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Health Care Workers in COVID-19: From Lockdown to Unlock and Beyond!

Charulata Londhe¹, Vikram Londhey²

Ever since the news of SARS COV-2 in other countries and then the virus itself reached India, the nation was looking up to the Healthcare workers (HCWs) as its saviours! The HCWs accepted this challenge positively and converted themselves into ‘COVID Warriors’. HCWs include not only doctors and nurses but also ward assistants, laboratory technicians, radiology technicians, dialysis technicians, operation theatre attendants, physiotherapists, occupational therapists, sweepers, ASHA workers, multipurpose workers and ambulance drivers as frontline workers.

The nation-wide lockdown changed the life of everyone. The brave ‘COVID warrior’ too had to adopt and adapt to the new lifestyle and the changes in the working environment. The challenges faced by the HCWs were multifaceted and multifactorial. For most of the existing medical disorders, there are established diagnostic guidelines and treatment protocols in place. But, COVID 19 being a new disease, there were no established guidelines initially. The disease too had its own bundle of surprises which the doctors learnt after treating the initial cases. The search for effective antiviral therapy had started from the beginning. But, so far no antiviral drug has been proven to reduce the mortality in clinical trials.¹

Understanding the pathogenesis of COVID-19 evolved from the severe acute respiratory illness involving viral pneumonia with ARDS and multi-organ failure to inflammatory cytokine storm, pulmonary vasculature thrombosis, risk of thrombotic stroke or myocardial infarction, to post-COVID lung fibrosis leading to long term hypoxia and post-COVID syndrome. Corticosteroids, anticoagulants, antivirals like Remdesivir or Favipiravir were subsequently added in the guidelines.

Keeping an update of the newer and ever evolving guidelines of testing, treatment, admission and discharge policy was another challenge. Sharing of experiences on online platforms and webinars helped for dissemination of knowledge to the frontline workers all over the country. The guidelines released by the Government authorities from time to time made the doctors more confident while performing their duties.

Public sector was first to come forward for screening, testing, isolation and treatment of COVID 19 cases. Initially, some HCWs had fear and resistance to work in COVID areas. It was overcome by conducting awareness programs on safety precautions, provision of personal protective equipment (PPE kits) and training on its use, N-95 masks, allotting COVID duties in rotation, provision of Hydroxychloroquine prophylaxis, inclusion in the COVID ‘Suraksha Kavach’ insurance scheme, provision for treatment of those infected despite using protective measures. Risk stratification was implemented while allotting duties in COVID areas; excluding HCWs above 55 yrs of age, with diabetes, hypertension, morbid obesity, asthma or pregnancy to minimise the risk of severe disease in HCWs. There was coordination between various departments for preparing signages, appealing the corporate sector and NGOs for donations via social corporate responsibility for mobilising the PPE kits, N 95 masks, sanitizers, pulse oximeters, face shields, etc.

As the number of cases started rising, there was revamping of infrastructure to start triage areas, isolation wards and COVID ICUs in existing hospitals, creating COVID care centres and dedicated COVID hospitals. The medical practitioners from all the ‘pathies’, from public as well as private sector were called for bridging the gap between the available human resources. Doctors from all specialities were pooled for COVID related work by stopping routine non emergency work. The private sector had to shut down elective non-COVID services. Some hospitals were fully converted into COVID hospitals, while some continued to provide COVID and Non-COVID care. While many practitioners initially had shut the clinics due to lockdown, later on opted for online consultation, telemedicine or limited OPD consultations with necessary precautions. Both, the public and private sectors worked hand-in-hand and have been successful to keep COVID fatality rate in India to as low as 1.48%.²

Prioritizing patients in resource limited setting based on disease severity and risk factors was another challenge for the COVID warrior. The challenge of conducting clinical trials for various upcoming therapies (which were used for off label indications in COVID) to COVID vaccines was successfully accepted and completed by researchers. Medical teachers had another challenge of conducting online teaching programs and college and University level examinations of graduate and postgraduate students amidst the pandemic.

The HCWs had to balance home front and the work front. HCWs working in COVID areas experienced dual stress of contracting infection themselves as well as carrying it back home to infect the near and dear ones. Absence of household helpers due to lockdown was an additional burden. Some HCWs faced harassment in residential areas due to fear of the spread of the disease. Many of them also had problems in

¹Associate Professor of Medicine, LTMMC and GH, Mumbai, Maharashtra; ²Associate Professor of Medicine, HBTMC and RN Cooper Hospital, Mumbai, Maharashtra
travelling to work place due to lack of public transport systems. Hence many HCWs in the public sector opted to stay away from their families in the temporary stay facilities provided by the administration.

The protection of HCWs and preventing them from contracting the infection was the topmost priority; as machinery and medicines can be procured in abundance but creation of skilled HCWs within short time is impossible. Despite all the necessary precautions, some of the HCWs did get infected with COVID either within the hospital or outside. As per an official statement released by the Central govt health ministry till 11th September 2020, 155 HCWs including 64 doctors had succumbed due to COVID-19 infection.3 The Indian Medical Association (IMA) National COVID-19 registry data suggests more than 1500 doctors have been infected with SARS-CoV-2 virus, at least 400 doctors succumbed, of which 40% were general practitioners, where 75% of them are above the age of 50 years.3 The positivity rate in healthcare workers is 18% in Telangana, 16% in Maharashtra, 14% in Delhi, 13% in Karnataka, 12% in Puduchery, and 11% in Punjab. This data was released by the secretary, Union Health Ministry.3

The next challenge was to keep up the morale of the HCWs as the pandemic continued for months. Various studies in different countries have reported increased rates of psychological stress, depression, anxiety, insomnia in HCWs.3,6 “This was due to higher risk of infection,7 disruption of routine work, COVID related duties in new wards or at different places, getting isolated or quarantined, death of any family member, friend or colleague; overburden of work due to quarantine of some staff and uncertainty about the future.

Another major issue was declaring death of COVID 19 patients, handling of dead body with dignity and tackling the emotional turmoil of relatives. The situation sometimes would turn into a violent war against the ‘COVID warrior’ and the doctors were rewarded by brutal attacks by hooligans and mental harassment and defamation by media and the public. The initial claps, thali banging, lightening of lamps and showering of flowers were later replaced by administrative disciplinary actions, enquiries, or police and court cases.

Life is slowly returning to a ‘new normal’ state as we are getting unlocked in a gradual phased-out manner. It is necessary to emphasize the importance of SMS: Social distancing, Masks and Sanitizer usage while restarting various activities. We have to be vigilant about resurgence of cases while we await the vaccine which is showing promising results in clinical trials. Establishment of new guidelines to deal with elective or emergency non-COVID conditions in order to provide timely treatment while minimizing the risk of COVID-19 infection in patients and HCWs is the need of the hour.

Now the COVID warriors have a sense of accomplishment after playing the various roles of team leader, teacher, researcher and a saviour. They have emerged as stronger, more resilient and more confident people than before.

References
3. Covid-19: India’s private doctors and government clash over pandemic response. doi: https://doi.org/10.1136/bmj.m3711 (Published 22 September 2020)
4. Coronavirus | TS healthcare workers have highest positivity rate in India. The HINDU 4 september 2020.
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Hepatitis C: A Tale of Three Nobel Laureates and the Ladder to Elimination

Ankita Singh¹, Sridhar Sundaram², Akash Shukla³

With this year’s Nobel prize in Physiology or Medicine awarded to Harvey J. Alter, Michael Houghton and Charles M. Rice for the seminal discovery of hepatitis C virus, the arduous journey of hepatitis C from its discovery to cure needs elucidation. According to WHO, an estimated 325 million people worldwide are living with hepatitis B and/or C, and for most of them, testing and treatment remains beyond reach.¹ The discovery of agents causing viral hepatitis represents a major breakthrough for medicine as millions of lives have been saved thanks to their discovery.

The primary mode of acquisition for infectious hepatitis was presumed to be feco-oral transmission till the early 1900s. There was an increased incidence of hepatitis amongst recipients of yellow fever vaccine during the Second World War.² There were intense attempts at identifying this new infectious agent of “Serum hepatitis”. However, no breakthrough was found till the early 1960s, when “paid-donor” pool started forming a greater fraction of blood products in most blood banks across the US with simultaneous rise in the incidence of post-transfusion hepatitis (PTH).³ The discovery of Au (Australia antigen) by Dr. Baruch Blumberg in 1964 and its association with hepatitis in patients receiving multiple blood transfusions was the landmark in the fight against viral hepatitis.⁴ The subsequent identification of the Dane particle in 1971 allowed development of screening tools, vaccine and drugs against hepatitis B (HBV). In 1976, FDA mandated the use of voluntary blood donation and screening for HBV, after which there was substantial decrease in the incidence of PTH. Blumberg was honoured with the Nobel Prize for his discovery in 1976. However, 10% patients receiving blood transfusion continued to develop hepatitis speculating a different agent, probably also a virus, responsible for PTH.

At NIH Clinical Centre blood bank, Dr. Harvey Alter and colleagues tested stored samples using newer and more sensitive Radioimmunoassay, and found that HBV was responsible for only 25-30% of cases of PTH. All the samples also tested negative for HAV. Since the biologic nature of this infectious agent/agents was still elusive, it was named “non-A non-B Hepatitis” (NANBH). Thereafter began a relentless search for the pathogen; establishing its transmissibility by serial inoculation in chimpanzees and physical characteristics of being a small 30-60 micron lipid-enveloped particle which increased its probability of being a virus from alpha or Flaviviridae family.⁵ Clinical characterization of NANBH was elucidated by Dr. Alter, as being majorly anicteric hepatitis with a chronic course leading to development of cirrhosis in about 20% patients.⁶ Despite all these advances, the virus remained unidentified as it could not be visualised directly under the microscope unlike Dane particle, nor could it be grown in any cell culture medium, and no viral protein or antigen could be isolated from the serum of infected patients or chimpanzees.

Michael Houghton and his colleagues at Chiron Corporation, California worked towards cracking the NIH panel code of NANBH using the novel molecular method of Proteomics. cDNA obtained from reverse transcription of RNA from infected human and chimpanzee plasma was inserted in a phage vector that was then used to transfect E.coli. After nearly 5 years and 6 million negative attempts, a reactive antigen clone was identified using which the entire genome was typed and it was substantiated that this virus belonged to Flavivirus family.⁷ The name NANBH was now officially changed to Hepatitis C. First and second-generation assays were developed to identify antibodies to this antigen and thus widespread screening of blood donors began in 1990.

The virus yet could not be replicated outside the human body, clouding the possibility of it causing hepatitis by itself. Charles M. Rice at Washington University accurately identified the problem being an incomplete genome characterization and discovered an end sequence deemed necessary for replication. With elimination of accumulated inactivating genetic variations and inclusion of this new replication sequence in the viral genome, Rice could replicate this viral genome after injecting it directly into the chimpanzee liver and demonstrating its presence in blood. With this, hepatitis C was established as the most common cause of post-transfusion hepatitis.⁸

Preliminary clinical trials evaluating the efficacy of recombinant interferon alpha in chronic hepatitis C were published in 1989 separately by Di Bisceglie et al and Davis et al.⁹ Both the studies concluded that interferon significantly improved transaminase levels and histology in patients with chronic HCV, however more than half the patients had relapse 6-12 months after discontinuing the treatment. Subsequent studies found greater response rates with pegylated form of interferon. With less frequent dosing (once weekly vs thrice weekly) and improved response rates, peg-IFN alpha largely replaced non-peg forms both for treatment and in clinical trials. In 2001, Manns et al. were the first to conclude that addition of ribavirin...
to peg-IFN alpha improved response rates.\textsuperscript{10} With this, Peg-IFN alpha 2b with ribavirin became the gold standard for treatment of chronic hepatitis C, with reported SVR rates ranging between 50% to 80%. However, this combination therapy was plagued by issues of compliance with significant adverse reactions, leading to discontinuation and lowered response rates.

The advent of directly acting antivirals (DAA) represents a paradigm shift in the treatment of Chronic HCV infection. The first class of DAA to be developed were NS3/4A protease inhibitors, Boceprevir and Telaprevir, approved for use in 2011. These were combined with peg-IFN (triple therapy) but were associated with significant adverse events. Subsequently NS5B polymerase inhibitor sofosbuvir was introduced and soon became the blockbuster agent with pan-genomic efficacy and was approved for use in 2014. It has been the backbone of therapy for HCV ever since. Other newer NS5A inhibitors like velpatasvir and daclatasvir were combined with sofosbuvir, bringing sustained viral response rates up to 95 to 97%.\textsuperscript{11} Introduction of DAs has allowed shorter duration, interferon-free pan-genomic treatment with high cure rates for all patients.

2015 marked the year of major advancement in the battle against hepatitis C with WHO adopting the 2030 agenda for sustainable development goals which called for global integrated efforts to combat viral hepatitis. In 2016, the Global Health Sector Strategy on viral hepatitis called for elimination of viral hepatitis as a major public health threat by 2030 (i.e. 90% reduction in incidence and 65% in mortality). US-based Gilead Sciences, Inc. granted generic licensing agreements to various India-based pharmaceutical manufacturers in 2014 for manufacture of sofosbuvir and ledipasvir, and distribution in 91 other developing countries. With the availability of generic drugs, which are priced far lower than the parent drug molecule, there was widespread access to chronic hepatitis C treatment, particularly in these developing countries which together account for more than half of the global HCV patients. This was a monumental step towards the goal of elimination of HCV. In India, the National Viral Hepatitis Control Program launched in 2018 aims to achieve 2030 SDG by an integrated initiative for prevention and treatment of hepatitis C and linking the program with existing national health programs like National AIDS Control Program. As part of the program, treatment centres have been established in all districts with free of cost treatment available to patients. For management of complex cases, model treatment centres are in place in 28 states.

To date, WHO has eradicated two diseases - smallpox caused by variola virus and rinderpest, a fatal disease of cattle. Eradication of both these diseases reied on prevention strategies (vaccine or health programmes based on awareness and harm reduction). Dracunculiasis is close to eradication with the key strategy being community education and patient identification.\textsuperscript{12} Various national control programs for diseases like vector-borne diseases (malaria & filaria) and tuberculosis having therapy as a pillar have been struggling for over 4-5 decades. In hepatitis C, due to poor proof-reading by viral RNA polymerase and high replication rate, there exists genetic variants in the same host known as quasi-species. This unique feature of HCV makes it difficult to mount an immune response and hinder the development of an effective vaccine.\textsuperscript{5} The deductions from these important data remains that while eliminating hepatitis C still remains onerous, eliminating it as a public health threat is attainable with community education and awareness, extensive screening, high risk behaviour modification, widespread access to therapy and reduction in mortality by better surveillance of chronic HCV patients.

References

Prevalence, Clinical Presentations and Treatment Outcomes of COVID-19 among Healthcare Workers at a Dedicated Hospital in India

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is rapidly spreading in India and across the world. Healthcare workers (HCWs) are at increased risk of contracting COVID-19 due to direct or indirect exposure to COVID-19 patients, and require special attention. Limited information is available about its effect in HCWs. Secondary transmission from HCWs is a possibility among patients, family members, and the community. Therefore, it is important to investigate the infection risk of HCWs and the clinical characteristics of affected cases and possible source of infection with exposure details. The aim of this study is to analyze the medical records of HCWs with COVID-19 retrospectively and carry out the analysis of the data of HCWs with COVID-19 at TNMC and BYL Nair Charitable Hospital (NH, COVID-19 Hospital) in Mumbai.

Interim analysis was carried out for the data collected from 6th April to 20th August 2020. Total 3711 HCWs (frontline, 74.32%, non-frontline, 25.68%) are working at NH Mumbai. We observed 11% prevalence of SARS-CoV-2 infection among HCWs, 4% co-infection and 1% mortality. Majority (85%) of the HCWs with COVID-19 were symptomatic and 15% were asymptomatic. Comorbidities were reported in 19% of HCWs with COVID-19. Hypertension and Diabetes Mellitus were the most common co-morbidities reported. More than 4% percent of HCWs with COVID-19 were also positive for plasmodium vivax Malaria. The results of the study will be useful for determining the impact of COVID-19 and adverse outcomes in HCWs, identifying probable mode of acquiring SARS-CoV-2 infection in HCWs. This is required for planning the strategies to handle the epidemic of COVID-19 among HCWs in Mumbai region, and at Maharashtra state level.

Introduction

Currently, there is a public health emergency due to COVID-19, an infectious disease caused by a novel coronavirus which is now called as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of 11th November 2020, 51.4 million confirmed cases of COVID-19, including 1.27 million deaths worldwide were reported as per WHO, of which India contributed 8.64 million confirmed cases of COVID-19 with more than 0.1 million deaths. SARS-CoV-2 had not been detected in humans before the current outbreak owing to which limited information is available about its effect in general population, and healthcare workers (HCWs).

Previous studies reported variation in SARS-CoV-2 infection rate in HCWs all across the globe (1-18%). Higher rates of COVID-19 were observed in HCWs who reported no exposure to COVID-19 patients. Recent study reported 44% of 200 HCWs had evidence of SARS-CoV-2 infection at any time-point, detected either by serology or RT-PCR. COVID-19 is caused by a new coronavirus strain SARS-CoV-2, first reported from Wuhan in China. Owing to its rapid spread globally, it was declared as a pandemic by WHO. HCWs have exposure to COVID-19 patients directly or indirectly or to the infectious materials. Secondary transmission from HCWs is a possibility among patients, family members, and the community. Therefore, it is important to investigate the infection risk of HCWs and the clinical characteristics of affected cases and possible source of infection with exposure details.

COVID-19 cases are on rise in India. Maharashtra state contributed 1.72 million cases with 45,325 deaths. Mumbai alone contributed to more than 0.26 million COVID-19 cases. As an epicenter of COVID-19 epidemic in Maharashtra, special attention in planning the strategies for combating COVID-19 for Mumbai city, especially HCWs who are most vulnerable.

Therefore, the present study aims to analyze the medical records of HCWs with COVID-19 retrospectively and carry out the analysis of the data of HCWs with COVID-19 at TNMC and BYL Nair Charitable Hospital (NH) (COVID-19 Hospital) in Mumbai. NH was declared as dedicated COVID-19 facility on 18th April under MCGM. The study will collect data from 1st March 2020 until 31st October 2020, on geographical location, clinical presentation, and possible source of infection, re-infection details, virus
Table 1: Comparative analysis of the Healthcare workers with COVID-19 reported from different countries

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Author et al., 2020</th>
<th>Country</th>
<th>Sample Size</th>
<th>Duration of data collection</th>
<th>Test used for detection of COVID-19</th>
<th>Prevalence of HCWs with COVID-19</th>
<th>Proportion of symptomatic HCWs</th>
<th>Prevalence of asymptomatic HCWs</th>
<th>ICU admission/ Death Severe or Critical disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lai X. et al.</td>
<td>China</td>
<td>110 positive and 335 random testing for asymptomatic carrier</td>
<td>40 days; January 1 to February 9, 2020</td>
<td>Nasopharyngeal swabs; RT-PCR</td>
<td>1.1% (110/ 9864)</td>
<td>No data available</td>
<td>No data available</td>
<td>HCWs with self-reported fever or (mild) respiratory symptoms were included in the study</td>
</tr>
<tr>
<td>2</td>
<td>Kluytmans et al., 2020</td>
<td>Dutch</td>
<td>86 positive</td>
<td>6 days; March 7 to March 12, 2020</td>
<td>Oropharyngeal swab; Semi-quantitative RT-PCR (45 cycles)</td>
<td>1% (86/9705)</td>
<td>No data available</td>
<td>No data available</td>
<td>Only mild symptomatic were included</td>
</tr>
<tr>
<td>3</td>
<td>Nguyen et al., 2020, app based study</td>
<td>UK USA</td>
<td>1922</td>
<td>31 days; March 24 to March 23, 2020</td>
<td>Not mentioned</td>
<td>2.747 % (1922/ 99,795)</td>
<td>96.7%</td>
<td>3-3% data not available</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Korth et al., 2020</td>
<td>Germany</td>
<td>316</td>
<td>28 days; March 25th, 2020 to April 21th, 2020</td>
<td>ELISA, Anti-SARS-CoV-2-IgG antibodies</td>
<td>1.6 % (5/316)</td>
<td>80%</td>
<td>20% Not included</td>
<td>Not included</td>
</tr>
<tr>
<td>5</td>
<td>Felice et al., 2020</td>
<td>Italy</td>
<td>98 underwent testing out of 388 respondents</td>
<td>12 days; March 25th to April 4th, 2020</td>
<td>Not provided</td>
<td>18/98 (18%)</td>
<td>Data not provided</td>
<td>33%</td>
<td>Not included</td>
</tr>
<tr>
<td>6</td>
<td>Treibel et al., 2020</td>
<td>UK</td>
<td>44 positive</td>
<td>March 23 to 5 weeks</td>
<td>Nasal swab</td>
<td>11% (44/400)</td>
<td>73%</td>
<td>27% (12/44)</td>
<td>Not included in the study</td>
</tr>
<tr>
<td>7</td>
<td>CDC COVID-19 Response Team, 2020</td>
<td>USA</td>
<td>9,282</td>
<td>58 days; February 12 to April 9, 2020</td>
<td>Not provided</td>
<td>18.80% (9,282/49,370)</td>
<td>92%</td>
<td>8%</td>
<td>184 (2%-5%) 27 (0.3%–0.6%)</td>
</tr>
<tr>
<td>8</td>
<td>Jha et al 2020</td>
<td>India</td>
<td>20 positive</td>
<td>39 days, 23rd March - 30th April 2020</td>
<td>Not mentioned</td>
<td>1.8% (20/1113)</td>
<td>50%</td>
<td>50%</td>
<td>Information not available Information not available</td>
</tr>
<tr>
<td>9</td>
<td>Barrett et al., 2020</td>
<td>USA</td>
<td>40 positive out of 546</td>
<td>15 days; March 24 to April 7, 2020</td>
<td>Oropharyngeal swabs, RT-PCR</td>
<td>7.3% (40/546)</td>
<td>75 (13.9%); COVID-19 symptoms in last week</td>
<td>65.9%</td>
<td>Not included in the study</td>
</tr>
<tr>
<td>10</td>
<td>Rivett et al., 2020</td>
<td>UK</td>
<td>61 positive</td>
<td>19 days; 6th – 24th April 2020</td>
<td>Throat + Nose self-swab, Real-time RT-PCR</td>
<td>4.8% (61/1268)</td>
<td>-</td>
<td>3% (31/1,032)</td>
<td>Not included in the study</td>
</tr>
<tr>
<td>11</td>
<td>Bongiovanni et al 2020</td>
<td>Italy</td>
<td>142</td>
<td>31 days, with 45 days follow up - 10th March to 10th April 2020</td>
<td>Nasopharyngeal swab</td>
<td>Study is about virus clearance</td>
<td>80.3% (114/142) 19.7% (28/142)</td>
<td>8.5%</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>Houlihan et al., UK 2020</td>
<td>UK</td>
<td>200 random</td>
<td>14 days; March 26 and April 8, 2020</td>
<td>Nasopharyngeal swabs RT-PCR twice per week and serology assays (ELISA and flow cytometry)</td>
<td>44% (87/200)</td>
<td>detected either by serology or RT-PCR</td>
<td>23% (42/200)</td>
<td>Asymptomatic were enrolled</td>
</tr>
</tbody>
</table>

COVID-19, Infectious disease caused by SARS-CoV-2 virus; RT-PCR, real-time reverse transcription– polymerase chain reaction; app, application; HCW- Healthcare Worker; ICU, Intensive Care Unit.

clearance duration and the outcome of the disease in HCWs with COVID-19 in NH. Herein we describe the protocol of study along with results of interim analysis.

Material and Methods

The present study is an observational retrospective monocentric study of data collection from Medical Case Records and interviews of HCWs with laboratory confirmed SARS-CoV-2 infection admitted or seeking treatment at NH, telephonically or by self-administered questionnaire.

Processes at NH

Temporary accommodation (hotels, schools) was provided outside the hospital campus for frontline HCWs. 7/7 days rotation (7 days off) with 6-hour shifts and frequent rotations was implemented to control exposure and stress among them.18 It was later changed to only symptomatic HCWs involved in care of COVID-19 and asymptomatic high-risk HCWs were tested between day 5-10 of contact or exposure.20 All HCWs were regularly trained for identifying common signs and symptoms of COVID-19, self-health monitoring and prompt reporting of symptoms and breach of PPE. Thermal screening was made available for all hospital staff and all by ICMR, all asymptomatic high-risk HCWs were tested between day 5-14 of contact or exposure.19

To implement the protocol, the aim was to follow a structured approach for detection and management of COVID-19 in HCWs at NH. The study protocol was presented in Table 1.
eligible frontline HCWs were provided with hydroxychloroquine chemoprophylaxis.

In case of exposure, nodal officer assessed the level of exposure and the risk. High risk contacts were quarantined for 14 days, and tested as per testing protocol by ICMR and actively monitored, and return to work if tested negative and remain asymptomatic after quarantine period. Symptomatic positive HCWs were categorized into mild, moderate or severe cases. Mild cases had an option of home isolation, or admission at COVID Care Center or NH.21

Aim of the study

The aim of the study is to conduct the retrospective analysis of the medical case records of the HCWs working at NH, diagnosed with COVID-19.

Research questions

a. What is the prevalence, clinical presentation and probable source of infection of COVID-19 among HCWs at NH?

b. What is the infection risk among HCWs while working in a dedicated COVID-19 hospital, because of occupational exposure?

c. How does the treatment of SARS-CoV-2 infection in HCWs influence the outcomes?

Objectives

a. To determine prevalence of SARS-CoV-2 infection amongst HCWs in NH

b. To study socio-demographic, probable source of infection/exposure, clinical presentations, co-morbidities, re-infection details, virus clearance, consistent use of PPE, and treatment outcomes in HCWs with COVID-19

Data collection instrument

NM and RG carried out literature search of the current evidences7-13 (Table 1) of outcomes of COVID-19 on HCWs. Based on this, we shortlisted the key parameters about which the information should be collected. Self-administered questionnaire was prepared to find out the possible source of infection, high risk exposure and transmission while working in a dedicated COVID-19 Hospital. It is also designed to capture missing data from medical case records. The questionnaire in the form of Google form was self-tested several times by the research team members and volunteers for validation purpose. Based on the feasibility and pilot testing, the case record form was modified and finalized by consensus of investigators.

Retrospective data collection

HCWs working in NH with COVID-19 will be identified from the Central Hospital data. These cases will be analyzed retrospectively from medical case record to understand the clinical presentation of COVID-19 among HCWs, document the outcome and also understand the response to treatment. They will be contacted telephonically by Co-Is, on phone number available from the central database to electronically document and obtain informed consent before reviewing the medical case records, after explaining information related to a study from patient information sheets in the language they understand. Wherever feasible and necessary, consent will be taken on the hard copy of the consent form. After the consent, they will be interviewed telephonically or will be asked to enter details in the self-administered questionnaire (google form) to find out additional information related to the possible source of infection, containment zone, missing socio-demographic details, and transmission while working in a dedicated COVID-19 Hospital. Data will be directly entered in the anonymized google excel sheet in the coded form.

Definitions

Viral clearance will be defined as having two consecutive negative swabs (oropharyngeal RT-PCR) repeated after 48-72 hours from each other, in the absence of symptoms.

Reinfection: Those cases presented a second confirmed COVID-19 episode. First SARS-CoV-2 infection was confirmed by RT-PCR positivity which was followed by a laboratory confirmed negative RT-PCR tests as per the National testing guidelines. HCWs readmitted for COVID-19 with a short duration (<15 days) will be excluded from study.

Co-infection: Clinical presentations of malaria, dengue and other monsoon related illnesses in the endemic region strongly overlap with that of COVID-19 and hence pose an additional challenge for differential diagnosis.

Data management, protection of privacy and confidentiality

The PI will monitor entry of individual data to ensure its accuracy real-time. Research team at NH will periodically review the data entered for gaps and discrepancies. No information will be collected related to the identity of the study participants. The names of the COVID-19 patients will not be entered in any of the documents. Each patient will be given a unique code number. The data of each Code no. will be entered accordingly. All precautions will be taken to maintain confidentiality of the records identifying the patient’s identity as well as the patient’s socio-demographic data. None of the COVID-19 patient’s details revealing the identity will be used in any reports and publications arising from this study. Only specific individuals within a research team will be able to access and edit data. The quality of the data will be regularly monitored by the PI. The data analysis to be carried out by PI and the research team

Expected Outcome

The proposed study is essential for a) Generating baseline information on sociodemographic data, clinical presentation, and adverse outcomes in HCWs with COVID-19 in NH, b) Determining the impact of COVID-19 and adverse outcomes in HCWs, c) Identifying probable mode of acquiring SARS-CoV-2 infection in HCWs and d) Together this data is required for planning the strategies to handle the epidemic of COVID-19 among HCWs in Mumbai region, and at Maharashtra state level.

Interim Analysis Results

NH was converted into a dedicated COVID-19 facility with since 18th April with 1043 beds and treated more than 6000 patients till 20th August. All the HCWs included in the study had RT-PCR confirmed COVID-19. The data was collected from 6th April to 20th August 2020. There are total 3711 HCWs [frontline (n= 2758, 74.32%), non-frontline (n=953, 25.68%)] working at NH Mumbai. Out of these, 413 were found to be infected with SARS-CoV-2 infection. Analysis of viral clearance was carried out in 402 HCWs.

The prevalence of SARS-CoV-2 infection detected on RT-PCR in the HCWs of NH was 11% during the first 5 months of COVID-19 pandemic. The
demographic, clinical characteristics of HCWs infected with SARS-CoV-2 are presented in Table 2. The median age of HCWs was 32 (IQR 27-44) years. Majority (95%) of the Doctors who were COVID-19 positive were less than 40 years of age. Twelve percent of the Nurses and 23 % of other HCWs were more than 50 years of age. Around 57% (236/413) of HCWs infected with SARS-CoV-2 were males and 43% (177/413) were females.

Out of total HCWs employed in different departments of NH includes, 2758 were working in clinical departments either OPD or Wards, 408 were working in other clinical departments and 545 had no contact with patients. The distribution of SARS-CoV-2 infected HCWs was as follows: 29% physicians, 26% nurses, 46% healthcare assistants and other staff. Majority (85%) of the HCWs with COVID-19 were symptomatic and 15% were asymptomatic. Comorbidities were reported in 19% of HCWs with COVID-19 (Figure 1). Of these, 23 HCWs had more than one co-morbidities. Hypertension and Diabetes Mellitus were the most common co-morbidities reported. More than 4% percent (18/413) of HCWs with COVID-19 were also positive for *plasmodium vivax* Malaria.

We observed 11% prevalence of SARS-CoV-2 infection in HCWs with 2% of readmission. We recommend universal testing of HCWs and double negative testing to label HCWs as fit to discharge to optimize staffing levels during this current pandemic. Testing should also be extended to family members and other close contacts. The HCWs are the most precious resource for every country. Symptomatic HCWs reported higher duration for virus clearance, two mortalities and 2% reinfection rate, indicate wearing mask and hand hygiene should be practiced by all HCWs even after recovery from first episode. Although we report comparable infection with SARS-CoV-2 virus, more symptomatic and reinfection could be result of high viral load in dedicated facility catering more than 1000 COVID-19 patients.

### Discussion

In the present study, the interim analysis suggested 11% prevalence of SARS-CoV-2 infection among HCWs, 4% co-infection and 1% mortality. The prevalence of SARS-CoV-2 infection among HCWs in our study is higher than Italy, similar to Netherlands and lower than UK, Spain. During the initial five months of pandemic, NH was the only dedicated COVID-19 hospital catering to Mumbai city and Mumbai Metropolitan Region. Despite the heavy work load of COVID-19 cases, there is reasonably low prevalence of COVID-19 in HCWs. Additionally, equal proportion of doctors, Nurses and other HCWs were found to be infected with SARS-CoV-2 during first 5 months of pandemic with may support the PPE protocols in place at our institution. We reported higher incidence of symptomatic infection in doctors and nurses (84%), other HCWs (87%). The mortality of HCWs with COVID-19 was low in our study. China reported comparatively high mortality of HCWs with COVID-19.

Front-line HCWs are at increased risk of COVID-19 as compared to the general population because of close contact with COVID-19 patients. Moreover, HCWs with infection could cause secondary transmission among patients, family members, and the community. Therefore, it is important to investigate the infection risk of HCWs and the clinical characteristics of affected cases and possible source of infection either from the community, hospital acquired or close contact with COVID-19 family members.

To the best of our knowledge, this is the first study among HCWs with COVID-19 in a dedicated COVID-19 Hospital in India for capturing data on clinical presentation, natural history of the disease (virus clearance), co-infections, reinfection, response to treatment, consistent use of PPE and transmission of SARS-CoV-2 infection. It is expected to generate data of the worst affected city in India in a very
systematic manner and its interim analysis would help other states to plan their strategies well in advance to manage HCWs infected with SARS-CoV-2.

