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Dr. Siddharth N. Shah
M.D., F.I.C.P., F.R.C.P (Edin), F.A.C.P (Hon)

03.11.1946 ➔ 25.03.2021

“The boundaries which divide life from death are at best shadowy and vague. Who shall say where the one ends, and where the other begins?”
—Edgar Allan Poe

Dr. Siddharth N. Shah, born on 3rd November 1946, left for his heavenly abode on 25th March 2021.

Dr. Siddharth was a distinguished Post graduate Teacher in Diabetes and Medicine. He was working as Consulting Physician & Diabetologist at the Saifee Hospital, SL Raheja Hospital, Bhatia Hospital, Reliance Sir H. N. Hospital, Mumbai and was Visiting Consultant to Central Railway Hospital, Byculla, Mumbai.

Not only was he a great clinician & teacher the cause of the physicians was also very close to his heart. He worked tirelessly for the same and reached the helm of affairs of the Association of Physicians of India (API) in various distinguished capacities viz. Director of Physicians Research Foundation 2019-2021 and President of API (2000-2001). He had also been the President of other prestigious societies viz. Hypertension Society of India and Diabetic Association of India, and Chairman of the ISCCM Mumbai Branch from 2004 - 2006. He has been the Executive Chairman of Hypertension Society of India. He was Editor-in-Chief of the 7th and 8th editions of the prestigious API textbook of Medicine, Journal of API (2009 – 2014), and Hypertension India Journal (1996 – 2007). He also served as Executive Editor of API Text Book of Medicine 11th Edition, JAPI and Journal of Diabetic Association of India. He contributed more than 175 articles in peer reviewed journals, textbooks and monograms.

It’s a very painful exercise to reminisce and write about my dear friend who is no more. He had all the qualities which a good doctor and human being his moto in life was serve, love, give, purify meditate relies be good do good be compassionate. These two lines depict his character. A god fearing man & was an ardent follower of the preachings of Shivani. I feel blessed to have known him from close quarters and had an over two decades of association with him. I worked with him at the API for over 2 decades. He was an exceptional individual it was so pleasant to work with him. Always in a good mood, positive and very professional. He really had a way with people. Everyone loved him and idolized him at various fora. He was laughing all the time. Thinking of him i immediately see his beautiful smile. He was both a valued colleague and a true friend. There are some people that make work worth it on the dreariest of occasions that was him. My heartfelt condolences to Mrs Shah may god give her and the family the strength and courage to deal with this irreparable loss.

Dr. Siddharth N. Shah was a delightful personality and contributed immensely not only in the scientific field but community at large. He will be sorely missed by all of us!!!

So let’s all pledge to continue the good work he started
Long Live Siddharth!!! Long Live API!!!

Dr. Yash Pal Munjal
Imm. Past Director - Physicians Research Foundation (PRF)
Sr. Consultant Endocrinologist,
Artemis Hospital and St. Stephen’s Hospital, Gurugram, Haryana
Remembering Prof. Dr. Siddharth N. Shah

Prof. Dr. Siddharth N Shah - an inspirational teacher, a beloved mentor, a jovial friend, a father figure, and a caring family man, left us all on Thursday 25th March 2021 at Mumbai.

Prof. Dr. Siddharth N. Shah was a graduate and post graduate from the prestigious Grant Medical College and Sir JJ Group of Hospitals, where he also served as a faculty from 1974 to 1981. He was a Fellow of the Royal College of Physicians of UK and a Fellow of American College of Physicians. He later joined Somaiya Medical College as a faculty in the department of Medicine. He served as a Post Graduate teacher later in Diabetology at TN Medical College, All India Institute for Diabetes and SL Raheja Hospital. He was also a faculty at the College of Physicians and Surgeons in Mumbai and was actively involved in developing capacity building courses for diabetes (both certificate and diploma). Over the span of last five decades, he served at several leading hospitals in the city including Bhatia Hospital, Sir HN Hospital, SL Raheja Hospital, BR Ambedkar Railway Hospital among many and was actively involved with clinical care and education. He was serving as the Director of the Physicians Research Foundation and API House Committee prior to his untimely demise.

He actively contributed to Association of Physicians of India, Hypertension Society of India, Cardiology Society of India, Indian Society of Critical Care Medicine and was one of the pillars of Diabetes Association of India. He was the backbone of Association of Physicians of India over the last three decades and was responsible for its growth and development. He left a palpable impact on the Hypertension Society of India and an international impact of the society by recently unveiling the Global Logo for Hypertension and the Indian Hypertension Guidelines. He served with distinction as the President of the scientific section of Diabetes Association of India and many other professional medical organisations. He published more than 175 research papers, authored several books including various editions of API Textbook of Medicine. He also founded the Asian Journal of Diabetology and Hypertension India journals.

He has left us all with countless memories of his teachings, his deep love for the field of science, academics, and his persistence in sharing his wisdom with all of us at Associations of Physicians of India (API). Above all his loving nature as a wonderful human being - made countless of us smile whenever we met him or spoke to him. We will miss his presence and his infectious smile - as his loss is irreplaceable to us all. As he would have liked us all to be the torchbearers of science, academics and above all service to the mankind - we shall continue to celebrate his legacy with various endeavours at API in his memory.

We pray to the almighty to give strength to his wife Geetaben (Obstetrician and Gynaecologist), his sons Yash (Ophthalmologist and Squint expert) and Ashiesh (Architect), along with his entire family to bear this irreparable loss and pray for sadgati and shanti.

Shashank R. Joshi, Mumbai
COVID 19 in India: Waves, Variants of Concern, Airborne Transmission

Shashank R Joshi

The novel coronavirus disease (COVID-19), caused by SARS-CoV-2 in 2021, is a tsunami-like outbreak relative to the previous outbreaks involving older coronavirus or swine flu (H1N1) or Spanish flu. With the number of COVID-19 cases now exploding worldwide, it is certain that transmission of SARS-CoV-2 is very high possibly airborne (aerosol droplet) and there are diverse spectrum of disease severity. The biological issues like genetic susceptibility and variability in the response to the virus are still being elucidated. Controlling current rates of infection and combating future waves require a better understanding of the routes of exposure to SARS-CoV-2 and the underlying genomic susceptibility to this disease. How individuals respond to SARS-CoV-2 exposure is becoming better understood in a global sense, but differences in the vulnerability of individuals to infection and in the spectrum of COVID-19 symptoms remain to be understood. It is known that advanced age and pre-existing conditions (e.g., metabolic, cardiovascular, pulmonary, and renal diseases) render a person more vulnerable to severe COVID-19. However, a surprising observation emanating from the current pandemic is the rate of hospitalization of younger, ostensibly healthy individual especially in the newer waves in 2021. Is there a vulnerability index of COVID 19 for India? What makes some people more vulnerable than others to SARS-CoV-2? What role do gene networks play in determining or influencing efficiency of infection, the immune response to infection, or the severity of COVID-19 symptoms? Our understanding of genetic susceptibility to SARS-CoV-2 infection and the severity of COVID-19 is still in its infancy. In addition to the genomics research, attention needs to be paid to the spread of the virus and how it can be prevented in India by breaking the chain of transmission.

