates in unvaccinated group compared to vaccinated group. A surge in mucormycosis in COVID-19 cases was noted with risk factors being diabetes mellitus and steroid therapy. The commonest site of mucormycosis was rhino-sinus region. Hypertension was the common co-morbidity in isolated COVID-19 cases. Incidence of breakthrough infections two weeks following second dose of vaccine was 14.2% and all the patients showed complete recovery. Hence, two doses of COVID-19 vaccine which offers 95% of protection is mandatory along with social distancing norms to combat the serious threats of ongoing COVID-19 infection.

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