Present study will give an insight about socio-demographic determinant of the clinical presentation and the proportion of asymptomatic/symptomatic HCWs with COVID-19 in a reasonably large cohort. It will also provide an insight disease severity and viral clearance among HCWs. Limited information is available from the published literature on these aspects among HCWs, especially co-infection in endemic areas for malaria and dengue and viral clearance. Together, this data will aid in planning the strategies to handle the epidemic of COVID-19 among HCWs. This data is extremely important to develop rational testing strategies for testing HCWs and preventing secondary transmission of SARS-CoV-2 or entire group of corona viruses among fellow HCWs, patients, family members, and the community.

Although there is no report on prevalence of SARS CoV-2 in HCWs in India, the London study13 and study from China2 strongly suggest that policies are needed urgently for regular testing/surveillance which will protect both HCWs and patients.

Information on high risk exposure like possible break of personal protective equipment (PPE), performed aerosol generating procedures (AGPs) without appropriate PPE or facial protection or having accidental exposure to body fluids; will be more beneficial to the society and HCWs. PPE supply chain and equitable access to PPE should be a part of the deliberate and informed decision making about resource allocation. Even also if there are disinfection protocols in place for PPE reuse, there is no surety for prevention of infection. Therefore, we strongly discourage reuse of PPE, and it should not be advocated. Risk for front-line HCWs exposed to COVID-19 patients, reusing PPE is more compared to those not reusing it.

Bongiovanni et al12 studied the natural history of COVID-19 infection in HCWs and analysed the time required to clear COVID-19 infection among HCWs. Their study demonstrated that symptomatic HCWs infected by COVID-19 need more than 30 days to clear the virus and these findings can be applied to the general population also. Clinical presentations of malaria, dengue and other monsoon related illnesses in the endemic region strongly overlap with that of COVID-19 and hence pose an additional challenge for differential diagnosis.26 We plan to study presentation and viral clearance among co-infections. Also there is no mention if any HCWs received prophylaxis (like Hydroxychloroquine) in any published literature, we are planning to address this issue in our study. The objectives and the protocol of the present study are at par with these international papers and will open up an opportunity at the international level for data comparison and planning strategies to deal with such pandemic.

Our study has some limitations. First, this a single centre study. Secondly, we are not confirming distinct SARS-CoV-2 strain on genome sequencing in HCWs. Based on our results, we hope to recommend practice of hand hygiene, physical distancing, and wearing of masks in public places even by the recovered patients. These observations need to be confirmed in a different populations so that policy can be developed for protecting HCWs during current pandemic of COVID-19.

Asymptomatic carriers poses greater risk to fellow HCWs and also to non-COVID patients seeking treatment. Universal testing would also alleviate workforce depletion and protect HCWs.27 Testing only those HCWs with symptoms surely is going to miss many infected. We therefore suggest universal or mass screening of all HCWs at regular intervals rather than screening only symptomatic HCWs and testing should also be extended to family members and other close contacts. Antibody testing at regular intervals, can be the alternative option especially in resource poor countries. The final data analysis is ongoing and results are expected to be available by December 2021.

Acknowledgements

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Trial Registration

Study is registered with Clinical Trial Registry of India (Registration no: CTRI/2020/09/027516).

Ethics Approval

The study was approved by the Ethics Committees of TNMC (No. ECARP/2020/78 dated 13.08.2020).

Contribution to Authorship

NM had full access to all of the data in the study and take responsibility for the Integrity of the data and the accuracy of the data analysis. Concept and design: NM, RG, AC, PL, and VR. Analysis, or interpretation of data: All authors. Drafting of the manuscript: NM, AM, KM, MG. Critical revision of the manuscript for important intellectual content: NM, RG, KM. Statistical analysis: NM, RG, AM, KM. Administrative and technical or material support: NM, SM, SR.

References

Physician Health in the Times of COVID-19

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Abstract

Background and Objectives: A virtual registry study evaluating real world evidence on physicians’ use of prophylactic regimens for protection against SARS-CoV-2. This paper summarizes the interim results.

Methods: Physicians at risk of acquiring SARS-CoV-2 responded to online questions at baseline and 7 weeks post-baseline. Baseline data included demographics, prophylaxis regimen (including “no prophylaxis”) and start date. Participants who provided complete week-7 data (information on type of health facility (COVID/Non-COVID), number of presumed/confirmed cases exposed to, PPE use, SARS-CoV-2 testing and symptoms, regimen adherence and inter-current illness) comprised the Completer population. Limited data (regimen adherence, SARS-CoV-2 testing) was collected for participants who failed to provide complete week-7 data. Those providing limited/complete information comprised the Evaluable population.

Results: Of 369 enrolled participants, 182 (mean age 42±11.05 years) comprised the Evaluable population. They showed a male preponderance (67.6%). Practitioners from Maharashtra (59.9%) and specialties of Pediatrics, Internal Medicine, Anesthesiology and Critical Care (63.2%) accounted for the majority. ICMR’s HCQ prophylaxis regimen was initiated by 125 (68.7%) participants with 31 (17%) initiating ‘No prophylaxis’: The highest adherence was for the ICMR-regimen (87.2%).

In the Completer population comprising 150 participants, 87 were exposed to presumed (81) and/or confirmed cases (60). Most exposures to confirmed cases (49, 81.7%) were high-risk. PPE use was generally high (75-100%). Most participants (94.7%) did not report an AE. The proportions with an AE was similar with ICMR regimen (5.9%) and no prophylaxis (6.5%).

Interpretation and conclusions: Physicians in India preferred ICMR’s HCQ regimen. The regimen appears to be safe and associated with a high level of adherence.
For participants on a prophylactic regimen, baseline date was date of start of prophylaxis. For participants on ‘No prophylaxis’, baseline date was date of enrolment.

Fig. 1: Study Design

chloroquine. Pharmacokinetic models demonstrated that HCQ (400 mg twice a day) achieves adequate free lung tissue concentrations. The Indian Council of Medical Research (ICMR), even in the absence of supporting clinical evidence, issued an advisory (an emergency usage authorization) recommending the use of HCQ for those at high risk of acquiring infection, viz. close household contacts of patients diagnosed with SARS-CoV-2 infection (post-exposure prophylaxis, PEP) and healthcare workers (pre-exposure prophylaxis, PrEP).

The need to generate confirmatory evidence to support (or refute) the use of HCQ persisted. The pandemic situation, consequent lockdown and busy schedules of physicians precluded a randomized controlled trial in India. It became readily apparent that real world evidence (RWE) on the use of HCQ would be critical to inform public health policy.

A central virtual registry was established to gather RWE on the relative protection against acquisition of SARS-CoV-2 infection of different prophylactic regimens being taken by physicians, in terms of efficacy, safety and, adherence (compliance). We herewith publish interim results in view of the need for quick dissemination of the observations related to risk factors, adherence and inter-current illnesses (adverse events).

Materials and Methods

This registry-based observational study commenced enrollment after receiving approval from an Independent Ethics Committee, Ripon Independent Ethics Committee (registration number ECR/299/Indt/TN/2018) and following registration in the Clinical Trials Register of India (CTRI2020/04/024482). Asymptomatic physicians registered with the Medical Council of India (MCI) or any of the State Medical Councils, who were of the opinion that they were at high risk of acquiring SARS-CoV-2 infection due to their profession and were willing to provide data for registration and registry conduct were eligible to participate. The participants were approached through social media platforms, emails and word of mouth publicity, and were requested to register online.

The information sought at registration included participant’s name, medical council registration details, email id and mobile number (participant and a designee). To ensure that only physicians were enrolled, physician credentials were verified with registers available at MCI and State Medical Council websites in the public domain. The information provided at registration remained confidential, as it contained personally identifiable information (PII). This registration data captured in a registration database was accessible only to a small operations team (but not to the Investigators) who sent reminders to participants encouraging them to remain compliant with study requirements.

Participants conveyed their agreement to participate through an e-consent process, registered and, if eligible, were given a username and password by secure means. Using these credentials, they were required to respond to a set of questions at enrollment and seven weeks from their baseline date (Figure 1). This data was captured in a (different) clinical database. The clinical data was stored within the electronic data capture (EDC) system that was compliant with 21CFR (Code of Federal Regulations and with the EU General Data Protection Regulation (GDPR) and the US Health Insurance Portability and Accountability Act (HIPAA) and applicable local laws. The EDC did not hold any personally identifiable information.

The baseline information sought included: gender, age, weight, height, place (state) of practice, specialty, presence of comorbid conditions (terms could be selected from a pick list [diabetes, hypertension, known QTc prolongation on ECG]) or entered as free text, which prophylaxis regimen used (including no prophylaxis) and prophylaxis start date for those who were on a prophylaxis regimen at registration.

The operations team reminded participants through email, voice messages and short message service (SMS) to complete their week 7 data. Data collected at week 7 was for the interval between the participant’s baseline date and week 7. It included the type of facility the physician worked at, number of presumed and confirmed cases exposed to, type of exposure to confirmed case (WHO grading), use of personal protective equipment (PPE) among those exposed to confirmed cases, results of any tests for SARS-CoV-2 infection, modified World Health Organization (WHO) ordinal symptom scale, adherence to the prophylaxis regimen, inter-current illness (adverse events [AEs]) and concomitant medications taken after their baseline date. Data collection utilized standard WHO definitions and methodologies to enable cross-comparison with other studies across different regions and geographies.

Participants who failed to complete their week 7 data were sent reminders for about two weeks. If no data were provided, the participant or designee was contacted over the phone (documented in a telephone contact form) or via email, and limited data pertaining to adherence to prophylaxis regimen and results of SARS-CoV-2 testing, were then entered into the database.
Statistical analysis software, SAS (SAS Institute Inc. Cary NC USA) version 9.4 for Windows, was used for generating the data outputs. The data is presented for two populations: “Completer” who completed the questionnaire at baseline and week 7, and the “Evaluable” population who provided all baseline data but limited (for adherence and prophylactic efficacy) week 7 data. Medical history, inter-current illnesses (AEs) and concomitant medications in free text were not coded using any coding dictionary. Terms that were similar (e.g. hypertension/ essential hypertension/ HTN/ controlled hypertension) and could be grouped together (e.g. under the term ‘Hypertension’) were identified prior to being summarized. Categorical variables are shown as frequencies and percentages, and continuous variables as means with standard deviations or medians with range as appropriate.

The registry commenced enrolment on 7th April 2020. This paper describes the experience of participants who completed study prior to 19th June 2020.

Results

As of the cut-off date (19th June, 2020), 475 participants had registered for the study, with 369 (77.7%) of them enrolling into the study (providing baseline data) (Figure 2). Of these 369 participants, 161 have not yet completed the study and 26 were lost to follow-up. There were 182 participants in the Evaluable population (provided follow-up data), 150 of them were part of the Completer population (provided complete follow-up data).

Table 1: Demographics at baseline

<table>
<thead>
<tr>
<th></th>
<th>Completers N=150 (%)</th>
<th>Evaluable N=182 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean, SD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>42.6, 11.04</td>
<td>42.3, 11.05</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>103 (68.7)</td>
<td>123 (67.6)</td>
</tr>
<tr>
<td>Female</td>
<td>47 (31.3)</td>
<td>59 (32.4)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>N: 149</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td>Mean, SD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>167.7, 9.01</td>
<td>167.7, 9.09</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>N: 149</td>
<td>181</td>
</tr>
<tr>
<td></td>
<td>Mean, SD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>72.85, 13.359</td>
<td>73.06, 13.604</td>
</tr>
</tbody>
</table>

Percentages for gender are based on the number ‘N’ in the column header. Height and weight were optional fields, N varied.

Table 2: Physician professional details

<table>
<thead>
<tr>
<th></th>
<th>Completers N=150 (%)</th>
<th>Evaluable N=182 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Currently Practicing in Maharashtra</td>
<td>91 (60.7)</td>
<td>109 (59.9)</td>
</tr>
<tr>
<td>Uttar Pradesh</td>
<td>10 (6.7)</td>
<td>11 (6.0)</td>
</tr>
<tr>
<td>Tamil Nadu</td>
<td>8 (5.3)</td>
<td>11 (6.0)</td>
</tr>
<tr>
<td>Kerala</td>
<td>6 (4.0)</td>
<td>7 (3.8)</td>
</tr>
<tr>
<td>Other states and UTs</td>
<td>35 (23.3)</td>
<td>44 (24.2)</td>
</tr>
<tr>
<td>Specialty</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatrics</td>
<td>60 (40.0)</td>
<td>74 (40.7)</td>
</tr>
<tr>
<td>Internal medicine</td>
<td>17 (11.3)</td>
<td>22 (12.1)</td>
</tr>
<tr>
<td>Anesthesiology</td>
<td>9 (6.0)</td>
<td>11 (6.0)</td>
</tr>
<tr>
<td>Critical care</td>
<td>7 (4.7)</td>
<td>8 (4.4)</td>
</tr>
<tr>
<td>Family practice</td>
<td>7 (4.7)</td>
<td>8 (4.4)</td>
</tr>
<tr>
<td>Pulmonary medicine</td>
<td>5 (3.3)</td>
<td>6 (3.3)</td>
</tr>
<tr>
<td>Other Medical specialties</td>
<td>21 (14.0)</td>
<td>23 (12.6)</td>
</tr>
<tr>
<td>Surgical specialties</td>
<td>17 (11.3)</td>
<td>23 (12.6)</td>
</tr>
<tr>
<td>Other specialties</td>
<td>7 (4.7)</td>
<td>7 (3.8)</td>
</tr>
</tbody>
</table>

Percentages are based on the number ‘N’ in corresponding columns; Other Medical specialties included cardiology, gastroenterology, emergency medicine, nephrology, hematology-oncology; Surgical specialties included obstetrics and gynaecology, general surgery, plastic surgery, urology, surgical oncology; Other specialties included pathology, pharmacology, community medicine, out-patient and administration.

Table 3: Concern about contracting COVID-19 by exposure – Evaluable population

<table>
<thead>
<tr>
<th>Concerned about</th>
<th>Exposure to Confirmed/ Presumed COVID-19 cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Presumed not confirmed Confirmed 14 (%)</td>
</tr>
<tr>
<td></td>
<td>N = 134 (%)</td>
</tr>
<tr>
<td>Yes</td>
<td>125 (93.3) 29 (85.5) 12 (85.7)</td>
</tr>
<tr>
<td>No</td>
<td>9 (6.7) 5 (14.7) 2 (14.3)</td>
</tr>
</tbody>
</table>

Percentages are based on the number ‘N’ in corresponding columns.

In this communication we present findings for the Evaluable population (N=182) except where the information is available only for the Completer population (N=150). Most of the 182...
As shown in Table 1, in the Evaluable population a male preponderance (123, 67.6%) was observed in the gender distribution. The age of the 182 participants ranged from 24 to 67 years with a mean age (SD) of 42.3 (11.05) years.

A majority of the participants (109, 59.9%) were from the state of Maharashtra followed by Uttar Pradesh and Tamil Nadu. The remaining states contributed less than 5% each, to the study population (Table 2). The most common medical specialities were Pediatrics, Internal Medicine, Anaesthesiology, Critical Care, Family Practice and Pulmonary Medicine (accounting for 70.9% of participants), a distribution consistent with physicians likely to be exposed to, and involved in the care of patients with SARS-CoV-2.

Of the 182 Evaluable participants, 134 had no exposure to SARS-CoV-2 cases (Table 3). However, most of these participants (125/134, 93.3%) were still concerned that they might contract SARS-CoV-2. Likewise, most participants among those with confirmed exposure (12/14, 85.7%) were also concerned about contracting SARS-CoV-2.

Table 4 provides the distribution of the prophylactic regimen based on the participants concern about contracting SARS-CoV-2 infection. Twenty seven (16.3%) participants did not take prophylaxis despite being concerned about developing SARS-CoV-2. Interestingly, 12 participants (7.5%) took prophylaxis despite not being concerned about contracting SARS-CoV-2 infection.

A selection of prophylaxis regimens was provided in a pick list. This comprised the ICMR regimen, HCQ or CQ alone (daily, weekly, twice weekly or another frequency) or HCQ or CQ in combination with another drug. Over 2/3rd (125/182, 68.7%) of participants were on the ICMR-recommended prophylaxis regimen, 31 (17%) participants had not initiated any prophylaxis at baseline. Other regimens were reported by less than 15% of participants. The other regimens (n, %) comprised HCQ weekly (12, 6.6%), CQ weekly (7, 3.8%), HCQ alone in another frequency (2, 1.1%), HCQ daily (2, 1.1%) and HCQ in combination, CQ daily or CQ in another frequency (1, 0.5%).

A summary table of the medical history for the 182 participants is provided in Table 5. Hypertension, diabetes mellitus, hypothyroidism and asthma were the most commonly reported comorbidities.

The participants were provided with a pick list of concomitant medications based on: potential for increasing risk of QTc prolongation (azithromycin, amodiaquine, alpha-2 blockers), ocular toxicity (tamoxifen), drug-drug interactions (e.g. cimetidine, digoxin, cyclosporin), to be independently considered as an anti-viral (lopinavir,
Table 9: Adherence to prophylaxis regimens – Evaluable population

<table>
<thead>
<tr>
<th>Regimen reported at week 7</th>
<th>Participants providing information regarding adherence (N=182)</th>
<th>Baseline Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ICMR prophylaxis (N=125) n (%)</td>
<td>No prophylaxis (N=31) n (%)</td>
</tr>
<tr>
<td>ICMR prophylaxis</td>
<td>109 (87.2)</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td>No prophylaxis</td>
<td>12 (9.6)</td>
<td>26 (83.9)</td>
</tr>
<tr>
<td>Other prophylaxis*</td>
<td>4 (3.2)</td>
<td>3 (9.7)</td>
</tr>
</tbody>
</table>

Percentages are based on number of participants who provided complete or limited data sets within each set. * - Other prophylaxis regimen comprises of all non-ICMR prophylaxis regimens. Subjects may have switched between any of the non-ICMR regimens.

Table 10: Adverse event summary – Completers

<table>
<thead>
<tr>
<th>Adverse Event Term</th>
<th>ICMR Prophylaxis (N=101) n (%)</th>
<th>No Prophylaxis (N=31) n (%)</th>
<th>Other prophylaxis (N=18) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergy</td>
<td>1 (1.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Constipation and Fissure</td>
<td>0</td>
<td>1 (3.2)</td>
<td>0</td>
</tr>
<tr>
<td>Fever</td>
<td>1 (1.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fungal Vaginitis</td>
<td>1 (1.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (1.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Inflammatory Bowel Disease</td>
<td>1 (1.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Malaise</td>
<td>1 (1.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mild Soreness in Throat</td>
<td>0</td>
<td>1 (3.2)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea for a Day after Taking HCQ</td>
<td>1 (1.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Oral Ulcer</td>
<td>1 (1.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>1 (1.0)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* - No AEs were reported by participants on ‘Other prophylaxis’; Percentages are based on the number of subjects who completed Week 7 data within corresponding column. Reported AE verbatim terms that are not summarized here: ‘None’ Participant id UNITY-MH-00065. ‘Cytokine storm’ Participant id UNITY-MH-0024. Subject reported this adverse event but was lost to follow-up.

In the Evaluable population, 64 of 182 participants (35.2%) were on at least one concomitant medication. There were 14 participants on ACE inhibitors. HCQ, CQ, alpha-2 blockers, amodiaquine were taken by less than 10 participants. None of the other medicines on the pick list were taken by any participant. As many as 59 of 182 (32.4%) were taking medications not on the pick list. The most common being anti-hypertensive drugs (beta-blockers, calcium channel blockers, angiotensin receptor blockers), anti-diabetic drugs (biguanide, dipeptidyl peptidase 4 inhibitor, sulfonylurea), drugs for asthma (steroids, bronchodilators, leukotriene antagonist), thyroid supplements, statins, anti-platelet agents. In general, the concomitant medications were consistent with the medical history of participants.

Post-baseline data

About a third of the participants were from a dedicated COVID-19 facility. Participants were exposed to presumed (n=81) or confirmed (n=60) cases of SARS-CoV-2 over the 7 week period. There were 87 participants who were exposed to a presumed or confirmed case (Table 6).

Information on the type of exposure was collected for participants exposed to confirmed cases (N=60) (Table 7). Most participants (49/60, 81.7%) had high risk exposures with confirmed cases, i.e., presence during aerosol generating procedures, involvement in direct patient care and/or having face-to-face contact within 1 meter.

Generally, the participants had exceptionally high use (always or most of the time) of common PPEs such as single-use gloves (95%), mask (100%), face shield (86.7%) and disposable gown (76.6%) (Table 8).

Most of the 182 participants (139, 76.4%) continued on the regimen they started with, suggesting a high degree of adherence to the prophylactic regimen. The adherence to the regimen was 87.2% (109/125) and 83.9% (26/31) for the ‘ICMR prophylaxis’ and ‘No prophylaxis’ respectively (Table 9).

The distribution of AEs by baseline prophylaxis regimen for the Completers is provided in Table 10. Most participants (142/150, 94.7%) did not report an AE. No AEs were reported in participants who reported use of ‘Other prophylaxis’ regimens. The proportion of participants with an AE was generally similar with ICMR prophylaxis and no prophylaxis (5.9% and 6.5%, respectively). In the ICMR and no prophylaxis arms, there were 6 participants with 9 AEs and 2 participants with 2 AEs respectively. In the ICMR prophylaxis treatment arm, two participants reported multiple AEs: a 47-year old female (UNITY-MH-00171) with hypertension (on treatment with amlopidine) reported allergy, malaise and headache, all events of ‘moderate’ intensity; and a 44-year old male without co-morbidities (UNITY-MH-00023) reported oral ulcer and tinnitus, both events of ‘mild’ intensity. Each symptom, sign or diagnosis was reported only once, attesting to a lack of pattern among these conditions. The single patient with inflammatory bowel disease (IBD) had a past history of IBD.

Discussion

The prospective Registry study has enrolled 475 participants (physicians) up to the cut-off date (19-Jun-2020). However, this communication represents an interim report of 182 physicians (150 providing complete set of information and 32 providing partial set of information) who provided data up to 7 weeks from the baseline date. The participant physicians (mean age 42.3±11.05 years) were drawn from multiple specialties (with pediatricians predominating) working in COVID and non-COVID healthcare facilities in various states (Maharashtra being the largest contributor) of India. Sixty physicians reported exposure to a confirmed-case of SARS-CoV-2 and, reported a high frequency of use of medical mask. An additional 27 physicians were exposed to a suspected case of SARS-CoV-2. About 69% of physicians chose the HCQ-based prophylaxis mentioned in the ICMR advisory, with 17% choosing no prophylaxis. Just over 14% selected one of the several other prophylactic regimens. Most physicians continued with the initial regimen, with the highest adherence rate of 87% being seen with the ICMR-advised regimen. Adverse events were reported infrequently (5-7%) and were particularly rare with ICMR prophylaxis.
generally rated as mild to moderate by the physicians.

This is one of the earliest COVID-19-related studies initiated in India. Only one COVID-19 study was registered in the CTRI prior to the study’s registration. The study has enrolled physicians of all age-groups, working in various levels (junior level resident doctors and middle and senior level consultants) of COVID and non-COVID healthcare facilities from all over the country. Therefore, the sample can be considered as representative of physicians in India. There was a preponderance of physicians working in Maharashtra. However, this can be understood in the context of Maharashtra being the most affected Indian state in this epidemic to date. Similarly, pediatricians accounted for about 40% of the physicians. This could be related to the fact that three of the authors (SBB, VN, SM) are pediatricians who practiced in Maharashtra who spread word about this study among their contacts. However, this does not deprive the study of its generalizability, as in many hospitals (especially, public hospitals) junior and middle level doctors were allocated duties irrespective of the specialty.

Most physicians (93%) were concerned about contracting SARS-CoV-2 infection. A vast majority of physicians chose to take prophylaxis and several factors may be responsible for this decision: easy communicability of infection, lack of definitive treatment options, perceived ‘common’ fatal outcome and the relative non-availability of PPE at some centers in the early stages of the epidemic in India9,10 may have weighed on the minds of physicians. The ICMR regimen was, by far, the most common regimen subscribed to, having been chosen by 69% of all physicians and by 83% of those who decided to take any prophylaxis. Although, no clinical data about efficacy of HCQ in preventing SARS-CoV-2 was available, the demonstration of its activity in laboratory studies11,12 may have influenced their decision. In addition, proactive recommendation by India’s premier and trusted medical research body, the ICMR, lack of data on alternative drugs/ regimens and established safety record of HCQ over the last 6 decades must have acted in favor of the ICMR regimen. It is noteworthy that ICMR prophylaxis was the choice of the highest number of physicians, irrespective of exposure (not exposed or exposed to presumed and/or confirmed case) and irrespective of whether the physician was concerned about developing SARS-CoV-2 infection or not.

Interestingly, a significant minority (19%) took no prophylaxis despite being concerned about SARS-CoV-2. Lack of clinical data regarding efficacy of any of the prophylactic regimes proposed, concern about the side-effects of the prophylaxis drugs and perceiving PPE as adequate protection, may have persuaded some not to take any prophylaxis.

Fifty-three (29%) physicians reported comorbidities such as diabetes, hypertension, hypothyroidism and asthma. Diabetes is associated with higher mortality rates in adults infected with SARS-CoV-2.13 It is, therefore, not surprising that 10 physicians with diabetes chose to take prophylaxis (ICMR regimen: 8, other regimens: two). The fact that in diabetic patients, hypoglycemia is a labeled adverse event of HCQ13 does not seem to have deterred the enrolled physicians with diabetes. It is possible that they felt assured by the fact that in India, HCQ is widely used in the management of diabetes.14

Sixty physicians exposed to confirmed COVID cases reported that high-risk exposure in the form of aerosol-generating procedure was, expectedly, much rarer as compared to face-to-face (within 1 meter) exposure and involvement in direct care. Given such significant exposure, the use of PPE was expectedly very high. Gloves and masks were used always or most of the time (95-100%). Face shield and gowns were used slightly less frequently (77-87%). The lower use of certain types of protective equipment may be related to the type of work (goggles and face-shields preferred only while performing aerosol-generating procedures) and availability. This information could also be a pointer to the need for and areas of training.

The adherence to the regimen was consistently high across prophylactic regimens (77-87%). ICMR prophylaxis was associated with the highest level of adherence (87%) followed by those not on any prophylaxis (83.9%). In ICMR-prophylaxis group, 12 stopped prophylaxis, while 4 chose to shift to other prophylaxis. This shift, we think, is unlikely to be related to adverse events, as adverse events were very infrequently reported (6%) and, when reported, were of mild to moderate nature. We suspect that papers that reported lack of efficacy,15,16 or even worse outcomes (paper subsequently retracted)17 in patients treated with HCQ may have influenced their decision. Improved availability of PPE as the pandemic progressed, concerns about potential to cause hypoglycemia (especially in those receiving concomitant anti-diabetic therapy) could be other factors responsible for the switch to ‘no prophylaxis’.

Across the study population, adverse events were infrequent, being reported in 5% of physicians. The events were heterogenous, occurred singly, and their profile does not suggest prophylactic drug-specific symptoms, signs or diagnoses. The physicians were on a variety of concomitant drugs that included anti-hypertensive drugs (beta-blockers, calcium channel blockers, angiotensinreceptor blockers), anti-diabetic drugs (biguanide, dipeptidyl peptidase 4 inhibitor, sulfonylurea), asthma drugs (steroids, bronchodilators, leukotriene antagonist) thyroid supplements, statins, anti-platelet agents and aspirin. It is noteworthy that despite these medications, adverse events were reported infrequently. It may be noted, however, that the real incidence of adverse events not reported in the study may be up to 2% (upper bound of the 95% confidence limit for zero events in 150 participants) based on the ‘rule of three’.18

This study has a significant first to its credit, being the first virtual registry study among physicians in India. Interestingly, the virtual registry design was necessitated by the circumstances around the pandemic and the accompanying lockdown, which precluded study start-up activities for a conventional study. This study was prospective and initiated early in the course of the pandemic in India. The study utilizes standard definitions and methodologies (e.g. for symptom scoring of participants who get infected with SARS-CoV-2,2 interventional drug,2 type of exposure,2 thereby enabling cross-comparison with other studies across
different regions and geographies. Real world experience on the use of different regimens (especially ICMR regimen, recommended early during the course of the pandemic in India), and PPEs (frequency of use, distribution of different PPEs) forms part of some of the new information provided. Most importantly, all this information is obtained from medical professionals, which ensures high quality of data across all the parameters evaluated.

A key limitation is the relatively low number of physicians who provided post-baseline information. This precluded a meaningful evaluation of the prophylactic efficacy of different regimens. It is hoped that we will have sufficient data to report on this parameter in the final report, wherein we will have more complete information from a larger number of physicians. Despite a skew in terms of regions and specialties of the participants, we think that informations from the study can largely be extrapolated to the general medical community, and even to all healthcare workers (HCW). We do not have physicians reporting on reasons behind their actions (choice of prophylaxis, shift of prophylaxis, etc.) However, this was deliberately done to keep the questionnaire short with a view to minimize the engagement time for busy physicians and to avoid participant fatigue.

The study findings indicate that physicians in India working in different types and levels of COVID and non-COVID healthcare facilities heeded to the ICMR advisory and preferred its HCQ-based regimen over other regimens. The regimen was safe and hence, was associated with a high level of adherence. If we are able to confirm the efficacy of HCQ in preventing SARS-CoV-2 infection in the full report, this information has potential utility in policy decisions. In addition, this is the first study from India reporting on exposure levels and types of exposures experienced by physicians. These data will be useful for making comparisons and delineating training issues.

References

Nationwide Survey on the Knowledge, Attitudes and Perceptions among the Indian Adult Population regarding COVID-19

Abdul Rahman Hakeem1*, Kavin Baskaran2, Sruti Chandrasekaran3, Jagadeesh Menon4, Mettu Srinivas Reddy5, Mohamed Rela6

Abstract
Background & Objectives: Nearly three months after its first recorded case, the progression of the coronavirus disease (COVID-19) pandemic has been slow in India so far, with relatively low number of cases and deaths. The behavior of the general public will probably have the most important bearing on the course of the disease over the next few months in India. We aim to study the awareness, attitudes and perceptions of COVID-19 among the adult Indian population.

Methods: A cross-sectional online survey was conducted using the ‘Google Survey Forms’ between 29th March and 14th April 2020 and distributed through email and various social media groups.

Results: There were 1502 respondents, majority were male (56.7%), between 30-49 years (47.7%). 90% of the respondents had either an undergraduate or postgraduate degree, with a third of them being in the healthcare sector (34.6%). Most of the respondents were aware of the common symptoms of COVID-19, but worryingly only a third (31%) were aware of the risk of spread from infected asymptomatic individuals, which is a major concern in India. Majority were aware of the modes of virus transmission, but only two-thirds (68.6%) were aware of the safe physical distance (6 feet) for maintaining social distancing. A majority of respondents were appreciative of the government interventions in containing the virus spread and would support further extension of lockdown if necessary.

Conclusion: Despite limitations of generalizability, this survey has identified areas which the public health authorities need to target in future information campaigns.

Introduction
The coronavirus disease 2019 (COVID-19) has infected over 12 million people worldwide and more than half a million have died. Even though India had its first COVID-19 infection as early as 30th January, there has not been an exponential increase in cases as noted in the US and Europe. The Indian government has been appreciated about the way it was quick to close its international borders and enforce early lockdown. With 1.3 billion people, densely populated areas, informal settlements, large masses of migrant daily wage and economically disadvantaged workers, it is a considerable challenge to sustain the good work that has been done so far. As of 10th July 2020, India has about 2,76,000 confirmed COVID-19 cases with more than 20,000 deaths.

But with the recent increase in cases, it is estimated that if the spread continues at the current rate, India could see between 500,000 to 1.3 million cases by the middle of August 2020. The behavior of the general public will have the most important bearing on the course of the disease in India.

The aim of our survey was to study the awareness of COVID-19 among the Indian population and their attitudes and perceptions towards the social distancing and lockdown strategies.