What makes some SARS-CoV-2 infected individuals extremely sensitive to the development of acute respiratory distress syndrome (ARDS) while others are asymptomatic? The impact of ACE2 gene and its protein on viral entry with TMPRSS as well as furin is well known. Genetic polymorphisms of either ACE2 or TMPRSS or furin can have impact on cellular invasion to facilitate rapid entry. Could it lead the virus bypass nose or throat and enter the lung or could it be more virulent are unanswered questions which are now being investigated. Variations in COVID-19 severity might be classified as (a) asymptomatic, (b) symptomatic but no hospitalization required, and (c) severely symptomatic with hospitalization urgently indicated. Elucidation of alleles of relevant genes associated with these three levels of severity to viral response might aid clinicians in dealing with possible future waves of this pandemic.

The second surge in India started very quietly from less exposed population clusters in some districts from where it’s rapidly spread to rest of India. Clearly in the second wave we are seeing a faster transmissible strain, but of unknown virulence. Currently the Indian variants of concern are being investigated by genome and public health experts to delineate if it’s an imported strain like UK, South African or Brazilian one or is a home grown mutant. The initial data suggested by Indian research agencies have identified a double mutant of E484Q and L454R strains. The public health strategy will still be the same. Worldwide more than a million sequences have been done and some have been designated as “Variants of concern”. CDC classifies them as B.1.1.7(British), P.1(Brazil), B.351(South African) American (California, New York), and Indian (B.1.617). SARS-CoV-2 variants bring concerns for increased spread and escape from both vaccine and natural infection immunity. Various factors driving SARS-CoV-2 variant evolution, include specific mutations, examine the risk of further mutations, and consider the experimental studies needed to understand the threat these variants pose. Plante et al. examine SARS-CoV-2 variants including B.1.1.7 (UK), B.1.351 (RSA), P.1 (Brazil), and B.1.429 (California). Some mutations can enhance virulence to make it more invasive as well as severity. Most have till date not been documented linked to severity but possible links with transmissibility can’t be ruled out.

Vaccine is the fourth pillar after the COVID appropriate behaviour of mask, distancing and sanitizing. The vaccine primary goal is to protect the most vulnerable from death and severe diseases. These are all early generation rapidly developed vaccines which are all in Emergency use authorisation (EUA) mode. India is part of the global alliance for vaccine and has risen above vaccine nationalism by exporting vaccine fulfilling its global obligations. We need to vaccinate all our vulnerable groups which can succumb to COVID19 independent of the age but must follow vaccine discipline. Even after vaccination with full doses we need to mask, avoid crowds or poorly ventilated spaces, distance and sanitize. Post vaccine COVID 19 needs investigation to study the phenomenon of immune escape or efficacy. Also the severity of the disease and phenotype of post vaccine COVID 19 needs to be studied. We should never unmask while speaking, when eating try to avoid public spaces in crowds but eat in safe zone and ensure that we don’t unmask as much as possible. We need to use safer masking strategies like doubling up, using mask braces, ensure its tight and well covered. There
has to be zero tolerance for violators of COVID norms, behaviour and protocols and we need to have a single-minded determination to conquer and decontaminate this nasty virus. We need to be proactive to clear the virus from our environment using mind and body strategies and build a strong COVID free India.²

The contribution of aerosol exposure to the transmission of SARS-CoV-2 has been under scrutiny. Many global scientists have emphasized that infected individuals represent emission sources of aerosol generated by routine behaviours—such as breathing, speaking, singing, coughing, and resuspension activity—all of which might be capable of transmitting disease.¹ SARS CoV-2 is a typical respiratory RNA virus which spreads via aerosol generation. As with any infectious respiratory disease, an infected individual can release aerosols and droplets containing SARS-CoV-2 by coughing or sneezing. The transmission efficiency of SARS-CoV-2 has proved to be high, with reported reproductive numbers greater than that of the 2009 H1N1 influenza virus.¹ SARS-CoV-2 have virus-containing aerosols and droplets can lead to short-range airborne transmission (~6 ft). Such aerosols (<10-μm diameter) and droplets (>10-μm diameter) can promote infection through (i) deposition on surfaces and subsequent hand-to-mouth/nose/eye transfer and (ii) inhalation. While suspended airborne droplets can persist in the air for several minutes, the smaller aerosols do not rapidly settle and can persist for longer durations (~minutes to hours). Once airborne, the characteristics of aerosols generated by cough or sneeze are dynamic, notably decreasing in size due to evaporative loss of water depending on ambient humidity and temperature levels. As the size of aerosols decrease, their ability to disperse in the air is enhanced. Therefore, inhalation of aerosol-borne SARS-CoV-2 is likely to be a relevant mode of viral infection, with the range of aerosol transmission extending beyond 6 ft of an infected individual. Beyond coughing and sneezing, normal speech and breathing can also generate aerosol. The size of aerosol generated by speaking and breathing is similar, ranging from 0.75 to 1.1 μm, but is notably smaller than those generated by coughing or sneezing, i.e. ~5 μm. The concentration of aerosol released by the combination of speaking and breathing for more than 4 min is equivalent to the amount of aerosol emitted for 30 s of singing or coughing.³ The volume of speech can further influence aerosol release, leading to variations in emission rates between individuals that may impact their capacity for viral transmission; this is relevant, in particular, for infected individuals that are pre-symptomatic or have asymptomatic illness.¹

The detection of SARS CoV2 in air both in indoor and outdoor spaces is now better understood and linked to virus viability in air; factoring both temperature and humidity. The northern hemispheric, temperate reginal waves in winters and the tropical Indian wave in hotter, humid environments merits scientific scrutiny. The high transmissivity of the virus suggests that a low dose might be sufficient to infect an individual; however, such studies have yet to evaluate the infectious dose of SARS-CoV-2.¹ Until scientific evidence emerges, it is useful for individuals to follow approaches that minimize their risk of infection by reducing their exposure level and duration of exposure. The combined use of masks and physical distancing can be effective approaches for decreasing exposure to airborne forms of SARS-CoV-2. Avoiding or minimizing the time in contact with these potential aerosol exposures would also be a critical parameter in lowering risk. Common approaches for mitigating airborne exposures include (i) identification of emission sources, (ii) prevention of viral shedding and inhalation exposure, and (iii) environmental controls. The key area of environmental controls leverages evidence of reduced exposures by improving ventilation, utilization of portable filtration devices, or other aerosol inactivation technologies, and cleaning practices to reduce exposure from resuspension. This topic of environmental controls is broad and complex and guidance approaches for mitigating airborne exposures would also be a critical parameter in lowering risk. Common approaches for mitigating airborne exposures include (i) identification of emission sources, (ii) prevention of viral shedding and inhalation exposure, and (iii) environmental controls. The key area of environmental controls leverages evidence of reduced exposures by improving ventilation, utilization of portable filtration devices, or other aerosol inactivation technologies, and cleaning practices to reduce exposure from resuspension. This topic of environmental controls is broad and complex and guidance approaches for mitigating airborne exposures would also be a critical parameter in lowering risk. Common approaches for mitigating airborne exposures include (i) identification of emission sources, (ii) prevention of viral shedding and inhalation exposure, and (iii) environmental controls. The key area of environmental controls leverages evidence of reduced exposures by improving ventilation, utilization of portable filtration devices, or other aerosol inactivation technologies, and cleaning practices to reduce exposure from resuspension.

standard n95 mask capable of filtering more than 99% of airborne aerosols compared to filtration efficiencies of surgical masks (~75%) and cloth coverings (~67%) that afford inward protection against for aerosols sized between 0.02 and 1 μm.⁴ A range of face coverings is available—including N95 respirator masks, surgical masks, and cloth coverings, each offering different efficiencies for inward protection (i.e., PPE) and outward protection (i.e., source control) from virus-laden aerosol and/or droplets.⁷

There is a need to double mask and do innovation in design and filtration efficiency of cloth masks both for adults and children which will be the key and as important as vaccine development to prevent the spread of the virus. While promoting the use of face coverings by the public, it is also essential to ensure cleaning protocols prior to reuse, and to reinforce the importance of continued physical distancing to prevent individuals from having a false sense of security. The real threats of recurrent waves of the pandemic loom large and the key will be behaviour change and preventive strategies including vaccine, identification of vulnerable groups and avoidance of viral contamination.

