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Original Article

Internal Medicine Section

SARS-CoV-2 Antibody Response in Patients with Co-morbidities in Kashmir's Ethnic Population: An Observational Cohort Study

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ABSTRACT

Introduction: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection risks in co-morbid patients are still unknown two years after the pandemic began. The prevalence of antibodies against SARS-CoV-2 infection is crucial for determining disease preventive and mitigation strategies. Obesity, type 2 diabetes, and chronic cardiovascular disease can raise the risk of Coronavirus Disease-2019 (COVID-19), which has a greater morbidity and fatality rate.

Aim: To determine the seroprevalence of SARS-CoV-2 (COVID-19) antibodies and their relationship to co-morbidities in Kashmir's ethnic population.

Materials and Methods: The present observational cohort study was done in the Department of Pulmonary Medicine at Chest Disease Hospital Srinagar, Jammu and Kashmir, India, from September 2020 to September 2021 and 1,846 co-morbid unvaccinated patients were chosen for the study. As per standard methodology, a cohort study was undertaken, a questionnaire was prepared, and demographic and associated parameters were recorded. All participants had their immune profiles tested, and the existence of Immunoglobulin G (IgG) antibodies for SARS-CoV-2 was determined using the chemiluminisence immunoassay technique. Chi-square and Fischers-exact test were used for stastical analyses and p-value <0.05 were taken as statistically significant.

Results: As per the present study estimates, demographic and socio-economic characteristic affected test attendants. The SARS-CoV-2 IgG antibody response among co-morbid patients were found to be 54.3%. The hypertension and diabetes were most prevalent co-morbidity found in the individuals (p<0.001).

Conclusion: Co-morbidities including hypertension and diabetes in an individual are more likely to have COVID-19 which can lead to death. COVID-appropriate conduct is required to limit infection transmission in the community, and immunisation is of paramount importance for all individuals. More research is needed to determine the risk of co-morbidities among Kashmir's ethnic community.

Keywords: Coronavirus disease-2019, Immunisation, Severe acute respiratory syndrome coronavirus 2, Vaccination

INTRODUCTION

SARS-CoV-2 or COVID-19 infectious disease causes severe and lethal symptoms, including flu-like symptoms, and fever. According to hundreds of clinical investigations, over 80% of cases have minor symptoms, whereas about 5% of cases, mostly older patients and those with co-existing diseases, develop serious symptoms such as severe respiratory distress syndrome and thromboembolism [1,2].

Due to the lack of identifiable COVID-19 symptoms, with the exception of Olfactory or Taste Dysfunction (OTD) [3,4], diagnoses were first based mainly on Real Time Polymerase Chain reaction (RT-PCR) testing to detect SARS-CoV-2 RNAs [5]. However, due to sample difficulties and the virus's rapid genomic change, the sensitivity and specificity were not sufficient [6,7]. Samples from the lower airway tract are required for reliable diagnosis, as described in prior SARS pandemic cases. In addition, for the initial PCR tests, the sequences of PCR amplicons were not unique, because the target sequences were the same as those of SARS, MERS, and other types of coronaviruses [8]. Several investigations revealed that the sensitivity of PCR tests was 60% [9,10]. This is particularly worrisome for those at high risk, such as the elderly and immune-compromised patients, because many asymptomatic patients with negative PCR testing can unknowingly transfer infection. The health officials began a massive case-finding and contact-tracing operation. The detection of cases was based on RT-PCR testing of nasopharyngeal samples.

Seroprevalence studies can estimate the percentage of the population that has produced antibodies to SARS-CoV-2, indicating current infection with the virus. It is possible to detect mild and asymptomatic infections that have not been subjected to RT-PCR testing. Furthermore, seroprevalence studies provide an estimate of the fraction of the population still vulnerable to infection, presuming antibodies confer partial or total immunity. Serological estimation of IgG antibodies are being researched throughout the communities in order to gain a complete picture of previous SARS-CoV-2 exposure in susceptible populations. It has been reported that SARS-CoV-2 has a five-day incubation period, with IgM antibodies appearing in 5-10 days and IgG antibodies appearing in roughly 10 days following symptom onset, with greater titers in severe cases than in mild cases [11,12]. The real temporal course of antibody titres on the other hand, is still unknown.