Materials and Methods
A cross-sectional online survey was conducted using the ‘Google Survey Forms’ between 29th March and 14th April 2020. The survey

Table 1: Demographics of all the respondents (N=1502)

<table>
<thead>
<tr>
<th>Respondents</th>
<th>No. of</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30 years</td>
<td>526</td>
<td>35.0</td>
</tr>
<tr>
<td>30-49 years</td>
<td>716</td>
<td>47.7</td>
</tr>
<tr>
<td>50-69 years</td>
<td>238</td>
<td>15.8</td>
</tr>
<tr>
<td>&gt;70 years</td>
<td>22</td>
<td>1.5</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>851</td>
<td>56.7</td>
</tr>
<tr>
<td>Highest degree</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No education</td>
<td>2</td>
<td>0.1</td>
</tr>
<tr>
<td>Up to school level education</td>
<td>294</td>
<td>19.6</td>
</tr>
<tr>
<td>Undergraduate</td>
<td>35</td>
<td>2.3</td>
</tr>
<tr>
<td>Postgraduation</td>
<td>193</td>
<td>12.8</td>
</tr>
<tr>
<td>State</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamilnadu</td>
<td>1069</td>
<td>71.2</td>
</tr>
<tr>
<td>Kerala</td>
<td>71</td>
<td>4.7</td>
</tr>
<tr>
<td>Andhra Pradesh</td>
<td>64</td>
<td>4.3</td>
</tr>
<tr>
<td>Karnataka</td>
<td>73</td>
<td>4.9</td>
</tr>
<tr>
<td>Telangana</td>
<td>32</td>
<td>2.1</td>
</tr>
<tr>
<td>Pondicherry</td>
<td>7</td>
<td>0.5</td>
</tr>
<tr>
<td>New Delhi</td>
<td>42</td>
<td>2.8</td>
</tr>
<tr>
<td>Uttar Pradesh</td>
<td>14</td>
<td>0.9</td>
</tr>
<tr>
<td>Maharashatra</td>
<td>70</td>
<td>4.7</td>
</tr>
<tr>
<td>Madhya Pradesh</td>
<td>7</td>
<td>0.5</td>
</tr>
<tr>
<td>Gujarat</td>
<td>11</td>
<td>0.7</td>
</tr>
<tr>
<td>Orissa</td>
<td>12</td>
<td>0.8</td>
</tr>
<tr>
<td>West Bengal</td>
<td>30</td>
<td>2.0</td>
</tr>
<tr>
<td>Are you a healthcare provider?</td>
<td>980</td>
<td>65.2</td>
</tr>
<tr>
<td>Doctor</td>
<td>294</td>
<td>19.6</td>
</tr>
<tr>
<td>Nurse</td>
<td>35</td>
<td>2.3</td>
</tr>
<tr>
<td>Other healthcare worker</td>
<td>193</td>
<td>12.8</td>
</tr>
<tr>
<td>Has anyone of your family or friends infected with coronavirus</td>
<td>8</td>
<td>0.5</td>
</tr>
<tr>
<td>Yes</td>
<td>1446</td>
<td>96.3</td>
</tr>
<tr>
<td>No</td>
<td>38</td>
<td>2.5</td>
</tr>
<tr>
<td>Don’t know</td>
<td>8</td>
<td>0.5</td>
</tr>
</tbody>
</table>

1Consultant HPB and Liver Transplant Surgeon, 2Third Year Medical Student, 3Consultant Endocrinology & Diabetology, 4Consultant Paediatric Gastroenterology & Hepatology, 5Director & Consultant HPB and Liver Transplantation, 6Chairman & Director, Institute of Liver Disease & Transplantation, Dr. Rela Institute & Medical Centre, Chennai, Tamil Nadu; 7Corresponding Author

Received: 21.10.2020; Accepted: 03.11.2020
Table 2: Knowledge of COVID-19 among the respondents

<table>
<thead>
<tr>
<th>What are the main symptoms of Coronavirus infection (COVID-19)?*</th>
<th>No. of Responses (n=1502)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>1282</td>
<td>85.4</td>
</tr>
<tr>
<td>Breathlessness (i.e. difficulty breathing)</td>
<td>1412</td>
<td>94.0</td>
</tr>
<tr>
<td>Running nose</td>
<td>695</td>
<td>46.3</td>
</tr>
<tr>
<td>Loose motions</td>
<td>397</td>
<td>26.4</td>
</tr>
<tr>
<td>Tummy pain</td>
<td>126</td>
<td>8.4</td>
</tr>
<tr>
<td>Can an adult or child without any symptoms of the infection transmit the virus?</td>
<td>128</td>
<td>8.5</td>
</tr>
<tr>
<td>Never</td>
<td>704</td>
<td>46.9</td>
</tr>
<tr>
<td>Possible</td>
<td>203</td>
<td>13.5</td>
</tr>
<tr>
<td>Very less when compared to those with symptoms</td>
<td>467</td>
<td>31.1</td>
</tr>
<tr>
<td>Can spread the infection similar to those with symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct (Droplet) infection by coughing/sneezing</td>
<td>1398</td>
<td>93.1</td>
</tr>
<tr>
<td>Touching surfaces contaminated with respiratory secretions</td>
<td>1331</td>
<td>88.6</td>
</tr>
<tr>
<td>Touching someone infected with the virus</td>
<td>898</td>
<td>59.8</td>
</tr>
<tr>
<td>Faecal contaminants in drinking water or food</td>
<td>256</td>
<td>17.0</td>
</tr>
<tr>
<td>Which is the best means available at present to prevent COVID-19 infection?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccination</td>
<td>12</td>
<td>0.8</td>
</tr>
<tr>
<td>Antibiotic prophylaxis</td>
<td>9</td>
<td>0.6</td>
</tr>
<tr>
<td>Wearing face masks</td>
<td>83</td>
<td>5.5</td>
</tr>
<tr>
<td>Social distancing</td>
<td>1398</td>
<td>93.1</td>
</tr>
<tr>
<td>What do you understand by Social Distancing?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staying at least 6 feet away from people</td>
<td>1031</td>
<td>68.6</td>
</tr>
<tr>
<td>Staying at least 2 feet away from people</td>
<td>462</td>
<td>30.8</td>
</tr>
<tr>
<td>Attend mass gatherings</td>
<td>5</td>
<td>0.3</td>
</tr>
<tr>
<td>Carrying routine travel without restrictions</td>
<td>4</td>
<td>0.3</td>
</tr>
<tr>
<td>What are the precautions you are currently taking in view of the COVID-19?*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staying isolated at home</td>
<td>1321</td>
<td>87.9</td>
</tr>
<tr>
<td>Minimising contact with visitors and family members</td>
<td>774</td>
<td>51.5</td>
</tr>
<tr>
<td>Going out of home, but with a mask</td>
<td>272</td>
<td>18.1</td>
</tr>
<tr>
<td>Not following any restrictions</td>
<td>2</td>
<td>0.1</td>
</tr>
<tr>
<td>Wearing a face mask can completely protect one from getting infected with the coronavirus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>True</td>
<td>231</td>
<td>15.4</td>
</tr>
<tr>
<td>False</td>
<td>1271</td>
<td>84.6</td>
</tr>
<tr>
<td>When they get infected, what age groups are most likely to die from the coronavirus infection?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>24</td>
<td>1.6</td>
</tr>
<tr>
<td>Young adults</td>
<td>20</td>
<td>1.3</td>
</tr>
<tr>
<td>Older adults</td>
<td>1458</td>
<td>97.1</td>
</tr>
<tr>
<td>Those with other health problems are most likely to die from COVID-19 infection than those without any health problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1319</td>
<td>87.8</td>
</tr>
<tr>
<td>No</td>
<td>183</td>
<td>12.2</td>
</tr>
</tbody>
</table>

*These questions have multiple responses

was disseminated through the social messaging platform - WhatsApp, Facebook and through emails. The questions focused on their awareness of the COVID-19 symptoms, knowledge of the modes of transmission and available means of prevention and treatment. In particular, we were keen to know their perceptions of the steps taken so far to control its spread. We used a 22-point questionnaire; demographics (6 questions), COVID-19 awareness (8 questions), attitudes and perceptions (6 questions) and concerns (2 questions). Opportunity was also provided for conveying any additional concerns or suggestions in a free-text format.

Categorical variables are expressed as the frequencies and proportions (%) and continuous variables are presented as the mean ± standard deviation. Categorical variables were analysed by Fisher’s exact or chi-square test and continuous variables by unpaired student t-test or one-way ANOVA (Analysis of Variance). As a significant proportion of the respondents were healthcare workers, we also compared responses of healthcare workers and the general public to understand the difference between the two cohorts. P value of <0.05 was considered as statistically significant. All statistical analysis was carried out using SPSS version 26.0 (SPSS Inc., Chicago, IL, USA).

Results

There were 1502 respondents, majority were in the age group of 30-49 years (47.7%) with a slight male preponderance (56.7%). More than 90% of the respondents had either an undergraduate or postgraduate degree. More than two-thirds of the respondents were from the state of Tamilnadu (71.2%), with rest of the responses from 12 other states and one union territory. A third of the responses (34.6%) were from a healthcare worker (doctor, nurse or other health care provider such as pharmacist, laboratory technician). Eight of the respondents (0.5%) reported confirmed infection with novel coronavirus (n-CoV-2) in their family or social circle, but a larger proportion (10.1%, n=152) had some respiratory illness in the last 4 weeks.

Table 3: Attitudes and Perceptions of COVID-19 among the respondents

<table>
<thead>
<tr>
<th>What will you do if you or your family members develop symptoms of flu such as fever, cough or sore throat?</th>
<th>No. of Responses (n=1502)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit hospital as soon as symptoms develop</td>
<td>771</td>
<td>51.3</td>
</tr>
<tr>
<td>Visit local doctor as soon as symptoms develop</td>
<td>174</td>
<td>11.6</td>
</tr>
<tr>
<td>Stay at home, wait for symptoms to get better and if they get worse attend hospital</td>
<td>555</td>
<td>37.0</td>
</tr>
<tr>
<td>Continue your routine work, as it is only common cold and should get better</td>
<td>2</td>
<td>0.1</td>
</tr>
</tbody>
</table>

South Korea is testing more than 5000 people per Million population and seems to have the coronavirus disease under control. In India, only 10 people are being tested per Million population. Do you think Indian Government should test more people for coronavirus infection, so as to quarantine them (i.e. placing them in strict isolation measures)?

Strongly Agree 881 58.7
Agree 421 28.0
Neutral 146 9.7
Disagree 36 2.4

Strongly disagree 18 1.2

I think the period of lockdown is much needed and Indian Government has done a very good job in implementing it.

Strongly Agree 1032 68.7
Agree 364 24.2
Neutral 77 5.1
Disagree 21 1.4

Strongly disagree 8 0.5

I will be happy to support if the Indian Government extends the lockdown period to more than 21 days, if it is needed to protect the community spread

Strongly Agree 983 65.4
Agree 360 24.0
Neutral 113 7.5
Disagree 34 2.3

Strongly disagree 12 0.8

Which medium do you commonly depend on for getting information regarding COVID-19 problem? (multiple responses)

Television 1235 82.2
WhatsApp 543 36.2
Newspaper 643 42.8
Friends 224 14.9
Facebook 12 0.8
Others (COVID sites, WHO sites, Government sites, YouTube, etc) 1031 68.6
Table 4: Comparison of demographics, knowledge and attitude between the healthcare workers and non-healthcare public

<table>
<thead>
<tr>
<th></th>
<th>Healthcare workers (n=522)</th>
<th>Non-healthcare public (n=980)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30 years</td>
<td>229 (43.9%)</td>
<td>297 (30.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>30-49 years</td>
<td>246 (47.1%)</td>
<td>470 (48.0%)</td>
<td>0.786</td>
</tr>
<tr>
<td>50-69 years</td>
<td>44 (8.4%)</td>
<td>194 (19.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥70 years</td>
<td>3 (0.6%)</td>
<td>19 (1.9%)</td>
<td>0.061</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>276 (52.9%)</td>
<td>575 (58.7%)</td>
<td>0.035</td>
</tr>
<tr>
<td>Highest degree</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No education</td>
<td>0 (0.0%)</td>
<td>2 (0.2%)</td>
<td>0.722</td>
</tr>
<tr>
<td>Up to school level education</td>
<td>31 (5.9%)</td>
<td>98 (10.0%)</td>
<td>0.009</td>
</tr>
<tr>
<td>Undergraduation</td>
<td>197 (37.7%)</td>
<td>412 (42.0%)</td>
<td>0.118</td>
</tr>
<tr>
<td>Postgraduation</td>
<td>294 (56.3%)</td>
<td>468 (47.8%)</td>
<td>0.001</td>
</tr>
<tr>
<td>State</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamilnadu</td>
<td>396 (75.9%)</td>
<td>673 (68.7%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Kerala</td>
<td>20 (3.8%)</td>
<td>51 (5.2%)</td>
<td>0.286</td>
</tr>
<tr>
<td>Andhra Pradesh</td>
<td>22 (4.2%)</td>
<td>45 (4.6%)</td>
<td>0.837</td>
</tr>
<tr>
<td>Karnataka</td>
<td>9 (1.7%)</td>
<td>63 (6.4%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Telangana</td>
<td>5 (1.0%)</td>
<td>27 (2.8%)</td>
<td>0.035</td>
</tr>
<tr>
<td>Pondicherry</td>
<td>6 (1.1%)</td>
<td>1 (0.1%)</td>
<td>0.937</td>
</tr>
<tr>
<td>New Delhi</td>
<td>21 (4.0%)</td>
<td>19 (1.9%)</td>
<td>0.027</td>
</tr>
<tr>
<td>Uttar Pradesh</td>
<td>4 (0.8%)</td>
<td>10 (1.0%)</td>
<td>0.837</td>
</tr>
<tr>
<td>Madhya Pradesh</td>
<td>4 (0.8%)</td>
<td>3 (0.3%)</td>
<td>0.905</td>
</tr>
<tr>
<td>Maharashtra</td>
<td>13 (2.5%)</td>
<td>57 (5.8%)</td>
<td>0.245</td>
</tr>
<tr>
<td>Gujrat</td>
<td>3 (0.6%)</td>
<td>8 (0.8%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Orissa</td>
<td>4 (0.8%)</td>
<td>8 (0.8%)</td>
<td>0.757</td>
</tr>
<tr>
<td>West Bengal</td>
<td>15 (2.9%)</td>
<td>15 (1.5%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Has anyone of your family or friends infected with coronavirus?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 (0.6%)</td>
<td>5 (0.5%)</td>
<td>0.870</td>
</tr>
<tr>
<td>No</td>
<td>504 (96.6%)</td>
<td>942 (96.1%)</td>
<td></td>
</tr>
<tr>
<td>Don’t know</td>
<td>15 (2.9%)</td>
<td>33 (3.4%)</td>
<td></td>
</tr>
<tr>
<td>Have you had any respiratory illness in the last 4 weeks which worried you because of the current COVID-19 problem?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>81 (15.5%)</td>
<td>71 (7.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>441 (84.5%)</td>
<td>909 (92.8%)</td>
<td></td>
</tr>
<tr>
<td>What are the main symptoms of COVID-19?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>448 (85.8%)</td>
<td>831 (84.8%)</td>
<td>0.647</td>
</tr>
<tr>
<td>Breathlessness (i.e. difficulty breathing)</td>
<td>495 (94.8%)</td>
<td>917 (93.6%)</td>
<td>0.388</td>
</tr>
<tr>
<td>Running nose</td>
<td>238 (45.6%)</td>
<td>457 (46.6%)</td>
<td>0.741</td>
</tr>
<tr>
<td>Loose motions</td>
<td>158 (30.3%)</td>
<td>239 (24.4%)</td>
<td>0.016</td>
</tr>
<tr>
<td>Tummy pain</td>
<td>49 (9.4%)</td>
<td>77 (7.9%)</td>
<td>0.357</td>
</tr>
<tr>
<td>Can an adult or child without any symptoms of the infection transmit the virus?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>31 (5.9%)</td>
<td>97 (9.9%)</td>
<td>0.012</td>
</tr>
<tr>
<td>Possible</td>
<td>235 (45.0%)</td>
<td>469 (47.9%)</td>
<td>0.319</td>
</tr>
<tr>
<td>Very less when compared to those with symptoms</td>
<td>59 (11.3%)</td>
<td>144 (14.7%)</td>
<td>0.080</td>
</tr>
<tr>
<td>Can spread the infection similar to those with symptoms</td>
<td>197 (37.7%)</td>
<td>270 (27.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>What are the modes of transmission of infection in COVID-19?</td>
<td>Direct (Droplet) infection by coughing/sneezing</td>
<td>492 (94.3%)</td>
<td>906 (92.4%)</td>
</tr>
</tbody>
</table>

186 out of 294 doctors were aware of 6 feet physical distance for ‘social distancing’; 27 of the 81 responses were from doctors; “132 out of 294 doctors would visit hospital as soon as flu symptoms develop.”

**Awareness of COVID-19**

Majority of the respondents were aware of the common symptoms of COVID-19, such as fever (85.4%), breathlessness (94%), but only one-fourth were aware of diarrhea (26%) as one of the symptoms. It is worrying that only a third (31%) of the respondents knew that the COVID-19 infection can be spread by asymptomatic patients similar to those with symptom. 13% and 8% of the respondents believed that asymptomatic people are either very less likely or will never spread infection compared to symptomatic patients respectively. Majority of the recipients were aware of droplet spread by coughing/sneezing (93.1%), spread through surface contact (88.6%), and touching infected person/secretions (59.8%). But only 17% were aware of the oral/faeco-oral route as one of the modes of transmission. 93.1% of the recipients understood the importance.

Which is the best means available at present to prevent COVID-19 infection?
- Vaccination: 3 (0.6%)
- Antibiotic prophylaxis: 1 (0.2%)
- Wearing face masks: 29 (5.6%)
- Social distancing: 489 (93.7%)

**What do you understand by Social Distancing?**
- Staying at least 6 feet away from people: 326 (62.5%)
- Staying at least 2 feet away from people: 192 (36.8%)
- Attending mass gatherings: 1 (0.2%)
- Carrying routine travel without restrictions: 3 (0.6%)

**What are you currently taking in view of the COVID-19?**
- Wearing a face mask can completely protect one from getting infected with the coronavirus: True: 431 (82.6%) False: 830 (84.7%)
- When they get infected, what age groups are most likely to die from the coronavirus infection?
  - Children: 9 (1.7%) Young adults: 4 (0.8%) Older adults: 509 (97.5%)

**What will you do if you or your family members develop symptoms of flu?**
- Visit hospital as soon as symptoms develop: 259 (49.4%) Visit local doctor as soon as symptoms develop: 43 (8.2%)
- Continue your routine outside work, as it is only common cold and should get better: 2 (0.4%)
Fig. 1: Comparison of attitudes and perceptions responses between healthcare workers (HCW) and non-healthcare public (NHP) of social distancing, but only two-thirds (68.6%) were aware of the safe physical distance of 6 feet (2 metres), which is recommended by the Centers for Disease Control and Prevention (CDC). A majority of respondents (97.1% and 87.8%) were aware that older adults and people with other health problems were high risk for COVID related mortality respectively. 15.4% of the respondents wrongly believed that wearing face mask can completely protect them from getting the COVID infection (Table 2).

Attitudes and perceptions of COVID-19

Only a third of the respondents (37.0%) were clear of the advice from the Indian Council of Medical Research (ICMR), which is to stay at home if they develop any flu-like illness and only if symptoms get worse, they should attend hospital. Worryingly, more than half of them (51.3%) will attend hospital for flu-like symptoms, which does risk a larger population. 86.7% of the respondents felt that the Indian Government should increase coronavirus testing from the current rate of 10 per million population, so as to prevent silent spread and hence enforce strict quarantine for the asymptomatic infected individuals. Their attitude towards the lockdown was very positive, with 92.9% felt that the Indian government has done a very good job in implementing it. This also meant that a vast majority (89.4%) would be happy to support further lockdown, more than 21 days (i.e.) beyond 14th April 2020 (Table 3).

Comparison between healthcare workers and non-healthcare public

Majority of the healthcare workers were of a younger age group and were more likely to have a postgraduate degree, when compared to the non-healthcare public. Being aware of the risk of transmission from asymptomatic people, the healthcare workers (15.5%) were more worried during a respiratory illness in the last 4 weeks, than the non-healthcare public (7.2%; P<0.001). Although majority of the non-healthcare public were aware of the common symptoms of COVID-19, their awareness of asymptomatic transmission was limited with only a fourth (27.6%) felt that spread can happen from those without symptoms. Interestingly, the non-healthcare public showed greater awareness of the recommended social distance to be maintained when compared to healthcare workers (71.9% vs 62.5%; P<0.001). It is infact worrying that only 186 out of 294 doctors (63.2%) were aware of this safe distance. Considering their pivotal role in this pandemic, healthcare workers were less likely to stay isolated at home (82.6%), when compared to non-healthcare public (90.8%; P<0.001). However, healthcare workers (41.8%) were more likely to wait and watch for symptoms to settle than non-healthcare public (34.4%; P=0.006) (Table 4). Both the healthcare workers and non-healthcare public were appreciative of the efforts taken by the government and would further support extension of lockdown, however, they would want government to increase the testing for coronavirus. Figure 1 shows the Likert scale responses with no difference in P value between the healthcare workers and non-healthcare public.

Concerns regarding COVID-19

Majority of them obtained their COVID-19 news from television (82.2%), newspaper (42.8%), WhatsApp (36.2%) and their friends (14.9%). They also gathered information from a number of official and unofficial COVID related sites, which did concern them regarding the validity of the information. Respondents reported wrong information received on social media platforms, difficult access to food and other basic amenities and job loss and economic meltdown, due to the prolonged lockdown as major concerns (Table 5).

Discussion

In a survey of 1502 sociodemographically diverse adult Indian population, we found that the respondents have good knowledge of the common symptoms of COVID-19 and the main modes of disease transmission. However, only a third were aware that asymptomatic individuals can spread the infection similar to symptomatic patients, which is a cause of concern. The ICMR reported that 80% of the infections in India are from asymptomatic carriers, which along with the low numbers of testing in India, is a cause of considerable concern. On the positive aspects, the participants were quite appreciative of the government interventions in containing the virus spread and would be happy to support further extension if lockdown extends beyond 14th April,
Table 5: An illustrative selection of concerns raised by the respondents regarding COVID-19

<table>
<thead>
<tr>
<th>Concerns regarding COVID-19:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>“What if the COVID-19 infection becomes like a regular flu? How long can we follow the lockdown?”</td>
<td></td>
</tr>
<tr>
<td>“Transparency in reporting the cases is important”</td>
<td></td>
</tr>
<tr>
<td>“If anybody gets infected and cured, will coronavirus affect them again?”</td>
<td></td>
</tr>
<tr>
<td>“Government should take steps to stop fake news and rumours”</td>
<td></td>
</tr>
<tr>
<td>“Will taking Hydroxychloroquine prevent one from getting COVID-19?”</td>
<td></td>
</tr>
<tr>
<td>“Why there is no mass testing for COVID-19?”</td>
<td></td>
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<tr>
<td>“Is climate change important role in spread of COVID-19?”</td>
<td></td>
</tr>
<tr>
<td>“Is India prepared when we move towards the COVID-19 peak?”</td>
<td></td>
</tr>
<tr>
<td>Misinformation on COVID-19:</td>
<td></td>
</tr>
<tr>
<td>“Alcohol is the best medicine for coronavirus, as it kills virus – yes or no?”</td>
<td></td>
</tr>
<tr>
<td>“What kind of food helps in preventing COVID-19 infection?”</td>
<td></td>
</tr>
<tr>
<td>“Government should provide Vitamin C tablets for immunity”</td>
<td></td>
</tr>
<tr>
<td>“Can high blood pressure patients recover from COVID-19 if they get infected?”</td>
<td></td>
</tr>
<tr>
<td>“Avoiding cold food is more important I think”</td>
<td></td>
</tr>
<tr>
<td>“Face masks will protect me, so I am not worried”</td>
<td></td>
</tr>
<tr>
<td>Concerns regarding prevention and cure:</td>
<td></td>
</tr>
<tr>
<td>“When will be getting a vaccine for COVID-19?”</td>
<td></td>
</tr>
<tr>
<td>“How is the government going to protect healthcare professionals”</td>
<td></td>
</tr>
<tr>
<td>“Create more testing facilities at the earliest”</td>
<td></td>
</tr>
<tr>
<td>“Why adequate PPE kits not available?”</td>
<td></td>
</tr>
<tr>
<td>Concerns due to lack of access and lockdown:</td>
<td></td>
</tr>
<tr>
<td>“Ensuring food, security and fulfilling basic needs of people under or near ‘Below Poverty Line’ is the need of the hour to avoid mass restlessness and starvation in the near future”</td>
<td></td>
</tr>
<tr>
<td>“Ensuring our police maintaining law and order also gets proper rest and food”</td>
<td></td>
</tr>
<tr>
<td>“Worried about job loss”</td>
<td></td>
</tr>
<tr>
<td>“Arrangement of food and shelter for migrant workers”</td>
<td></td>
</tr>
<tr>
<td>“Strict action must be taken against those who violate lockdown”</td>
<td></td>
</tr>
<tr>
<td>“Concerns is buying fruits and vegetables for high cost”</td>
<td></td>
</tr>
<tr>
<td>“One hour exercise outside should be allowed like in the Western countries”</td>
<td></td>
</tr>
<tr>
<td>Other general concerns:</td>
<td></td>
</tr>
<tr>
<td>“Government should have quarantined all the International inbound passengers during the initial phase itself; we were late in undermining the onset and transmission”</td>
<td></td>
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<tr>
<td>“People who are driving outside during lockdown, their diving license should be cancelled”</td>
<td></td>
</tr>
<tr>
<td>“Why are private hospitals not empowered so that more cases can be monitored and isolated”</td>
<td></td>
</tr>
<tr>
<td>“How to meet financial commitment as an employer, when the source of business from outside India is shut completely?”</td>
<td></td>
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<tr>
<td>“Very less awareness in poor population”</td>
<td></td>
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<tr>
<td>“All deaths reported as pneumonia or ARDS, should have novel coronavirus tested”</td>
<td></td>
</tr>
<tr>
<td>“Has the government started building temporary hospitals for the possibility of stage 3 infection?”</td>
<td></td>
</tr>
<tr>
<td>“Trade with China should be cut off internationally, as the spread of COVID-19 seems intentional”</td>
<td></td>
</tr>
<tr>
<td>“Economic downfall is my biggest concern”</td>
<td></td>
</tr>
<tr>
<td>“Lockout should extend”</td>
<td></td>
</tr>
<tr>
<td>“Thousands of people are gathering at bus stations, why Government is not taking necessary steps to avoid this”</td>
<td></td>
</tr>
</tbody>
</table>

which has now been revised to 3rd May.\ootnote{15} The lack of awareness of asymptomatic spread, false reassurance regarding the protection provided by a face mask and steps to be taken in case of any flu-like symptoms should be key areas to target in information campaigns by the public health authorities and the media.

Although social media plays a key role in spreading awareness and knowledge about public health, it also spreads fake news, misconception and myths, which is a major concern in mitigating the spread of COVID-19.\ootnote{16,17} Majority of the respondents are to an extent, confused by the information available on various social platforms. Their concern with the current situation was apparent by the fact that 3100 questions were asked by 1502 respondents, an average of 2.1 questions per person. With the ease of internet access and over 350 million social media users in India, a large proportion of the populace are unaware of the right source for fact checking.\ootnote{18} A majority of the fake news issue with social media can be controlled if safe social media usage is practiced and we stop the practice of forwarding messages from unconfirmed sources.\ootnote{17,19,20} The healthcare authorities should use social media along with the traditional media in a positive way to build public trust, cooperation and better adherence to social distancing and lockdown restrictions.\ootnote{16,21}

A surprising finding in this survey was that respondents in the healthcare sector were as likely to have misconceptions and concerns and COVID as the general public. Infact, it does appear that in some areas the non-healthcare respondents appeared to be more clued in. This again reiterates the need for better public messaging and active involvement of healthcare worker community in this area.\ootnote{22,23}

The major limitation of this survey is that the respondents are from a young and well educated demographic in India with access to mobile phone and social media. This would hence be a niche group very different from the vast Indian demographic of semi-literate or illiterate individuals. The responses to questions regarding their knowledge of COVID cannot be generalized and should be considered as the knowledge level of the top percentile of the population, with the majority having much lesser information. It is also likely that most of the respondents of the survey are in a secure job, so their attitudes to the national lockdown and possible extension will not reflect the majority of the population working in the unorganized sector. However, the findings of this survey do identify major areas that public health education programs should target.

Author contribution

ARH, JM and MSR planned and designed the study. ARH, KB, SC and JM disseminated the survey and collected the responses for the study. ARH performed the statistical analysis and wrote the manuscript. SC, JM and MSR reviewed the manuscript, which was finalised by MR.

Abbreviations

ANOVA: Analysis of variance; CDC: Centers for Disease Control and Prevention; COVID-19: Coronavirus disease 2019; ICMR: Indian Council of Medical Research; nCoV: Novel coronavirus

References

Post COVID Inflammation Syndrome: Different Manifestations Caused by the Virus

Chandrashekara S1*, Prakruthi Jaladhar2, Shruti Paramshetti2, Veena Ramachandran2, Sayid Fahad Nizar2, Devaraj Kori3

Abstract

Background: Incidence of viral pneumonia has been reported in several patients diagnosed with COVID-19. The infection has also been linked to the development of inflammatory syndromes and related clinical manifestations.

Result: The present study discusses four cases of COVID infection showing varying clinical features. The post-COVID inflammation syndrome was associated with non-specific inflammation and post viral arthritis in three cases. One other subject had vasculitis leading to central retinal artery occlusion.

Conclusion: As the number of cases of COVID-19 cases has been increasing globally, it is advisable that physicians consider the possibility of post-COVID manifestations while examining patients with non-specific inflammation. A short course of NSAIDs and hydroxychloroquine regimen has been found to be beneficial for alleviating symptoms, and in rare cases with organ threatening inflammation, steroids may be required.

COVID-19 infection, which was first reported as a cluster of pneumonia from Wuhan, China, in December 2019, has rapidly emerged as a global pandemic. However, the recent trends from the country shows an exponential increase in daily spike and the total cases has crossed 68 lakhs mark, according to the Health Ministry data published on October 10, 2020. The officially confirmed deaths from the disease is around 1,05,554.

Though the COVID infection is acute, it can trigger several inflammatory pathways. Though pathophysiology of immune response is unclear, there are reports of several post-infection complications including reactive arthritis and post-infection fibrosis.14 The present study deals with a case series on post COVID inflammation syndrome involving non-specific inflammation and retinal vasculitis.

CRAO following COVID

A 66-year-old male suffering from leukoderma was referred for evaluation and management of rashes over the legs, polyarthitis and sudden unilateral blurring of vision following COVID infection (Figure 1). Further investigations revealed that he had elevated D dimer (1450 ng/mL) and ferritin (590 ng/mL) levels, but negative for antiphospholipid antibody (APLA), ANA, and ANCA. The ophthalmic evaluation suggested bilateral panuveitis along with right eye central retinal artery occlusion (CRAO) with retinitis and macular vessel vasculitis. Based on the history, examination findings and investigations, a diagnosis of post-COVID hyperinflammatory syndrome was made. He was initiated with pentoxifylline 400 mg, aspirin 75 mg, and before tapering dose of...
A 78-year-old male with a history of diabetes mellitus and bronchial asthma on regular treatment presented with fever for 20 days, and pain and swelling along with burning sensation in both lower limbs (Figure 2). Further investigation revealed that he had elevated CRP (18.80 mg/L), ESR (48 mm/hr), D dimer (1134 mg/dL), lactic acid dehydrogenase (488 U/L), ferritin (450 mg/dL). He was positive for COVID IgG antibody (6.8 mg/dL). On the basis of history and investigation, diagnosis of hyperinflammatory syndrome following COVID infection was made. He was started with anti-inflammatory medication celecoxib 200 mg twice daily.

A 31-year-old lady presented with multiple joint pain for past one week, following an episode of fever with chills 25 days ago. Fever was treated by a local physician with antipyretics and a course of antibiotics. Fever subsided in 3 days and the patient continued to have malaise following fever episode. Since the previous investigation revealed that she was negative for chikungunya IgG, she was referred to our centre for further evaluation. Clinical investigations revealed that she had raised ESR and CRP, with other serarkers like RF, anti-CCP, ANA being negative. However, she was found to be positive for COVID IgG testing. She was diagnosed to have post-COVID-19 arthritis and was initiated with hydroxychloroquine 200 mg twice a day with anti-inflammatory drugs.

### Discussion

The occurrence of post-infective and para-infectious arthritis following a viral infection is not rare, but with the current pandemic, the incidence has increased. Several clinical forms of post-viral arthritis have been described. Chikungunya infection is the commonest to produce such arthritis. Chikungunya could be distinguished from other virally-mediated arthritis by the pattern of joint pain, skin rash, and muscle, bone or back pain, and absence of thrombocytopenia, poor circulation and respiratory or gastrointestinal symptoms. Whereas for dengue, joint pain and arthritis, and presence of thrombocytopenia, leukopenia, and nausea are early predictors. The syndrome of polyarthritis, post-infection arthritogenic alphaviral infections, may be mediated through an unknown autoimmune response due to the presence of cross-reactive epitopes between viral and human proteins. Absence of a robust cytokine response during acute infection is correlated with the development of chronic joint pain. Low TNF alpha, IL-13, IL-2, and IL-4 during acute infection are predictive of chronic joint pain in chikungunya. There are several studies to illustrate the possibility of development of arthritis, as the direct invasion of the synovium and the joint tissue by the virus causes immune complex formation and deposition in the joint tissue, and immune dysregulation.

With an exception of the patient who developed CRAO, other patients had milder and less stormy disease course. One of the patients had asymptomatic infection and was tested based on her history of contact. Arthritis, as a post-viral phenomenon in COVID-19, appears to be having a different mechanism compared to the complication of CRAO. All three patients who had arthritis had robust antibody response and had not progressed to oxygen dependency.

Arthritis is seen as a post-COVID manifestation. It is generally benign and respond to NSAID. It is highly important to distinguish this manifestation from other causes of arthritis.