References

2. Joshi SR. How to defeat the virus and build a COVID-free India. Indian Express 2021; 8.
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As I begin to write this editorial, India had recorded this year’s worst single-day spike in coronavirus disease cases. This is of concern as it follows a decline in the daily new cases since the last few months of the last year.

The global pandemic of coronavirus disease (COVID-19), while being a communicable infectious disease, had much wider health implications. In fact, our experience with the pandemic and the measures taken to contain its spread and impact have rekindled the discussion on the relevance and importance of the ‘mental health’ component of the concept of holistic health.

The rapidity and scale of the spread of the infection, fear of acquiring the infection, limited know how about the disease, lack of an effective treatment, coupled with the infodemic (too much information including false or misleading information in digital and physical environments during a disease outbreak) surrounding the disease created an atmosphere of concern and uncertainty. Many countries responded by imposing nationwide lockdowns that were aimed at breaking the chain of transmission of the virus and contain the spread of the infection. The consequent restrictions on movement, difficulties with day-to-day living, forced and unplanned migration, change in daily routines, economic hardships and concerns about vocations, all contributed to a stressful experience that continued for months at a stretch. While Work from Home (WFH) was offered as a possible way out from the situation created by the office premises being shut, it disrupted the work-life balance by blurring the boundaries between the two and added to the already heightened stress levels. The increased stress levels were observed across diverse population groups and settings. A systematic review and metaanalysis of the published studies during the COVID-19 pandemic reported a prevalence of 29.6% (95% confidence limit: 24.3–35.4) of stress among the general population (total sample size of 9074 across the included studies).1

Besides the experience of the heightened psychological distress, an increase in rates of various mental disorders including anxiety, depression, and post-traumatic stress disorder were also reported. Again, these findings were reported from diverse population groups across different countries. The pandemic adversely impacted the psychological wellbeing of the health care workers as well.2

Isolation, lack of social support and limited opportunities for in-person interactions made the handling of the psychological distress even more challenging. The restricted access to and disruption of the existing support systems is expected to have triggered maladaptive coping behaviors such as increased substance use and screen time. Studies have reported an increase in number and frequency of use of tobacco and electronic cigarette, and alcohol among the smokers and alcohol users, respectively during the pandemic.3,4

Suspension of the on-campus activities, remaining confined to home, increase in spare time and disruption of the daily routine created an environment that was conducive to increased use of the digital devices and internet-based activities among the students. An increase in gaming behavior was documented among the college students during the pandemic.5 Additionally, increased access of the Over the Top (OTT) platforms also contributed to the increased screen time. A lack of guidelines on screen time did not help the cause as parents continued to grapple with their concerns about the increased screen time of their children. While the concerns about the increased screen time have more commonly been expressed for students, populations across different age groups including children, adolescents, young adults, and older age groups also had an increase in the same over the past months.

As the pandemic posed challenges of associated mental health implications, it also exposed the shortcomings of the existing health care systems to offer the services for mental and addictive disorders. Many countries struggled catering to in need for the mental health services during the pandemic. The limited mental health care infrastructure- a result of limited investment in mental health care over the years- coupled with the diversion of the existing health resources to the COVID care, strained the already overburdened systems even further.

As COVID-19 continues to burden the health systems, there are various learning from our experience with the pandemic. Some of these are briefly discussed here.

First, there is a need to integrate the mental health in the overall health care delivery systems more intricately. While mental health has always been considered an essential component of holistic health, the approach to mental health care delivery has mostly been piece meal. However, over the past few years there has been a growing acknowledgement of the need to integrate mental health care delivery with other non-communicable diseases (NCDs). The current pandemic has taught that such an integration needs to extend beyond the NCDs. While the heightened psychological distress as well as an increase in mental and addictive disorders was reported among the various sections of the population (those infected with the novel coronavirus, those diagnosed
with coronavirus disease, the care providers, health care workers, general public) during the pandemic, the long-term mental sequelae to the pandemic remain to be explored. There is a need to realign the health policies and health care delivery systems to cater to the mental health needs of the population with an aim to ensure the effective, accessible and affordable Universal Health Coverage (UHC). There should be an increase in the public health spending on services for mental health and addictive disorders. There is also a need to develop newer avenues and approaches to mental health care delivery. One of the key developments of the past few months has been the growth of the digital health. Despite of its inherent limitations, the digital health has emerged as an important tool for health systems. There is a need to leverage on the digital technology and incorporate the same in health care delivery as well as capacity building of the health care professionals.

Second, there is a need to realign the focus of the health care systems that currently is centered around disease detection, disease cure, disability prevention and, to some extent, disease prevention. The health care sector needs to invest in health promotion as a priority area. The emphasis should be to build the resilience of the population and development of effective coping strategies against distress among them. Given the impact of the recent pandemic on a large section of population in form of increased levels of psychological distress, this is a much-needed investment going ahead. Also, the mental health care needs of the health care workforce should be a priority and it should be ensured that these do not go undetected and unattended.

Third, the COVID-19 pandemic highlighted the need to approach certain aspects of modern living besides and beyond the pathological realm. Rather than dichotomizing these as pathological and non-pathological, it shall be prudent to approach these as lifestyle issue. Screen time is one such issue. There is a need to develop evidence-based recommendations on screen time across different age groups. This should help address the issues such as increase in gaming behavior and use of OTT platforms and use of screens for education and work-related reasons. Currently such recommendations exist only for those aged five years or less.

Fourth, it is important to ensure that the correct public health messages are communicated in correct way. ‘Physical distancing’ should have been preferred in-lieu of ‘social distancing’ as an infection transmission prevention strategy during the pandemic. This would have helped in highlighting the importance of much needed social connectedness during the pandemic while maintaining physical distancing.6 Also, media-an important stakeholder in public mental health- should play a more productive, constructive and proactive role. Avoiding miscommunication and misattribution of information during the pandemic times can do a great good. Media reports on the association of the #PlayApartTogether campaign (a promotional campaign on gaming) with the public health agencies during the pandemic conveyed the wrong public health message.7 Given that the situation due to the COVID-19 pandemic could serve as a risk factor for an increase in the public health burden due to gaming disorders, it was of paramount importance that such miscommunication was avoided.

The COVID-19 pandemic has led to lot of morbidity, mortality and socio-economic hardships. However, it is important that the learning from this human experience is used to establish a system that is better equipped, accessible, affordable and sustainable to support the mental health needs of the people in future.

