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Original Research Article

Seroprevalence of SARS-CoV-2 specific IgG antibodies among eye care workers in South India

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ABSTRACT

Purpose: Health care workers are at higher risk of acquiring the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. This study aims to understand the seroprevalence of anti-SARS-CoV-2 IgG antibody among the eye care workers in South India.

Methods: The participants included eye care workers from the nine eye care centres. All the participants were interviewed with a questionnaire to obtain essential information about socio-demographics, past contact with COVID-19 patients and additional information as recommended by Indian Council of Medical Research, India. Serum samples were tested for anti-SARS-CoV-2 IgG antibodies by ELISA.

Results: A total of 1313 workers were included and 207 (15.8%) were positive for the SARS-CoV-2 IgG antibody. The seropositivity was higher in the moderate risk group (19.5%) followed by low (18.6%) and high risk (13.7%) groups. The seropositivity was significantly higher among i) day scholars compared to hostellers (OR - 2.22, 1.56 to 3.15, \( P < 0.0001 \)), ii) individuals with history of flu-like illness (4.57, 3.08–6.78, \( P < 0.001 \)) or who were symptomatic or in contact with COVID 19 positive cases (2.2, 1.02–4.75, \( P = 0.043 \)) and iii) individuals with history of systemic illness (2.11, 1.39–3.21, \( P < 0.001 \)). Individuals (11.97%) who had no history of contact or any illness were also seropositive.

Conclusions: The effectiveness of the protective measures taken against COVID infection was evident from the lower percentage of seropositivity in the high risk group. The study highlighted the need to create awareness among individuals to follow strict safety measures even in non-work hours and also in social circles.

1. Introduction

The first few cases of COVID-19 in India was reported on 30 January 2020 [1]. Since then, 1,12,44,786 cases with 1,57,930 deaths have been reported in India till March 9th, 2021 (https://www.mygov.in/covid-19/?cbps%2B1). Clinically the spectrum of SARS-CoV-2 infection is varied, from asymptomatic to severe respiratory failure to multiorgan dysfunction syndrome leading to death. Identification and isolation of the affected individuals is mandatory to prevent further spread in the community. This becomes significant when individuals with co-morbid conditions can succumb to the infection. Therefore, understanding the incidence and prevalence of the disease in the community is essential. Laboratory confirmation is based on the analysis of throat and/or nasal swabs by Reverse Transcriptase quantitative – Polymerase chain reaction (RT-qPCR). Since detection of the antigen is transient and it is not possible to carry out RT-qPCR for a population-based study. On the other hand serosurveillance is the best method to measure population exposure to past COVID infections as well as understand existence of protective immunity by specific antibodies.

A recent serosurvey in Iceland indicated the persistence of SARS-CoV-2 antibodies over four months of the study period [2]. This was in contrast to the previous reports on short lived humoral immunity in the

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COVID-19 patients [3]. The national serosurvey in India conducted in early May 2020, 0.73% adults were reported to be exposed [4] which increased to 7.1% during August–September 2020 [5]. Similarly, the serosurveillance by the Greater Chennai Corporation indicated the prevalence of COVID-19 infection among men was 19.3% and 23.7% in September 2020 among women in Chennai [6]. Continuation of such

surveys is essential in the long-term to understand and develop strategies to contain the transmission/pandemic.

Seroprevalence studies are helpful to understand incidence of symptomatic vs asymptomatic infection [7,8]. Serosurveys also help to estimate the total number of infected individuals in the population [4]. Health care workers are at higher risk for acquiring as well transmitting the infection to others because of their constant contact with patients or co-health care workers [9]. Understanding the prevalence among the eye care workers is very much essential since they need to be in close proximity with the patients while examination or triaging, which makes them more susceptible to infection. In addition, most ophthalmic practices have higher volume of patients compared to other practices. As one of the route of spread is through asymptomatic carriers, the volume seen in eye clinics add to increased risk. In this study, a serosurveillance for anti-SARS-CoV-2 specific IgG antibodies was carried out among the 1313 eye care workers working across nine centres of Aravind Eye Care System.