### References

Effectiveness of Convalescent Plasma Therapy in the Treatment of Moderate to Severe COVID-19 Patients: A Systematic Review and Meta-Analysis

Bikash Ranjan Meher¹, Biswa Mohan Padhy², Smita Das³, Rashmi Ranjan Mohanty⁴*, Kanhaiyalal Agrawal⁵

Abstract

Though Convalescent plasma therapy (CPT) is being used for management of COVID-19, the evidence is still equivocal. So, we carried out this study to evaluate the currently available data to provide evidence about CPT in COVID-19 patients. RCTs and observational studies with sample size with more than 5 were included in the analysis. Out of 196 studies, 12 studies were selected for systematic review and meta-analysis was carried out for 6 studies having a control arm. For dichotomous values, risk ratio (RR) and 95% confidence interval was expressed.

Main outcomes: All-cause mortality, clinical improvement by day 7 and viral detection by day 7 were the defined outcome measures before starting of data extraction.

Result: For 6 studies (2 RCTs and 4 observational studies) with 474 patients, the overall pooled RR for all-cause mortality was 0.61 (95%CI: 0.37 to 0.99, P= 0.04). Only RCTs and only observational studies for all-cause mortality showed pooled RR of 0.60 (95% CI: 0.33 to 1.10, P=0.10) and 0.48 (95% CI: 0.17 to 1.36, P= 0.17) respectively. There was risk of bias in the studies due to randomization process and confounding. Sensitivity analysis was carried out only for observational studies. The overall pooled RR for clinical improvement by day 7 and viral detection by day 7 were 1.12 (95%CI: 0.96 to 1.31, P=0.16) and 0.19 (95%CI: 0.09 to 0.60, P< 0.0001).

Conclusion and relevance: Though the review suggests modest utility of CPT in reducing all-cause mortality, improving clinical outcome, and early viral clearance, it should be interpreted cautiously.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a global problem since its outbreak in December 2019 in China.¹ By mid-August, approximately 20 million people got infected and 0.7 million succumbed to death worldwide due to coronavirus disease -19 (COVID-19).² Although antimalarials chloroquine and hydroxychloroquine, antivirals remdesivir and favipiravir, and the antibiotic azithromycin are being repurposed for the treatment of COVID-19 no specific drug or treatment has yet proven effective.³⁴ The current management is mostly limited to general supportive care and symptomatic treatment. Convalescent plasma (CP) is the liquid part of blood collected from patients who have recovered from an infection. It contains high level of antibodies and is usually considered safe for use. There are instances in the past where CP has been used in the treatment of infectious diseases like Severe Acute Respiratory Syndrome-1 (SARS -1), Middle East respiratory syndrome (MERS), and Ebola.⁵⁶ A study of patients with severe pandemic influenza A (H1N1) revealed that those on convalescent plasma therapy (CPT) had low fatality as compared to patients not treated with CP.⁷ Similarly, shorter hospital stays and reduced mortality were observed in patients with SARS who received CP when compared with patients who received only methylprednisolone.⁸

Due to these encouraging outcomes in respiratory infections, CPT is currently being explored as one of the treatment options in patients suffering from COVID-19. Although US-FDA has not yet formally granted approval for routine use of CP in COVID-19 patients, it has recently issued emergency use authorization.⁹ Few randomised clinical trials (RCT) and observational studies have been performed to evaluate the efficacy and safety of CP in COVID 19.¹⁰⁻¹¹ Based on this limited data, some systematic reviews and meta-analysis have been conducted.¹²⁻¹⁴ However, the evidence regarding the use of CPT is still equivocal. As the situation is evolving and newer studies are being reported across the world, we carried out this systematic review and meta-analysis to evaluate the currently available data and provide evidence on the effectiveness of CP in COVID-19 patients. This may help physicians and policymakers to make an informed decision for management of COVID-19 patients.

Materials and Methods

Development and registration of protocol

The PRISMA-P guidelines was followed for writing the protocol. It was registered in prospective register of systematic review (PROSPERO) with registration number CRD42020203901.
Secondary outcomes
1. Clinical improvement in the form of change in WHO ordinal score for clinical improvement in COVID 19 patients within 7 days of CPT.\(^{20}\)
2. Change in RT-PCR status of COVID 19 patients within 7 days of CPT.

Information source
The Cochrane Library, PubMed, EMBASE, and SCOPUS were searched for articles on CPT in moderate to severe COVID 19 from inception till 20th August 2020. We also searched the Pre-print servers medRxiv and bioRxiv. For unpublished data we checked the International Clinical Trials Registry Platform (ICTRP).

Search strategy
A combination of subject terms and keywords using the PICO method were employed. Medical Subject Headings (MeSH) as well as keyword variants of all relevant terms were used for the search. The algorithm was designed on a combination of keywords, and Boolean operators like: “Convalescent plasma therapy” OR “Plasma therapy” OR “Hyperimmune serum” AND “COVID 19” OR “Severe acute respiratory syndrome coronavirus 2”.

The reference lists of retrieved articles were also checked for additional information.

Data extraction and management
Four review authors (RRM, BRM, SD, KA) independently extracted and assessed the quality of data according to the predefined eligibility criteria following Cochrane Collaboration’s guidelines. Disagreements were resolved by discussion and consultation with fifth review author (BMP). The extracted data was recorded in a pre-designed data extraction format which includes basic information, study design, patient characteristics, treatment details, and outcome measures.

Assessment of risk of bias in included studies
The risk of bias in studies included for meta-analysis was assessed by Cochrane risk of bias tool. We used version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) and Risk of Bias in Non-Randomized Studies - of Interventions (ROBINS-I) for RCTs and observational studies respectively.

Types of studies
All types of studies including RCTs and observational studies with or without control arm with sample size more than 5 were included in the analysis. The systematic review was conducted for all studies whereas meta-analysis was performed only for studies with a control arm.

Types of Participants
Adult human subjects of both gender with a diagnosis of RT-PCR confirmed moderate to severe COVID 19 treated in hospital with CP along with other modes of treatment were included in the study.

Moderate COVID 19 was defined as any patients requiring oxygen therapy with pneumonia in X-RAY chest and/or HRCT thorax. Severe COVID 19 was defined as any patient with X-RAY chest and/or HRCT thorax finding of pneumonia requiring non-invasive/invasive ventilation and/or requiring presser support/renal replacement therapy/ECMO.

Following are the exclusion criteria of our study:
1. The studies in which, the efficacy/outcome of CPT has not been measured or could not be extracted in terms of WHO ordinal score for clinical improvement in COVID 19.\(^{20}\)
2. The studies with sample size less than 5.

Types of intervention
In all the included studies, the intervention was administration of CP in moderate to severe COVID 19 patients along with usual treatment irrespective of the dose, timing, and frequency of administration of CP.

Types of comparator
For RCTs and observational studies having control arm, the comparison was change in study outcomes between usual treatment with and without CPT.

Outcome measures
Primary outcome
1. All-cause mortality: Death in COVID 19 patients due to any cause during the available period of follow up in the studies.

Secondary outcomes
1. Clinical improvement in the form of change in WHO ordinal score for clinical improvement in COVID 19 patients within 7 days of CPT.\(^{20}\)
2. Change in RT-PCR status of COVID 19 patients within 7 days of CPT.

Identification
- Studies identified through database searches (n=196)
- Studies screened by title/abstract (n=196)
- Full text evaluated (n=20)
- Studies included (n=12)
- Systematic review (n=12)
- Meta-analysis (n=6)
- RCT=2
- Observational study=4

Screening
- Studies excluded by title/abstract (n=176)
- Studies excluded [Not meeting the inclusion criteria] (n=8)

Eligibility

Included
- Meta-analysis
- Observational study
- RCT
- Systematic review
- Studies screened by title/abstract
- Full text evaluated
- Studies included

Included
- Studies identified through database searches
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Fig. 1: PRISMA flowchart of study selection process

Information source
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Primary outcome
1. All-cause mortality: Death in COVID 19 patients due to any cause during the available period of follow up in the studies.

Secondary outcomes
1. Clinical improvement in the form of change in WHO ordinal score for clinical improvement in COVID 19 patients within 7 days of CPT.\(^{20}\)
2. Change in RT-PCR status of COVID 19 patients within 7 days of CPT.
Table 1: Characteristics of included studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Study period</th>
<th>Study population</th>
<th>Primary outcome (all-cause mortality)</th>
<th>Secondary outcome (with in day 7)</th>
<th>Additional comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>With CPT</td>
<td>Without CPT</td>
<td>With CPT</td>
</tr>
<tr>
<td>Li et al 2020</td>
<td>China</td>
<td>February to April 2020.</td>
<td>n= 52</td>
<td>Median age-70</td>
<td>8/51</td>
<td>12/50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Male-27</td>
<td>Median age-69</td>
<td>(One patient withdrew from the study)</td>
<td>6/47</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Female-25</td>
<td>male-33</td>
<td></td>
<td>(One patient received CPT after randomization)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Moderate disease-23</td>
<td>female-18</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Severe disease-28</td>
<td>moderate disease-22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zeng et al 2020</td>
<td>China</td>
<td>April 2020</td>
<td>n=6</td>
<td>Median age-61.5</td>
<td>5/6</td>
<td>14/15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Male-5</td>
<td>Median age-73</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Female-1</td>
<td>Male-11</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Moderate-0</td>
<td>Female-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Severe-6</td>
<td>Moderate-0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duan et al 2020</td>
<td>China</td>
<td>January to February 2020.</td>
<td>n=7 instead of 10</td>
<td>Median age-52.5</td>
<td>0/7</td>
<td>3/10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(3 participants in treatment group were baseline RT PCR negative before intervention)</td>
<td>Male-6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Female-4</td>
<td>Moderate-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Severe-3</td>
<td>Moderate-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Male-25</td>
<td>Median age-63</td>
<td>(historic matched control)</td>
<td>3/10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Female-14</td>
<td>Male-33</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Moderate-14</td>
<td>Female-10</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Severe-25</td>
<td>Moderate-7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gharbharan et al 2020</td>
<td>Netherland</td>
<td>April to June 2020.</td>
<td>n = 43</td>
<td>Median age-63</td>
<td>6/43</td>
<td>11/43</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Male-33</td>
<td>Median age-61</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Female-10</td>
<td>Male-29</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Moderate-1</td>
<td>Female-14</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Severe-42</td>
<td>Moderate-7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rasheed et al 2020</td>
<td>Iraq</td>
<td>April to June 2020.</td>
<td>n =21</td>
<td>Median age-63</td>
<td>1/21</td>
<td>8/28</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Moderate-0</td>
<td>Moderate-0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Severe-21</td>
<td>Moderate-0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studies without control arm</td>
<td>Shen et al 2020</td>
<td>China</td>
<td>January to March 2020.</td>
<td>n=5</td>
<td>Median-60</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Male-3</td>
<td>Admission to CPT duration varies from 10 to 22 days</td>
<td>0</td>
<td>5(100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Female-2</td>
<td>Disease severity:</td>
<td>0</td>
<td>5(100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Moderate-0</td>
<td></td>
<td>0</td>
<td>5(100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Severe-5</td>
<td></td>
<td>0</td>
<td>5(100)</td>
</tr>
</tbody>
</table>
Data analysis

Cochrane Program Review Manager 5.3 software was used for the meta-analysis. For dichotomous values, risk ratio (RR) and 95% confidence interval was expressed in accordance with Cochrane Handbook for Systematic Reviews of Interventions. $I^2$ statistic was used to check heterogeneity among eligible studies. The random-effect model was used for data synthesis.

Assessment of publication bias

Funnel plot was used to assess the presence of publication bias. We also used Egger’s test (Comprehensive meta-analysis software: Evaluation version) for quantifying the asymmetry due to publication bias.

Grade of evidence

GRADE profiler software (V 3.6.1) was used for quality assessment of the evidence.

Results

Description of studies

The database search resulted in 196 studies. After screening and removal of duplicates, 20 studies were selected for evaluation of the full text, among those 12 studies were selected for systematic review and meta-analysis as per our inclusion criteria. Out of those, 12 studies, only 6 studies having a control arm (2 RCTs and 4 observational studies) with 474 patients were included in the meta-analysis. The PRISMA flowchart of study selection is depicted in Figure 1.

Out of 5546 patients in the 12 studies included in this review, 5243 patients had received CPT along with usual care. For the 6 studies included in the meta-analysis, the RCTs provided data about 189 patients. In the 4 studies included in the meta-analysis, the usual treatment group had received CPT after randomization. Among these, 2 studies (Rasheed et al, Zeng et al) had a total of 27 patients in the CPT group and 43 patients in the usual treatment group. The other 2 studies (Duan et al and Liu et al) had 10 and 39 patients respectively in the CPT group and used historical control groups for comparison. Among all the 6 studies, 44 cases were moderate COVID 19 and 125 cases were severe COVID 19 in the CPT group. Similarly, in the control group, 29 cases were moderate COVID 19 and 107 cases were severe COVID 19. The data regarding the severity of COVID 19 in the historical control group were not available. As the study by Liu et al had not reported the exact number of deaths, we calculated the numbers from the reported percentages (13% for CPT and 25% for the usual treatment group). The characteristics of studies included for meta-analysis and systematic review are depicted in Table 1.

Risk of bias in included studies

The risk of bias assessment of all studies included in the meta-analysis was carried out for the primary outcome (all-cause mortality). The use of RoB-2 reported that both the RCTs had “some concerns” regarding the risk of bias. In the 4 observational studies included in the meta-analysis, there was “critical” risk of bias in all. The result of the risk of bias assessment of RCTs and observational studies is depicted in Figure 2.

Effects of intervention

In the 6 studies with control arm included in the meta-analysis, the effect of administration of CP in addition to usual therapy was assessed by measuring the pooled effect on the primary and secondary outcomes. The forest plots for primary and secondary outcomes are depicted in Figures 3, 4. Primary outcome (all-cause mortality)

All 6 studies in the meta-analysis had reported a reduction in all-cause mortality with the use of CP. Test for heterogeneity for the pooled studies
Among the studies and the pooled RR was 0.48 (95% CI: 0.17 to 1.36), which indicated a beneficial but statistically non-significant effect of adding CP (P=0.17). The study by Zeng et al., accounted for the heterogeneity and when it was removed in sensitivity analysis, the test for heterogeneity became non-significant (Chi² = 1.32, df=2, (P=0.52), I²=0%). The RR did not change considerably and was 0.41 (95% CI: 0.14 to 0.87) and significantly favoured the addition of CP compared to usual therapy only (P=0.02).

**Secondary outcomes**

**Clinical improvement by day 7**

All the 4 studies included in the meta-analysis reported clinical improvement by day 7 and were analysed for this secondary outcome.

The test of heterogeneity was not significant (Chi²=1.38, df=3, (P=0.71), I²=0%). The random effect model revealed that adding CP led to non-significant clinical improvement by day 7 compared to usual therapy only (RR=1.12, 95% CI: 0.96 to 1.31, P=0.16).

**Virus detection by day 7 (RT-PCR)**

Out of the 4 studies, only 2 studies that reported the detection of virus by RT-PCR by day 7 were included in the analysis. The test for heterogeneity was not significant (Chi² =0.27, df=1, (P=0.60), I²=0%) and the random effect model revealed that the RR for detectable viral load by day 7 was 0.19 (95%CI: 0.09 to 0.60). This implied that there is a statistically significant reduction in the detection of the virus with RT-PCR by day 7 in patients who were administered CP compared to patients on usual therapy only (P<0.0001).

**Publication bias**

Funnel plot suggested the presence of publication bias due to asymmetry. Egger's test was statistically significant for publication bias for the primary outcome of all-cause mortality (Intercept -1.67, 95% CI: -2.31 to -1.02, P=0.001).

**Grade of evidence**

For all the outcomes (primary and secondary), the evidence was assessed using GRADE profiler. For all-cause mortality, in all the 6 studies included in the meta-analysis, there was moderate evidence for adding CP to usual therapy as the anticipated absolute effect was 112 fewer deaths per 1000 patients compared to usual therapy alone. However, the quality of evidence was very low. Even when data from only the two RCTs were considered, moderate evidence for the use of CP was found with 99 fewer deaths per 1000 patients compared to usual therapy alone. However, the quality of the evidence was still low.

Similarly, moderate evidence was found for the secondary outcomes of clinical improvement by day 7 and virus detection with RT-PCR by day 7 with the addition of CP with the anticipated absolute effect of 68 more showing improvement by day 7 and 538 fewer being RT-PCR positive by day 7 per 1000 patients, compared to usual therapy alone. The quality of the evidence for these two outcomes was low and very low respectively.

In the 6 studies without control arm not included in the meta-analysis, all-cause mortality ranged from 0% to 23% suggesting a modest effect of adding CP to usual therapy.23-28 Clinical improvements by day 7 was reported to be 100% in 2 studies.24,25

The detailed analysis of the summary of evidence is depicted in Table 2.

### Table 2: Risk of bias assessment of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
<th>D4</th>
<th>D5</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al 2020</td>
<td>S</td>
<td>L</td>
<td>SC</td>
<td>L</td>
<td>L</td>
<td>SC</td>
</tr>
<tr>
<td>Gharrbaran et al 2020</td>
<td>SC</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>SC</td>
</tr>
<tr>
<td><strong>Domains:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D1: Bias due to randomization process</td>
<td>Low (L): Some concern (SC):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D2: Bias due to deviation</td>
<td>High (H):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D3: Bias due to missing outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D4: Bias due to measurement of outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D5: Bias due to selection of reported result</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

**Post-publication bias**

Egger's test was statistically significant for publication bias for the primary outcome of all-cause mortality (Intercept -1.67, 95% CI: -2.31 to -1.02, P=0.001).
Discussion

In this systematic review and meta-analysis, we have attempted to include all the contemporary evidence regarding the use of CP in COVID-19 patients. As there were only 2 published RCTs, we combined them with observational studies for estimating the pooled effect. Though there is a difference in methodology and substantial heterogeneity between RCTs and observational studies, there are many examples of meta-analysis combining them due to several reasons like an insufficient number of RCTs, lack of long-term outcomes in RCTs, evaluation of safety and efficacy in real-life scenarios. Moreover, the test of heterogeneity in the 6 pooled studies was not statistically significant. The
pooled estimate suggested a statistically significant reduction in all-cause mortality when CP was added to usual therapy with RR of 0.61 (P= 0.04). However, the significant effect should be considered cautiously as the upper limit of the 95% CI of the RR was 0.99 and quite close to 1.

We also conducted subgroup analysis taking RCTs and observational studies separately into consideration and found that pooled effect from neither the RCTs nor the observational studies favoured the addition of CP in significantly reducing all-cause mortality. The observational study by Zeng et al, accounted for the heterogeneity and when it was removed in sensitivity analysis, the test for heterogeneity became non-significant. The RR of 0.41 (95% CI: 0.14 to 0.87) after the removal of Zeng et al, showed a significant reduction in all-cause mortality with the addition of CP in the pooled observational studies. This finding was also supported by the observational studies without control groups where all-cause mortality ranged from 0% to 23%. The possible reasons for the variability in the effect may be attributed to delay in initiating CPT (median duration 21 days), elderly patients (median age > 50 years), and presence of comorbidities like diabetes, hypertension, obesity, pre-existing lung diseases, and associated organ failure.

The RR of 1.12 for clinical improvement by day 7 suggested some benefit with CPT that was not statistically significant. Apart from the above-listed conditions, other possible contributors for limited clinical improvement might be the shorter duration of follow up (7 days), variability in dose, and timing of CP administration in the absence of well-defined guidelines. However, there was a significant decrease in virus detection by RT-PCR by day 7 when CP was added to usual treatment (RR 0.19, P <0.0001). Early viral clearance may decrease the possibility of immune hyperactivity, cytokine storm and shorten the disease course, apart from limiting the transmission of infection.30

Though we have included a greater number of studies, our findings are broadly in concurrence with some of the systematic reviews on the efficacy of CPT in COVID-19.17,18 We have excluded the large observational study by Joyner et al from the meta-analysis as it was without a control arm.27 Additionally, we also excluded the study by Chen et al as it was not a primary study and was based on data compiled from 3 other observational studies.31 Inclusion of both these studies could have contributed to the significant reduction in all-cause mortality, greater clinical improvement, and higher viral clearance reported by a recent meta-analysis from India.19

**Strength and Limitations**

Our review has included a greater number of studies covering wide geographies and patients with different ethnicities. The WHO ordinal scale for clinical improvement was used for greater objectivity. Since we conducted the meta-analysis by pooling data from RCTs and observational studies, subgroup analysis and sensitivity analysis was carried out to confirm the robustness of our test.

Limitations of the study are the inclusion of studies with small sample sizes and high risk of bias. Other limitations include variations in patient profile, concomitant medications, dose and timing of CPT and follow up time.

**Conclusion**

This review suggests the modest utility of CPT in reducing all-cause mortality, improving clinical outcome, and early viral clearance in patients with COVID-19. However, in view of low to a very low quality of evidence currently available, clinicians should interpret our findings with caution. Currently, many clinical trials are ongoing, and clear recommendations...
Table 2: Grade of evidence for included studies

Convalescent plasma compared to No convalescent plasma for COVID-19

Bibliography: Meta-analysis

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No of Participants</th>
<th>Quality of the evidence (GRADE)</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effects</th>
<th>Risk with No convalescent plasma</th>
<th>Risk difference with Convalescent plasma (95% CI)</th>
<th>Study population</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>472 (6 studies1)</td>
<td>VERY LOW1,2</td>
<td>RR 0.61 (0.37 to 0.99)</td>
<td>Anticipated absolute effects</td>
<td>Risk with No convalescent plasma</td>
<td>Risk difference with Convalescent plasma (95% CI)</td>
<td>288 per 1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>‘due to risk of bias, publication bias’</td>
<td></td>
<td></td>
<td>Study population</td>
<td>112 fewer per 1000</td>
<td>(from 3 fewer to 181 fewer)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Moderate</td>
<td>Study population</td>
<td>99 fewer per 1000</td>
<td>(from 166 fewer to 25 more)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>187 (2 studies)</td>
<td>LOW1,2</td>
<td>RR 0.60 (0.33 to 1.10)</td>
<td>Anticipated absolute effects</td>
<td>Risk with No convalescent plasma</td>
<td>Risk difference with Convalescent plasma (95% CI)</td>
<td>247 per 1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>‘due to risk of bias, publication bias’</td>
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<td></td>
<td>Study population</td>
<td>159 fewer per 1000</td>
<td>(from 254 fewer to 110 more)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>282 (4 observational studies)</td>
<td>VERY LOW1,2</td>
<td>RR 0.48 (0.17 to 1.36)</td>
<td>Anticipated absolute effects</td>
<td>Risk with No convalescent plasma</td>
<td>Risk difference with Convalescent plasma (95% CI)</td>
<td>306 per 1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>‘due to risk of bias, publication bias’</td>
<td></td>
<td></td>
<td>Study population</td>
<td>68 more per 1000</td>
<td>(from 25 fewer to 175 more)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>336 (4 studies2)</td>
<td>LOW2</td>
<td>RR 1.12 (0.96 to 1.31)</td>
<td>Anticipated absolute effects</td>
<td>Risk with No convalescent plasma</td>
<td>Risk difference with Convalescent plasma (95% CI)</td>
<td>565 per 1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>‘due to risk of bias, publication bias, large effect, plausible confounding would change the effect’</td>
<td></td>
<td></td>
<td>Study population</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>217 (studies)</td>
<td>QUALITY OF EVIDENCE</td>
<td>RR 0.09 (0.03 to 0.27)</td>
<td>Anticipated absolute effects</td>
<td>Risk with No convalescent plasma</td>
<td>Risk difference with Convalescent plasma (95% CI)</td>
<td>655 per 1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Study population</td>
<td>530 fewer per 1000</td>
<td>(from 386 fewer to 596 fewer)</td>
</tr>
</tbody>
</table>

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio; GRADE: Working Group grades of evidence; High quality: Further research is very unlikely to change our confidence in the estimate of effect; Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.; Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.; Very low quality: We are very uncertain about the estimate.

will only emerge following their completion and publication in the future.

Author contribution

RRM developed the concept. Search, data extraction, and quality assessment was carried out by RRM, BRM, SD, KA. Resolution of disagreement was carried out by BMP. Statistical analysis, and statistical inferences was done by BRM and BMP. Manuscript was written by RRM, BMP, and BRM. The final version was approved by all authors for publication.

Acknowledgement

We are thankful to Dr. Rituparna Maiti, of Department of Pharmacology, AIIMS, Bhubaneswar for his constructive suggestions during conduct of this study.

References

The Syndromic Spectrum of COVID-19 and Correlates of Admission Parameters with Severity-outcome Gradients: A Retrospective Study

Anil Gurtoo¹, Aparna Agrawal¹, Anupam Prakash², LHMC Medicine COVID-19 Investigator Group³, Ravinder Kaur⁴, Manoj Jais⁵, Rama Anand⁶, Sunita Sharma⁶, Shailaja Shukla⁶, Ritu Singh⁷

Abstract

Background: Clinical and laboratory features of COVID-19 may have regional variations. This study aimed to discern their association with severity of illness and mortality in tertiary setup of Delhi, India.

Methods: Retrospective data of hospitalised COVID-19 patients over 3 months (end March to June 2020) were evaluated for symptom profile, blood investigations and chest radiograph data and classified according to COVID-19 severity and as survivors and non-survivors.

Results: Average age (n=182) was 46.1 years, male to female ratio 1.4:1. Fever (51.1%), cough (49.4%) and breathlessness (48.3%) were the commonest symptoms (alone and in combination) and meta-analysis [published online ahead of print, 2020 Feb 13]. JAMA 2020; 323:1582-1589. doi:10.1001/jama.2020.4783

Conclusion: Greater prevalence of symptoms (alone and in combination) and derangements in blood biochemistry are seen in severe COVID-19 compared to mild or moderate cases, and also in non-survivors compared to survivors.

Introduction

The world is faced with the COVID-19 pandemic, a disease which has gained entry in the International Classification of Diseases (ICD), and is set to enter the texts of medicine. A pandemic can have varying manifestations since it affects human beings across countries, continents with different topographies, across different geographic regions, and in different contexts.
The collected data was segregated according to the severity of COVID-19 (as per the MoHFW, Government of India guidelines) into three categories—mild, moderate and severe—and the clinical features and investigative profile outlined in these three categories of severity. Also, collected data was tabulated in two groups of survivors and non-survivors (mortality group), and likewise clinical features and investigative profile outlined in these two groups.

Various clinical, laboratory and radiological parameters were analysed for proportions of various signs and symptoms at presentation, means and standard deviations were calculated for various durations and laboratory parameters. Statistical analyses were further performed to see for differences by applying ANOVA to compare between the severity categories, and Student’s t-test between survivors and non-survivor groups. Chi-square test was used for statistical analysis in case of data which was non-parametric. P<0.05 was taken as significant.

**Results**

Total number of COVID-19 patients was 182 with mean age of 46.1 ± 16.4 years, and male to female ratio of 1.4:1. Common symptoms encountered in the patients are tabulated in Table 1. Fever, cough and breathlessness were the three main symptoms with which patients were admitted to the hospital, each witnessed in approximately half of the patients. About one in ten patients had productive cough (11% of those having cough at presentation). 4 patients were found to have ageusia and 6 patients had anosmia. However, since this symptom was not noted in the initial days of the pandemic, the exact proportion of patients who had such symptoms cannot be calculated.

Table 2 shows various clinical parameters in mild, moderate and severe COVID-19 patients. Symptoms at presentation included fever and

### Table 1: Common Symptoms encountered in COVID-19 patients

<table>
<thead>
<tr>
<th>Symptoms (Number of Patients)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (n=178)</td>
<td>91 (51.1%)</td>
</tr>
<tr>
<td>Cough (n=182)</td>
<td>90 (49.4%)</td>
</tr>
<tr>
<td>Breathlessness (n=176)</td>
<td>85 (48.3%)</td>
</tr>
<tr>
<td>Myalgia (n=180)</td>
<td>18 (10.0%)</td>
</tr>
<tr>
<td>Abdominal Pain (n=170)</td>
<td>12 (7.1%)</td>
</tr>
<tr>
<td>Loose Motion (n=170)</td>
<td>11 (6.5%)</td>
</tr>
<tr>
<td>Chest Pain (n=173)</td>
<td>10 (5.8%)</td>
</tr>
<tr>
<td>Sore Throat (n=128)</td>
<td>4 (3.1%)</td>
</tr>
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</tr>
<tr>
<td>Sore Throat (n=128)</td>
<td>4 (3.1%)</td>
</tr>
</tbody>
</table>

**Table 2: Association between Severity and clinical parameters at admission**

<table>
<thead>
<tr>
<th>All Parameters</th>
<th>Severity</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total No.</td>
<td>Mild (n = 61)</td>
</tr>
<tr>
<td>Age (Years)</td>
<td>38.6 ± 15.4</td>
<td>46.4 ± 14.6</td>
</tr>
<tr>
<td>Gender</td>
<td>107</td>
<td>33/107 (30.8%)</td>
</tr>
<tr>
<td>Gender</td>
<td>0.426</td>
<td></td>
</tr>
<tr>
<td>Fever duration prior to admission (days)</td>
<td>4.05 ±3.32</td>
<td>5.81 ± 5.7</td>
</tr>
<tr>
<td>Fever Duration After Admission</td>
<td>1.7 ± 1.1</td>
<td>2.8 ± 2.2</td>
</tr>
<tr>
<td>Fever Total Duration (Days)</td>
<td>5.4 ± 3.3</td>
<td>8.1 ± 6.7</td>
</tr>
<tr>
<td>Fever + Breathlessness (Present)</td>
<td>5.9 ± 3.5</td>
<td>8.1 ± 6.7</td>
</tr>
<tr>
<td>Fever + Cough (Present)</td>
<td>6/36 (10.1%)</td>
<td>13/61 (21.3%)</td>
</tr>
<tr>
<td>Fever + Cough + Breathlessness</td>
<td>5/60 (8.3%)</td>
<td>12/59 (20.3%)</td>
</tr>
<tr>
<td>Present (n=170)</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Comorbidities (present)</td>
<td>125</td>
<td>11 (15.8%)</td>
</tr>
<tr>
<td>Pulse Rate (beats per minute)</td>
<td>92.8 ± 12.4</td>
<td>94.4 ± 14.8</td>
</tr>
<tr>
<td>Respiratory Rate (per minute)</td>
<td>16.8 ± 2.4</td>
<td>19.2 ± 4.6</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>139.2 ± 144.7</td>
<td>116.4 ± 16.6</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>75.1 ± 115.5</td>
<td>74.4 ± 9.3</td>
</tr>
<tr>
<td>Saturation of O2 on room air</td>
<td>97.6 ± 1.2</td>
<td>95.8 ± 2.7</td>
</tr>
</tbody>
</table>

**Methodology**

The first COVID-19 patient was admitted at LHMC on 27th March 2020. This study is a retrospective study based on data collected and collated from the medical records of COVID-19 patients from March to end June 2020. The study was approved by the Institutional Ethics Committee. All clinical data of admitted patients was filled in a COVID-19 Clinical Case proforma, which was part of the official case file. A total of 182 case record proformas were analysable. All clinical features, laboratory features and radiological findings for the purpose of the study were collected from the COVID-19 Clinical Case proforma and transcribed on to Microsoft Excel. Since it was a retrospective study, few case records were incomplete, so the denominators for various symptoms which were analysable are indicated against each symptom. Also many new features (symptom/laboratory abnormalities) were added later to the initial features, as the disease progressed and new data came to light. Complete blood counts and biochemical parameters were performed on separate autoanalyzers, while the chest x-rays of covid patients were digitally obtained. Chest X-rays (n=98) were scored based on a 18-point severity scale called Brixia. Parameters which were collected and tabulated under different headings included—documented symptom profile in entirety, haemoglobin, total leucocyte counts (TLC), absolute neutrophil and lymphocyte counts (ANC and ALC), platelet count, neutrophil to lymphocyte ratio (NLR), random plasma glucose, serum urea, serum creatinine, serum bilirubin, serum transaminases (ALT and AST) and Brixia score on chest X-ray.

The collected data was segregated according to the severity of COVID-19 (as per the MoHFW, Government of India guidelines) into three categories—mild, moderate and severe and the clinical features and investigative profile outlined in these three categories of severity. Also, collected data was tabulated in two groups of survivors and non-survivors (mortality group), and likewise clinical features and investigative profile outlined in these two groups.

Various clinical, laboratory and radiological parameters were analysed for proportions of various signs and symptoms at presentation, means and standard deviations were calculated for various durations and laboratory parameters. Statistical analyses were further performed to see for differences by applying ANOVA to compare between the severity categories, and Student’s t-test between survivors and non-survivor groups. Chi-square test was used for statistical analysis in case of data which was non-parametric. P<0.05 was taken as significant.
Breathlessness at presentation was 67% respectively in the severe category, and 72% and 52% in the moderate category, and 72% and 40-45% patients of the mild category. 