During COVID-19, the immune system plays a critical role, and immunological dysfunction is linked to disease severity. COVID-19 patients with severe lymphopenia and an overactive innate immune response that results in hyperinflammation are linked [13]. Many COVID-19-related co-morbidities have an impact on immune system function, which has a direct impact on COVID-19 responsiveness. Furthermore, the plethora of medicines recommended to manage these co-morbidities will influence COVID-19 progression and limit new COVID-19 therapeutic options. As the COVID-19 pandemic spreads, epidemiological evidence suggests that obesity, type 2 diabetes, and chronic cardiovascular disease can worsen the disease's severity, resulting in a worse prognosis and outcome [14,15]. Although SARS-CoV-2 IgG and neutralising antibodies have been found to be greater in severely or critically ill COVID-19 patients during both the acute and convalescent stages, less investigations focusing exclusively on patients with metabolic disorders have been conducted. Because diabetes, obesity, and hypertension are

becoming more common, it's critical to understand the particular characteristics of COVID-19 infection in persons with these co-morbidities [16,17]. The aim of present study was to observe antibody response of SARS-CoV-2 in ethnic population of Kashmir.

MATERIALS AND METHODS

The present cohort study was conducted at Department of Pulmonology, Chest Disease Hospital, Srinagar, from September 2020 to September 2021. In this study, a questionnaire was prepared by Researchers as per World Health Organisation (WHO), Format [18], in both International English and Vernacular Language which included demographic history such as (name, age, sex, occupation), RT-PCR testing, major co-morbidities, symptoms of COVID -19. The ethical clearance was approved by Institutional Ethical Committee (IEC) under Ref No: 1020/ETH/GMC. Participants were explained about the aim of the study in their local language and were interviewed by experienced medicos. Consent was taken before filling the questionnaire. For cohort research, this report follows the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guideline. The sample size was calculated by using G Power software. All the recommended tests were done free of cost and study was supported by Department of Pulmonology GMC Srinagar.

Inclusion criteria:

- Unvaccinated co-morbid patients (COVID-19 RT-PCR positive).
- The patients or their attendants who gave consent was included in the study.
- Ethnic Kashmiri patients.

Exclusion criteria:

- Vaccinated candidates.
- Non ethnic Kashmiri patients.
- Patients on chemotherapy or radiotherapy.

Study Procedure

Before taking the blood sample procedure was explained to each participant by doctor and consent was taken. Under all aseptic precaution around 3-5 mL venous blood sample was withdrawn from each participant by a trained laboratory technicians (phlebotomists). Red-top serum tube with a clot activator was used into which blood sample were transferred. For clotting to take place the blood sample were allowed to stand for approximately 30 minutes. The blood samples were centrifuged for 10 minutes at 3000-5000 revolutions per minute (rpm) . After calibration stored sample were tested for SARS-CoV-2 specific antibodies. Calibration of automatic immunoassay analysers were done before each testing to enhance efficacy.

Serological IgG antibody testing for SARS-CoV-2: Fully Automated Cobase e411 immunoassay analyser was used to conduct antibody testing. The analyser works on the principle of Electro-Chemiluminisence (ECL), technology is used to detect antibodies to SARS-CoV-2 in human serum. It gives excellent low-end sensitivity and broad dynamic ranges. The sensitivity according to a study 88.48% (76.62-84.34) and specificity was 100%. Seropositive if the index value for SARS-CoV-2 specific antibody was above 1.00 as suggested by the manufacturer protocol.