2. Materials and methods

2.1. Definition of study population

This is a cross sectional study conducted among the eye care workers from nine centres of Aravind Eye Care System, South India. This study was reviewed and approved by the Institutional Ethics Committee and adhered to the tenets of the Declaration of Helsinki. Blood samples were collected from a total of 1313 eye care workers who were available during the study (19th August to 28th August 2020). The participants included all employees above 40 years including the leadership team, Medical consultant, mid-level ophthalmic assistants (MLOPs), administrative and support staff who were actively participating in the day-to-day management of the hospital. Among <40 years group, all employee doctors, MLOPs - day scholars (>23 years) and hostellers (2 per room of 6 occupants), laboratory personnel, drivers, cleaners, and employees diagnosed/with symptoms of COVID-19 infection. The individuals were grouped as high, moderate or low risk based on their work location and interaction with the patients irrespective of the departments.

2.2. Questionnaire

Before collection of blood samples, the participants were interviewed with a questionnaire to obtain essential information on various recommended characteristics and history of COVID 19 according to Indian Council of Medical Research, India. The study participants were categorized into six groups such as 1) Symptomatic COVID positive person, 2) Asymptomatic COVID positive person, 3) direct contact of lab confirmed COVID positive person, 4) Symptomatic Influenza like Illness (ILI) person (since 1st April 2020), 5) direct contact of Symptomatic Influenza like Illness (ILI) person, and 6) No history of contact or illness. Apart from those general demographic information, type of PPE used, travel history, previous history of COVID signs and symptom, pre-existing Medical conditions and previous COVID test (RT-qPCR, CT-scan, antibody tests) details if done were also collected.

2.3. Sample collection and storage

From each eye care worker, 5 mL of peripheral venous blood was collected followed by serum separation and storage at –80 °C until further processing.

2.4. Detecting serum IgG against SARS-CoV-2

During the time of this study COVID vaccines were not available and all the participants developed the antibody only through infection. Anti-SARS-CoV-2 Immunoglobulin IgG antibody was detected by ICMR approved Enzyme-Linked Immunosorbent Assay (ELISA) (COVID Kavach™, Zydus Cadila Healthcare Limited, India) kit. Developed

**Table 1**

| s.no | Details | n  | %   |
|------|---------|----|-----|
| 1.   | Total   | 1313| 100.0|
| 2.   | Location |     |      |
| 3.   | Madurai | 457 | 34.8 |
| 4.   | Coimbatore | 314 | 23.9 |
| 5.   | Pondicherry | 203 | 15.5 |
| 6.   | Chennai | 87  | 6.6  |
| 7.   | Tirunelveli | 85  | 6.5  |
| 8.   | Tirunelveli | 51  | 3.9  |
| 9.   | Salem   | 20  | 1.5  |
| 10.  | Thien   | 63  | 4.8  |
| 11.  | Dindigul | 33  | 2.5  |
| 12.  | Female  | 932 | 71.0 |
| 13.  | Male    | 381 | 29.0 |
| 14.  | Age group (years) |     |      |
| 15.  | <20     | 148 | 11.3 |
| 16.  | 21–30   | 365 | 27.8 |
| 17.  | 31–40   | 262 | 20.0 |
| 18.  | 41–50   | 275 | 20.9 |
| 19.  | 51–60   | 164 | 12.5 |
| 20.  | >60     | 99  | 7.5  |
| 21.  | Department |     |      |
| 22.  | Accounts | 16  | 1.2  |
| 23.  | Administration | 171 | 13.0 |
| 24.  | Catering | 14  | 1.1  |
| 25.  | Cleaner | 65  | 5.0  |
| 26.  | Counseling | 51  | 3.9  |
| 27.  | House Keeping | 86  | 6.5  |
| 28.  | Laboratory | 30  | 2.3  |
| 29.  | Maintenance | 75  | 5.7  |
| 30.  | Medical consultant | 138 | 10.5 |
| 31.  | Medical Records | 75  | 5.7  |
| 32.  | Out Patients | 138 | 10.5 |
| 33.  | Operation Theatre | 205 | 15.6 |
| 34.  | Pharmacy | 13  | 1.0  |
| 35.  | Refraction | 42  | 3.2  |
| 36.  | Security | 61  | 4.6  |
| 37.  | Store | 12  | 0.9  |
| 38.  | Transport | 35  | 2.7  |
| 39.  | Ward | 49  | 3.7  |
| 40.  | High | 791 | 60.2 |
| 41.  | Moderate | 226 | 17.2 |
| 42.  | Low | 296 | 22.5 |
| 43.  | Hostel | 467 | 35.6 |
| 44.  | Day scholar | 846 | 64.4 |
| 45.  | COVID associated Total | 162 | 12.3 |
| 46.  | Symptom |     |      |
| 47.  | fever | 87  | 6.6  |
| 48.  | cough | 50  | 3.8  |
| 49.  | Nasal discharge | 36  | 2.7  |
| 50.  | Sore Throat | 58  | 4.4  |
| 51.  | Anosmia or hypogeusia | 22  | 1.7  |
| 52.  | Breathelessness | 8  | 0.6  |
| 53.  | Headache | 36  | 2.7  |
| 54.  | Chest pain | 2  | 0.2  |
| 55.  | Nausea | 4  | 0.3  |
| 56.  | Vomiting | 4  | 0.3  |
| 57.  | Diarrhoea | 8  | 0.6  |
| 58.  | Body ache | 36  | 2.7  |
| 59.  | Fatigue | 12  | 0.9  |
| 60.  | Total | 132 | 10.1 |
| 61.  | Lang disease | 12  | 0.9  |
| 62.  | Liver disease | 2  | 0.2  |
| 63.  | Diabetes | 87  | 6.6  |
| 64.  | Hypertension | 42  | 3.2  |
| 65.  | Renal disease | 1  | 0.1  |
| 66.  | Malignancy | 2  | 0.2  |
| 67.  | Heart disease | 11  | 0.8  |