References

6. Balhara YPS, Kattula D. ‘Physical distancing’ in-lieu of ‘Social distancing’ [The BMJ [Internet]. [cited 2021 Mar 19]; Available from: https://www.bmj.com/content/369/bmj.m17111r-3
COVID-19: Elevated von Willbrand Factor at Hospital Admission Predicts Clinical Outcomes

Dinesh Jothimani1, Ezhilarasan Kailasam2, Balaji Nallathambi3, Silas Danielraj3*, Hemalatha Ramachandran4, Kirthika Narayanan5, Akila Rajakumar6, Ilankumar Kaliamoorthy7, Gomathy Narasimhan8, Mohamed Rela8

Abstract
Background: Recent studies reported higher thromboembolic complications in COVID-19 with associated mortality. The virus SARS-CoV-2 utilizes ACE2 receptors expressed in endothelial cells. Von Willebrand factor (VWF), released from the vascular endothelium following an injury results in platelet adhesion and aggregation.

Objectives: To study the role of VWF antigen level and other factors associated with thrombogenesis in COVID-19 patients and to correlate with their clinical outcome.

Methodology: A prospective study where COVID-19 patients underwent VWF antigen level, fibrinogen, platelet count, activated partial thromboplastin time, international normalized ratio, Protein C, Protein S, Antithrombin III and D-dimer at the time of hospitalization.

Results: 30 (85.7%) out of 35 COVID-19 patients had elevated VWF antigen level during hospitalization. Twenty-one (60%) patients developed complications with significantly elevated VWF antigen level (P= 0.037). There was a positive correlation between VWF antigen level and number of complications in COVID-19 patients. Eleven patients (31.54%) who developed Acute Respiratory Distress Syndrome (ARDS) had a statistically higher VWF antigen level compared to patients with no ARDS (mean 235.1 vs 182.1%; P= 0.024). Patients who died with thrombogenesis in COVID-19 patients and to correlate with their clinical outcome.

Conclusion: Our study shows that patients with COVID-19 have elevated VWF antigen level correlating with complications and poor outcome.

Background
COVID-19 pandemic caused by SARS-CoV-2 is increasing rapidly in several countries across the world. As of 14th December 2020, 72,655,939 cases have been reported, with a case fatality rate of 2.23%. Despite stringent measures such as social distancing, wearing masks, and imposing lockdown in controlling the disease, the second wave of COVID-19 has emerged in many countries across the world, thus showing no decline in the daily infection. Mortality of COVID-19 is higher in patients, with advanced age, diabetes mellitus, hypertension, and obesity.2

The understanding of COVID-19 has changed significantly since the beginning of the pandemic. Initial studies from China demonstrated COVID-19 as predominantly a respiratory viral illness with fever and flu-like symptoms. The virus utilizes ACE2 receptors in type 2 alveolar cells causing significant lung damage leading to Acute respiratory distress syndrome (ARDS).3 Subsequent studies revealed COVID-19 involvement in other systems such as vascular endothelium, gastrointestinal system, liver, and heart due to the abundance of ACE2 receptors in these tissues.4,5 Higher endothelial expression of ACE2 receptors in these organs attracts binding of SARS-CoV-2 spiked protein.6 This causes widespread disruption and damage to the endothelial lining. Endothelial disruption, the release of proinflammatory cytokines further damages the endothelium leading to edema and increased leakiness resulting in Acute Respiratory Distress Syndrome (ARDS).

Up to 25% of COVID-19 patients have shown to develop thromboembolic complications, particularly in those with severe disease.7 Atypical presentation of COVID-19 with Myocardial Infarction and stroke have been described.8 Currently thromboembolic complications are the most common cause of morbidity and mortality among COVID-19 patients. Post-mortem studies revealed alveolar edema, interstitial lymphocytic inflammation, and importantly, a higher proportion of COVID-19 patients were found to have extensive fibrin thrombi with activated megakaryocytes involving smaller blood vessels.9 Distinctly, these patients were found to have severe endothelial damage, loss of endothelial cell tight junctions, widespread microthrombi and alveolar capillaries. COVID-19 patients developed significant endothelial damage in comparison to influenza

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COVID-19 patients admitted to our institute between 1st July 2020 to 12th July 2020 was carried out following informed consent at the time of hospitalization. All patients above 16 years of age with COVID-19 were included in the study. Patients who were already on antithrombotic agents or anticoagulants, pregnant women and patients unwilling to participate were excluded. All hospitalized COVID-19 patients underwent investigations as per the unit protocol and inflammatory markers such as C-reactive protein (CRP), ferritin, Interleukin-6 (IL-6), and lactate dehydrogenase (LDH). Radiological investigations were carried out upon clinical indications to assess COVID-19 disease severity. Following parameters were tested at the time of hospital admission: VWF antigen level, fibrinogen level, platelet count, Activated partial thromboplastin time (aPTT), International normalized ratio, Protein C, Protein S, AT III, and D-dimer. COVID-19 patients received corticosteroids, anticoagulants, antibiotics, antiviral medications, and vitamin supplements as per our institution protocol.

**Materials**

About 3.0ml blood was collected in a Greiner bio-one citrated (3.2% disodium citrate) vacutainer at the time of hospital admission. Laboratory analysis was performed on the citrated plasma after separation based on the following methods VWF antigen level using latex enhanced immunoassay, fibrinogen level using clot-based assay, D-Dimer using high sensitive latex enhanced immunoassay. Similarly, Protein C and AT III using automated chromogenic assay, Protein S activity was carried out using a clot-based assay with fully automated Haemostasis analyzer ACL TOP-750 (Instrumentation Laboratory-a Werfen company, USA). The normal reference range of VWF antigen level expressed in percentage (%) was calculated according to the patient’s blood group. For blood group O the reference range was 41.1% to 125.9% and for non-O blood group 61.3% to 157.8%. Normal range were set as following, fibrinogen 220-496 mg/dL, D-Dimer 0-250 ng/mL, Protein C 70-140 %, Protein S 63.5-149 %, AT III 83-128 %. Instrumentation Laboratory Normal Control was processed with each batch of the run to monitor the method performance. The obtained control result agreed with the certified values. The performance of these tests was correlated with COVID-19 severity and clinical outcomes. Clinical complications were defined as patients requiring ICU stay, worsening lung infiltrates accounting for ARDS, prolonged hospital stay, multi-organ dysfunction or death.

**Ethics Approval**

Institutional Ethics Committee approval obtained.

**Statistical analysis**

Data entries was analyzed using Statistical Package for the Social Sciences (SPSS Statistics v21.0) software. Descriptive statistics were used to summarize the basic features and the visualization of the data. Mean, standard variation, frequency and percentage of variables were calculated.

Student t-test was utilized to compare the means in factors associated with thrombosis with respect to patients COVID-19 disease severity, complications and clinical outcome. Correlation coefficient (r) and scatter plots were used to quantify the association between the thrombogenic factors, and inflammatory markers.

Univariate regression analysis was used to infer the relationships between the VWF antigen level (X or Dependant variable) and the independent variables (Y) such as duration of hospital stay, ferritin, CRP, and IL6. P-value of <0.05 was considered as statistically significant.