STATISTICAL ANALYSIS

Data was entered into a Microsoft Excel spreadsheet. Statistical Package for the Social Sciences (SPSS) 16.1 was used for statistical analysis (Chicago, IL). The IgG index was compared between mild to moderate instances and severe to critical cases, as well as in relation to co-morbidities, using the Chi-square and Fischers-exact test. p-value <0.05 were taken statistically significant.

RESULTS

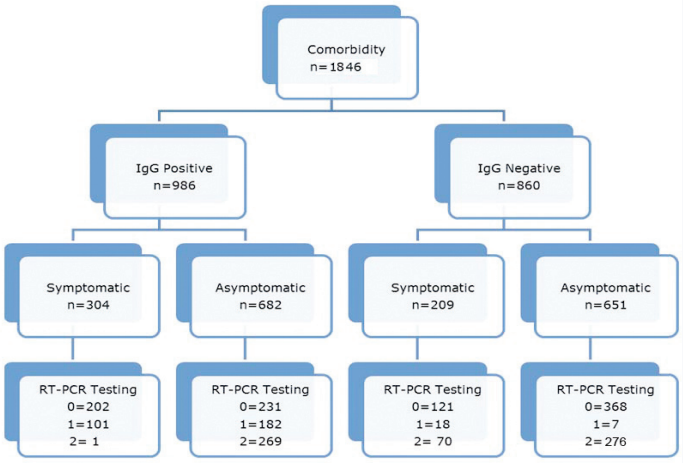
A total of 1,846 co-morbid people were tested for SARS-CoV-2 antibodies. Antibodies against SARS-CoV-2 was established in 986 co-morbid persons. The mean age was 45±5.5 (45.75) years, and the bulk of the participants were men. The majority of those surveyed 1645 (89.1%) were non healthcare workers, while 201 (10.9%) were healthcare workers. The most prevalent co-morbidities was hypertension 1020 (55.2%) and diabetes mellitus 434 (23.5%) followed by thyroid dysfunction 227 (12.2%). Out of 1846, 513 (27.7%) were symptomatic. 308 (16.7%) out of the 1846 people tested positive for COVID-19. 986 (53.4%) individuals out of 1846 developed antibodies against SARS-CoV-2. Seroprevalence was 551 (55.8%) among rural population as compared to urban population 435 (44.2%). The antibody IgG response was investigated in terms of demographics and co-morbidities. It was discovered that the antibody reactivity and non reactivity numbers in the table are described independently [Table/Fig-1]. In this study seroprevelance was seen in (2.5%) and (1.2%) in Chronic Obstructive Pulmonary Disease (COPD) and asthma patients, respectively. Antibody response seen in Chronic Kidney Disease (CKD) was (1.2%) and chronic liver disease was (0.60%) Chronic heart diseases (0.2%). Among 1846 (0.5%) had cancer, SARS-CoV-2 antibody response was nil among them. In present study, subjects having co-morbidities like diabetes mellitus and hypertension were statistically significant (<0.005).

Characteristics		Antibody Negative (n=860, 45.5%)	Antibody Positive (n=986, 53.4%)	Total N=1846, (100%)	p-value (Chi-square test)
Age (Years) (M±SD)		(44±5.5) 44.78	(39±4.5) 39.54	(45±5.5) 45.75	0.009
Occupation	Healthcare worker	72 (8.4%)	129 (13.1%)	201 (10.9%)	0.001
	*Non Healthcare worker	788 (91.6%)	857 (86.9%)	1645 (89.1%)	
Residence	Urban	428 (49.8%)	435 (44.1%)	863 (46.8%)	0.017
	Rural	432 (50.2%)	551 (55.9%)	983 (53.2%)	
Gender	Male	510 (59.3%)	503 (51.0%)	1013 (54.9%)	0.0004
	Female	350 (40.7%)	483 (49.0%)	833 (45.1%)	
Contact history	Yes	61 (7.1%)	81 (8.2%)	142 (7.7%)	0.382
	No	799 (92.9%)	905 (91.8%)	1704 (92.3%)	
Real Time Polymerase Chain Reaction (RT-PCR) confirmatory test	Positive	25 (2.9%)	283 (28.7%)	308 (16.6%)	0.0001
	Negative	346 (40.2%)	270 (27.4%)	616 (33.4%)	
	Not done	489 (56.9%)	433 (43.9%)	922 (49.9%)	
Chief complaints**	Yes	209 (24.3%)	304 (30.8%)	513 (27.8%)	0.001
	No	651 (75.7%)	682 (69.2%)	1333 (72.2%)	
Hypertension (HTN)	Yes	532 (61.9%)	488 (49.5%)	1020 (55.3%)	0.0001
	No	328 (38.1%)	498 (50.5%)	826 (44.7%)	