*one individual may have more than one associated symptom or illness.*
indigenously by ICMR-NIV, Pune this kit is reported to have a sensitivity of 92.1% and specificity of 99.7%. The serum samples were incubated at 56°C for 30 min and diluted 1:100 in dilution buffer. The tests were performed as per the manufacturer’s instructions and final OD at 450 nm was measured in Spectra max M3 micro plate reader (Molecular Devices, USA).

### 2.5. Statistical analysis

The data collected using the Google form was downloaded as Microsoft excel sheets and the data were checked and validated. For all the data, Mean (SD) and frequency (percentages) were calculated, univariate logistic regression analysis with odds ratio (95% confidence

| Table 2 | SARS-CoV-2 IgG antibody prevalence for different sociodemographic characteristics. |
|---------|---------------------------------------------------------------|
| S. no   | Details                                                                 | Positive % | Negative % | Total  |
| 1.      | Total                                                                 | 207        | 1106       | 1313   |
| 2. Age group | <20                                           | 16         | 132        | 148    |
| 3.      | 21–30                                          | 39         | 326        | 365    |
| 4.      | 31–40                                          | 46         | 216        | 262    |
| 5.      | 41–50                                          | 63         | 212        | 275    |
| 6.      | 51–60                                          | 30         | 134        | 164    |
| 7.      | >60                                            | 13         | 86         | 99     |
| 8. Gender | Female                                         | 150        | 782        | 932    |
| 9.      | Male                                           | 57         | 324        | 381    |
| 10. Departments | Accounts                                     | 2         | 14         | 16     |
| 11.     | Administration                                 | 39        | 132        | 172    |
| 12.     | Catering                                       | 4         | 10         | 14     |
| 13.     | Cleaner                                        | 7         | 58         | 65     |
| 14.     | Counseling                                     | 11        | 40         | 51     |
| 15.     | House Keeping                                  | 14        | 72         | 86     |
| 16.     | Laboratory                                     | 4         | 26         | 30     |
| 17.     | Maintenance                                    | 13        | 62         | 75     |
| 18.     | Medical consultant                             | 9         | 129        | 138    |
| 19.     | Medical Records                                | 16        | 59         | 75     |
| 20.     | Out Patients                                   | 19        | 119        | 138    |
| 21.     | Optical                                        | 7         | 30         | 37     |
| 22.     | Operation Theatre                              | 27        | 178        | 205    |
| 23.     | Pharmacy                                       | 4         | 9          | 13     |
| 24.     | Refraction                                     | 5         | 37         | 42     |
| 25.     | Security                                       | 9         | 52         | 61     |
| 26.     | Store                                          | 2         | 10         | 12     |
| 27.     | Transport                                      | 9         | 26         | 35     |
| 28.     | Ward                                           | 6         | 43         | 49     |
| 29.     | Risk based on patient contact                  | 108       | 683        | 791    |
| 30.     | Moderate                                       | 44        | 182        | 226    |
| 31.     | Low                                            | 55        | 241        | 296    |
| 32. Place of stay | Hostel                                    | 45        | 422        | 467    |
| 33.     | Day scholar                                    | 162       | 684        | 846    |
| 34. COVID-19 Category | 1: Symptomatic COVID positive person       | 6         | 85.71      | 14.29  |