**Results**

35 COVID-19 patients underwent tests for thrombosis at the time of hospitalization, with a median age of 50 (IQR:44.5-55.7) years and male-female ratio of 1.69:1. Fever (n= 18; 51.4%) and dry cough (n= 11; 31.4%) were the most common presenting symptoms. Twenty-three (65.7%) patients had underlying co-morbidities such as diabetes mellitus (n= 14; 40%) and hypertension (n= 11; 31.4%).

Thirty (85.7%) COVID-19 patients had elevated VWF antigen level (Blood group-O:41.1-125.9%; Blood group A, B and AB:61.3-157.8%) at the time of hospital admission (overall mean:198.1); whereas 4 (13.3%), 3 (8.5%), 0 (0%), 0 (0%), 3 (8.5%), 1 (2.9%) ,5 (14.3%) and 14 (40%) patients had abnormal levels of fibrinogen, platelets,
Table 1: Comparison of factor levels between COVID-19 patients with complications and without complications

<table>
<thead>
<tr>
<th>Complications (n= 21;60%)</th>
<th>No complications (n= 14; 40%)</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td><strong>Pro-coagulant factors</strong></td>
<td></td>
<td></td>
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<tr>
<td>VWF (O group:41.1-125.9 %; non-O group:61.3-157.8 %)</td>
<td>216.1 ± 71.6</td>
<td>183.58-248.88</td>
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<td>Fibrinogen (238-496 mg/dL)</td>
<td>385.5 ± 129.4</td>
<td>323.18-447.97</td>
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<td>Platelet (150-450 ×10^9/L)</td>
<td>250.7 ± 95.2</td>
<td>206.17-295.33</td>
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<td>APTT (25-35 secs)</td>
<td>33.0 ± 14.1</td>
<td>26.06-39.96</td>
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<td>INR (0.90-1.15)</td>
<td>1.01 ± 0.12</td>
<td>0.96-1.07</td>
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<td><strong>Anti-coagulant factors</strong></td>
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<tr>
<td>Protein C (70-140 %)</td>
<td>94.8 ± 20.9</td>
<td>85.29-104.33</td>
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<td>Protein S (63.5-149 %)</td>
<td>99.8 ± 28.9</td>
<td>86.73-113.06</td>
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<td>ATIII (83-128 %)</td>
<td>98.3 ± 14.1</td>
<td>91.92-104.75</td>
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<td><strong>Pro-fibrinolytic factors</strong></td>
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<tr>
<td>D-dimer (0-250 ng/mL)</td>
<td>894.6 ± 2268.8</td>
<td>-359.83-2149.03</td>
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Fig. 1: Correlation between VWF antigen level and the number of complications

Complications vs no complications

Twenty-one (60%) COVID-19 patients developed complications during the study period. Patients who developed complications had significantly elevated VWF antigen level compared to those with no complications (mean 216.1 vs 172.7 %; P= 0.037). Other parameters showed no statistical difference; fibrinogen level (mean 385.5 vs 301.6 mg/dL; P= 0.054), platelet count (mean 250.7 vs 277.4 ×10^9/L; P=0.471), APTT (mean 33.0 vs 33 secs; P=0.495), INR (mean 1.01 vs 1.02; P= 0.807), Protein C (mean 94.8 vs 97.1 %; P= 0.795), Protein S (mean 99.8 vs 103.5 %; P= 0.683), AT III (mean 98.3 vs 97.8 %; P= 0.953) and D-dimer (mean 894.6 vs 248.4 ng/mL; P= 0.297) as illustrated in Table 1.

Out of 21 patients who had complications, 10 (47.6%), 3 (14.2%), 4 (19%), 4 (19%) had one, two, three, and four complications respectively. Detailed analysis is presented in the supplementary table.

On further analysis, there was a positive correlation between VWF antigen level and the number of complications in COVID-19 patients (Figure 1).

COVID-19: ICU vs non-ICU Patients

Eight (22.8%) patients required ICU support. Table 2 illustrates the levels of thrombotic factors between ICU and non-ICU patients. COVID-19 patients requiring ICU had a significantly higher levels of VWF antigen level (mean 252.9 vs 182.7 %; P= 0.006), fibrinogen (mean 432 vs 326.7 mg/dL; P= 0.037) and D-dimer (mean 2075.7 vs 253.7 ng/mL; P= 0.043). Platelet count (mean 246.2 vs 263.9 ×10^9/L; P= 0.672), INR (mean 1.09 vs 0.99; P= 0.04), APTT (mean 38.7 vs 29.9 secs; P= 0.361), Protein C (mean 92.7 vs 96.6 %; P= 0.572), Protein S (mean 96.6 vs 102.7 %; P= 0.488) and AT III (mean 96.7 vs 98.3 %; P= 0.804) were not different between the groups. The Odds ratio of COVID-19 patients requiring ICU support with VWF antigen level >200% requiring ICU support was 11.08 (95%CI:1.24-99.15; P= 0.006).

Prolonged Hospital Stay

Twenty-one patients (60%) had ≥7 days of hospital stay. Patients with prolonged hospital stay had significantly increased VWF antigen level (mean 216.2 vs 172.7 %; P= 0.037). There was a significant logarithmic correlation between VWF antigen level and the duration of hospitalization in COVID-19 (Figure 2). However, there was no statistical significance noted among the other parameters.

ARDS vs no ARDS

Eleven patients (31.54%) developed ARDS. Patients with ARDS had statistically higher VWF antigen level compared to patients with no ARDS (mean 235.1 vs 182.1 %; P= 0.024).

Dead vs Alive

Four (11.4%) COVID-19 patients died during the study period. Patients who died had higher VWF antigen (mean 289.9vs 187 %; P= 0.002), lower...
platelet count (mean 159.3 vs 275 ×109/L; P= 0.01) and elevated D-dimer (mean 4265.3 vs 278.5 ng/mL; P= 0.001) in comparison to alive patients. (supplementary table)

**Correlation between thrombogenic factors and inflammatory markers**

COVID-19 patients with elevated VWF antigen level had higher inflammatory markers, such as ferritin (mean 459.2 [95% CI:250-668] vs 63.3 mg/dL [95%CI:26–152.8]; P= 0.001), LDH (mean 287 [95%CI:229-346] vs 185.8 U/L [95%CI:163-209]; P= 0.002), CRP (mean 46.8 [95%CI:21-72] vs 1.2 mg/dL [95%CI:0.27-2.2]; P= 0.001) and IL-6 (mean 49.3 [95%CI:27.7-70.9] vs 3.5 pg/mL [95%CI 2.3-4.7]; P= 0.00) compared to patients with normal VWF antigen level. In addition, the was a positive correlation between VWF antigen level with ferritin (r= 0.628), CRP (r= 0.611) and IL-6 (r= 0.782) levels. (Table 3)

**Discussion**

COVID-19 is associated with a higher incidence of thromboembolic complications, particularly in those with severe and progressive disease. Autopsy studies revealed widespread endothelial damage with extensive microvascular thrombosis involving pulmonary as well as systemic vasculature. Our study demonstrates that 85.7% of COVID-19 patients admitted to the hospital have elevated VWF antigen level. A similar study published earlier showed elevated VWF antigen in 94% of COVID-19 patients.16 Interestingly, the cut off values of VWF antigen level varies depending on the blood group. Blood group O patients tend to have a higher cut off level than the non-blood group O. We stratified and adjusted VWF antigen level accordingly for better results.