Diabetes Mellitus (DM)	Yes	106 (12.3%)	328 (33.3%)	434 (23.5%)	0.0001
	No	754 (87.7%)	658 (66.7%)	1412 (76.5%)	
Chronic Heart diseases (CHD)	Yes	17 (2.0%)	2 (0.2%)	19 (1.0%)	0.0002
	No	843 (98.0%)	984 (99.8%)	1827 (99.0%)	
Thyroid dysfunction	Yes	114 (13.3%)	113 (11.5%)	227 (12.3%)	0.255
	No	746 (86.7%)	873 (88.5%)	1619 (87.7%)	
Asthma	Yes	28 (3.3%)	12 (1.2%)	40 (2.2%)	0.003
	No	832 (96.7%)	974 (98.8%)	1806 (97.8%)	
Chronic Obstructive Pulmonary Disease (COPD)	Yes	38 (4.4%)	25 (2.5%)	63 (3.4%)	0.028
	No	822 (95.6%)	961 (97.5%)	1783 (96.6%)	
Chronic Kidney Diseases (CKD)	Yes	19 (2.2%)	12 (1.21%)	31 (1.7%)	0.105
	No	841 (97.8%)	974 (98.5%)	1815 (98.3%)	
Chronic Liver Disease	Yes	2 (0.2%)	6 (0.60%)	8 (0.4%)	0.297
	No	858 (99.8%)	980 (99.4%)	1838 (99.6%)	
Cancer	Yes	4 (0.5%)	0	4 (0.21%)	0.046
	No	856 (99.5%)	986 (100%)	1842 (99.8%)	

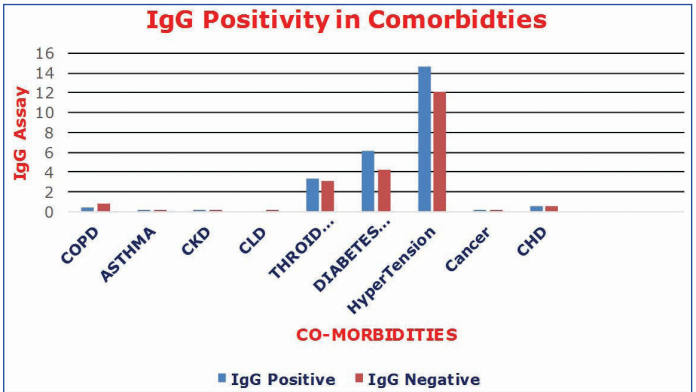
[Table/Fig-1]: General characteristics and association with antibody response (IgG) in co-morbid individual.
**Non healthcare workers comprises of people from the occupations other than medical, which include individuals involved in business, banking, education etc.
**Chief Complaints like (Fever, dry cough, sore throat dysgusia, anosmia, shortness of breath)

[Table/Fig-2] shows a full description of the patients with co-morbidities. Present study had 1846 co-morbid people. The stratification analysis was shown using a flow chart.