| 35.     | 2: Asymptomatic COVID positive person         | 2         | 100.00     | 0.00   |
| 36.     | 3: Asymptomatic direct contact of lab confirmed COVID positive person | 9 | 23.08 | 76.92 |
| 37.     | 4: Symptomatic Influenza like Illness (ILI) person | 51 | 38.35 | 61.65 |
| 38.     | 5: Asymptomatic direct contact of Symptomatic Influenza like Illness (ILI) person | 7 | 24.14 | 75.86 |
| 39.     | 6: Asymptomatic Non-COVID person               | 132       | 971        | 1103   |
| 40.     | Past Travel history                            | 12        | 61         | 73     |
| 41.     | COVID associated Symptoms*                     | 70        | 92         | 162    |
| 42.     | Fever                                          | 43        | 44         | 87     |
| 43.     | Cough                                          | 22        | 28         | 50     |
| 44.     | Nasal discharge                                | 15        | 21         | 36     |
| 45.     | Sore throat                                    | 18        | 40         | 58     |
| 46.     | Anosmia or hyposxia                            | 16        | 6          | 27     |
| 47.     | Breathlessness                                 | 5         | 3          | 8      |
| 48.     | Headache                                       | 18        | 18         | 36     |
| 49.     | Chest pain                                     | 1         | 0          | 2      |
| 50.     | Nausea                                         | 2         | 0          | 4      |
| 51.     | Vomiting                                       | 2         | 0          | 4      |
| 52.     | Diarrhoea                                      | 4         | 4          | 8      |
| 53.     | Body ache                                      | 17        | 19         | 36     |
| 54.     | Fatigue                                        | 6         | 6          | 12     |
| 55.     | Systemic illness*                              | 35        | 97         | 132    |
| 56.     | Lung disease                                   | 2         | 10         | 12     |
| 57.     | Liver disease                                  | 1         | 1          | 2      |
| 58.     | Diabetes                                       | 25        | 62         | 87     |
| 59.     | Hypertension                                   | 10        | 32         | 42     |
| 60.     | Renal disease                                  | 1         | 0          | 1      |
| 61.     | Malignancy                                      | 0         | 2          | 2      |
| 62.     | Heart disease                                  | 5         | 6          | 11     |
| 63.     | Hospitalized for COVID-19                      | 16        | 15         | 31     |

* one individual may have more than one associated symptom or illness.
interval) was performed for risk assessment using STATA 14. P value less than 0.05 consider as statistically significant.

3. Results

3.1. Social demographic features

The mean age of the study population was 37.5 ± 14.7 years (age range 18–87 years). Among the 1313 participants, 381 (29%) were males and 932 (71%) were females with mean age of 50.3 ± 12.5 years and 32.3 ± 12.1 years respectively. The highest number of individuals 365 (27.8%) were in the age group 21–30 years followed by 262 (20.0%) in 31–40 years, 275 (20.9%) in 41–50 years, 164 (12.5%) in 51–60 years, 148 (11.3%) in <20 years and 99 (7.5%) in >60 years. The majority of the participants were staff in the operation theatre (number, percentage: 205, 15.6%), outpatient department (138, 10.5%), administration department (171, 13.0%) and medical consultants (138, 10.5%).

3.2. Risk categorisation

Majority of the staff (791, 60.2%) belonged to the high risk group comprising the medical consultants, outpatient and operation theatre staff. The moderate risk group (226, 17.2%) included the individuals from housekeeping, security, transportation, administration, out-patient (triaging of patients and investigations) and optical (Sales). The low risk group (296, 22.5%) includes staff (not in contact with patients) from administration, maintenance, cleaners, out-patient department, catering, accounts, optical technicians (manufacturing) and stores. The detailed demographics were summarized in Table 1.