Our data shows that COVID-19 patients requiring ICU care had significantly higher VWF antigen level in comparison to non-ICU patients (mean 252.9 vs 182.7 9.9%; P= 0.006). In addition, we found a clear association between elevated VWF antigen level and COVID-19 patients with complications. The levels were much higher in patients with ARDS (mean 235.1 vs 182.1 %; P= 0.024), prolonged hospital stay (mean 216.9 vs 172.7 %; P= 0.037), and in particular, in those who died (mean 289.9 vs 187 %; P= 0.002) compared to those with no ARDS, with shorter hospital stay (<7 days) and survived. The mortality rate in our COVID-19 patients with elevated VWF antigen level was 11.4%. Our mortality was slightly lower compared to a study by Ladikou et al, where the mortality rate was 16.7%, involving 24 patients.17 However, a larger study by Helms et al, in COVID-19 patients with ARDS showed a mortality of 8.7% S and a much higher median VWF antigen level compared to our study (455% vs 216.3%).18 These features may be an indication of accelerated prothrombotic state in patients with severe COVID-19. Further analysis showed a positive correlation between VWF antigen level and the number of complications. We do not know whether elevated VWF antigen level is a consequence or cause of complications. We evaluated the VWF antigen level at the time of hospital admission when the patient did not have clinical complications. This indicates that elevated VWF antigen level may occur prior to the onset of complications. Interestingly, in comparison with other studies, the median VWF antigen levels were low in our study. Patients with mild COVID-19 in our series had a VWF antigen level of 197.7% whereas, in a study by Cugno et al, the median level was 263%. Similarly, in patients with severe COVID-19, the levels were 216.6% in our series as compared to 455% from the west. It is unclear whether these differences explain the lower mortality in our series of COVID-19 patients.19

Elevated inflammatory markers such as ferritin, CRP, and IL-6 were associated with severity in COVID-19. Our data showed a clear correlation between VWF antigen level and inflammatory markers. In addition, there was a positive correlation between the VWF antigen level and the severity of inflammation.

Non-survivors in our series had higher VWF antigen level, lower platelets, and elevated D-dimer. This probably represents the onset of DIC as a terminal event leading to death. In concurrence, both ours and the study by Berger et al, showed higher mortality in patients with elevated D-dimer levels compared to patients with normal levels (20% vs 2% in our study vs 29.9% vs 10.8%).20 Overall, our study shows elevated VWF antigen level in patients with COVID-19 which correlates with disease severity, complications, and mortality. Elevated VWF antigen probably an indication of underlying endothelial injury could be due to caused directly by SARS-CoV-2 virus or secondary to systemic inflammation or maybe an immune dysfunction leading to endothelitis.

Our study is limited by smaller patient numbers, based predominantly on VWF antigen level and other routine clinical parameters. We do not know the baseline VWF antigen level in the general population. However, our study throws open to a number of questions that need further research.

In conclusion, our study shows that COVID-19 have elevated VWF antigen level correlating with complications and poor outcome. Larger studies.

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**Table 2: Comparison of thrombotic factors in COVID-19 patients requiring ICU and non-ICU**

<table>
<thead>
<tr>
<th>Factor</th>
<th>ICU (n= 8; 22.8%)</th>
<th>Non-ICU (n= 27; 77.2%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pro-coagulant factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VWF (O group:41.1-125.9%; non-O group:61.3-157.8%)</td>
<td>252.9</td>
<td>253.7</td>
<td>0.804</td>
</tr>
<tr>
<td>Fibrinogen (238-496 mg/dL)</td>
<td>432.0</td>
<td>326.7</td>
<td>0.043</td>
</tr>
<tr>
<td>Platelet (150-450 ×10^9/L)</td>
<td>246.2</td>
<td>263.9</td>
<td>0.994</td>
</tr>
<tr>
<td>APTT (25-35 secs)</td>
<td>38.7</td>
<td>29.9</td>
<td>0.456</td>
</tr>
<tr>
<td>INR (0.90-1.15)</td>
<td>1.09</td>
<td>0.99</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>Anti-coagulant factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein C (70-140%)</td>
<td>92.7</td>
<td>96.6</td>
<td>0.86</td>
</tr>
<tr>
<td>Protein S (63.5-149%)</td>
<td>96.6</td>
<td>102.7</td>
<td>0.286</td>
</tr>
<tr>
<td>Antithrombin III (83-128%)</td>
<td>96.7</td>
<td>98.5</td>
<td>0.852</td>
</tr>
<tr>
<td><strong>Pro-fibrinolytic factors</strong></td>
<td>D-Dimer (0-250 ng/mL)</td>
<td>2075.7</td>
<td>192.4</td>
</tr>
<tr>
<td><strong>Discussion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

COVID-19 is associated with a higher incidence of thromboembolic complications, particularly in those with severe and progressive disease. Autopsy studies revealed widespread endothelial damage with extensive microvascular thrombosis involving pulmonary as well as systemic vasculature. Our study demonstrates that 85.7% of COVID-19 patients admitted to the hospital have elevated VWF antigen level. A similar study published earlier showed elevated VWF antigen in 94% of COVID-19 patients.16 Interestingly, the cut off values of VWF antigen level varies depending on the blood group. Blood group O patients tend to have a higher cut off level than the non-blood group O. We stratified and adjusted VWF antigen level accordingly for better results.

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In conclusion, our study shows that COVID-19 have elevated VWF antigen level correlating with complications and poor outcome. Larger studies.
Table 3: Correlation between Thrombogenic factors and inflammatory marker levels

<table>
<thead>
<tr>
<th>Inflammatory markers</th>
<th>CRP</th>
<th>LDH</th>
<th>Ferritin</th>
<th>CK</th>
<th>IL-6</th>
<th>Fibrinogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pro-coagulant factors</td>
<td>VWF</td>
<td>0.611</td>
<td>0.545</td>
<td>0.628</td>
<td>0.246</td>
<td>0.782</td>
</tr>
<tr>
<td></td>
<td>fibrinogen</td>
<td>0.701</td>
<td>0.615</td>
<td>0.603</td>
<td>-0.017</td>
<td>0.544</td>
</tr>
<tr>
<td></td>
<td>Platelet</td>
<td>-0.090</td>
<td>-0.113</td>
<td>-0.004</td>
<td>-0.151</td>
<td>-0.121</td>
</tr>
<tr>
<td></td>
<td>APTT</td>
<td>0.314</td>
<td>0.079</td>
<td>0.104</td>
<td>0.023</td>
<td>0.140</td>
</tr>
<tr>
<td></td>
<td>INR</td>
<td>0.403</td>
<td>0.272</td>
<td>0.246</td>
<td>-0.074</td>
<td>0.328</td>
</tr>
<tr>
<td>Anti-coagulant factors</td>
<td>Protein C</td>
<td>-0.238</td>
<td>-0.298</td>
<td>-0.164</td>
<td>-0.230</td>
<td>-0.227</td>
</tr>
<tr>
<td></td>
<td>Protein S</td>
<td>-0.132</td>
<td>0.049</td>
<td>0.120</td>
<td>-0.173</td>
<td>-0.070</td>
</tr>
<tr>
<td></td>
<td>Antithrombin III</td>
<td>-0.146</td>
<td>0.107</td>
<td>-0.072</td>
<td>-0.051</td>
<td>-0.194</td>
</tr>
<tr>
<td>Pro-fibrinolytic factors</td>
<td>D-dimer</td>
<td>0.254</td>
<td>0.505</td>
<td>0.535</td>
<td>0.43</td>
<td>0.499</td>
</tr>
</tbody>
</table>

are required to ascertain the utility of VWF antigen level in patients with COVID-19, particularly with the commencement of the second wave in several countries.