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Survivors (n=122)</th>
<th>Non-survivors (n=60)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC (x 103/ microlitre)</td>
<td>27 7.95 ± 4.4</td>
<td>40 11.39 ± 6.7</td>
<td>0.009</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>27 11.7 ± 2.3</td>
<td>38 11.3 ± 2.7</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Investigation parameter Mild COVID-19 Moderate COVID-19 Severe Covid-19 p-value

Breathlessness was observed in only 14.7% of mild cases, 45.2% of moderate and 89% of severe cases. Highly significant association of severity of COVID-19 was seen with increasing age, presence of fever, cough, breathlessness at admission, alone and in different combinations (p < 0.001). Duration of some symptoms like fever and breathlessness also had a bearing on severity. Patients with higher total duration of fever (average 11 days) and presence of fever after admission were more likely to have a severe disease (p < 0.003). Presence of breathlessness after admission (4 days in severe and 2 days in mild COVID category) was also associated with greater likelihood of severe COVID-19 (p=0.049). However, duration of breathlessness and fever prior to admission did not bear any effect on severity. Low oxygen saturation and increased respiratory rate were also highly significant as they were the defining criteria. High pulse rate, was also found to be significantly associated with disease severity. Patients with presence of chest pain or altered sensorium were more likely to be suffering from moderate to severe COVID-19.

Of out 182, 60 patients (32.9%) expired. On correlating the age of patients with their outcome (Table 3), we found that average age of patients who died (54.8 ± 13.8 years) was significantly higher than those who survived (41.7 ± 16 years, p <0.001). The survival rate reduced with advancing age (χ² = 36.2, p <0.001) declining from 90% in 18-30 years age group to 18% in 71-80 years age group (Table 3). All three octogenarians in the study survived. Average total duration of fever was higher in the non-survivor (mortality) group compared to the survivor group (p <0.001). Average total duration of breathlessness in the mortality group was 7.5 ± 4.1 days, which was comparable to the survival group (6.5 ± 3.9 days, p =0.183). When fever, breathlessness and cough were present together it had a significant impact on the prediction of mortality (47.2% in mortality group and 19.1% in survival group, Chi square - 14.433, p < 0.001). 125 (68.7%) patients had co-morbidities. 90% patients in the mortality group as against 59% patients in the survival group had one or more comorbidities (p < 0.001). In the mortality group, 51.1% of patients had diabetes, 35% had hypertension, 5.6% had chronic obstructive pulmonary disease (COPD), 3.3% had chronic liver disease (CLD) and 1% had chronic liver disease (CLD) and 1% had...
kidney disease (CKD).

Table 4 highlights the investigational parameters according to severity of COVID-19 in the study group. TLC, ANC, NLR, blood urea and serum transaminases significantly increased while ALC decreased as severity of COVID-19 worsened. Around half of the patients in moderate and three-fourths in severe COVID-19 had transaminitis while elevated blood urea levels were present respectively in one-third and two-thirds cases, which was significantly more when compared to mild cases (p<0.001).

Table 5 indicates the investigational findings compared between the survivor and the mortality groups. TLC, ANC, NLR were significantly higher in mortality group compared to survivors (Student t test, p value of 0.0004, 0.002, 0.048 respectively). ALC was significantly reduced in mortality group compared to survivor group (p = 0.015). Haemoglobin and platelet counts were similar in mortality and survivor groups (Table 5). Significantly higher values of blood urea were observed in mortality group compared to survivors (Student unpaired t test, p = 0.003), however no significant difference in creatinine values were observed in survival and mortality groups. 64.9% (24/37) patients had raised blood urea>40 mg/dL in mortality group compared to 25.8% (16/62) in survivors (p = 0.00012) while 40.5% (15/37) had creatinine >1.2mg/dL in non-survivors compared to 17.9% (11/61) in survivor group (p = 0.014). AST and ALT values were normal in 57-58% patients in the survivor group compared to 24-27% patients in the mortality group. Degree of transaminitis was significantly more in the mortality group compared to the survivor group (p<0.001). 53 (29%) patients of our study group had diabetes. The severity of COVID-19 in diabetics was more compared to non-diabetics (p-value < 0.001). Mild, moderate and severe COVID-19 in diabetics was 13.21%, 33.96% and 52.83% while in non-diabetics, it was 41.86%, 34.88% and 23.26 % respectively. The survival among diabetic patients in each category of COVID-19 severity was poorer than non-diabetic patients (mild- 85% vs. 98.1%, moderate- 67% vs. 86.7% and severe- 14.4% vs. 26.7%).

Chest X-ray was available for 98 patients- of which 59 were in the survival group and 39 in the mortality group. Patients were aggregated into 3 classes of graded severity, according to brixia scores. Greater involvement (higher score) was seen with greater severity of COVID-19. Score of <9 (81.3% vs. 15.4%), 10-12 (15.2% vs. 28.2%), and ≥ 12 (3.4% vs. 56.4%) were observed in the survivor and non-survivor groups, respectively. Analysis of the data showed higher Brixia severity scores in the mortality group (Chi square test, p<0.001).

Discussion

COVID-19 symptomatology has varied from totally asymptomatic patients to mildly symptomatic with fever and constitutional symptoms, to pneumonia, adult respiratory distress syndrome (ARDS) and extrapulmonary manifestations. Since COVID-19 is a new disease, caused by the novel coronavirus (SARS-CoV-2), the spectrum of disease symptoms and manifestations has been unfolding gradually as we progress into the pandemic. The realisation is growing that COVID-19 will continue to be another of these diseases with which we will have to live along. So it is imperative that we understand this disease and recognise the spectrum of syndromic profile of this new disease. As highlighted by our study, a number of clinical features stand out, displaying a syndromic spectrum for COIVD-19.

Our study showed an association of severity and outcome (mortality) of COVID 19 with increasing age. Average age of presentation increased as severity of COVID-19 illness increased, being 38.6 years in mild, 46.4 years in moderate and 53.5 years in severe COVID-19. The average age of mild cases was very similar to the figure of 35.5 ±16.6 years reported in another Indian study.4 Age > 60 years has been considered to be a risk factor for COVID-19 illness and severity. Notably, our cohort was much younger, and 37.9 % patients who were more than 60 years of age had severe disease. Relation of increasing age and mortality was reported early on in the pandemic from China itself.5 But all the three octogenarian patients in our study survived. All of them had mild COVID-19, and two of them had no co-morbidities while one of them had hypertension and diabetes. Although
58.7% of the patients in our study were male, however gender predilection was not observed with the severity or outcome of COVID-19.

The commonest symptoms were fever (51%), cough (49%) and breathlessness (48.3%) in our study, as has been universally reported around the world.6 Fever proportion in COVID has been reported variably in different studies, and as high as 96% and 98.6% in some studies,5,7 these variations could result from varying admission criteria and the site of care (ICU/isolation ward) where study was conducted. In our study, fever was present in 72% of the patients having severe disease but in less than 50% of mild and moderate category of patients. Duration of fever also had a bearing on the severity and outcome in our study; mean duration of fever was found to be 6.3 days in patients who recovered and 12 days (i.e. twice) in those who succumbed to the illness (p = 0.003). Published literature is lacking on the duration of symptoms and its association with mortality. Duration of fever and other symptoms could be used as an important marker for risk stratification and prognosis. Further multicentric studies will need to be conducted to establish the same. Cough was present in the majority of patients with severe disease (67.2%), but was less common in mild and moderate category of patients (41%). Dry cough was noted in 90% of patients which has been reported in other studies too.8 Breathlessness was present in 89% of patients in severe category and 14% of mild category patients. When symptoms were analysed in combinations viz., fever, cough and breathlessness together, a significant association was found to be present with severity and mortality (p<0.001). Constellation of symptoms have not been reported in other studies but we found it to be an important marker of prognosis.

Chest pain was present in 5.8% of patients in our study. None of the patient with mild disease had chest pain. In a study done by Bhandari et al chest pain was reported in 6.3% patients,9 whereas it was present in 23.1% patients in a Chinese study done by Zhao et al.10 Sore throat was present in miniscule number (3.1%) and myalgia in just 10% patients in our study, while other workers reported similar or higher numbers (sore throat-5% and 20.9% and myalgia-11% and 16.5%).7,8 Three patients were found to have altered sensorium in our study and all three had severe disease and expired. Similar findings were reported by Chen et al wherein all but one out of 25 patients with altered sensorium expired.7 Amongst comorbidities, diabetes was found to be the most common (29.1%) comorbidity in our study. Hypertension was present in 24.7% of the patients. Another study from Central India reported similar rates for diabetes (25.2%) and hypertension (24.9%) in their study cohort.11 Presence of comorbidities was associated with high risk of mortality (Relative risk: 2.6 for diabetes and 1.63 for Hypertension). In a single-centre Italian survey from Milan, diabetes prevalence was shown to be 14.9% among 410 hospitalized individuals with COVID-1912 which is lower than our study. Prevalence rates of diabetes in US patients hospitalized with COVID-19 was ranging from 22.6 to 37.2%13,14 which is similar or even higher than our study. Kumar et al. reported a pooled data of COVID patients which was showing higher proportion of severe disease [odds ratio of 2.75 (95% CI: 2.09–3.62; p < 0.01)] and mortality [odds ratio of 1.90 (95% CI: 1.37–2.64; p < 0.01)] in diabetic patients.15 In our study, random blood sugar values at admission greater than 200 mg/dL (n=26) were associated with significantly higher mortality compared to patients presenting with <200mg/dL (p<0.0001), and in fact, out of the 12 diabetics who had admission blood sugar values >300 mg/dL, none survived. Very limited number of studies to date have analyzed the outcomes of severity and mortality, stratified on the level of glycaemia, in patients with diabetes and COVID-19. Interestingly, Bode et al.16 reported a significantly higher percentage of death (41.7 vs. 14.8%, p < 0.001) in patients with COVID-19 (n = 184) who had uncontrolled hyperglycemia (defined as ≥22 blood glucose value, >180 mg/dL within any 24-hour period). The data reviewed above clearly indicate that diabetes is a risk factor for disease progression towards severe illness and death.

Transaminitis was reported as part of COVID-19 as early as March 2020, with approximately one-third patients in Wuhan, China the epicentre of the pandemic, and lower rates varying from 6% to 22% outside of Wuhan. (17) However, one-third of our mild COVID-19 patients had transaminitis, approximately half of the moderate patients and over three-fourths of the severe COVID-19 patients had transaminitis. Similar relation of degree of transaminitis to severity of COVID illness has also been reported from China.18 The exact mechanism of liver involvement is hitherto unknown, but many factors may be contributing singly or in combination viz. the viral infection itself, use of potentially hepatotoxic drugs, systemic inflammatory response, hypoxia secondary to respiratory distress syndrome, multiple organ dysfunction, and co-morbidities affecting the liver. A recent study has reported SARS-CoV-2 like particles in the hepatocytes and attributed direct viral infection as the contributor to hepatic impairment in COVID-19.19 The degree of transaminitis was more as well as the proportion of patients having transaminitis was higher among the non-survivors compared to the survivor group. This finding of ours is corroborated by a meta-analysis which showed that deranged liver chemistries may indicate severe COVID-19 and could also predict mortality.20 Elevated blood urea was also observed in our patients, more (65%) in severe COVID-19 and more (65%) among COVID-19 non-survivor category. Acute kidney injury (AKI) incidence in COVID-19 patients has been found in up to 15% patients, and around 25% in critically ill patients,21 which are much lower than reported in our study population. Elevated kidney functions have been reported in one-fourth to one-third of patients only, but haematuria and proteinuria may be seen in 50-60% of patients. The cytokine storm along with direct viral cytopathic effect is the likely cause of renal involvement, though pre-renal factors, ARDS induced hypoxia, multiorgan dysfunction and underlying comorbidities also play a role.

In our study, leucocytosis, neutrophilia and lymphopenia are seen more as the severity of COVID-19 increases, and were associated with poor survival. The mean neutrophil-to-lymphocyte ratio was much higher in the severe COVID-19 patients at admission and also very high in the non-survivor patient category. Comparable results have been reported in a retrospective
analysis from Wuhan, wherein the highest tertile of NLR (5.1-19.7) was associated with 5.9-fold greater incidence of severity of COVID-19 compared to the lowest tertile (0.6-2.5). They postulated that COVID-19 may act only on lymphocytes, primarily T-lymphocytes causing lymphopenia and elevated NLR. Elevated NLR has been accepted to be an independent risk factor for prediction of critical illness in COVID-19 patients. Notably, neutrophilia and leucocytosis was not observed by Kong M et al, which is in contrast to our study and may be attributed to an inflammatory response or simultaneous existence of infections prevailing in our study population in the tropical countries. The inflammatory response hypothesis is also supported by another group of workers from China, who have not only reported neutrophilia, but also related the parallel increase of neutrophil counts with increasing lung involvement on CT scans. They postulated that excess neutrophils and neutrophil extracellular trap (NET)-associated genes in COVID-19 patients may be responsible for neutrophil-mediated lung injury and thus neutrophils are implicated in the pathogenesis of severe disease. Greater involvement on chest radiographs (as indicated by Brixia score) was observed with greater severity of illness and also associated with poorer survival in our COVID-19 patients.

Conclusion

The present study outlines the clinico-biochemical profile of COVID-19 patients stratified in to mild, moderate and severe categories, and also comparison is made of the profile between survivors and non-survivors. Our study highlights that the symptom duration and number of symptoms increase as severity of illness increases, and when all three of fever, cough and breathlessness are present, the prognosis needs to be guarded. Also, diabetes and hypertension continue to be the commonest comorbidities encountered, and their presence as well as hyperglycemia (>200 mg/dL) at admission carries a poor prognosis. Degree of transaminitis and renal parameters worsen as we encounter increasing disease severity, and higher values are also noted among non-survivors. Neutrophilia, lymphopenia, high NLR and high Brixia score (on chest radiograph) are observed more in the severe COVID-19 group and among the non-survivors. Being a retrospective study, it has limitation of incomplete data, but the same has been mentioned in each table for purposes of brevity. This study brings forth a comprehensive profile of various parameters in COVID-19 patients, which has not been brought out till now, and will serve as an interesting read for physicians managing COVID-19 patients.

References

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**Composition:**
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**Indications:**
Glycomet GP is indicated for the management of patients with type 2 diabetes mellitus (T2DM) when diet, exercise and single agent (metformin hydrochloride or glimepiride alone) do not result in adequate glycemic control.

**Dosage and Administration:**
Dosage of Glycomet GP should be individualized on the basis of effectiveness and tolerability while not exceeding the maximum recommended daily dose of glimepiride USP 4 mg and metformin hydrochloride BP 3 g. Initial dose: 1 tablet of Glycomet GP should be administered once daily during breakfast or the first main meal. Do not crush or chew the tablet. In several cases, the tablet may remain intact during transit through the gastrointestinal (GI) tract and will be eliminated in faeces. If patients could not be advised about intactness of all drug components, has already been released during transit. **CONTRAINDICATIONS:**
- Lactation.
- Severe hepatic insufficiency.
- Chronic alcoholism.
- Severe hypokalemia.
- Severe hypocalcemia.
- Hypersensitivity to metformin or glimepiride.

**Adverse Reactions:**
For glimepiride - Hypoglycaemia; temporary visual impairment; gastrointestinal symptoms like nausea, vomiting, abdominal pain, or discomfort may occur. For metformin - Gastrointestinal symptoms like nausea, vomiting, abdominal pain may occur. In case of lactic acidosis, patient should be hospitalized immediately.

**References:**
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Status of Health-care Workers in Relation to COVID-19 Infection: A Retrospective Study in a Level 4 COVID Hospital in Eastern India

Abhra Banerjee¹, Kheya Mukherjee²*, Debojyoti Bhattacharjee³, Debanjan Garai⁴, Roopsa Chakraborty⁴

Abstract

Introduction: Healthcare workers (HCWs) have a high risk of acquiring SARS-CoV-2 infection, due to repeated occupational exposure, long working hours, stress and fatigue. In India, there is lack of data regarding the prevalence of COVID-19 amongst HCWs due to absence of routine screening programme within the hospital premises. We have designed this study in order to improve our understanding of the incidence of SARS-CoV2 within the health care workers working in a level 4 COVID hospital in Kolkata.

Materials and Methods: A retrospective observational study was conducted at the Department of Microbiology, ID&BG Hospital, Kolkata upon health care workers who presented with symptoms suggestive of Covid 19 and their direct contacts. Oropharyngeal and nasopharyngeal swabs collected from the participants were subjected to Real time RT-PCR for detection of E, RDRP and ORF1B N gene for Covid 19 detection.

Result: Out of the 274 HCW tested, 75 (27%) of total HCWs were found to be positive. Among them 33(44%) were frontline workers and rest of them 42 (56%) were non-frontline workers. Predominance of SARS-CoV2 infection was found in male HCWs (57%) than female HCWs (43%). HCWs younger than 45 years (68%) were more infected.52 (69%) HCWs presented with symptoms like fever, sore throat, bodyache, loss of sensation of smell, coughs etc. 23 (31%) were asymptomatic with history of direct contact with Covid-19 positive cases.

Conclusion: Heath care workers are at higher risk of being exposed to SARS-CoV2 and could potentially has a role in transmission in and out of the hospital. Hence, routine screening of both symptomatic as well as asymptomatic hospital staff is essential for early diagnosis to prevent transmission of COVID 19 infection.

Introduction

Coronavirus is a group of virus that belong to the family of Coronaviridae. The virus is known to cause infection in both animals and humans. Human coronaviruses can cause mild disease similar to a common cold, or more severe disease like MERS - Middle East Respiratory Syndrome or SARS – Severe Acute Respiratory Syndrome. A new strain of coronavirus had emerged in Wuhan, China in December 2019. It’s presence in humans previously has not been identified. On 31 December 2019, the World Health Organization (WHO) following reports of a cluster of viral pneumonia cases of unknown cause in Wuhan, Hubei, launched an investigation in January 2020. After about eight thousand new cases of coronavirus infection emerged globally, affecting 19 countries, WHO declared the outbreak a Public Health Emergency of International Concern (PHEIC) on 30 January of this year. The disease was officially named by WHO as coronavirus disease (COVID-19) and causative organism as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Upon realization of the gravity of the danger that loomed ahead, WHO further went on to declare COVID-19 a pandemic on 11th March 2020. As of 13th August 2020, 20.6million people have been infected with and the total no. of deaths were 753,918 deaths bringing the crude mortality rate to 3.66%. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was found to spread efficiently through respiratory droplets and contact routes. Covid 19 infected persons have primarily common presenting symptoms like fever, fatigue, dry cough and myalgia. Some patients in particular had diarrhoea, nausea, vomiting, new-onset anosmia or ageusia. Dyspnoea had developed in a section of this population after few days. A considerable proportion of the SARS CoV-2-infected individuals did not have any noticeable symptoms. These people however had virus in their oral and nasal secretions thereby acting as asymptomatic carriers and spreaders of the infection.

Transmission potentials of SARS-CoV-2 being high in close contact population via aerosols and droplets and lack of definitive antiviral therapy are the reasons behind its wide-scale spread. Evidence indicates that healthcare workers (HCWs) are particularly at risk of acquiring SARS-CoV-2 infection, due to repeated occupational exposure, long working hours, psychological stress and fatigue. Reports from Center for Disease Control (CDC) as of 9th April 2020, have shown that of the total 315,531 COVID-19 cases in the US, 9,282 were HCWs. In India during early
days of transmission, only symptomatic people with travel history and or their close contacts were being tested. There is lack of specific registered data so far regarding the prevalence of COVID-19 amongst HCWs especially from India. We have designed this study in order to improve our understanding of the incidence of SARS-CoV2 within the health care workers working in a level 4 COVID hospital in Kolkata and to determine the COVID-19 virus exposure risk and possible avenues of infection in health-care workers.

Materials and Methods

A retrospective observational study was conducted at the Department of Microbiology, ID&BG Hospital, Kolkata from 1st June 2020 to 31st August 2020. The study proposal was approved by Institutional Ethics Committee. During this study period, all health care workers of ID & BG Hospital who presented with symptoms suggestive of COVID 19 infection like fever, dry cough, sore throat, body ache, lack of taste and smell etc. and health care workers who were in direct contact with a patient or any laboratory or its surrounding or after performing any procedure were verified by verbal communication.7

Presence of co-morbid conditions like Diabetes Mellitus, cardiovascular and respiratory disease, hypertension, hepatic and renal disorders or any serious health issue including malignancy were documented.

Informed consent was taken and oropharyngeal and nasopharyngeal samples were collected in viral transport media (Hi-Media) from all cases.

Oropharyngeal swab (e.g. throat swab) was taken by tilting the patient’s head back 70 degrees and rubbing synthetic fiber swabs with plastic shafts over both tonsillar pillars and posterior oropharynx without touching the tongue, teeth, and gums. The swab was placed immediately into sterile tubes containing 2-3 ml of viral transport media. Next, nasopharyngeal swab was taken by tilting the patient’s head back 70 degrees and inserting flexible swab through the nares parallel to the palate until resistance is encountered or the distance was equivalent to that from the ear to the nostril of the patient the swab was gently rubbed and rolled. The swab was left in place for several seconds to absorb secretions before removing.8

Real time RT-PCR for diagnosis of COVID-19 was done at ICMR-NICED, Kolkata according to ICMR protocol.

For Real time RT-PCR the TaqPath™ RT-PCR COVID-19 Kit (Applied Biosystem) was used to detect the E gene, RdRp gene and ORF1B gene and N gene. The controls included in the CDC 2019-nCoV Real-Time RT-PCR Diagnostic Panel are No Template Control (NTC), 2019-nCoV Positive Control (nCoVPC) and Human RNase P (RP).

Assay of E gene is the first line screening assay. When all controls exhibit the expected performance and if the Ct value for E assay is <36 it is considered a positive and confirmatory assay has to be performed. Assay of RdRp and N gene assay is confirmatory. If the RNase P growth curve does cross the threshold line within 36.00 cycles (< 36.00 Ct) and Ct values for both RdRp and N assays are <36 it is considered a positive test.9

Statistical Analysis

Statistical analysis of the data was performed using Statistical Package for Social Sciences (SPSS 20) and inferences were drawn. Comparison of continuous variables between case sub groups was evaluated using Student’s t test. Categorical variables were compared using Pearson’s chi-square test ($\chi^2$) test. Probability value $p<0.05$ was considered to be statistically significant at a confidence limit of 95%.

Result

Out of 677 health care workers working in this hospital within the specified time period 274 (41%) were tested for SARS-CoV2 which included 165 male and 109 female HCWs. 75(11%) of total HCWs were found positive (Figure 1). Among them 33(44%) were frontline workers and rest of them 42 (56%) were non-frontline workers (Figure 2). Predominance of SARS-CoV2 infection was found in male HCWs (57%) than female HCWs (43%) (Figure 3). HCWs younger than 45 years (68%) were more infected than HCWs more than 45 years. Overall, 74 of 75 HCWs (99%) with covid-19 had non-severe disease while only 1 (1%) died. Among the 75 covid-19 positive HCWs 52(69%) presented with symptoms like fever, sore throat, bodyache, loss of sensation of smell, cough etc. and 23(31%) were asymptomatic with history of direct contact with covid-19 positive cases (Figure 4).

Discussion

Health care workers are at most risk of getting SARS-CoV2 infection as they are involved in patient care and could have a role in hospital transmission of the disease. Protecting HCWs is of utmost importance because unlike inanimate infrastructural development in pandemic time like procuring...
ventilators or building dedicated covid wards human resource cannot always be generated urgently.\(^{10,11}\)

**Worldwide different studies conducted in different places showed a varying rate of positivity among HCWs.** Sikkema RS et al. in their study in three different hospitals in Netherlands found 2%, 5% and 8% infectivity rate among HCWs. Earlier reports from Wuhan, China showed a lower infection rate of 1.1%,\(^{11,13}\) Similar study from India by Jha et al. showed infection rate among HCWs was 1.8%.\(^{6}\)

In sharp contrast, Italy had reported a high infection rate of 20% among HCWs.\(^{12}\)

In our study the higher infection rate among HCWs (27%) might be a result due to inadequate wearing of PPE, prolonged exposure to infected patients, work overload and inadequate self hygiene. In addition to this the HCWs might have been infected from community as the study period also coincided with the period in which infection rate among Indian population was also quite high.\(^{11}\)

In this study HCWs younger than 45 years were more infected compared with the HCWs aged 45 years or older which were in concordance with other studies from China, Netherlands and India.\(^{11,13,6}\)

In countries with available data, it appears that female healthcare workers are being infected in higher numbers than their male counterparts but in our study we got more male HCWs were infected than female.\(^{13}\) Gender is hypothesized to play an important role in determining a person’s risk of exposure to Covid 19 from the environment. In the Indian society, male are more habituated in smoking, drinking alcohol outdoors requiring removal of face masks. Moreover, they are involved in occupations that involve close human contact more than female. In this study infection rate among non-frontline HCWs (56%) were more than frontline (44%) which was also found in a study by Lai X et al. at Wuhan, China. This can be explained by availability of better PPE and better practice of self hygiene by the frontline workers than non-frontline workers.\(^{14}\)

In this study though 69% of the COVID 19 positive HCWs were symptomatic but 31% asymptomatic cases was also detected. As there have been instances of transmission of COVID 19 from asymptomatic cases most of whom do not seek medical assistance, laboratory testing of asymptomatic infection is recommended to screen for high-risk population such as close contacts of covid positive cases for prevention and control of the disease.\(^{15,16}\) Like other studies our study also revealed that maximum of the HCWs had mild or moderate disease. This can be explained by several reasons. In our study most of the HCWs were young adults. Early symptoms were more easily noticed by HCWs which lead to early diagnosis, treatment and better outcome. The protection of HCWs is essential. The transmission of HCWs is essential to do routine screening of asymptomatic hospital staff to detect COVID 19 infection rapidly. Early diagnosis will not only help to initiate treatment and better outcome for HCWs but also prevent transmission of COVID 19 infection within health care setting.

**Conclusion**

Health care workers are at higher risk of being exposed to SARS-CoV2 and could potentially have a role in hospital transmission. To protect HCWs all necessary preventive and protective measures to be taken to minimize occupational hazards and health risks.

As this study revealed that non-frontline workers are at a higher risk of infection, special attention needs to be taken to protect them.

**References**


Pancreatic Injury in COVID-19 Patients

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Abstract

Background and Aim: Coronavirus disease 2019 (COVID 2019) outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may cause multisystem dysfunction. We studied pancreatic injury (serum amylase and serum lipase levels) in COVID-19 patients.

Methods: A retrospective study involving 42 COVID-19 patients (diagnosed by real-time PCR) admitted to a tertiary care hospital was conducted. Serum amylase and serum lipase levels were analysed in relation to severity of COVID-19 and mortality.

Results: Mean age of patients was 50 ± 16 years, with male to female ratio of 3.7:1. Serum amylase was elevated in 14 patients (33%). Serum lipase was elevated in 7 out of 29 patients (24.1%). Mortality was seen in 18 patients (42.8%). Serum amylase or lipase did not correlate with severity of COVID-19 or its mortality. However, both patients who had high lipase (>3 times) expired.

Conclusion: The prevalence of hyperamylasemia in patients of COVID-19 was 33%, while that of elevated lipase was 24.1%. Pancreatic injury failed to show any statistically significant relation to severity or outcome of COVID-19.

Introduction

WHO declared COVID-19 a pandemic on 11th March, 2020. In India, as of August, 26, 2020, there were 7,07,267 active cases, and 59,449 have died of the disease 1. The disease is associated with severe respiratory illness but has been reported to have multisystem involvement, including cardiovascular, neurological and gastrointestinal manifestations. While abdominal symptoms such as pain and diarrhea are a known presentation, little is known about pancreatic injury as a complication of COVID-19 infection. In this study we aimed to study the effect of COVID-19 disease on markers of exocrine pancreatic injury i.e. serum amylase and lipase, and determine their association with disease severity and outcome in COVID-19 patients.

Methods

A retrospective study was conducted in patients diagnosed as COVID-19 positive (on basis of positive RT-PCR for nCoV-2019) admitted to Lady Hardinge Medical College and associated hospitals, New Delhi. In addition to standard clinical examination, and routine blood haematology and biochemistry, serum amylase (normal range- 28-100 U/L) and serum lipase (normal range- 11-81 U/L) were done by enzymatic methods IFCC on Beckman Coulter analysers. CT imaging could not be done due to logistic issues and resource limitation in the face of pandemic and hence, diagnosis of pancreatitis as per Atlanta classification was not possible.

The patients were stratified as mild, moderate and severe based on symptoms, oxygen saturation by pulse oximetry and radiological findings, as mentioned in the guidelines for management of COVID-19, Ministry of Health and Family Welfare (MoHFW), Government of India.2

We analysed the clinical symptom of pain abdomen suggestive of pancreatitis and biochemical values in our patients, and correlated them with severity of COVID-19 and the outcome.

Other causes of acute pancreatitis such as gall stones, chronic alcoholism, trauma, drugs, hypertriglycerideremia, hypercalcemia and hypotension were excluded in all patients. A total of 42 analysable cases were studied, wherein serum amylase was available, for all, and serum lipase level was available for only 29 of these patients.

The data was analysed by Microsoft Excel and SPSS version 26.0 (SPSS Inc., Illinois, USA). The categorical variables were compared by Chi-square method. Cut-off for statistical significance was taken as a p value <0.05.

Results

The mean age of the study group (n=42) was 50 ± 16 years with a male to female ratio of 3.7:1. Out of the 42 COVID-19 patients included in the study, 18 patients (42.9%) expired; 14 males (out of 33 males, 42.4% males) and 4 females (out of 9 females, 44.4% females).

Serum amylase levels were elevated in 14 patients (33%), while levels more than three times the upper-limit of normal were seen in 3 (7.1%) patients. Simultaneous elevation of lipase was seen in 7 patients. Lipase levels more than 3 times the upper-limit of normal were seen in 2 patients.

Out of the 14 patients with elevated amylase levels, 6 patients (42.9%) expired, but only one of these had level more than three times upper-limit of normal. However, serum amylase levels did not have any association with mortality (Chi-square test, p= 0.932) (Figure 1). Out of the 7 patients with elevated lipase, both patients with levels more than three times upper-limit of normal expired, however, this was not statistically significant (Chi-square test, p= 0.331) (Figure 2). Six patients had elevation of both amylase and lipase, out of which 4 patients

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COVID-19. Acute pancreatitis, diagnosed employing the revised Atlanta classification was reported from Copenhagen in two out of three family members with COVID-19 infection.3 Gadiparthi et al have described a case of acute pancreatitis in a Covid-19 patient on a background of hypertriglyceridemia and newly-diagnosed Type-2 DM.4 Wang et al. from Wuhan, China defined pancreatic injury as any abnormality in amylase (normal range, 0–90 U/L) or lipase (normal range, 0–70 U/L), and their study reported that at admission 17% of 52 patients with COVID-19 had slightly abnormal amylase or lipase. It was suggested that pancreatic injury in COVID-19 might be caused directly by the cytopathic effect mediated by local SARS-CoV-2 replication or caused indirectly by systemic responses to respiratory failure or the harmful immune response induced by SARS-CoV-2 infection, which also leads to damage in multiple organs.5 Our study also highlights hyperamylasemia in one-third of the patients.

In our study group, patients with hyperamylasemia did not have hypertriglyceridemia or hyperglycemia, except one patient with diabetes who was well-controlled on oral anti-diabetic drugs.

Table 1: Amylase and Lipase Levels in Covid-19 patients according to severity

<table>
<thead>
<tr>
<th>Amylase (n=42)</th>
<th>Total</th>
<th>Clinical Severity of COVID-19</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Normal</td>
<td>28</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>1-3 x ULN</td>
<td>11</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>&gt; 3 x ULN</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Lipase (n=29)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>22</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>1-3 x ULN</td>
<td>5</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>&gt; 3 x ULN</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Both Amylase and Lipase (n=29)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both Normal</td>
<td>17</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Both raised 1-3xULN</td>
<td>5</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Both raised, but one is raised 1-3xULN and other is raised &gt;3xULN</td>
<td>6</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Both raised &gt;3xULN</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 1 highlights the severity of Covid-19 in association with elevated amylase and lipase levels. Out of total 42 patients, 12 patients had mild disease, 15 moderate and 15 had severe disease. Elevated amylase was seen in 3 out of 12 patients with mild disease (25%), 6 out of 15 patients with moderate disease (40%) and 3 out of 15 patients with severe COVID-19 (33.3%). Elevated lipase levels were seen in 4 out of 10 patients with moderate disease (40%) and 5 out of 15 patients with severe COVID-19 (33.3%). Out of 6 patients with elevations of both amylase and lipase levels, 3 had moderate disease and 3 had severe COVID-19. One patient with elevation of both amylase and lipase levels > 3 x ULN had moderate disease. There was no association of severity of COVID-19 with degree of elevation of amylase or lipase levels.