3.3. Seroprevalence of SARS-CoV-2 IgG among eye care workers

Among the 1313 eye care workers from nine centres, 207 (15.8%) individuals were found to be positive for the SARS-CoV-2 IgG antibody. Table 2 summarize the prevalence of SARS-CoV-2 IgG antibody among different socio demographic characteristics. The highest positive prevalence was observed at Theni 47.6% (30/63), followed by Tirunelveli 28.3% (24/85), Madurai 24.3% (111/457), Chennai 16.1% (14/87) and Tirupathi 11.8% (6/51). A low prevalence of less than 10% was observed in centres at Dindigul 9.1% (3/33), Pondicherry 4.4% (9/203), Coimbatore 2.9% (9/314) and Salem 5% (1/20) (Fig. 1). The highest seroprevalence of 22.9% was observed in the age group of 41–50 years followed by 18.3% among 51–60 years, 17.6% in 31–40 and 13.1% among >60 years individuals (Fig. 2A).There was no difference in the prevalence among the female (16.1%) and male (15.0%) staff. In terms of department, the highest prevalence was seen among the pharmacy staff (30.8%), followed by staff from the catering (28.6%), transport (25.7%), administration (22.8%) and counseling (21.6%) (Fig. 2B).The prevalence based on the patient contacts risk category indicated that the majority of seropositive individuals belonged to the moderate risk group (19.5%), followed by low risk (18.6%) and high risks (13.7%) (Fig. 3A). Among the high risk category, seropositivity was highest among the operation theatre and medical record department staff (Fig. 3B); housekeeping and security in moderate risk group (Fig. 3C); and administration and maintenance department in the low risk category (Fig. 3D). A higher seropositivity was seen among the day scholars (19.1%) compared to the hostellers (9.6%) with significant odds ratio of 2.22 (1.56–3.15) with P < 0.0001 (Supplementary Table 1).

A seroprevalence of 23.08% and 24.14% was observed in the individuals either in contact with COVID positive (category 3) or flu like symptoms (category 5) respectively. In addition, 11.97% individuals who had no previous contact history or illness (category 6) were positive for SARS-CoV-2 antibody. A higher positivity of was observed among symptomatic individuals diagnosed with flu like illness38.35% (category 4). Further, among the nine laboratory confirmed COVID positive individuals (category 1 and 2), eight (88.8%) were found to be positive for the antibody by ELISA including two who were asymptomatic (category 2). One of the COVID positive who didn’t have antibodies was an asymptomatic COVID detected as part of the contact tracing. Compared to the normal individuals (category 6), the seropositivity was significantly higher in individuals who were symptomatic or were in contact.
with COVID positive cases. Among the individuals with history of systemic illness (lung disease, liver disease, diabetes, hyper tension, renal disease, malignancy and heart disease), 26.5% were seropositive with 2.11 (1.39–3.21) fold increased risk with P < 0.001 (Supplementary Table 1).

4. Discussion

This is, to our knowledge, the first study reporting seroprevalence of antibodies against SARS-CoV-2 among a representative group of eye care workers in a COVID-19 high burden country. This study also represents all the eye care workers including the cleaners, laboratory technicians, administrative staff and security staff who have not been included in the reports on health care workers so far. The state government initiated the lock down from 24th March 2020 followed by relaxation for essential travels later from 16th July 2020. Aravind Eye care systems were functional during the lock down period with limited staff on rotational basis. Further analysis indicated that among the seropositive individuals, there is an increased mortality in doctors and health care workers [12]. Recent studies showed the prevalence of SARS-CoV-2 antibodies among the health care workers 6.4% in Belgium [13] and 13.7% in New York [14].

The report by Indian Council of Medical Research, New Delhi showed the low (0.78%) prevalence of SARS-COV-2 antibody in mid May 2020 [4] which increased to 7.1% during August to September 2020 among adult population in India [15]. In Tamil Nadu, the total PCR COVID confirmed cases were 8,55,121 with 12,518 deaths till March 9th, 2021 (https://www.mygov.in/covid-19/?cbps%C2%BC1). In this study, 15.8% of eye care workers tested positive for COVID-19 IgG antibodies (highest 47.6% in Theni and lowest 2.9% in Coimbatore). The seroprevalence among Chennai staff was 16.1%, similar to that reported by the Greater Chennai Corporation Study [6]. Another report by ICMR in September identified an increase in seropositivity to 33.4% in Chennai and 7.2% (from 2.5% in May 2020) in Coimbatore [16]. These reports highlight the increasing trend in the number of individuals exposed to COVID-19 infection in the population.