This study was approved by the hospital’s internal ethical committee.

Declarations

Ethics Approval

Institutional Ethics Committee approval obtained

References

In Hypertension Management

Rx

Olsertain
Olmesartan Medoxomil 20 mg & 40 mg
SURE-SHOT BP Drop

In T2DM patients

Rx
ADD

Glimy
Glimepiride 1/2/3/4 mg Tablets

Sureshot BP drop – Nearly 80% patients treated with Olmesartan 40 mg reached target blood pressure < 130/80 mm Hg.


T2DM: Type 2 diabetes mellitus
BP: Blood pressure
Unusual Observations of Neurological Cases in Patients with Simultaneous Corona Infection - (A Hospital-Based Study)

Debashis Chakraborty¹, Amit Haldar²

Abstract
Among the several cases of Coronavirus, presenting with mainly respiratory symptoms, in our Isolation ward, it was observed that there were cases which presented with neurological symptoms. Such cases apparently appeared initially as normal neurological varied presentations. However, due to strong suspicion related to certain unusual aspects, both clinical and investigation based and also due to failure of treatment, as done in such cases, we surmised that they could be related to Corona. This article describes 6 such cases, which were initially in suspected area, awaiting SAARS CoV2 report and later seen either in Corona ward if positive or in ward or intensive ward when they became twice negative. Initially they were treated on routine neurological lines but later on confirmation of SAARS CoV2, treatment patterns were changed due to non responsiveness to conventional treatment and variation in the progress were observed.

Introduction
The 2020-novel coronavirus (SAARS CoV2) has been declared a world pandemic by WHO. Initially named novel coronavirus, is a single-stranded RNA virus with a spike studded envelope, mimicking a crown, from where the name has been derived. In addition to the respiratory system involvement, recent evidence has shown that SARS-CoV-2 can affect other organ systems including nervous, vascular, digestive, urinary, haematological and so on.⁸ Here in this article, we have described such cases which presented as routine neurological cases. However, their behaviour was different, especially, in response to standard treatment regimens.

Methodology
In this article, we discussed neurological cases, who presented atypically like no high fever, cough etc but were proved to be positive for SAARS-CoV2.

Whenever there was a suspicion from either history or associated complains, they were admitted in separately without contact with normal cases. Once found positive, they were shifted to Isolation ward and if negative, and stable to ward/Intensive care units. These neurological cases are described including their presentation and management.

Results

Case 1
A cardiothoracic surgeon, who had previous history of diabetes, hypertension and CAD, was already on dual antiplatelets and statins. He presented with sudden onset gait disturbance and a transient period of detachment from surroundings for few minutes. It was found that he had diarrhoea 2 weeks back which was better. Neurological examination showed only a mildly ataxic gait. MRI however showed a mild lesion in parieto-occipital area along with multiple scattered small old infarcts in b/l MCA and ACA territories.

Conservative treatment continued with increasing the dose of antiplatelets and statins. However in his routine blood tests, his counts revealed both leukocytopenia and thrombocytopenia on 3 consecutive days and his gait deteriorated further. Chest CT, initially showed ground glass appearance, later, improved. He was then prescribed HCQS along with his other medications. Gradually his gait improved, with physiotherapy and repeat MRI was normal. Although by this time his counts became normal. Idea is to keep in mind haematological changes in stroke in a patient of corona.⁵

Case 2
A young 19-year female with a history of travel to Delhi, without any known history of epilepsy, presented with 3 episodes of generalised tonic clonic seizures at home. After the last attack she did not regain consciousness and was brought to hospital ER. Since there was a history of travel, she was kept in isolation instead of routine ICU.

At bedside there was no apparent neurodeficit. Although she was arousable but very drowsy. She continued to have 2 further attacks and then became completely unconscious, with GCS 4. Her blood gasses showed acidosis and she was intubated & fully ventilated. She was initially loaded with Fosphenytoin and kept at 150 mg thrice daily. The convulsions stopped. Pupils were small and non-reacting.

A bedside EEG, showed evidence of continuous spike and wave discharges, and assuming she was in non-convulsive status, she was started on Midazolam infusion up to 0.4mg/kg/hr. In the meantime, her routine blood examination showed a leukocyte count of 3500/L, Haemoglobin 9 gm/l and platelets 70000. CXR was normal. MRI showed patchy hyperintensities b/l in paraventricular areas. Corona test was positive.

She was added Lopinavir with Ritonavir combination and HCQS. Next day repeat EEG showed intermittent spikes, but no status.

Gradually Midazolam was tapered over 72 hrs and she could be extubated on 5th day by which time she regained

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ORIGINAl ARTIcle

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and on ventilator. At that point he was gradually recovering, and his chest symptoms, signs and ventilator requirements were coming down. Gradually he was weaned, conscious throughout, and shifted to medical ICU, after SAARS CoV2 was negative with tracheostomy. It was very difficult to bring him to t-piece and hence tracheostomy had to be kept for airway protection. He then complained of bodyaches with mild weakness of all 4 limbs. A CPK was sent and it was found to be over 2000. However, bromocriptine was not started as this was not thought to be due to NMS and after about 5 days his CPK came down to around 500. Clinically he had grade 4/5 power in 4 limbs both proximally and a bit more distally. Bedside Electrophysiology showed normal sensory SNAPs but CMAP were reduced along with reduction in conduction velocity as well. Due to his still mildly raised INR, and Liver enzymes, lumbar puncture was not ventured, and so we could not prove therefore any albumin-cytological dissociation.

In this case we found motor neuropathy, although we cannot conclude whether his neuropathy was related to Coronavirus or prolonged ventilation. But he definitely had myopathy, which is reported in Coronavirus\(^1\) and his high initial CPK was contributory too.

**Case 5**

A thirtyfive year old lady, with corona having mild sore throat and low-grade fever had been recovering and except a little patchy opacity in left base in initial Chest X-ray, was otherwise asymptomatic. While she was in ward, after becoming SAARS CoV2 negative she complained of severe headache. She has been a known episodic migraineur since several years. She was extremely anxious from admission and required regular counselling.

On the 10\(^{th}\) day she started complaining of increasing intensity of headache and she started incessant vomiting. She was put on i/v fluids, Ondansetron and Pantoprazole and paracetamol thrice but showed no improvement. Her lab electrolytes showed Sodium 121meq and Potassium 3.2. She was given necessary supplementation and dexamethasone (steroid) 4mg thrice was added.

She was sedated. 2days later her headache reduced and by 4\(^{th}\) day, her i/v medicines and fluids were stopped. However, steroids were tapered off in 5 days. She was put on Amitryptiline 25 mg at bedtime and Zolmitriptan nasal spray SOS. She became fit by day 17. We concluded that this status migranosus could be related to sudden changes in inflammatory markers\(^2\) in brain as a consequence of Corona. However, existing literature was not sufficient to verify this hypothesis.