Discussion

Pancreatic inflammation is reportedly known to occur with illnesses caused by several viruses viz. mumps, cytomegalovirus, coxsackievirus B virus and HIV. In the novel coronavirus (nCoV-SARS-2019) disease the primary organ of damage has been the respiratory system. Effect on other systems has been variable, and several associations have been reported based on clinical observations. One such clinical observation of acute pancreatitis in an admitted COVID-19 patient prompted us to retrospectively study the proportion of patients who demonstrated pancreatic injury in COVID-19. Only one patient complained of abdominal pain, and was provisionally diagnosed to have acute pancreatitis. The patient was managed conservatively with bowel rest, fluid resuscitation and analgesia. The disease course was complicated by worsening respiratory illness, requiring mechanical ventilation, and resulted in mortality.

No other confounding factors such as derangement of kidney function were seen in these patients. Only one patient was diabetic, who was well-controlled on oral medications.
COVID-19 has been associated with gastrointestinal symptoms including abdominal pain, and viral RNA has been identified in the gastrointestinal tract of patients with COVID-19. Whether the pancreatic injury is due to direct viral invasion, or secondary to hypoxic effects or cytokine-mediated injury, is difficult to surmise at this juncture. Further studies on extra-pulmonary effects of COVID-19 will help us understand its pathophysiology.

In conclusion, while pancreatic injury may be seen in one-third of patients with COVID-19, acute pancreatitis is uncommon. One should be careful if there is simultaneous elevation of amylase and lipase, as it may be associated with a worse prognosis.

References
Randomized Comparative Clinical Study of First Global Omalizumab Biosimilar with Innovator Product in Moderate to Severe Persistent Asthma

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Abstract

**Purpose of study:** Omalizumab the first anti-IgE antibody is proven with several real-world studies and meta-analyses as important adjuvant in severe allergic asthma. This study was undertaken for the first omalizumab biosimilar to establish clinical biosimilarity and interchangeability with originator product.

**Materials and Methods:** In this randomized, double-blind comparative study 105 subjects (70 subjects in the study group and 35 subjects in the reference group) were dosed up to week 16 as double blind phase and responders entered open label phase till week 24. All responders at week 16 received study product in open-label phase of the study as per their dosing schedule till week 24. The additional efficacy assessment visit was performed till week 24. Safety follow up visit was performed in responders at week 26. The pharmacokinetic (PK) and pharmacodynamic (PD) assessment was planned in 48 subjects after first dose of omalizumab.

**Results:** In double blind phase, 4 (5.80%) asthma exacerbations were reported in study arm compared to 1 (2.86%) asthma exacerbation in reference arm with no statistically significant difference (p>0.05). The time to first asthma exacerbation was 53 days in study arm compared to 62 days in reference arm. In study and reference arm, the mean change from baseline in forced expiratory volume in one second (FEV1%) was 7.51 and 5.98 at week 4; and 12.30 and 8.94 at week 16 respectively while mean change from baseline in forced expiratory volume in one second/forced vital capacity (FEV1/FVC%) was 4.20 and 4.06 at week 4 and 6.77 and 7.10 at week 16 respectively (no statistically significant difference, p>0.05). At week 16, 4 (5.80%) subjects in study arm had 50-75% inhaled corticosteroids (ICS) dose reduction compared to 2 (5.71%) subjects in reference arm. The proportion of subjects with meaningful improvement in Asthma Quality of Life Questionnaire (AQLQ) (improvement in overall AQLQ score ≥0.5), mean change in overall Asthma Control Questionnaire (ACQ) score and proportion of responders based on Global evaluation of treatment effectiveness (GETE) assessment also was similar at 16 weeks. A total of 101 adverse events were reported out of which 63 were reported in the study or biosimilar arm and 38 were reported in the reference or innovator arm. Two serious adverse events (SAEs) were reported, one in each arm. No deaths occurred during this study and the safety observations are consistent with the known safety profile of omalizumab. All the samples analysed in this study were negative for anti-omalizumab antibodies. There was no significant difference in the PK and PD evaluation.

**Conclusion:** The evaluation of pharmacokinetics, pharmacodynamics, efficacy, safety and immunogenicity was concluded to show no meaningful clinical difference of the biosimilar omalizumab with the reference product.

Introduction

Optimum treatment of severe asthma represents a major unmet need. It affects a relatively small proportion of the asthma population (approximately 5%-10%), and even less (<1%) for severe uncontrolled eosinophilic asthma. Despite improvement in outcomes, severe asthma is still a cause of mortality.\textsuperscript{1} About 10% of all asthma patients require additional therapy to achieve asthma control. Allergic asthma is an example of an asthma phenotype and omalizumab, a monoclonal antibody that neutralizes serum immunoglobulin IgE, is a specific targeted treatment which was developed as a result of an understanding of the underlying mechanism of allergic asthma. Omalizumab has been widely used in clinical practice for over a decade as an add-on therapy to treat patients who have severe refractory allergic asthma. When administered at therapeutic doses, omalizumab rapidly reduces free serum IgE levels by over 95% and also results in the reduction of receptor density on the mast cells or basophils, in turn leading to a decreased allergen-stimulated mediator release response.\textsuperscript{2} Omalizumab is a recombinant DNA-derived humanised IgG1 monoclonal antibody produced in Chinese hamster ovary cells. It was originally constructed as a murine antibody selectively binding to human IgE.\textsuperscript{3} Biosimilars of biologic drugs should follow strict regulatory process as is required for approval of biosimilars. For example, the EMA (European Medicines Agency) regulatory requirements ensure the same high standards of quality, safety and efficacy for biosimilars as for originator biologicals, and include a rigorous comparability exercise with the reference product.\textsuperscript{4} This study was undertaken as an extensive...
clinical comparison of efficacy and safety of the first global biosimilar of omalizumab against the original innovator product to establish absence of any clinically meaningful difference and interchangeability.

**Materials and Methods**

This was a randomized, double-blind, active-control, parallel-group, comparative clinical study to evaluate efficacy, PK, PD, safety and immunogenicity of first biosimilar of omalizumab (study arm) with originator or innovator omalizumab (reference arm) in patients with moderate to severe persistent asthma.

The study was conducted in compliance with the ethical principles that originated in the Declaration of Helsinki and International Conference on Harmonization-Good Clinical Research Practice (ICH-GCP) and Schedule Y regulations with the registration number CTRI/2017/10/010093. In this study, a total of 112 subjects were randomized (73 subjects in the study group and 39 subjects in the reference group) in order to dose 105 subjects with the study medication i.e. 70 subjects in the study group and 35 subjects in the reference group. A sample size of 105 subjects in a 2:1 ratio (study: reference) was based on assumption of 80% power and effect size i.e reduction in number of asthma exacerbations with the use of omalizumab. The randomization schedule was generated by the statistician which was managed centrally. For PK population, the randomization took in to account the 1:1 ratio of test and reference arm and also the 4 weekly and 2 weekly schedule of drug administration (e.g. block / stratified / any other applicable randomization). In order to maintain blindness, an unblinded person was employed in the study during the blinded activities who maintained the blinding records and codes for medications and was responsible for release of medications and maintaining the logs. All details of blinding for this study were recorded in the Study Pharmacy Manual.

Omalizumab was administered at a dose of 150 mg to 375 mg subcutaneously every 2 or 4 weeks as recommended in prescribing information. Doses (mg) and dosing frequency were determined based on baseline serum total IgE level (IU/mL) measured before the start of treatment and body weight (kg). Subjects received study or reference product at the recommended dose till week 16. For most controlled medications, full response may be evident at 3 to 4 months according to Global Initiative for Asthma (GINA) guidelines. All responders at week 16 received study product in open-label phase of the study as per their dosing schedule till week 24. The additional efficacy assessment visit was performed till week 24. Safety follow up visit was performed in responders at week 26. All subjects were on a high dose of ICS and LABA (long acting inhaled β2-agonist) prior to screening which were continued during the study. In addition, other medications for asthma were also allowed during the study.

The PK and PD assessment was planned in 48 subjects (24 from each group i.e., 1:1 ratio of study and reference group) after first dose of omalizumab. Concentrations of serum total omalizumab (i.e., the sum of free omalizumab and omalizumab bound to IgE) were determined for PK assessment and concentrations of serum free and total IgE were determined for PD assessment. PD assessment was done using same sampling points. Single dose PK analysis was performed for time points up to 360 hours after first dose administration. Immunogenicity samples were collected from all subjects at baseline (pre-dose), at week 16 and week 24 or at withdrawal visit. The figure 1 shows the study flow chart.

Male and female patients between 18-65 years of age, with the diagnosis of moderate to severe persistent asthma >1 year duration and who met the criteria of positive prick skin test to at least one perennial allergen within the past 1 year or at screening were selected. Total serum IgE level 76 to 700 IU/mL, 12% increase in FEV1 or 200mL of absolute value of FEV1 over baseline value within 20-30 minutes of taking up to 4 puffs of Short-Acting Beta Agonists (SABA) documented within the past year or at screening or at baseline prior to randomization, FEV1 < 80% of predicted normal value for the patient at baseline and multiple documented severe asthma exacerbations despite daily high dose ICS plus LABA were the main inclusion criteria.

Patients with prior hospitalisation or an emergency visit for asthma within the 4 weeks before the screening visit, patients with history of near fatal or life-threatening (including intubation) asthma within the past one year prior to screening visit and patients with a history of allergic reactions attributed to compounds of similar chemical or biologic composition to omalizumab product or its any excipients and with prior use of omalizumab (or any biological treatment of allergic
asthma) were excluded. Exclusion also applied to patients with known history of systemic (injectable or oral) corticosteroid medication use within one month prior to the screening visit, patients with significant non-reversible active pulmonary disease and patients with any concurrent severe and/or uncontrolled medical conditions.

Primary efficacy endpoint was the incidence reduction of clinically significant asthma exacerbations from the time after first study dose administration till week 16. Secondary efficacy endpoints included mean change in pulmonary function test measured by FEV1 and FEV1/FVC at 8, 12,16 weeks; reductions in ICS doses at 8, 12,16 weeks; time to first asthma exacerbation till week 16; proportion of patients with reductions in ICS doses at 8, 12,16 weeks; overall proportions of responders with meaningful AQLQ improvements at week 16; proportion of patients in each category of GETE at 16 weeks; mean change in total asthma symptom score at week 8, 12 and 16 from baseline; PK parameters (C\text{max} and AUC\text{C-o}) and PD changes assessed for single dose of study and reference product and evaluation of safety and immunogenicity. All responders in both treatment arms continued treatment with study drug in the open-label phase up to week 24. This provided additional safety information on study product.

Statistical analysis plan (SAP) was prepared to describe the statistical methods to be employed in the study and the data presentations required for this study. Statistical analyses were performed using the SAS® statistical software (Version: 9.4; SAS® Institute Inc., USA). PK and PD analysis was performed using non-compartmental model of Phoenix WinNonLin® version 8.0 Pharsight application.

## Results

### Demographic and Other Baseline Characteristics

Out of 69 subjects included in PP population from study biosimilar arm, 39 (56.52%) were females and 30 (43.48%) were males. The mean age of these subjects was 38.96 years, mean height was 157.44 cm, mean weight was 24.44 kg/m². The demographic characteristics of the subjects enrolled in study and reference arms were comparable for age, height, weight and BMI (Table 1).

### Primary Efficacy Analysis

In study arm, 3 (4.35%) subjects had at least one asthma exacerbations compared to 1 (2.86%) subject in reference arm who required hospitalization and was reported as a serious adverse event (SAE). In study arm, 4 (5.80%) asthma exacerbations were reported till week 16 compared to 1 (2.86%) asthma exacerbation in reference arm. The difference in incidence of clinically significant asthma exacerbations between the two treatment arms was not statistically significant (p>0.05) (Table 2).

### Secondary Efficacy Analysis

The time to first asthma exacerbation was 53 days in study arm compared to 62 days in reference arm.

In study and reference arm, the mean change from baseline in FEV1(%) was 7.51 and 5.98 at week 4; 9.48 and 8.93 at week 8; 12.06 and 7.93 at week 12; and 12.30 and 8.94 at week 16 respectively with no statistically significant difference between the two arms at any visit. In study and reference arm, the mean change from baseline in FEV1/FVC(%) was 4.20 and 4.06 at week 4; 5.13 and 6.52 at week 8; 6.48 and 4.90 at week 12; and 7.10 at week 16 respectively. There was no statistically significant difference in change from baseline in FEV1/FVC(%) between the two arms.

Up to week 8, 2 (5.71%) subjects in study arm had 50-75% ICS dose reduction and 1 (1.45%) subject in reference arm had 25-50% ICS dose reduction. At week 16, 4 (5.80%) subjects in study arm had 50-75% ICS dose reduction compared to 2 (5.71%) subjects in reference arm, whereas, one (1.45%) subject in study arm had 25-50% ICS dose reduction compared to 3 (8.57%) subjects in reference arm. Overall in the study, 5 (7.25%) subjects had at least one reduction in ICS dose in study arm and 5 (14.29%) subjects had at least one reduction in ICS dose in reference arm.

For AQLQ score, the Minimal Important Difference (MID) i.e. the smallest difference in score which patients perceive as beneficial has been established as 0.5. In study

### Table 1: Demographics and baseline characteristics (per protocol [PP] population)

<table>
<thead>
<tr>
<th>Parameter</th>
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<th>Reference arm (N=35)</th>
<th>Overall (N=104)</th>
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<tr>
<td>Male</td>
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<tr>
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<td>n (%)</td>
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<td>28 (80.0%)</td>
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<td>Mean</td>
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<td>p-value (b.)</td>
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### Table 2: Incidence of clinically significant asthma exacerbations till week 16 (PP population)

<table>
<thead>
<tr>
<th></th>
<th>Study product (N=69)</th>
<th>Reference product (N=35)</th>
<th>Difference in Proportions between Treatment groups</th>
<th>95% CI of Treatment difference</th>
<th>P value</th>
<th>Total (N=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Exacerbations</strong></td>
<td>4 (5.80%)</td>
<td>1 (2.86%)</td>
<td>2.86%</td>
<td>(-0.0489, 0.1061)</td>
<td>0.0576</td>
<td>5 (4.80%)</td>
</tr>
<tr>
<td><strong>Number of patients with at least one Exacerbation</strong></td>
<td>3 (4.35%)</td>
<td>4 (2.86%)</td>
<td>1.43%</td>
<td>(-0.0585, 0.0871)</td>
<td>0.1835</td>
<td>4 (3.84%)</td>
</tr>
<tr>
<td><strong>Number of Exacerbations requiring Hospitalization</strong></td>
<td>0 (0.00%)</td>
<td>1 (2.86%)</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>1 (0.96%)</td>
</tr>
</tbody>
</table>

NE-Not Evaluable
and reference arm, the proportion of subjects with meaningful improvement in AQLQ (improvement in overall AQLQ score ≥0.5) was 36.23% and 34.29% at week 4 and 57.97% and 77.14% at week 16 respectively. The proportion of patients with MID in AQLQ score was comparable between the two treatment arms.

In study and reference arm, the mean change in overall ACQ score was -0.58 and -0.34 at week 4; -0.85 and -0.62 at week 8; -1.10 and -0.96 at week 12 and -1.30 and -1.33 at week 16 respectively. Significant changes (improvement) were seen within each treatment arm up to week 16 (Table 3). The difference in mean change in ACQ score between the two treatment arms was not statistically significant (p>0.05) at any visit.

Based on GETE assessment at week 16, the proportion of responders (sum of excellent and good response) was 82.61% in study arm compared to 85.71% in reference arm. The difference between two arms was statistically not significant (p>0.05). The proportion of patients in each category of GETE at 16 weeks is presented in Table 4.

In the PK assessment, concentrations of total omalizumab (i.e., the sum of free omalizumab and omalizumab bound to IgE) were determined in serum samples by a specific enzyme-linked immunosorbent assay (ELISA). In study arm, the mean C_{max} and AUC_{0-360} were 60.46 μg/mL and 19108.04 μg x hr/mL respectively. In reference arm, the mean C_{max} and AUC_{0-360} were 24.52% respectively and in reference arm, the coefficient of variation for C_{max} and AUC_{0-360} was 26.08% and 22.71% respectively. The 90% confidence interval for AUC_{0-360} was within the acceptable limits for bioequivalence (80-125%). The comparable area under curve (AUC) data signify the equivalent total extent of absorption of study and reference products. The assessment of trough concentration data shows that the steady state of omalizumab was achieved by week 12 for both arms, which is in line with the results reported in literature.

Descriptive statistics of PD parameters of free and total IgE for test and reference products are shown in Table 5. For free IgE, in study arm, the mean C_{min} and T_{min} were 23.43 ng/ml and 124.50 hrs respectively and the mean maximum percent decrease from baseline level was 74.05% after first dose, whereas in reference arm, the mean C_{min} and T_{min} were 24.88 ng/ml and 278.86 hrs respectively and mean maximum percent decrease from baseline level was 69.515% after first dose. Similarly for total IgE, in study arm, the mean C_{max} and T_{max} were 678.51 ng/ml and 296.73 hrs respectively and mean maximum percent increase from baseline level was 112.60% after first dose while in reference arm, the mean C_{max} and T_{max} were 24.88 ng/ml and 278.86 hrs respectively and mean maximum percent increase from baseline level was 137.408% after first dose. The difference in C_{max}, T_{max} and maximum percent increase from baseline level for free IgE and total IgE was statistically not significant between the two treatment arms (p>0.05).

Safety assessment

In this study, 105 randomized subjects received at least one dose of study medication (study or reference product) as per protocol. Therefore, 105 subjects (70 in study arm and 35 in reference arm) were included in safety assessment. A total of 102 adverse events were reported out of which 63 were reported in the study or biosimilar arm and 39 were reported in the reference or innovator arm. There were 28 (40.00%) subjects in study arm and 19
(54.29%) subjects in the reference arm with at least one treatment emergent adverse event and there were 27 (38.57%) subjects in study arm and 18 (51.43%) subjects in the reference arm with at least one treatment emergent adverse event (TEAE) related to study medication. In this study, 02 SAEs were reported. Out of these, one SAE (acute exacerbation of bronchiial asthma) was reported in reference arm and one SAE (spontaneous abortion) was reported in study arm. No deaths occurred during this study. One subject from reference product arm was discontinued from the study due to treatment emergent adverse events. As per the available literature, the safety observations are consistent with the known safety profile of omalizumab. Therefore, considering the disease condition and the safety profile of the study medication, the adverse events reported during this study did not raise any new safety concern. All the immunogenicity samples analysed in confirmatory assay were negative for anti-omalizumab antibodies. There were no apparent immunologically mediated safety or efficacy concerns reported in this study.

Discussion

Several ‘real-world’ studies and updated reviews have concluded that omalizumab was effective in: reducing asthma symptoms, exacerbations, and work/school days lost; improving asthma control; improving lung function; decreasing healthcare utilization; lowering the use of other asthma medications; and enhancing quality of life, while presenting a similar safety profile as that of the randomized controlled trials.5 Biosimilars have to be demonstrated highly similar to the reference product by extensively analysing (i.e., characterizing) as well as comparative clinical study to demonstrate absence of clinically meaningful difference.6 Comparative human PK and PD data to demonstrate similarity with reference innovator product is considered the most sensitive clinical study evaluation. It supports a demonstration of biosimilarity with the assumption that similar exposure (and PD response) provides similar efficacy and safety (i.e., an exposure-response relationship exists).7 Based on PK data, the biomilar omalizumab (study product) and reference product showed comparable PK profile. The steady state of Omalizumab was achieved by week 12 for both study and reference products, which is in line with the results reported in literature. The change in free and total IgE levels were comparable between both the treatment arms demonstrating the similar PD profile of the two products. The reduction of serum free IgE is a surrogate marker of omalizumab efficacy. Hence, the similar reduction seen in Free IgE level after study and reference treatment further strengthens the hypothesis that the two products have comparable efficacy profiles. The comparable efficacy and safety data further supports the bioequivalence of the two products. The study omalizumab biosimilar has shown comparable efficacy profile to that of reference product as evident from the efficacy variables analysed between the treatment arms. The incidence of asthma exacerbations and number of subjects with at least one asthma exacerbation was comparable between two treatment arms. The two treatment arms were also comparable with respect to the secondary efficacy measures viz. pulmonary function test parameters (FEV1 and FEV1/FVC), proportion of subjects with meaningful improvement in AQLQ and ACQ score, mean change in overall AQLQ and ACQ score and GETE responder rate with similar trends seen across the majority of treated patients.

The incidence of adverse events was comparable between two treatment arms supporting the similarity in safety profile. Overall, both drugs were well tolerated. The safety profile observed during this study is in line with known safety profile of omalizumab. Immunogenicity samples from all subjects were negative for anti-drug antibodies (ADA) against omalizumab. There were no apparent immunologically mediated safety or efficacy concerns reported in this study. The study results have established that there is no statistically significant difference between the biosimilar omalizumab and reference product in the evaluation of PK, PD, efficacy, safety and immunogenicity.

Conclusion

The comprehensive evaluation in the study proves the clinical comparability of the biosimilar omalizumab and reference product. There was no clinically meaningful difference in the biosimilar omalizumab and reference product and this first biosimilar of omalizumab can be interchangeable to the innovator reference product in the management of moderate to severe persistent asthma. Therefore, based on this comparability, it is proposed that study omalizumab biosimilar may be considered as a viable alternative to reference product in patients with moderate to severe persistent asthma.

Acknowledgements

We acknowledge the contribution of investigators who contributed to the generation of the study data: Dr. Narendra Khippal, Jaipur; Dr. Jyothi hathiholi, Belagavi; Dr. Ashish Deshmukh, Aurangabad; Dr. Sushant Meshram, Nagpur; Dr. Ramesh Chandra Sahoo, Mangalore; Dr. Sumer Choudhary, Nagpur; Dr. Amit Sambare, Pune; Dr. Anand Kumar, Kanpur; Dr. Manish Jain, Jaipur; Dr. Rahul Lokhande, Pune; Dr. Nikanth Awad, Mumbai.

References

Anosmia, Ageusia and COVID-19

Partha S Ray

Abstract

COVID-19 is certainly the greatest global health problem now and for the foreseeable future. Clinicians and scientists from all over the world have been producing evidence to understand the epidemiology, clinical profile and prognostic factors of COVID-19. In the last six months a large list of COVID-19 symptoms including loss of taste and smell have emerged which can be used for screening and risk stratification. Robust workup of this evidence will help to reach strong conclusions to advance clinical medicine, epidemiology, public health, immunology and evidence-based treatment options in the spectrum of disease that we now know as COVID-19.

The olfactory nerve had largely been forgotten by neurologists till COVID-19 pandemic changed the world.1 Millions of global citizens have been infected and hundreds of thousands have died from the scourge of this 125 nm RNA virus.2 Billions of global citizens live in fear and anxiety trying to begin to adapt and reset to the “new normal”.

With COVID-19 being a new clinical entity through the novel SARS-Cov-2 virus, about which we are still discovering the genetic structure and mutations and the varied host immune response that it generates, the clinical phenotype is progressively widening as newer symptoms become strongly correlated with this virus specifically.3

What was initially thought to be a respiratory virus in keeping with the previous strains of coronaviruses,4 it is now turning out to be the cause of a systemic illness affecting all organs and systems. Importantly, only recently the very high rate of asymptomatic infection5 is being recognised from a public health standpoint and as the risk of a second wave looms large globally the necessity to identify patients with nonclassical symptoms of a viral illness or novel symptoms like anosmia and loss of taste becomes necessary. These individuals who carry a very high viral load (viral loads in the patient’s nasal cavity were higher than the viral loads in the pharynx in both symptomatic and asymptomatic individuals hinting that the nasal cavity was the first gateway for the initial infection) need to be recognised to avoid it’s spread in the face of stringent global lockdown measures and self-isolation and quarantine mandatory requirements and the effect it has had on people’s lives and livelihoods so far.

Olfaction is a primitive sense that has from an evolutionary perspective helped with feeding and mating behaviour. Human research into the mechanisms behind the detection of odours and how the brain reconstructs the sensory stimuli into a “smell map” of the world has advanced during the last 20 years. The 2004 Nobel Prize in Physiology and Medicine was awarded to Axel and Buck, USA for discoveries of odorant receptors and the organisation of the olfactory system.6

The odorant receptors on the surface of sensory olfactory neurons show significant species variability and specificity. Mice have 1200 odorant receptors (OR) while humans have less than 400 (Figure 1).

Olfaction plays a larger role in emotional processing, memory, and social behaviours. Olfactory function provides critical information about the environment, which is why substantial circuitry is dedicated to processing olfaction and multisensory integration. Irritant orders like onion or ammonia stimulate the trigeminal nerve and must not confound olfactory nerve assessment of odour!

It is not common for people to consciously appreciate the range of information provided by the sense of smell and taste from detecting warning odours in the environment to building our more pleasurable experiences. This process involves a complex neural network including the temporal lobe, the amygdala, the insula and a large part of the limbic lobe. Thus, the loss of taste and smell should not be considered only as a sensory symptom but also as a complex psycho sensorial syndrome.7

Anosmia if it comes on gradually, if long-standing, unilateral or if there is cognitive impairment is a late reported symptom. In COVID-19 the acute loss of smell and consequent impact on flavours of food described by patients as loss of taste, makes detection easier but dependent on subjective reporting.8,9

Anosmia has been difficult for individuals to perceive, as human species have not actively used their sense of smell with specific daily functions. We utilise smell mainly as a generalised phenomenon.10

As a clinical sign, Neurologists have long fallen out of practice in examining the olfactory system formally at the bedside and standardisation of utilising specific smell kits for bedside testing has
the common occurrence of head injuries leading to anosmia\textsuperscript{11} and the onset of the neurodegenerative disorders with disturbance of smell sensation as we have noted in Parkinson’s disease and Alzheimer’s disease as early disease biomarkers.

The utilisation of University of Pennsylvania Smell Identification Test (UPSIT – 40 unit score) at the bedside and lesser versions (Q-SIT 20 unit score) of the same are expensive and cumbersome and time-consuming leading to the olfactory nerve acquiring the status of the “forgotten nerve” or unexplored nerve in clinical neurology practice. This has now proven to be a limitation to research and standardisation.

Review of ENT literature shows broad categorisation of anosmia into conductive and sensorineural types. The sensorineural anosmia implies dysfunction of the olfactory epithelium and can be permanent or have longer time course to recovery. In conductive or obstructive anosmia there is impairment of the travel of odorants to the intact olfactory epithelium resulting in temporary anosmia. Infections resulting from endemic strains of human coronavirus do cause conductive anosmia as well. Disruption of olfactory epithelium following local infection is also known to occur.

Imaging of the olfactory nerve, bulb and tract and olfactory pathways including fMRI studies and Diffusion tractography with dedicated protocols on high-resolution MRI is only recently being undertaken and has shared a lot of information on the structural alterations in the olfactory bulb and tracts\textsuperscript{12} (Figures 2 and 3). Evoked potential studies – olfactory evoked potentials are a more objective way of studying the olfactory system.

In COVID-19 the frequency of anosmia ranges between 22% to 68% dependent on case ascertainment tools.\textsuperscript{13} Olfactory dysfunction after SARS Cov infection was also reported in the past, and in other coronavirus infections: however, it represents a rare occurrence. In COVID-19 patients ageusia and anosmia are not accompanied by nasal obstruction or other rhinitis symptoms majorly. This indicates probable direct damage of the virus on the olfactory and gustatory receptors.

Retrograde propagation to higher-order neurons in the olfactory pathways has been best studied in the case of Herpesvirus.\textsuperscript{14} Retrograde spread via the olfactory and trigeminal nerve results in herpes simplex encephalitis and late viral reactivation respectively. In these post-HSE patients a more “central” pattern of olfactory impairment involving limbic areas has been noted. Since we are yet to realise the nature of CNS involvement in COVID-19 such similar patterns would come to light if there was retrograde propagation via the olfactory bulb.

In a study, patients with anosmia did not present with nasal obstruction. Anosmia during viral rhinitis with nasal obstruction usually resolves within three days. In COVID-19 amelioration of anosmia would take 9 days.\textsuperscript{15} Thus, the symptom of post viral olfactory loss in relation to different kinds of viruses including coronavirus such as HCoV-229E needs further investigation.

Disturbance of taste sensation with smell has also been reported. The definition of taste disorders varies greatly with dysgeusia in 33% and ageusia in 20%. Gustatory taste bud mediated sensations are largely limited to the basic taste qualities of sweet, sour, bitter, salt and umami. With the exception of such sensations all “tastes” are flavour sensations from olfactory receptor stimulation by volatiles entering from the nasopharynx during deglutition.\textsuperscript{16} The tendency
Fig. 2: MR imaging shows probably microbleeding (methemoglobin) in the left olfactory bulb of a patient (case 1) with COVID-19 and anosmia. The left olfactory bulb (long arrows) has partial hyperintensity on precontrast fat-suppressed T1WI (A) and also on postcontrast fat-suppressed T1WI (B) and STIR (C).

Fig. 3: The coronal postcontrast fat-suppressed T1WI shows hyperintensity suggestive of enhancement or methemoglobin in the olfactory bulbs of 4 patients with COVID-19 (A–D; cases 2–5) compared with a healthy patient with normal olfactory bulbs (E and F). The coronal postcontrast fat-suppressed T1WI in 3 patients with COVID-19 (A–C; cases 2–4) shows that both olfactory bulbs (long arrows) are small oval images that are hyperintense with contrast, having signal intensity higher than the intensity of the cortex. D. A patient (case 5) with COVID-19 shows hyperintensity only on the left bulb (long arrow), the right olfactory bulb being normal (short arrow). In a healthy 60-year-old man, the coronal T2WI (E) and the postcontrast fat-suppressed T1WI (F) demonstrate normal olfactory bulbs (long arrows), which are isointense to the cortex and normally hypointense on postgadolinium sequence (F).

for many persons with smell loss to misconstrue their problems as taste loss must be considered in studies relying only on self-report. This ambiguity calls for further research to employ quantitative taste tests to definitely establish whether SARS-Cov-2 can also damage taste afferents or in rare cases more central taste related brain regions.

Research: A scarcity of advanced neuro imaging studies, difficulties obtaining histopathological tissue specimens and the absence of viral cultures of infected olfactory neural epithelium compound the difficulties in studying the phenomena of viral rhinitis.

Genetic heterogeneity of SARS-Cov and polymorphisms ACE2: Benvenuto et al17 have compared the complete genomes of 15 virus sequences from patients treated in different regions of China with other coronaviruses. The observed mutations of surface proteins (spike-S-protein and nucleocapsid-N-protein) confers stability to the viral particle. These mutations become clinically relevant as the spike protein enables viral entry and N protein in viral transcription and assembly efficiency. The biological behaviour of the virus and the choice of human receptor of entry would change which might explain potential clinical differences between patients from different world regions. ACE2, the receptor of SARS-Cov-2 entry could be specific to certain populations. Some ACE2 variants could reduce the association between human ACE2 and SARS-Cov S-protein. This would influence the susceptibility, symptoms and outcomes of COVID-19 infection. Moreover, variants of the ACE2 gene suggested that there will be a lot of ACE2 polymorphisms and expression levels between Asian and European populations.18 The mutations and polymorphisms will be determinant in studying the viral behaviour and relation to the host that would be a matter for research and understanding of the clinical spectrum of COVID-19 illness.

Not having had good validated baseline data in regards to anosmia analysis from previous coronavirus and other rhinovirus epidemic studies in regards to objective analysis of anosmia and dysgeusia,19 we are having scientific challenges in being able to be certain to definitely identify these as earliest biomarkers of COVID-19 that would necessitate isolation strategies. In addition, the effect of anosmia as a drug side effect needs to be considered as well (e.g. Macrolides and others).20

The sheer numbers of patients who will potentially exhibit sequelae to COVID-19 in the coming months and years leaves room for due concern and a vigilant clinical approach.

Take Home Message: COVID-19 is certainly the greatest global health problem now and for the foreseeable future. Clinicians and scientists from all over the world have been
producing evidence to understand the epidemiology, clinical profile and prognostic factors of COVID-19. In the last six months a large list of COVID-19 symptoms including loss of taste and smell have emerged which can be used for screening and risk stratification. Robust workup of this evidence will help to reach strong conclusions to advance clinical medicine, epidemiology, public health, immunology and evidence-based treatment options in the spectrum of disease that we now know as COVID-19.

References


COVID-19 and Tuberculosis: A Meeting of Two Pandemics!

Udita Gupta1, Anupam Prakash2, Sonali Sachdeva1, Ghan Shyam Pangtey2, Akshita Khosla1, Ramesh Aggarwal2, Ritika Sud2, Shubha Lakshmi Margekar2

Abstract

Coronavirus disease 2019 (COVID-19), causes serious respiratory illness manifesting as pneumonia, adult respiratory distress syndrome and respiratory failure. Amidst the rising number of cases and deaths, it is imperative to not forget Tuberculosis (TB) which is another pandemic existing since centuries. Tuberculosis is still the leading infectious killer worldwide, and therefore, it is crucial to reflect on the interaction between the two diseases. Evidence suggests that both COVID-19 and tuberculosis have a synergistic relationship, boosting detrimental effect of each other, disrupting existing health care models, and also worsening the clinical outcomes in terms of morbidity and mortality. This review aims to draw attention towards this pertinent clinical issue, and tries to unravel the intricate relationship between COVID-19 and tuberculosis, as also the role of BCG vaccination to combat the COVID-19 pandemic.