[Table/Fig-2]: Stratification analysis of participants having co-morbidities in the study.
0-Not done, 1-Test Positive, 2-Test Negative

Antibody response was seen more in those with hypertension 488 (49.9%), diabetes mellitus 328 (33.2%), thyroid dysfunction 113 (11.4%), COPD 25 (2.5%), Asthma 12 (1.2%), CKD 12 (1.21%), CLD 6 (0.6%), and Cancer (0%), as shown in [Table/Fig-3].



[Table/Fig-3]: Immunoglobulin IgG status in individuals having co-morbidities.
*CHD: Chronic heart disease; CKD: Chronic kidney disease; CLD:Chronic liver disease; COPD: Chronic obstructive pulmonary disease

DISCUSSION

The present study was the first study of its kind in ethnic population of Kashmir having COVID-19 infectious disease with co-morbidities. The seroprevalence survey was conducted in concomitant COVID-19 patients at GMC Srinagar's Department of Pulmonology. The seroprevalence research estimates the percentage of the population who has been exposed to SARS-CoV-2 and has generated antibodies against the virus. Exposure to SARS-CoV-2 virus to individuals having co-morbidities like Diabetes Mellitus, Hypertension etc, leads patient more vulnerable due to weak immune system and eventually to mortality, many studies reported that in different ethnic populations of world. As per reports of Central of Disease Centre (CDC, USA) 2021 research analysis, they have found, within 1-3 weeks after infection, antibodies (IgG) can be found in serum. The IgG and IgM rises simultaneously but IgM antibody weans off more frequently than IgG. IgG persists for several months but duration is not known. However, antibody test is not used to diagnose acute SARS-CoV-2 infection [19]. Present study provides crude estimation of seroprevelance IgG antibodies against SARS-CoV-2 in co-morbid individuals. The high rate of antibody response (IgG) were perceived in rural , non healthcare workers, middle aged male with co-morbidties (such as hypertension, diabetes mellitus, thyroid dysfunction). The seroprevalence in our study 986 (53.4%) among co-morbid individuals (1846), which was different with other study done by Khan SM et al., on general population in Srinagar city and they reported 26.9% of seroprevelance in co-morbid patients [20]. The highest seroprevelance was present in individuals higher age (>55 years). Age based antibody response needs further studies to understand the concept of immune response of SARS-CoV-2. Study done by Khan SM et al., reported 3.8-5.2% antibody response among 55-70 years age group [20]. Several studies suggest that SARS-CoV-2 antibodies are higher in older age group with co-morbidity [21].

As per present study data, the males shows antibody response (54.9%) that suggests they were in predominance as compared to opposite gender (45.1%). SARS-CoV-2-specific IgG antibodies seroprevelance did not differ significantly by gender, however it was slightly greater in males (54.9%). These findings were in line with what is known in the recent studies [20,21]. Some research have revealed that there is a gender difference in seroprevelance, with females having lower antibody levels.

In present study 89.1% were non healthcare workers and 10.9% healthcare workers. The study conducted in Srinagar by Salim et al, Khan SM et al., also found higher seroprevelance among non healthcare workers [20]. Probable suggestive reason could be that non healthcare works doesn't follow proper precautions to prevent COVID-19 infection. Urban regions are more densely populated than

rural ones, illness transmission in the population is accelerated. As a result, the seroprevelance of SARS-CoV-2-specific IgG antibodies in urban regions is expected to be greater. Present study estimated a seroprevelance of 44.1% in urban areas against 55.9% in rural areas.