A high prevalence of SARS-CoV-2 seropositivity was observed among eye care workers who were working in areas with moderate risk of acquiring the infection. This group includes eye care workers from housekeeping, catering, medical records, optical, pharmacy and drivers. This moderate category of eye care workers may come in direct contact with patients and may work closely with them, but with minimal contact time during their stay in the hospital. No significant correlation of seropositivity was observed among these risk groups. The lower seroprevalence among the higher risk groups might be due to the fact that they mostly comprised of the medical professionals who were always in full personal protection and well aware of the risks especially while taking care of patients as well as in other social settings, which may be lacking in other groups.

Further analysis indicated that among the seropositive individuals, day scholars had higher seropositivity across all risk categories (68.5% in high risk group, 87.3% in moderate risk group and 90.9% in low risk group). This was further confirmed by the significant correlation of seropositivity compared with the hostelers categorized in moderate and high risk group. The day scholars commuted to the centres using their own mode of transports due to the non-availability of public transportation at that time. Hence, the exposure to SARS-CoV-2 may be purely due to the spread through their social circles. The highest seroprevalence identified among the non-medical eye care workers including cleaners, catering and administrative staff might be due to the lack of knowledge, as well their constant mobility and contact with many person outside the health care setup. The risk of SARS-CoV-2 infection in the ancillary healthcare workers has not been documented so far.

The major concern of the SARS-CoV-2 infection is that a significant proportion of infected individuals never develop any noticeable symptoms yet they carry the virus and also transmit it [17]. In our study population, 11.97% of asymptomatic eye care workers were identified to be positive for SARS-CoV-2 IgG antibodies. The presence of SARS-CoV-2 antibodies reported has been reported to be higher among COVID positive cases as well as those with COVID-19 symptoms [5,18,19]. In concordance the seropositivity was significantly higher among individuals with COVID associated symptoms. The association of high incidence and severity of COVID-19 was reported in individuals with
various systemic illnesses including diabetes, hypertension or other respiratory illness [20]. Similarly, in this study individuals with any systemic illness had higher seropositivity compared to the healthy individuals.

5. Conclusions

The prevalence of SARS-CoV-2 infection will persist in the community for longer period and it is essential to evaluate and understand its community prevalence. This study provides insight about the seroprevalence among the eye care workers and thus highlights the level of risk amongst the eye care workers. The major concern for the spread of SARS-CoV-2 is through asymptomatic carriers. Hence the high patient volume and close proximity working environment add to increased risk for the eye care workers. The significant higher seropositivity among day scholars across all risk groups highlights the fact that transmission through the social circle may be more significant than work setting, wherein the protective measures were followed. Hence the awareness needs to be created that it is equally important to follow strict safety measures like wearing face masks, frequent hand washing and maintaining physical distancing in non-work hours, especially in social circles. Limitation of the study is that, only the staff available during the time of sample collection was included. Additional longitudinal studies with more representative number of eye care worker are required for better understanding the seroprevalence and also to evaluate the persistence of antibodies upon SARS-CoV-2 infection. Similar studies are required to monitoring the communal prevalence and help in taking precaution for safety of both patients and health care workers.

CRediT authorship contribution statement

Rajapandian Siva Ganessa Karthikeyan: Conceptualization, Methodology, Validation, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Mr. Gunasekaran Rameshkumar: Conceptualization, Methodology, Validation, Investigation, Data curation, Writing – review & editing, Visualization, Dr. Chidambaranathan Gowri Priya: Conceptualization, Validation, Data curation, Writing – review & editing, Visualization, Dr. Prajna Lalitha: Conceptualization, Validation, Resources, Writing – review & editing, Supervision, Project administration, Ms. Ramamoorthi Devi: Validation, Data curation, Visualization, Mrs. Mani Iswarya: Validation, Data curation, Visualization, Dr. Ravilla D. Ravindran: Conceptualization, Resources, Writing – review & editing, Supervision, Project administration.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijmmb.2021.06.014.

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