Introduction

It has been less than a year since the first novel coronavirus (SARS-CoV-2) case was described in Wuhan, China, and yet it has quickly escalated the ladder and COVID-19 has become a pandemic, arguably the largest outbreak world has witnessed in more than a century. But, one should not forget tuberculosis (TB), which is an already existing pandemic, declared as a global health emergency by WHO in 1993. One-quarter of the world’s population is infected by Mycobacterium tuberculosis and half of this population is concentrated in merely 8 countries- China, India, Pakistan, Bangladesh, Indonesia, Philippines, Nigeria, and South Africa.1 The superimposition of the coronavirus pandemic over tuberculosis is bound to have a significant impact, especially in emerging economies. Glaziou used predictive models to estimate the impact of COVID-19 pandemic on tuberculosis and has estimated a 13% increase in tuberculosis deaths in 2020, mainly due to a 25% decrease in case detection rate.2 In 2018, tuberculosis was responsible for 1.5 million deaths1 making it the topmost infectious
killer, and now coronavirus is just slightly behind. Data about concurrent COVID-19 and tuberculosis infection is scarce, hence we sought to provide a brief review of available literature on the same.

Prevalence of COVID-19 disease in tuberculosis patients

Tuberculosis and COVID-19 are both primarily respiratory illnesses, the difference being the insidious onset of tuberculosis compared to the acute viral illness that COVID-19 is. Both diseases notoriously spread through droplet nuclei, and respiratory symptoms such as fever, cough, breathlessness, and malaise are also very similar in the two. Simultaneous tuberculosis and COVID-19 can also exist in the same person and there exists the possibility of one disease augmenting the other as a transient decrease in cellular immunity may lead to new infection (COVID-19) or lead to reactivation of latent infection (tuberculosis). Importantly, tuberculosis and COVID-19 share common social predispositions viz., overcrowding, poverty and pollution as well as similar risk factors such as advanced age, diabetes, malnutrition, immunosuppression, and other chronic respiratory illnesses. A meta-analysis showed that patients with pre-existing chronic respiratory disease had more than two times likelihood of getting infected (odds ratio of 2.46). Since, tuberculosis is known to have varied presentations, it is imperative to anticipate important interactions between the two diseases and understand the same. A diagnosis of COVID-19 does not exclude underlying tuberculosis, and in tuberculosis-endemic settings, if the acute COVID-19 illness extends beyond two weeks, it is imperative to consider tuberculosis as a concomitant infection. Otherwise also, national tuberculosis guidelines in India do state that any fever and cough that extends beyond 2 weeks should be investigated for tuberculosis. Hence, in the COVID era, it is more pertinent that COVID patients who demonstrate delayed or slow recovery, possibility of co-infection with tuberculosis should be entertained and promptly ruled out.

Tadolini et al described a cohort of 49 patients with concurrent tuberculosis and COVID-19 infection. 26 (53.0%) had tuberculosis before COVID-19, 14 (28.5%) had COVID-19 first and nine (18.3%) had both diseases diagnosed within the same week. Although this study had its limitations, it proved the association between tuberculosis and COVID-19. The three subgroups can be put under the umbrella of old/active TB cases, which were probably unmasked by COVID-19 infection.

Another observational case-control study conducted by Liu et al in China with 36 confirmed COVID-19 cases reiterated the above findings. Controls were selected from another case-control study on bacterial/viral pneumonia and tuberculosis infection data for them was sought and comparisons made. Cases were grouped according to the severity of COVID-19 infection (mild/moderate, severe/critical) and the status of Mycobacterium tuberculosis infection was sought in these patients using IGRA (interferon-gamma release assay). The prevalence of tuberculosis infection in COVID-19 patients was found to be 36.11%, which was higher compared to the control arm which consisted of two groups with bacterial (20%) and viral pneumonia patients (16.13%). Notably, tuberculosis infection (36.11%) was found to be more common than other comorbidities viz. diabetes (25%), hypertension (22.2%), coronary heart disease (8.3%), COPD (5.6%). This is an important observation as tuberculosis has not been studied as a comorbidity for COVID-19 infection compared to the extensive research about the effect of non-communicable diseases such as hypertension, diabetes, and coronary artery disease on COVID-19 outcomes.

A case series of 4 COVID-19 patients from Singapore with atypical radiographic features was reported. Ground glass opacities, multifocal patchy consolidation and peripheral interstitial changes are considered typical radiographic findings in COVID-19 patients. In spite of a confirmed COVID-19 diagnosis, the pulmonary radiologic findings in these four patients appeared to be more consistent with those of tuberculosis. This highlights the importance of entertaining a differential of other pulmonary pathologic conditions such as tuberculosis causing atypical radiographic features in patients of COVID-19.

Diagnostic uncertainty due to non-specific clinical features and radiological findings for tuberculosis can lead to missing of the diagnosis. Tuberculin skin tests and IGRA have been widely used for screening of tuberculosis, although it is not a sure-shot diagnostic tool. The results are influenced by host’s immune response after Mycobacterium tuberculosis (or BCG) exposure and this increases the possibility of diagnostic errors. Increasing age, low blood lymphocyte count, high body mass index and immunosuppressive therapies can be associated with false negative results. Further, an excess of inflammatory markers is known to affect the sensitivity of IGRA and the high value of C-reactive protein (CRP) might be a confounder for false negative results. Moreover, high CRP and low peripheral blood lymphocyte counts have been observed within a few days of exposure to SARS-CoV-2, and this may contribute to false negativity of IGRA.

Impact of tuberculosis on COVID-19 severity

Tuberculosis and COVID-19 are linked bi-directionally; the temporary immunosuppression induced by tuberculosis may increase the susceptibility of patients to COVID-19, and COVID may, in turn, also increase susceptibility to tuberculosis.

According to a modelling analysis by STOP-TB partnership in collaboration with John Hopkins University and WAHIDSA, a 3-month lockdown and a protracted 10-month restoration could lead to an additional 6.3 million cases of tuberculosis and an additional 1.4 million tuberculosis deaths during 2020-2025, implying a setback of 5-8 years due to the COVID-19 pandemic. Each month taken to return to normal tuberculosis services would incur, in India, an additional 40,685 deaths between 2020 and 2025.

Pre-existing tuberculosis disease and underlying lung condition will affect the clinical categorization (for severity) of COVID-19. The severity of COVID-19 in patients with tuberculosis was also studied by Liu et al in 36 patients with 78% patients being in the severe/critical category, while mild/moderate cases were just 22% of the total (p=0.0049). Similarly, the rate of disease progression was significantly faster, i.e; the time period between infection and development of symptoms in patients with concurrent tuberculosis and COVID was less (6.5±4.2 days) compared to patients...
without tuberculosis (8.9±5.2 days), and between symptom development and being diagnosed as severe disease was 3.4±2.0 days in concurrent infection vs 5±0.5 days in SARS-COV-2 alone.3

Motta et al2 described 2 cohorts with a total of 69 patients with tuberculosis (including post-tuberculosis sequelae) and COVID-19. In all cases, COVID-19 worsened the prognosis of tuberculosis patients and/or resulted in death. Mortality is likely to occur in elderly individuals specially if they have comorbidities. Higher mortality rates can be expected in settings where advanced forms of tuberculosis frequently occur and are caused by drug-resistant strains of Mycobacterium tuberculosis.

The long-term effect of this virus on lung function will be discerned only in the times to come. SARS-CoV-2 infection is known to initiate an aggressive inflammatory response, called the “cytokine storm”. Cytokines such as interleukin-1β, interferon-γ, tumor necrosis factor-α, interleukin-2, interleukin-4, interleukin-10 increase significantly and contribute to disease severity.10

**The potential impact of COVID-19 on tuberculosis**

The Ministry of Health and Family Welfare, India have released an advisory on 26th August 2020,13 stating that prevalence of tuberculosis among COVID-19 patients is 0.37% – 4.47% and recommended bi-directional screening for COVID-19 and tuberculosis. It has also advised for tuberculosis screening in all cases of influenza-like illnesses (ILI) and severe acute respiratory illness (SARI). Tuberculosis is reportedly associated with a 2.1-fold increased risk of severe COVID-19 disease. In the period from January to June 2020 compared to previous year, an overall decline in tuberculosis notification by 26% has been observed due to the COVID-19 pandemic.

Similarly, Hogan et al used established transmission models to estimate the potential additional impact of COVID-19 on tuberculosis, human immunodeficiency virus (HIV) and malaria epidemics. It is estimated that in high-burden settings, deaths due to HIV, tuberculosis, and malaria could increase by up to 10%, 20%, and 36%, respectively over the next 5 years. Due to COVID-19 suppression strategies, the major impact for tuberculosis is likely to be from reductions in timely diagnosis and its subsequent treatment.4

A retrospective study was done by Buensono et al10 in Sierra Leone, a small town of Africa, to study the impact of COVID-19 in a high tuberculosis burden setting, wherein tuberculosis incidence and directly observed therapy (DOT) administration was compared to previous years. A significant drop of confirmed tuberculosis cases was noted. The number of presumptive cases of tuberculosis, that might have other respiratory diseases, decreased in March and April 2020. Moreover, no DOT was presumably administered in April 2020.

Coinfection with tuberculosis and SARS CoV-2 is of particular concern due to several reasons. COVID-19 itself or use of immunomodulators in moderate to severe COVID-19 may lead to reactivation of latent tuberculosis in high endemic areas like India as demonstrated by Pathak et al14 in mouse models by activation of a stem cell defense mechanism that accelerates activation of dormant tuberculosis. Their findings point to a potential increase of tuberculosis post-COVID. Mandal et al in their review highlighted that characteristics of COVID-19 progression are similar to fatal central nervous system tuberculosis, and suggested that some anti-tubercular therapeutic strategies can be helpful for SARS-CoV-2 treatment.17

Use of immunosuppressive agents for COVID-19 remains an area of concern, as it can potentially increase the risk of reactivation of latent tuberculosis. Also, possibility of drug-drug interactions (e.g., Rifampicin and Lopinavir/ritonavir) and additive hepatotoxicity due to simultaneous use of antitubercular drugs with agents for COVID-19 cannot be overlooked.15

**Is BCG vaccine protective against COVID-19?**

Another hypothesis which has generated widespread interest is the role of Bacille Calmette-Guerin (BCG) vaccine for protection against COVID-19. As on date, the status of BCG vaccine remains to prevent serious tuberculosis infection when administered in infants. It confers protection from tuberculosis by enhancing cellular immunity. IFN-γ is a key cytokine produced by CD4+ T cells and mediates macrophage activation and resistance to Mycobacterium tuberculosis via cellular immune mechanisms.15 However, the NSE (nonspecific effects) of the vaccine are the ones which are considered to confer protection against coronavirus, and one of these NSE is trained immunity. Trained immunity is defined as the enhancement in the innate immune responses to subsequent infections, which is different from the cellular immunity important for prevention against tuberculosis. It is believed to be achieved through epigenetic and metabolic programming of immune cells (monocytes and/or natural killer cells) which allows them to mount an enhanced response to pathogen-associated molecular patterns (PAMPs- from bacteria or viruses) and to activate adaptive responses efficiently which is non-specific, thus promoting host defence.20 This is the plausible mechanism why a vaccine for tuberculosis can lead to protection against multiple pathogens, like the protection conferred by the BCG vaccine to salmonella, and its use in bladder cancer.21

A study that involved both BCG vaccination at birth and delayed vaccination showed a reduced mortality rate in the birth vaccinated group. This effect is attributable to the BCG-based prevention of a range of conditions, including respiratory infections, neonatal sepsis, and fevers.22 Similarly, BCG vaccination of elderly patients over a period of three months was observed to result in a reduction in the incidence of acute upper respiratory tract infections.23

In another interesting study done by Escobar et al,24 a correlation between the BCG index, and COVID-19 mortality in different socially similar European countries was observed. Every 10% increase in the BCG index was associated with a 10.4% reduction in COVID-19 mortality. Moreover, COVID-19-related deaths were significantly higher in countries with higher quality of life when compared to developing countries even after correcting for confounding factors. This is in contrast to the general expectation that high income countries would have lower mortality rates due to better healthcare systems. An inverse relation has been demonstrated with the ‘BCG
vaccine coverage' and COVID-19 mortality, even after adjusting for morbidity, PCR-tests, age, universal health coverage, numbers of medical doctors, elevated total cholesterol and healthy life expectancy. But no such relation of BCG vaccination was evident with COVID-19 morbidity [25].

Clinical trials are ongoing to evaluate the efficacy of BCG vaccination on COVID-19 outcomes. BCG vaccination of health-care workers is being conducted in several countries to see if it can offer protection against COVID-19. A study in Germany is also evaluating VPM1002, a recombinant vaccine strain derived from BCG, if it can protect health-care workers and elderly from COVID-19[26]. It is important to note that, since BCG is a live attenuated vaccine, there is limited data on the safety of its administration to elderly people and it should also be avoided in immunocompromised individuals.[27]

Conclusion

Co-infection with tuberculosis in patients with COVID-19 should always be suspected especially in patients with severe features, prolonged clinical course and atypical radiographic findings. Timely initiation of treatment should be our priority in these subsets of patients, especially in high tuberculosis burden settings. Large scale prospective studies are required to study the actual impact of COVID-19 on the already existing tuberculosis pandemic on all fronts including health, social and economic fronts. Not only this, it is important to initiate randomized controlled trials to ascertain the interactions of the various drugs used for COVID-19 and tuberculosis, so as to prevent deleterious side effects and manage post- tuberculosis as well as post-COVID sequela.

References

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Drug Resistant Seizure Disorder in Young Patient

Prashant Kumar Panda¹, Sourabh Agstam², Jitender Mokta³, Anita Sharma⁴, Yash Paul Sharma⁵

Introduction

A 7 year old female presented to the out patient department with the complaints of repeated episodes of loss of consciousness since childhood. She was on 3 different types of antiepileptic drugs for last 2 years, still seizures were not controlled. General physical examination and systemic examination were within normal limits. An electrocardiogram (ECG) was advised for cardiac evaluation. While undergoing electrocardiographic testing, patient again had an episode of syncope. ECG was recorded prior to syncope, during syncope and after syncope. Prior to syncope ECG (Figure 1) showed marked T wave alternans and prolong QT during episode of syncope ECG (Figure 2) showed torsades de pointes which reverted without intervention and subsequent ECG (Figure 3) showed marked QT prolongation (QTc-524 msecs) with bifid T waves suggesting a diagnosis of long QT syndrome. Patient was started on beta blocker propranolol at the dose of 40 mg twice a day which was increased to 80 mg twice a day. Patient was asymptomatic after initiation of propranolol and there was marked decrease in QTc interval (448 msec, Figure 4) duration after that.

Congenital long QT syndrome is an important cause of sudden cardiac death and difficult to recognize in young population.¹ The exact prevalence in the population is not known because of its variable expression. The current population estimate ranges from 1 in 2000¹ to 1 in 3000.² It has autosomal dominant mode of inheritance. LQTS may present at any time from fetal life onward. Presentation varies from asymptomatic to repeated episode of syncope to sudden cardiac death. These patients are commonly mistaken for seizure disorder and treated for same. Long QT syndrome (LQTS) is an arrhythmogogenic ion channel disorder characterized by severely abnormal ventricular repolarization resulting in prolongation of the QT interval in ECG. Untreated, it has a high mortality rate; and with treatment, it has a excellent survival. Arrhythmias in LQTS1 patients occur during sympathetic stimulation like swimming, in LQTS2 arrhythmias occur during auditory stimulus emotional stress and in LQTS3 malignant arrhythmias occur during rest and sleep.³ T wave alternans in patients with long QT syndrome is a marker of electrical unstability and it should alarm the physician regarding impending arrhythmias.⁴

References


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An Interesting Case of Upper Gastrointestinal Bleed

Piyush Manoria

A 45 year old male, who was chronic daily alcoholic was admitted with complaints of pain in abdomen since 3 months, hematemesis and melena since 3 days. Pain in abdomen was epigastric in location, radiating to back, intermittent and increases with meals. There was no prior history of any liver disease or gastrointestinal bleeding. On examination he was having tachycardia and hypotension. Per abdomen examination revealed epigastric tenderness. Laboratory studies showed haemoglobin of 5.6 gm/dl, raised serum amylase to 994 U/L, normal liver and renal function tests. After initial resuscitation, upper gastrointestinal endoscopy was performed which showed fresh blood in second part of duodenum without any identifiable source (Figure 1). Then a side view endoscopy was done which showed ooze of blood coming out from papilla (Figure 2). His ultrasonography of abdomen followed by contrast tomography was done which revealed changes of chronic pancreatitis with a cystic mass of size 7x5x5 cm in head of pancreas with pseudoaneurysm of splenic artery with active bleeding into the cyst. It was followed by a coil embolization of the ruptured aneurysm which stopped his gastrointestinal bleed.

Hemosuccus pancreaticus is defined as bleeding from the pancreatic duct into the gastrointestinal tract via the ampulla of vater. It’s one of the rarest causes of upper gastrointestinal bleed and constitutes less than 1 % of its cases. It occurs mostly due to complications of acute or chronic pancreatitis, pancreatic malignancy or vascular malformations. It’s mostly caused by rupture of a pseudoaneurysm into pancreatic duct or pseudocyst. Arteries involved in decreasing order of frequency are splenic, gastroduodenal, pancreaticoduodenal, gastric and hepatic artery. Its one of the cause of obscure gastrointestinal bleed as bleeding is intermittent in it due to formation and dissolution of clot in main pancreatic duct or pseudocyst and needs side view endoscopy for its accurate diagnosis. In only 30 % of cases endoscopy can detect active ooze of blood from papilla and negative endoscopy doesn’t completely rule out its possibility. It should be suspected whenever there is abdominal pain and hyperamylasemia along with gastrointestinal bleed. CT angiography is the initial investigation of choice. Interventional radiological treatment in the form of embolization is the treatment of choice. Surgical treatment is indicated when radiological treatment fails or is not available. So its high index of suspicion should be kept in mind in any case of obscure gastrointestinal bleed as its early diagnosis will reduce the morbidity and mortality.

References

Heerfordt–Waldenström Syndrome

Sanjay K Mahajan1, Roshan Thakur2, Madan Kaushik1, Rajiv Raina3

Abstract
Heerfordt’s-Waldenström syndrome is a very rare presentation of neurosarcoidosis characterized by parotid gland enlargement, facial palsy, anterior uveitis and fever. World over only few cases of this syndrome have been reported. We present such a case of Heerfordt–Waldenström syndrome.

Introduction
Sarcoidosis is a disease of unknown etiology. Heerfordt–Waldenström syndrome is a very rare presentation of neurosarcoidosis characterized by parotid gland enlargement, facial palsy, anterior uveitis and fever. World over only few cases have been reported. Dr. Christian Heerfordt first described this constellation of symptoms in 1909, and later Dr. Jan Waldenstrom described association of these symptoms with sarcoidosis. This syndrome is also known as Heerfordt’s syndrome, also referred to as uveoparotid fever, Heerfordt–Mylius syndrome, Heerfordt–Waldenström syndrome, and Waldenström’s uveoparotitis.

Case History
A 32 years old female presented with easy fatigability, facial asymmetry associated with worsening facial droop and slurring of speech. She also had dryness of mouth associated with difficulty in chewing food especially solid food and required to take plenty of water for chewing and swallowing food for last 6 months. For last 4 months she had low grade fever, cough and dyspnoea on exertion. There was also history of diminution of vision, grittiness in eyes, redness of eyes, undocumented and unintentional weight loss and painless swelling bilateral side of the neck. She was a diagnosed as hypothyroidism and was on treatment and had oligomenorrhea.

Her physical examination revealed pallor, bilateral non tender enlarged parotids, multiple palpable firm non tender cervical lymph nodes and conjunctival congestion. There were multiple hyper pigmented macules and papules over her shin bilaterally. In CNS examination, right sided facial infra nuclear palsy (Figure 1). Rest of examination was unremarkable. Her fundus examination and Shirmer’s test were normal. Slit lamp examination was suggestive of cells and flare in bilateral anterior chamber suggestive of anterior uveitis. Antinuclear Antigen, Anti Ro and Anti La were negative. HBsAg, Anti HCV and HIV by ELISA were also non reactive.

Hemogram revealed hemoglobin 11 gm%, ESR 27 mm in 1st hour. TSH was 3.6 IU/ml and serum biochemistry was normal. Her serum calcium levels were 12 mg/dl. X-ray Chest revealed hilar LAP on right sided (Figure 2A) Serum ACE levels were 148U/L, serum iPTH levels were normal and Tuberculin test showed was anergy. Pulmonary function tests revealed mild restrictive pattern. HRCT chest (Figures 2C) revealed bilateral hilar, pre-tracheal and right para-tracheal lymphadenopathy (Pawnbroker’s sign or 1-2-3 sign or Garland sign Figure 2B), and ground glass haze in bilateral subpleural apices (Scadding stage III). Histopathology of salivary gland revealed multiple giant cells (Figure 3A) and naked non caseating granuloma (Figure 3B) without evidence of lymphocytic infiltration. Shirmer’s test was negative, thus Sjogren’s syndrome was ruled out. This patient was also having Scadding stage III pulmonary involvement.

Our patient had all four features of Heerfordt’s–Waldenström Syndrome i.e. fever, bilateral parotitis, right infranuclear facial nerve palsy and anterior uveitis along with raised serum angiotensin converting enzyme (ACE) levels and evidence of non caseating granuloma on biopsy. She was started on oral steroids (Prednisolone 60 mg). Symptoms of the patient improved considerably however while tapering the dosage of steroid, she again had flare up of symptoms and dosage of Prednisolone again escalated. She improved, discharged from hospital on tapering dosages but developed intolerance to steroids and Methotrexate 10 mg once a week was added. Her symptoms started improving and on follow up visits at 3 months and 6 months, she was doing well on Prednisolone 10 mg OD and Methotrexate 15 mg once a week.

Discussion
Sarcoidosis is a systemic disease characterized by non caseating granuloma formation affecting multiple organs, occurring mainly in 3rd and 4th decades of life. It affects mainly lungs but can also lead to ocular, cutaneous, extrathoracic lymph node.

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hepatic, splenic, neurological or cardiac involvement in decreasing order. Only 5% of sarcoidosis cases have neurological involvement and only about 0.3% of patients of neurosarcoidosis can present as Heerfordt’s syndrome.³

Rarely sarcoidosis can present as Heerfordt’s syndrome as initial presentation also, as in our case. Diagnosis is considered complete if all four characteristics (fever, parotitis, anterior uveitis, and facial nerve palsy) are present or otherwise considered incomplete. Facial nerve palsy can be unilateral or bilateral. Diagnosis of this syndrome is made by constellation of symptoms along with raised serum angiotensin converting enzyme (ACE) levels and evidence of non caseating granuloma on biopsy.⁴

Differential diagnoses for non caseating granuloma formation are infections, vasculitis, malignancy, autoimmune disorders. Differentials for facial nerve palsy are idiopathic facial nerve palsy, Lyme disease, Gullian Barre Syndrome, leprosy, Sarcoidosis, Sjogren’s syndrome, connective tissue disorder, amyloidosis, Melkerson Rosenthal Syndrome, adenocarcinoma and HIV can present as facial nerve palsy.⁵

The exact cause of facial nerve palsy in this syndrome is not certain; it can be either due to direct involvement of nerve or involvement of the nerve in the parotid gland. Very rarely Sjogren’s syndrome and Sarcoidosis can coexist showing both non caseating granuloma and lymphocytic infiltration on histopathology.⁴ But in our case patient presented as sicca complex but there was no suggestion of Sjogren’s syndrome, Shirmer’s test was negative and there was no evidence of lymphocytic infiltration on histopathological examination.

Very rarely sarcoidosis can present with neurological complaints as presentation. Neurosarcoidosis (except 7th CN palsy) commonly leads to chronic disease and the patients, who require steroids initially, also have tendency to develop chronic disease.

There are only case reports of Heerfordt’s-Waldenström Syndrome in the literature and randomised control trials of treatment are not available. The patients are treated as neurosarcoidosis.² The patients of neurosarcoidosis should be treated with higher doses of steroids. Non-responders and/or those with intolerant to steroids, cytotoxic / immunosuppressive drugs can be used. Methotrexate, azathioprine, cyclosporine, mycophenolate mofetil, infliximab, all can be used. Methotrexate is one of most commonly used and studied drug of these all.

Overall prognosis is good in Sarcoidosis, 2/3rd of cases resolve spontaneously and 1/3rd will have chronic disease. Out of which about 5% result in fatality. Common causes of death are progressive pulmonary fibrosis, cardiac or neurological involvement.² Risk factors for chronic disease include pulmonary fibrosis, lupus pernio, bone cysts, cardiac or neurologic disease (except 7th CN palsy) and renal calculi due to hypercalciuria.²

References
Case Reports of Two Interesting Patients with Sea Snake Envenomation

S Senthil Kumar¹, S Ragunanthanan², D Ramesh¹, V Rajendran¹, S Sridhar¹

Abstract
Sea Snakes have the most potent venom among snakes known to mankind and a few species are implicated in human fatalities.¹ Commonest Sea snake in the Indian Sea is Enhydrina Schistosa.² Mortality is high in spite of therapy because of multiple complications. This is a Case report of two Fishermen who were bitten by Sea Snake and developed complications.

Introduction
Sea snakes are marine reptiles and probably the most abundant reptile on Earth, mainly found in tropical and sub tropical waters of Indian Ocean and Pacific ocean.¹ Sea snakes are closely related to Australian Elapids with two subfamilies, Hydrophiinae and Laticaudinae. The Sea snakes are distinguished from the land snakes by their laterally compressed Fin like tail (Figure 1). This paddle like tail is their characteristic feature which increases their swimming ability. The venom apparatus of Sea snakes are rudimentary with 2-4 short hollow maxillary fangs associated with a pair of venom producing glands. Though all Sea Snakes are venomous, majority (80%) of them fail to produce any features of envenomation because of their shallow fangs and insignificant venom injected upon the victim. Usually bite does not produce any pain or evoke inflammatory response. In several areas of Coromandel coast (East coast of India), Enhydrina Schistosa is the sea snake most frequently encountered or caught by humans.² Enhydra Schistosa commonly called as Hooknosed or Beaknosed sea snake in ENGLISH and ‘Valakadyn’ meaning –‘Strong Biter’ in Tamil. Heatwole describes that majority of death due to sea snakes are because of E. schistose.³ Its venom is very potent and toxic. Most often the victims of sea snake bites are fishermen because of their profession. Here we present case records of two victims of sea snake envenomation.

Case summary 1
Case 1
- 34 year old fisherman went for fishing by boat in the Bay of Bengal 7 kms from Thiruvottriyur beach near Chennai on 23/7/15. Around 11:00 am, while he was sorting out the fishes in the net, the sea snake which was in the net has bitten his right thumb. Within 60 minutes he developed drooping of eye lids and myalgia. He was rushed to the shore immediately and taken to a nearby private hospital, he was then referred to Government General Hospital, Madras Medical College for further management. He was admitted in GH on 23/7/15 afternoon.

- At the time of admission he had drooping of eyelids, diplopia, slurring of speech and difficulty in swallowing. EOM Restricted in all directions. Pt was tachypneic with a Respiratory rate of 28/min and low Spo2. JVP not elevated. No h/o local pain and swelling over the bite site. Cardiac examination revealed tachycardia, hypotension, normal Heart sounds with no murmur. Respiratory examination revealed bilateral air entry with fine Inspiratory cracks up to midscapular region.

- In view of Respiratory Distress pt was immediately intubated and started on mechanical ventilation with appropriate settings. ET showed pink frothy secretions s/o Pulmonary Oedema. Bedside ECG- showed sinus tachycardia. Whole Blood Clotting Time (WBCT) done at the time of admission and further repeated tests at appropriate intervals were normal. Patient was started on Injection Dopamine infusion for correcting hypotension and further dose titrated according to BP.

- Urgent bedside Echocardiography was done. It revealed reduced Ejection Fraction, DYSKINETIC LV

Fig. 1: Entire view of sea snake

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they have come to normal on 4th and 5th days respectively. He was discharged with stable vitals later.

Case 2

54 Yr old fisherman with normal medical history went fishing in the Ennore sea near Chennai. He was bitten by a sea snake while clearing the catch. Within minutes pt developed drooping of eyelids and slurring of speech. He was rushed to the shore immediately by fellow fishermen and admitted in government General Hospital, Madras Medical College.

On admission he had drooping of eyelids and complained of myalgia (Figure 3). He was hemodynamically stable. Single breath count was 20 and maintained normal oxygen saturation. Cardiac and Respiratory system were normal. Serial WBCT were normal. His urine was high coloured (Figure 4). Biochemical parameters showed elevated renal parameters with Hyperkalemia (potassium - 6.4). His CPK was grossly high 14,530 with urine myoglobin positive. CPK MB fraction was also elevated with 360 units. Urgent bedside Echo was done showed mild global hypokinesia with EF – 54%. He was immediately taken up for Hemodialysis with hyperkalemia correction.

Repeat Renal parameters, potassium and CPK remained elevated after 12 hours of Hemodialysis. He was taken up for another cycle of Hemodialysis 16 hrs after admission. His urine output gradually decreased. He suffered a lethal cardiac arrest after 30 hours of admission and could not be resuscitated despite of 30 mins. Cardio pulmonary Resuscitation.

Discussion

Sea Snake bites are often neglected and poorly reported by the patients. The pathophysiology and clinical features in patients with significant envenomation are so rapid that life threatening complications progress within minutes to few hours and are often dramatic. There were a few case reports about Sea Snake envenomation in the International Toxicology Community. Sea Snake Bite is a Novel experience to many Doctors. However there is a lack of epidemiologic data concerning Sea Snake bites in our Country which has a Vast Coastline. This case report elaborates the clinical features along with complications of Sea Snake envenomation and highlights the treatment options.

Enhydrina Schistosa (Figure 5) is one of the most toxic snake known to be more dangerous than most of its terrain counterparts. Most relevant toxins of E schistosa are Neurotoxins and Myotoxins. Many studies about the constituents of E schistosa venom have been done.

S.P. Gawade et al\(^5\) describes that E Schistosa venom had atleast three neurotoxins Enhydrotoxin A, Enhydrotoxin B, Enhydrotoxin C. Most of them cause post synaptic neuromuscular blockade resulting in neuroparalysis presenting as acute onset descending Quadriaparesis commonly.

Palani Damotharan et al\(^6\) concluded that E schistosa venom had significant Proteolytic, Cytolytic and Hemotoxic activities

Nget Hong Tan et al\(^7\) comprehensively describes the Acidic phospholipase A2
activity, which was isolated from E schistosa venom. Phospholipase is a highly active enzyme that exerts more deleterious myotoxic, neurotoxic, cardiotoxic effect and pro-inflammatory in nature. Phospholipase A2 acts both as a neurotoxin and myotoxin. It breaks /hydrolysis of phospholipids and cause pores in biological membrane. It binds to cellular receptors causing physiological alteration and catalyses the hydrolysis of glycerophospholipids to Free Fatty Acids. It causes lysis of RBCs and inhibits oxidative phosphorylation and causes severe inflammatory swelling, rhabdomyolysis, renal insufficiency and induces neuronal inflammation in mammals.

Histopathological study of sea snake envenomation had described widespread hyaline necrosis in skeletal muscles where regeneration and repair occurred 1-2 weeks after the bite. Some victims had necrosis of upto 60% of muscle mass.4

Marsden and Reid noted that myonecrosis occurs rapidly and would be clinically apparent even within half hour of bite. Multiple organ dysfunction were a common result in sea snake envenomation. Congestion and centrilobar necrosis in the liver was a common finding. Most important cause of early death in cases of sea snake envenomation was hyperkalemia and cardiovascular collapse.

Case I presented with Neurological manifestations and also had Myocarditis resulting in Cardiogenic Shock and Pulmonary oedema. He responded to medications and reversal of LV Dysfunction was also confirmed with a repeat Echocardiogram. Case II had severe Rhabdomyolysis with Hyperkalemia and deteriorated fast despite 2 cycles of Hemodialysis and died due to Sudden Cardiovascular collapse.

Management of Sea Snake envenomation involves Resuscitation with Airway Care, Breathing and Circulation(ABC) initially. A normal coagulation profile with absent local reaction at the bite site is a common presentation. Prompt recognition of clinical features and complications pertaining to Rhabdomyolysis, Myotoxicity, Myocarditis, Nephrotoxicity and Neurotoxicity is Life saving. Forced Alkalline Diuresis is useful when there is Rhabdomyolysis with myoglobinuria in preventing a catastrophic Renal failure, however cardiotoxicity if present, restricts this option. Hence Hemodialysis will be the more appropriate therapy for severe Rhabdomyolysis and Renal toxicity. Continuous Cardiac monitoring is very important for the first few hours as victims may develop Acute Cardiac Decompensation, Shock and Arrhythmias. In our country, specific Anti Snake Venom for Sea Snake envenomation is not available. However, in Australia Tiger Snake Antivenom are being used because of the close relationship of Tiger snake and Sea snake venoms.10

Prompt identification of complications predominantly Cardiotoxicity and Neurotoxicity and resuscitation with appropriate therapy forms the corner stone of management. Polyvalent ASV which is available in India, is not indicated in the management of Sea Snake envenomation. In spite of intensive therapy mortality is high in Sea snake envenomation because of Myocarditis with pulmonary oedema/ arrhythmia and Renal failure.