Present study data also reports that the, 8.2% gave history of contact with a known lethal COVID-19 infection. 304 (30.8%) out of 986 were symptomatic IgG positive. Among symptomatic only 101 (33.2%) were RT-PCR positive. 202 (66.4%) had never undergone any microbiological testing. Majority 682 (69.1%) co-morbid individuals were asymptomatic. Among them 182 (27.2%) were RT-PCR positive. 231 (33.8%) had never undergone microbiological testing. Robust testing and vaccination should be encouraged among general population to overcome the burden of unknown infection and thus decreases the total number of infected cases. Asymptomatic individuals become a potential source of transmission of disease. Especially young socially active asymptomatic individual becomes a source of infection to the elderly family member [21,22]. One participant was IgG positive symptomatic RT-PCR negative. This can be due to false negative RT-PCR thermal inactivation, faulty technique, microbiological testing done at a date later than appearance of symptoms or false positive antibody test or poor B cell response. Small number of studies have been conducted so far regarding antibody detection in RT-PCR negative [23]. A 209 (24.3%) were symptomatic IgG negative out of them 18 (8.6%) were RT-PCR positive. Study was conducted in Wuhan among RT-PCR positive cases out of 310 only 2 patients were negative for both IgG and IgM antibodies [24]. [Table/Fig-4], shows studies done on seroprevelance in SARS-CoV-2 and co-morbidities [20,25-28]. In majority of the studies done in other parts of country, they found hypertension and diabetes are major co-morbidities related to lethality of COVID-19 patients and shows significant antibody response. Individuals with co-morbid conditions are associated with severe COVID-19 disease, hospitalisations and poor outcome. Mortality is observed more in elderly population with pre-existing co-morbid. Ageing and co-morbidity causes various changes in immune system and incapacitates the immunity to fight against infections [29]. In present study 49.5% hypertensive patients developed SARS-CoV-2 antibodies. A study conducted in Srinagar among general population reported that (12.1%) were hypertensive followed by thyroid dysfunction (8.5%), diabetes mellitus (5.0%) had developed antibodies [25]. Hypertension has been reported as highest pre-existing co-morbidity in COVID-19. Angiotensin Converting Enzyme (ACE) inhibitors increases the ACE2 expression this increases risk of COVID among hypertensive patients. Patient receiving non Angiotensin Receptor Blocker (ARB) and Angiotensive Converting Enzyme (ACEI) were also found to develop severe diseases. More literature is required to support role of ACE in worsening COVID in hypertensive patients. WHO suggests continuing of these drugs in COVID-19 infection because of their beneficial role [30]. In present study 33.3% diabetic patients developed SARS -CoV-2 antibodies. Diabetic patients have impaired immunity due to hyperglycaemia and chronic inflammation. All these factors leads increases oxidative stress and more severe COVID-19 diseases. DPP4 inhibitor is used in treating diabetes patients it impairs innate immunity [30]. In present study seroprevelance is seen in (2.5%) and (2%) in Chronic Obstructive Pulmonary Disease (COPD) and asthma patients respectively. Individuals with pre-existing respiratory disease are at more risk of developing life threatening COVID-19 disease. A 0.95% COPD patients were infected with COVID-19 in USA. In China 0.90 % asthma patients were infected due to COVID-19 [30]. Antibody response seen in Chronic Kidney Disease (CKD) was (1.2%) and chronic liver disease was (0.60%). In meta-analysis 0.83% had CKD among COVID-19 patients. ACE2 receptors in CKD patients does not increases the susceptibility to SARS-C0V-2 infection. Study conducted in China showed that 3% COVID -19 patients had chronic liver disease [30]. Chronic heart diseases (0.2%) is associated with high mortality and morbidity because cardiovascular diseases are treated with renin angiotensin system inhibitor and heart is highly expressed with ACE2 receptors. These patients are at a high risk of thromboembolism and arythmias [30]. Among 1846 (0.46%) had cancer. SARS-CoV2 antibody response was nil. In other literatures the incidence of cancer was low among COVID -19 patients. 0.92% malignancy cases were reported in large Meta-analysis [30]. In our study 11.4% thyroid disease patients developed antibody response. A study conducted by Hariyanto TI and Kurniawan A described, a significant association between thyroid disease and COVID-19. Thyroid hormone plays important role in innate immunity dysfunctioning of thyroid gland results in dysregulation of innate