Note

The photographs are used after getting appropriate permission from Patient I and relatives of Patient II.

References

Connection between humans and animals is imprinted in our collective subconscious and to some extent moulds our emotional world. The new field of Animal Assisted Therapy (AAT) utilizes this connection to further human wellbeing. It is rapidly growing and developing throughout the world in the educational and rehabilitative frameworks. There are many studies geared towards examining the unique therapeutic effects of animals on a patient’s emotional, social and physiological state.

Animals used in the therapy may be domesticated pets, farm animals and marine mammals- like dolphins. Dogs are most commonly used in the therapy, apart from guiding or assisting dogs for the disabled. Emotionally, animals provide unconditional love, uninhibited affection, warmth and acceptance. Patients feel a sense of meaning and security, which strengthens their sense of ability and self image. Animals inculcate compassion and empathy in patients; they also induce a sense of calmness, reduce anxiety and stress and diminish loneliness and depression. The feeling of anger and frustration is lessened, allowing better self control and emotional adjustment.

Caring for animals also strengthens a patient’s sense of responsibility and commitment to task and improves morale, communication, and quality of life.

Sigmund Freud (1856-1939) kept many dogs and often had his dog Jo-fi present during his pioneering sessions of psychoanalysis. He believed that dogs had a “special sense” of judging persons character and noticed that the presence of dog was reassuring. It encouraged them to relax and confide Florence Nightingale also appreciated the benefits of pets while treating ill individuals. Earliest reported use of AAT was for the mentally ill and founded as early as 1792 at the Quaker Society of Friends York Retreat in England. Dr. Boris Levinson accidentally discovered the use of pet therapy with children in 1961. He left his dog alone with a difficult child, and upon returning found the child talking to the dog with improved mood. He then studied many other cases and realized the value of an animal in treating certain medical situation. He coined the term Pet therapy in 1964.

Animals are used in a variety of settings such as hospitals, mental institutions, prisons and at home. Therapists use animals as a form of motivation after developing a bond between animal and the client. Motor and verbal skills are improved greatly. A positive social interaction with animals is translated to positive human interactions. Therapist monitors improvement with interactions and judges positive social outcome. Children receive more benefits from the therapy. Pets promote kindness in children and motivation is increased with animal interaction.

Presence of pets/animals helps victims of sexual assault feel more comfortable in the therapy settings. It reduces anxiety, depression, and other post traumatic stress symptoms. The positive feelings that pet therapy induces during therapy sessions with sexual assault victims goes far beyond just sessions.

The three stamps issued by Israel in 2009 display individuals interacting affectionately with animals (bottom), which allow patients to feel needed, meaningful, worthy and capable at every point in the process.

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Presence of pets/animals helps victims of sexual assault feel more comfortable in the therapy settings. It reduces anxiety, depression, and other post traumatic stress symptoms. The positive feelings that pet therapy induces during therapy sessions with sexual assault victims goes far beyond just sessions.
Beyond COVID-19: Evidence-Based Consensus Statement on the Role of Physiotherapy in Pulmonary Rehabilitation in the Indian Context

Narasimman Swaminathan¹, Mariya Jiandani²*, Praveen J Surendran³, Prasobh Jacob⁴, Anjali Bhise⁵, Gaurang Baxi⁶, Poorvi Devani⁷, Bela Agarwal⁸, V Sundar Kumar⁹, Nicole Maria Pinto⁹, Umanjali Damke¹⁰, Pralhad Prabhudesai¹¹

Abstract
Post COVID-19 sequelae includes breathlessness, weakness, fatigue, decreased exercise tolerance and impaired quality of life. Physiotherapy based rehabilitation program is an essential component for post COVID-19 patients in facilitating maximum functional recovery. Expert consensus statements are available from the developed countries. There is a need for a guidelines to manage post COVID-19 sequelae in Indian context. The objective of this consensus statement is to provide evidence informed guidelines for post COVID-19 physiotherapy management as a component of pulmonary rehabilitation. This consensus statement was developed by expert panel across India. Published literatures were appraised and used to prepare the recommendations. This is the first of its kind of work providing preliminary guidelines for post COVID-19 physiotherapy.

Introduction
The rapid spread of novel coronavirus (SARS CoV-2) disease across the globe has created an unprecedented public health crisis. Healthcare delivery systems across globe nations are still struggling to fight the pandemic. Involvement of respiratory system during the acute stage of infection, especially with the onset of adult respiratory distress syndrome (ARDS) requires admission to critical care settings. However, there is a glimmer of hope as recovery rates from the infection are steadily increasing and so are the drop in the mortality rates. Previous experience with the epidemics of SARS in 2002-2003 and MERS in 2012 has revealed the prolonged disabling effect brought in due to involvement of respiratory system and multi-system complications resulting in impaired physical, social and mental functioning amongst the critical care survivors.¹⁻³

The post-acute effects of COVID-19 are being recognised by patient groups, clinicians and researchers alike. Though post-acute COVID-19 is presenting as a syndrome affecting multiple organs and systems including Respiratory, Cardiovascular, Gastro-intestinal, Central, Peripheral and Autonomic Nervous Systems; lung impairment seems to be at the core of functional limitations. Fatigue caused by various systemic and organic factors, reductions in muscle strength and endurance, activity limitation, and participation restriction, is becoming a major concern as they are known to affect the quality of life significantly.⁴ It is important to restore function to premorbid state by timely and appropriate intervention. Since this is a new health emergency, the evidence base for effective intervention strategies are limited. Full-fledged randomised clinical trials to test the effects of interventions, though essential, are not feasible to be executed within a short period of time. However, professional recommendations are essential to guide clinicians to cater to their patients using the most appropriate scientific methods, until high-quality evidence is available through RCTs.

Purpose
The purpose of this document is to systematically review the available evidence on the role of physiotherapy in post COVID-19 pulmonary rehabilitation, and map the evidence with experts consensus.

This evidence based consensus statement is aimed to:-
1. Identify the screening and assessment strategies for Post COVID-19 physiotherapy care
2. Propose an evidence-based protocol for Post COVID-19 physiotherapy management as a part of pulmonary rehabilitation.
3. Identify research need and priorities in Post COVID-19 physiotherapy care

Preamble
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data宸umbed by patient groups, clinicians and researchers alike. Though post-acute COV-19 is presenting as a syndrome affecting multiple organs and systems including Respiratory, Cardiovascular, Gastro-intestinal, Central, Peripheral and Autonomic Nervous Systems; lung impairment seems to be at the core of functional limitations. Fatigue caused by various systemic and organic factors, reductions in muscle strength and endurance, activity limitation, and participation restriction, is becoming a major concern as they are known to affect the quality of life significantly. It is important to restore function to premorbid state by timely and appropriate intervention. Since this is a new health emergency, the evidence base for effective intervention strategies are limited. Full-fledged randomised clinical trials to test the effects of interventions, though essential, are not feasible to be executed within a short period of time. However, professional recommendations are essential to guide clinicians to cater to their patients using the most appropriate scientific methods, until high-quality evidence is available through RCTs.

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Introduction
Preliminary literatures report that post COVID-19 sequelae includes breathlessness during activities, fatigue, impaired functional activities and decreased quality of life. Long term impairments documented during SARS and MERS outbreaks is applicable to the

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current COVID-19 pandemic. Similar to earlier respiratory infections restrictive lung pathology due to residual fibrosis is identified as a classical feature of COVID-19. Associated sarcopenia, cardiometabolic dysfunction along with Critical illness neuropathy and myopathy causing lower extremity weakness and cognitive impairments are observed in post COVID-19 survivors.

Pulmonary Rehabilitation is an established intervention in management of patients with chronic respiratory dysfunctions as it alleviates dyspnoea, reduces symptoms and improves functional capacity.

**Scope**

This consensus statement, underpinned with emerging and past evidence, provides recommendations for physiotherapy management in Pulmonary Rehabilitation of Post COVID-19 patients within the Indian Context. These Recommendations would benefit the health care teams, especially physiotherapists, across various health care setups involved in Post COVID-19 care.

**Methodology**

For the purpose of developing this evidence-based consensus guidelines, a four-phase process was adopted.

Phase I

The lead authors identified a core group of experts to prepare this guideline. The core group of experts were selected on the basis of their speciality, experience and involvement in COVID-19 rehabilitation. Few members of this guidelines also contributed to publishing the first consensus guideline on physiotherapy management of acute COVID-19 care. An initial online meeting of the subject experts was conducted on 05/08/2020 where the need for this consensus guidelines was reiterated. The meeting also finalised the process to be adopted for development of the consensus guidelines and defined the objectives.

Phase II: Evidence Synthesis: A sub group was formed and was tasked with systematic search of literature and review of evidence.

Search Strategy:

A systematic literature search was carried out on the common electronic database COVID-19 Medline, EMBASE, Emcare, PubMed - LitCovid and Cochrane. The literature search was executed on 12th August 2020 using the following terms:

Search terms:
1. “COVID-19 or SARS-CoV-2 or SARS-CoV-2 OR SARS or MERS
2. Recovery or post COVID syndrome
3. Physiotherapy or Breathing exercise or Respiratory muscle training
4. Exercise prescription
5. Pulmonary rehabilitation
6. Rehabilitation
7. And #2 and #3 and #4 and #5 and #6

The search was restricted to English language. Three members (Pj, PjS, SK) screened the abstract independently for inclusion using Rayyan QCRI web application. Screened abstracts were further analysed by authors Mj and NS. Consensus on including the full text screening was arrived through a web conference, where all the members of the team participated in the deliberations. Full texts were screened, summarised and graded independently by four members (NS, Mj, Pj, PjS) of the team. The process of flow of literature search is as in Figure1.

Phase III: Delphi Process

Phase II and III ran concurrently. For phase III, a modified Delphi approach was used to gain consensus on various aspects of post COVID-19 physiotherapy assessment and treatment. For this purpose, two web meetings were conducted for developing a, structured questionnaire to obtain consensus from the therapists practising in India. The questionnaire was prepared following detailed deliberations among experts involved in Post COVID-19 care and having expertise in respiratory physiotherapy.

**Fig. 1: Flow chart for inclusion of literatures (PRISMA chart)**
The questionnaires consisted of five sections:

a. consent to participate in the Delphi exercise;
b. demographic details of the participants;
c. details of their experience in COVID-19 care;
d. components of physiotherapy assessment and investigation; and
e. outcomes and management of Post COVID-19 rehabilitation.

In addition to snowball sampling strategy via email and professional social media groups, a concerted attempt was made to reach out to practicing cardiorespiratory physiotherapy experts across the country. In order to ensure adequate representation of therapist from across the country, potential experts were contacted through phone and requested to participate in the Delphi exercise.

Four members (BA, PS, GB, and NP) independently analysed the response to the Delphi process and summarised their findings using a consensus process. The results of the Delphi exercises were discussed and summarised during the third meeting. The results of the Delphi exercise were mapped against the evidence synthesised through systematic literature search and was used for drafting the recommendations.

**Phase IV: Expert Consensus Process**

Physiotherapy experts in the field of cardiorespiratory across India were approached through online survey. 48 recommendations prepared based on the preliminary evidence search, were circulated among the experts for consensus. Experts also provided their personnel opinions on physiotherapy management of Post COVID-19 diagnosis.

Survey was administered between 19 August to 10th September 2020 by using google form. Physiotherapists across India based on their clinical expertise and involved in managing COVID-19 patients were approached. A consensus on assessment, outcome measures and physiotherapy intervention were obtained. Total number of 79 physiotherapists responded to the survey.

Forty Items which reached more than 80% consensus with Cronbach’s alpha more than 0.74 were included in the recommendations. ISCCM guidelines were used to grade the recommendations. For items that reached requisite cut-off but did not have evidence, they were considered for inclusion as useful practical points (UPP). The criteria adopted for grading the quality of evidence are summarized in Figure 2.

**Fig. 2: Criteria for quality of evidence levels and grading of strength of recommendations used in formulation of current recommendations**

(MJ, NS, AB, Pj, PJS, GB, PS, SK).

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**Patients likely to benefit**

The core group recommends the following inclusion and exclusion criteria for enrolment into physiotherapy programme along with physician consultation:

**Inclusion**

- Patients who had prolonged hospital stay
- Received ventilatory or oxygen support during acute care.
- Patients with reduced effort tolerance
- Patients on supplemental oxygen
- Patients having hypoxemia on activity and or rest

**Exclusion**

- Having any of the following symptoms or complains:
  - breathlessness on exertion
  - fatigue
  - leg /muscle/joint pain
  - weakness
  - sleep disturbance warranting post viral fatigue syndrome

**Settings:** Physiotherapy assessment and intervention may vary depending on the disease severity, patient related daily functional limitation, investigations, infrastructure availability and the setting.

**In-patient care: Refers to individually tailored program provided when the patient is still admitted in the hospital after diagnosis of COVID-19 in the pre discharge period in continuation of post admission physiotherapy care.**

**Home based / Community based care: Refers to individually tailored program carried out at home post discharge from the hospital or isolation centres or home isolation or community setting not earlier than three weeks post COVID-19 diagnosis or COVID negative laboratory test.**

**Centre based: Refers to individually tailored program provided on outpatient face to face consultation at the institute or rehabilitation centres six weeks after diagnosis of COVID19 or a negative RT-PCR laboratory test.**

**Telerehabilitation: Refers to individually tailored program provided using social media platforms such as video call, zoom, WhatsApp, skype etc or through telemedicine centre can be initiated not earlier than three weeks post COVID-19 diagnosis or COVID-19 negative laboratory test after discharge from hospital or isolation centres or on home isolation based on patient needs.** It is preferred mode in view of infection control during the pandemic and for
patients who are unable to access rehabilitation care.\textsuperscript{5,17–19}

Timing of initiation of Physiotherapy: As per available evidence the timing of initiating rehabilitation can be initiated 6-12 weeks after hospital discharge.\textsuperscript{17,18} However, experts participated in this consensus process recommends that rehabilitation can be initiated as early as 3 weeks post diagnosis based on patient needs and functional limitations. (Cronbach’s $\alpha =0.807$; ICC= 0.741)

The recommendations are as follows:

1. **Recommendations for pre enrolment screening:**\textsuperscript{10,17,18,20} [Level 3A]

   1.1. Prior screening for any associated myocardial involvement or pulmonary embolism by the physician is mandatory.

   1.2. Any relevant investigations as advised by the treating physician such as D Dimer values, ECG changes, Echocardiography, cardiac enzyme levels should be noted by the therapist.

   1.3. Patients with suspected myocarditis, acute chest pain, oedema feet, excessive sweating or any such signs of associated cardiac involvement or with raised inflammatory markers should not be included in Post COVID-19 rehab till physicians order.\textsuperscript{10}

   1.4. Patients with symptoms of giddiness should be evaluated for the source of symptoms before enrolment.

2. **Recommendations for Initial assessment\textsuperscript{20–22}**

   It is recommended that a detailed assessment in the post-acute phase (3-12 weeks post diagnosis) based on a consensus (Cronbach’s $\alpha =0.807$; ICC =0.741).

   2.1. Demographic data [UPP]

   2.2. COVID-19 history [UPP]

   Presentation of COVID-19 symptoms

   Duration of COVID-19 symptoms

   Severity of COVID-19 symptoms

   Type of oxygen support during COVID-19 status

   Hospitalization vs home quarantine details

   Number of days after COVID-19 lab test negative

   Perceived limitations in activities of daily living at discharge or time of assessment post COVID-19.

   Medical management including

   respiratory support

   2.3. Co-morbidities\textsuperscript{10,17,18,20} [Level 3A]

   Metabolic disorders

   Pre-existing respiratory or cardiac ailments

   Pre-existing neuro muscular disorders

   Any other reported co morbidities or new co morbidities post COVID-19

2.4. Investigations:\textsuperscript{10,17,18,20} [Level 3A]

   Haematological reports (Routine Complete Blood Count (CBC) and Lipid Profile and Blood Sugar level and HbA1c in Diabetes )

   Inflammatory markers (if available)

   Chest X ray, HRCT,

   Last available PFT, ABG

   Routine cardiac investigations

2.5. Vital signs assessment: All the vital signs (heart rate, blood pressure, oxygen saturation, respiratory rate) should be monitored pre, throughout session and in recovery. [UPP]

2.6. Temperature should be checked for presence of fever.

2.7. Respiratory system: Assessment of respiratory system is recommended for presence of airway secretions, pattern of breathing and overall posture for use of accessory muscles during rest and routine activities. [UPP]

   External Oxygen support

   Oxygen saturation at rest and during activity

   MRC Dyspnoea score

   Breath holding capacity

2.8. Neuro-musculoskeletal System:\textsuperscript{10,17,18,20}

   It is recommended to assess pain, sensory motor assessment, balance and coordination. In the experience of therapist many patients were observed to report paraesthesia post covid 19. Appropriate outcome measures related to symptoms has to be used.

   Gait and use of assistive devices should be evaluated in-case of neurological or musculoskeletal dysfunction

2.9. Functional Evaluation:

   Six minute walk test (6MWT):\textsuperscript{23,24} [Level 2A]

   In case of Teleconsultation the 6MWT should not be attempted [UPP]

   If the patient is unable to walk for six minutes use of two minute walk test to assess activity induced desaturation may be considered.\textsuperscript{25} [Level 2A]

   30 second sit to stand or 1 minute sit to stand test (1-MSTST)\textsuperscript{26} is recommended as functional test for lower extremity.\textsuperscript{27} [Level 2A] In case of tele consultation it should be done with caution. [UPP]

   Post COVID-19 functional Status score can be used to grade impact of psychological status on functional limitation\textsuperscript{28} [Level 2A]

2.10. Fatigue evaluation: Visual Analog Scale for Fatigue (VAS-F)\textsuperscript{29,30} or Fatigue Severity Scale (FSS)\textsuperscript{31,32} can be used in patients with fatigue as predominant symptom limiting function. [Level 2A]

2.11. Screening for psychological impairment: As psychological impairments are prominent in post COVID-19 patients, it is recommended to screen for anxiety and depression and appropriate referrals to other disciplines is recommended.\textsuperscript{10,11,13,17,18,20} [Level 3A]

2.12. Nutritional Assessment: Evaluation of loss of weight and BMI should be considered as patients have reported loss of weight and muscle mass post COVID-19 and referral to the dietician to be considered.\textsuperscript{17,18,20} [Level 3A]

3. **Recommendation for post covid-19 patient categories and physiotherapy treatment goals**

   In the initial phase from 3-6 weeks the goal would be to promote physical functioning to carry out activities of daily living without desaturation. Patient education and counselling for resumption of activities within and outside the home environment becomes important. Depending on the category of severity, the need and patient goals may differ. Table 1 categorizes the patients into mild, moderate and severe pulmonary impairments and Table 2 identifies physiotherapy treatment goals as per category.

4. **Recommendations for Physiotherapy interventions:**

   The treatment for a post COVID-19 patient should be individualized\textsuperscript{17} and the protocol would depend on the severity of impairment. Physiotherapy interventions should be directed towards respiratory exercises, endurance and strength training,
4.1. Respiratory Exercises:

4.1.1. Breathing exercises [Level 3A]

Breathing exercise to improve inspiratory capacity and recruit diaphragm are suggested.

Inspiratory breath-holds may prove useful in improving lung compliance and recruiting collapsed alveoli. An inspiratory hold for 3 seconds enables collateral ventilation and increase in opening up of obstructed lung regions.

Breathing control and pursed lip breathing: Patients may be taught pursed lips expiration to control breathing, maintain patency of airways, decrease respiratory rate and dynamic hyperinflation during exercise training.

4.1.2. Positioning: [Level 3A]

It is recommended to continue with positioning techniques in patients with breathlessness. Dyspnoea reliving positions are suggested for patients when they feel breathless during exercise sessions.

4.1.3. Airway Clearance Techniques: [Level 3A]

Active airway clearance techniques may be prescribed for patients who has retention of secretions or difficulty in expectoration. Techniques such as active cycle of breathing (ACBT) and autogenic drainage (AD) may be considered.

4.1.4. Lung Volume Expansion exercises [Level 3A]

Chest expansion exercises with proprioceptive feedback with emphasis on thoracic expansion is recommended.

Thoracic Expansion exercises: It is important to incorporate thoracic expansion exercise and rib cage mobility in view of anticipated restricted nature of the disease.

Incentive spirometer: Single use devices such as incentive spirometer may be used for lung expansion to improve respiratory capacity. [UPP]

4.1.5. Respiratory Muscle training: [Level 3A]

It is recommended to avoid overloading the muscles during respiratory muscle training.

Inspiratory Muscle Training (IMT): Devices such as inspiratory muscle trainer that load the respiratory muscles can be used. 2 sessions of 10 minutes of respiratory rehabilitation per week for 6 weeks. [Level 2A]

Non-threshold load training for the inspiratory muscle, started from 3 cm H2O and slowly increased thereafter, 10 to 15 minutes, 1 time/day. [Level 3A]

4.2. Exercise prescription: The Frequency, intensity, type and time (FITT) of exercises would vary depending on the patient category.

General Considerations:

4.2.1. Exercise Program: In order to achieve maximum benefit, exercise program should be of minimum 6-12 weeks with 2-3 supervised sessions per week of at least 30 minutes duration. [UPP]

4.2.2. Oxygen support and monitoring during exercise: [Level 3A]

Continuous monitoring of oxygen saturation is recommended for Patients who requires oxygen support or at risk of desaturation. Exercise induced desaturation needs to be evaluated prior to exercise prescription.

The oxygen requirement should be re-evaluated during the follow-up visit.

The patient should be advised to maintain SpO2 above 88% at rest and during activity.

4.2.3. Along with saturation, Resting blood pressure should be checked if possible for normally acceptable ranges, and resting heart rate <100 beats per minute. [UPP]

4.3. Recommendations for Exercise prescription for specific patient categories.

4.3.1. Aerobic and resistance training exercise should be applied as per FITT principle, (frequency, intensity, type and time). The recommendations based on category of patients for exercise is as in Table 3.

4.3.2 Special Considerations: [Level 3A]

Exercises should be titrated to the level of tolerance without desaturation below 88% for patients in severe and moderate category. Combination of face to face and tele-rehab session can be considered for patients with mild impairment. [UPP]

5. Recommendation for termination of Exercises: [Level 2A]

5.1. It is recommended to terminate the exercise session immediately if the patient shows the following (ACSM)

Oxygen saturation (SpO2) drops < 88%.

Develops symptoms, such as palpitations, sweating, chest tightness, and shortness of breath

Leg cramps
Physical or verbal manifestation of severe fatigue

Exercise induced hypotension

Uncontrolled hypertensive response to exercises (SBP > 260 mmHg; DBP > 115 mmHg) specially for known hypertensive patients

temperature fluctuation (> 37.2° C), exacerbation of respiratory symptoms and fatigue that are not alleviated after rest


Patients with severe pulmonary impairments as well as patients with moderate pulmonary impairments may benefit from energy conversation techniques following principles:

6.1. Pacing:

Pacing helps to have enough energy to complete activities.

Activities should be broken up into smaller tasks and spread them throughout the day.

Introduce rests in between as a part of activities, that will help to recharge energy. Plan 30–40 minutes of rest breaks between activities.

It is recommended to sit and rest wherever possible between the activities.

6.2. Planning: It is recommended to plan as follows

Plan daily and weekly routine so that activities are spread out throughout.

Pace out more demanding activities. Collect all the items you need before you carry out a particular task to save energy.

Perform strenuous activity when energy levels are high change the time of an activity:

6.3. Prioritizing:

It is recommended to prioritize the activities than doing all together. Also consider another person’s help in completing some activities which can be shared.

6.4. Positioning:

It is recommended to position oneself such that excess energy is not wasted while doing any work.

Breathing should be coordinated with body movements.

Positions to relieve breathlessness as in 4.1.2 should be used.


The patients should be informed about the following:

Disease, its nature and known course of infection, involvement of the lung and other systems of the body.

Interpretation of reports and tests.

Breathing strategies, airway clearance and use of devices.

Role and rationale of medications including oxygen therapy.

Type of exercise to be performed, its frequency and duration of each session.

Benefits of exercise and physical activity. They should also be given general instructions about the program and follow up.

Energy conservation techniques.

Importance of sleep, nutrition and hydration.

Self-monitoring with pulse oximeter (indicate values drop more than 3% or saturation <90 on activity and or rest) and rate of perceived exertion (as per prescription of intensity on Borgs Scale).

Information about symptoms and advisory for immediate reporting to physician and or physiotherapist. The importance of social distancing, hand washing and wearing a mask should be emphasized.

Difficulties faced should be identified and addressed along with changes in health related behaviour.

Appropriate tools of patient education in the form of charts, leaflets and videos in language understood by the patient should be used.

8. Recommendation for relaxation:39,44 [Level 3A]

As these patients undergo stress and emotional fatigue it is suggested to train them in relaxation techniques like Laura Mitchell39,40 or passive relaxation. It is important that relaxation be practiced daily for a duration of at least 10 minutes.

Progressive relaxation techniques is found to have reduced anxiety and improved quality of sleep among COVID-19 patients.

9. Recommendation for Outcome measures: [UPP]

9.1. The following outcome measures are recommended in documenting the progress in post COVID-19 rehabilitation: (Cronbach’s α =0.849; ICC=0.838)

Borgs Scale of Rate of perceived exertion

MRC Dyspnoea grade

Fatigue Severity Scale or VAS-F

Six Minute Walk Test

Two minute walk test

Timed up and go test

L test for Functional Mobility

30 second Sit to stand Test / One minute Sit to stand test

Grip strength

Functional Independence Measure or physical performance battery

Post COVID-19 Functional Status Scale

10. Recommendations for referral for other disciplines as multidisciplinary approach: [UPP]

As per patient needs and associated system dysfunction an multidisciplinary and inter professional collaborative effort should be considered.

Depending up on the assessment findings referral to relevant disciplines should be initiated

Speech and swallowing problems may referred to a speech therapist

Symptoms suggestive of PTSD may need a referral to a psychologist

Lack of taste/appetite may need a referral to a diettian

Severe Fatigue may require a referral to occupational therapist

11. Recommendation for infection control practices:20,21 [Level 3A]

Considering the virulence and infectivity of COVID-19 post 3 weeks being still unknown, we recommend the following:

Patients should continue individualized rehabilitation under the premise of strengthening protection and prevention against other infectious diseases.10,21

Therapeutic interventions that can increase the risk of infection, such as instructed cough, expiration training, and tracheal compression, should be minimized.21

A sealed plastic bag should be used to cover the mouth during expectoration to prevent infection.21

Clinicians should follow preventive measures wear appropriate personal protective equipment’s according to
Table 3: Recommendations for Exercise prescription for specific patient categories

<table>
<thead>
<tr>
<th>Components of Exercises</th>
<th>Patient Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Moderate</td>
</tr>
<tr>
<td>Frequency(^{11,16}) [Level 3A]</td>
<td>2 to 3 times/day and all days of week</td>
</tr>
<tr>
<td></td>
<td>Minimum 2-3 sessions per week</td>
</tr>
<tr>
<td>Intensity [UPP]</td>
<td>Very Low intensity exercises RPE of 9-12 (20-point scale) or RPE of 1-3 (10-point scale)</td>
</tr>
<tr>
<td></td>
<td>Upper and lower extremities free exercises.</td>
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<tr>
<td></td>
<td>Treadmill and cycle ergometer if available. Balance exercises in sitting and standing. Uni-lateral lower limb exercises can be added as per tolerance.</td>
</tr>
<tr>
<td>Time/Duration(^{11,16}) [Level 3A]</td>
<td>Minimum 2-3 sessions per week</td>
</tr>
<tr>
<td></td>
<td>Minimum of 15 minutes and progress up to 45 minutes according to patients’ tolerance.</td>
</tr>
</tbody>
</table>

**Summary**

The recommendations are based on evidence available in literature at the time of development and expert consensus of physiotherapist. They serve as a framework to guide patient management post COVID-19. They are adapted to suit the Indian context in urban and rural setup and were under consideration by Society of Indian Physiotherapist for endorsement at the time of publication. All patients enrolled in physiotherapy should be screened by physician prior for exclusion and red flags if any. Physiotherapy along with pharmacotherapy and multidisciplinary approach is known to benefit a large cohort of patients with pulmonary and systemic involvement. The above recommendations are intended to benefit patients with all categories of pulmonary impairment.

**Research needs**

Available post COVID-19 rehabilitation guidelines are based on the expert consensus. Since the post COVID-19 sequelae is yet to be established, there is need for high quality RCTs to document the effectiveness, type, intervention dosage, safety and feasibility of physiotherapy protocol in post COVID-19 rehabilitation.

**Acknowledgements**

References


The COVID Infodemic - How Much is Too Much?

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Sir,

In the wake of the pandemic there has been a spate of publications on the subject. While good research is central to dealing with a pandemic of this proportion there appears to be a deluge of sub-standard publications.

To get an objective idea about the barrage of publications a MEDLINE search was performed using the search term “COVID”[All Fields] OR “corona”[All Fields] OR “SARS‑COV2”[All Fields]. The search was limited to the English language and only to publications in the year 2020. This resulted in an overall 67,702 publications of which 572 were in dental and 1074 were in the nursing journals. The publication type included Meta-analysis (n=339, 0.5%); clinical trials (400, 0.5%); randomized controlled trials (237, 0.3%); systemic reviews(1.4%) and review articles(6785,10%). Isolated reports and commentaries constituted bulk of the publications (58964, 87%) followed by review articles (6785, 10%). Clinical trials constituted only 400(0.5%) of these publications and Randomized clinical trials forming an even smaller part (237, 0.3%) of these publications.

Thirteen papers so far have been “retracted” or “withdrawn” in MEDLINE indexed journal alone. The maximum number of retractions/withdrawals have occurred in Lancet group of publications (n=3). During this time 434 papers were published in the Lancet on the subject. A summary of different PubMed indexed journals where such withdrawals have taken place has been provided in Table 1.

In the “Journal of The Association of Physicians of India” (JAPI) during this time 44 papers were published. The clinical area covered was diverse with most of the papers (n=7) looking at risk factor analysis for COVID-19. The role of Chest CT was discussed in 3 and hydroxychloroquine was studied in 2. Liver and lung diseases were addressed in 3 papers each. Neurological diseases in 2 and Acute Care, Oncology, Ethics, Anti-coagualtion Cardiac, Diabetes was addressed in 1 paper each. Rest of the manuscripts covered other areas. The publication rate in JAPI has steadily increased too with just one publication in March to a plateau of 8 during June, July and August. The publication numbers are expected to peak with 6 publications in October (Figure 1). No retraction or withdrawals has taken place in JAPI. In fact the only paper from India that has been retracted was published in DRJI (Directory of Research Journal Indexing) and is disregarded as a reliable indexing platform by many.

The issue with the publication explosion is not limited to only the journals but also to registered trials. A similar search on the ClinicalTrials.gov resulted in 3787 listings. Of these 418 were completed, 54 were already withdrawn, 19 were suspended and 22 were terminated, 1972 were recruiting and 892 had yet to begin recruitment.

Knowledge about the causative agent, identification of risk factors for poor outcome and efficacy of treatment can only be established through research. But this research has to follow the basic principles of research ethics. In order to facilitate important research in an expeditious fashion many health authorities have adopted fast track policy for ethics approval in COVID research. Also, journals have relaxed the requirements of peer review in order to provide important scientific information in the public domain in a timely fashion. While these measures were intended to have a positive impact on COVID- research it has also led to an unprecedented explosion in the number of publications, most of which is sub-standard and does not contribute anything to science. It is about time that “due diligence” is exercised in publishing papers on COVID with peer review being encouraged if not mandated.

Table 1: PubMed indexed journals where retraction/withdrawal occurred

<table>
<thead>
<tr>
<th>Journal</th>
<th>Total Publications on COVID/Corona/Sars-Cov-2</th>
<th>Retracted/Withdrawn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rev Neurol</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Korean J</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Anesthesiol</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes Technol Ther</td>
<td>424</td>
<td>3</td>
</tr>
<tr>
<td>New England Journal of Medicine</td>
<td>362</td>
<td>1</td>
</tr>
<tr>
<td>Curr Oncol Rep</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Ann Intern Med</td>
<td>189</td>
<td>1</td>
</tr>
<tr>
<td>Int J Nurs Stud</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Ann Diagn Pathol</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Travel Med Infect Dis</td>
<td>165</td>
<td>1</td>
</tr>
<tr>
<td>ACS Appl Mater Interfaces</td>
<td>102</td>
<td>1</td>
</tr>
</tbody>
</table>

Fig. 1: Publication Trend in the Journal of The Association of Physicians of India (JAPI) - March-15th October 2020

References

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2. Boots. Available from [URL].
3. FDA. Available from [URL].
4. WHO. Available from [URL].

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