Name of authors (publication year)	Place of study	IgG positivity	Highest co-morbidity
Inbaraj LR et al., 2021 [25]	South india	Seroprevalence was 12.4%	Hypertension and diabetes was 16.3% (95% CI: 9.2-25.8) and 10.7% (95% CI: 5.5-18.3) respectively
Murhekar MV et al., 2021 [26]	70 districts across 20 states and 1 union territory where 3 previous rounds of serosurveys were conducted.	Nearly two-thirds of individuals aged ≥6 years from the general population and 85% of HCWs had antibodies against SARS-CoV-2 by June–July 2021 in India	Of the 28,975 individuals who participated in the survey, 2,892 (10%) were aged 6-9 years, 5,798 (20%) were aged 10-17 years, and 20,285 (70%) were aged ≥18 years; 15,160 (52.3%) participants were female, and 21,794 (75.2%) resided in rural areas. The weighted and test-adjusted prevalence of IgG antibodies against S1-RBD and/or nucleocapsid protein among the general population aged ≥6 years was 67.6% (95% CI 66.4% to 68.7%). Seroprevalence increased with age (p<0.001) and was not different in rural and urban areas (p=0.822).
Chowdhury I et al., 2022 [27]	A total of 77 patients (age 18 – 70 years) infected by SARS-CoV-2 were enrolled for this study	The median value of serum IgG was significantly higher in hospital-treated patients than in hometreated patients (p<0.001)	Hospital treated patients develop higher antibodies in comparison to home treated patients.
Khan SM et al., 2020 [20]	2906 persons >18 years of age selected from hospital visitors across District Srinagar participated in the study	Age- and gender-standardised seroprevalence was 3.6% (95% CI 2.9% to 4.3%)	The seroprevalence of SARS-CoV-2 specific IgG antibodies is low in the District. A large proportion of the population is still susceptible to the infection
Kumar D et al., 2022 [28]	A hospital-based survey was carried out among 1279 conveniently selected HCPs from September 2020 to January 2021 in Himachal Pardesh.	A total of 29 (2.3%) were already tested positive for COVID-19 (RT-PCR: 22; Rapid Antigen Test: 7) before the survey, and the overall prevalence of IgG antibody was 12.7% among the participants (Male: 12.8%; Females: 12.5%)	HCPs were tested about six months after the initiation of the COVID-19 pandemic in the state and demonstrated a high and expected level of seroprevalence.
Present study (2022)	Srinagar	The seroprevalence in present study is 986 (53.4%) among co-morbid individuals (1846). The highest seroprevelance was present in individuals higher age (>55 years). The majority of those surveyed 1645 (89.1%) were non-healthcare workers	The most prevalent co-morbidities was hypertension 1020 (55.2%) and diabetes mellitus 434 (23.5%) followed by thyroid dysfunction 227 (12.2%). The seroprevalence among cancer patient were nil.

[Table/Fig-4]: Seroprevelance studies on Antibody response in COVID-19 and co-morbidities in other States/UT of India [20,25-28].

immunity [31]. Further studies should be conducted with large sample size to estimate antibody response in co-morbid cases. Also it is recommended that the government authorities, therapists, and doctors need to increase public awareness of correct COVID-19 behaviours and appropriate precautionary measures need to be followed in letter and spirit in order to mitigate the transmission of the lethal disease. Patients with co-morbidities who are susceptible to infection should need to be taken extra precautions.

Limitation(s)

In present study sample size was constraint, more study are needed on large sample size across the districts of Kashmir, India.

CONCLUSION(S)

Antibody positivity among co-morbid people is insignificant, with the exception of hypertension and diabetes. More research is needed in all of Kashmir's districts in this regard. Acceptable behaviour, sufficient ventilation, and hygienic practices, in combination with governmental, business, and municipal health leadership, prevents an infectious disease from spreading. Because a greater population is still vulnerable to COVID-19, maintaining public health measures and increasing immunisation access are crucial to protect this groups health from disease, as severe COVID-19 can be visibly burdensome. Co-morbid individual have poor outcome and associated with high mortality and morbidity.

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