**Case 6**

75-year-old diabetic, hypertensive, Covid patient, although well controlled, presented with fever, cough and typical ground glass CT chest appearance. He was treated conservatively with antibiotics, steroids and HCQS. He was recovering as far as his respiratory symptoms and signs were concerned. Suddenly on the seventh day he started complaining of uncoordinated movement of left upper limb with difficulty in vision. On examination it was found he had a right homonymous hemianopia and left sided cerebellar signs. MRI brain showed that he had a left cerebellar and left occipital infarcts and MR angio of neck showed complete occlusion of left vertebral artery. He was immediately started on dual antiplatelets and statins. His blood counts were normal, but D-Dimer was highly raised, around 900. He was shifted to medical ICU for better monitoring and also to detect any intermittent arrhythmia as the nature of the CVA was also thought to be an embolic episode.

Echo and Holter were normal. His symptoms persisted, but after 5 days of Heparin infusion, his D-Dimer reduced and repeat MRI and angio were same. A CT angio of lungs (done to rule out pulmonary embolism) was normal. His stay was quite prolonged, physiotherapy continued, and he was discharged on 21\(^{st}\) day with normal D-Dimer and residual neurodeficit.

**Discussion**

From the above cases, it is clear that Coronavirus can cause a spectrum of neurological disorders. However, the presentations were not causative but necessarily observations only.

Different modes of both Anterior and posterior circulation CVA, Epilepsy
including status, myopathy, doubtful critical illness neuropathy, headaches – even amounting to status migranosus, were new to us in a background of Coronavirus due to different presentations and response to different forms of therapy.

The above Pie chart depicts the different types of cases of Neurology seen in patients of corona cited in Figure 1. (Legend and citation given in figure - A Summary of the Clinical Presentations in the case studies). In concert with COVID positive results in 6 admitted patients.

Deaths from COVID-19 are chiefly due to a major immune inflammatory response and diffuse alveolar damage. The body responds to the infection by recognizing the viral RNA when it is replicating within the host cell using downstream signalling cascades with intracellular receptors. This in turn, leads to several downstream signalling cascades with the end result of producing an army of defence cytokines to curb the viral spread. The pro-inflammatory cytokine up regulation (interleukin (IL)-1, IL-6, TNF, and interferon γ) in this disease is a valid target for anti-TNF therapy. Blockade of TNF alone is clinically effective in many diseases, despite the presence of other pro-inflammatory cytokines and mediators.

This severe immune storm which takes place in the entire Neural-axis as well as the whole body has been figuratively described in the above picture, titled Corona and the central nervous system, mechanisms of tropisms and presentation in the above picture cited in Figure 2. (Legend and citation in figure given - Corona and the Central Nervous System. Mechanisms of Tropism and Presentations.) It not only emphasises the immune storm in the brain and entire neural axis but the whole body in general.

Finally the 6 cases has been summarised in a table, given below and named as Table 1 (Cited as summary of case studies).

**Conclusion**

**SAARS CoV2 is a highly contagious disease that has become a pandemic.** Patients infected may show neurological symptoms at the commencement. These cases are intriguing and important, and one has to consider these above observations as having possible association to Corona in their pathogenesis. Neurologists should scrutinise these symptoms closely and have a high index of suspicion when evaluating patients in an endemic area. Early recognition may help initiate treatment and isolation so as to prevent clinical worsening and spreading of the virus. Since the pathogenesis of the novel Coronavirus still remains to be explained accurately, vaccine development is a monumental task. Until these efforts are fruitful, strict monitoring of patients and carefully selected treatment routines, particularly for those with unusual neurological features are essential.

**Acknowledgement**

**COVID Team:** 1. Sibabrata Banerjee, MD(Medicine), 2. Yashis Paliwal, MD, Chief Intensivist, 3. Raja Dhar, MD, MRCP (UK), Director-Pulmonology.

Statiscal and graphic help has been done by Miss Sukanya Chakraborty is a scholar at the Indian Institute of Science Education and Research (IISER), Berhampur, majoring in the...
High Mortality Unaffected by Age, Gender and Steroid Use is the Hallmark of COVID-19 in Diabetes: Observations from a Retrospective Analysis during Peak of 2020 Pandemic in India

Ramesh Aggarwal¹, Aparna Agrawal², Anil Gurtoo³, Vivek Suman¹, Shivraj Meena¹, Anupam Prakash⁴*

Abstract


Methods: Records of admitted COVID-19 patients suffering from diabetes or having admission hyperglycemia (random plasma glucose ≥200 mg/dL) between March to August 2020 were analysed for severity and outcomes of COVID-19, presence of comorbidities, steroid use, and correlated with hyperglycemia.

Results: 71 COVID-19 patients (severe disease - 35, moderate- 17, mild- 19) were studied. Mortality was 52.1% (mild disease-27.3%, moderate- 43.5% and severe-72.7%). Mortality was similar across age and gender. Prevalence of comorbidities was similar in survivors (20.6%) and non-survivors (24.3%). Newly detected hyperglycemia at admission was noted in 9 patients, two-thirds of which had severe COVID-19 and 5 expired (55.5%). Higher values of plasma glucose at admission (295.9 vs. 236.4 mg/dL, p=0.047) and high fasting plasma glucose values (210.3 vs. 166.5 mg/dL, p=0.043) were observed among non-survivors.

Conclusion: COVID-19 in diabetes patients requiring admission carries high mortality, irrespective of age, gender, presence of comorbidities and steroid use. However, admission hyperglycemia and high fasting plasma glucose values are associated with higher mortality.

Introduction

Diabetes is one of the major illnesses affecting 8.8% of the world population representing almost 415 million people. Diabetes is known to predispose an individual to increased risk for infections. Studies in the past have shown a J-curve type of relationship between HbA1c and the chances of being admitted in hospital with respiratory infection. COVID-19 pandemic seized the world in 2020, but diabetes impacted COVID-19 as one of the prime adverse prognostic factors. An increased risk of infection in diabetics was reported during previous outbreaks of severe acute respiratory syndrome, Middle East respiratory syndrome and H1N1 influenza virus. Evidence is gradually emerging that not only diabetes but hyperglycemia in the early phase of the disease may determine the severity of the disease. However, published literature is lacking on how Diabetes patients getting admitted with COVID-19 have behaved. The present study outlines the severity and outcomes in patients...
Table 1: Comparison between Group A (Non Survivors) and Group B (Survivors)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group A Non Survivors (n=37)</th>
<th>Group B Survivors (n=34)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in years)</td>
<td>55.1 ± 11.9 (33-82)</td>
<td>55.1 ± 12.63 (33-85)</td>
<td>0.475</td>
</tr>
<tr>
<td>Male to Female ratio</td>
<td>23:14</td>
<td>21:13</td>
<td>0.972</td>
</tr>
<tr>
<td>Age of Males (Mean ± SD in years)</td>
<td>53.3 ± 12.34 (33-82)</td>
<td>56.5 ± 13.03 (33-85)</td>
<td>0.2</td>
</tr>
<tr>
<td>Age of Females (Mean ± SD in years)</td>
<td>58.0 ± 10.94 (40-80)</td>
<td>52.9 ± 12.12 (42-85)</td>
<td>0.13</td>
</tr>
<tr>
<td>New Onset Hyperglycemia (n=9)</td>
<td>5 (26.4%)</td>
<td>9 (24.3%)</td>
<td>0.71</td>
</tr>
<tr>
<td>Steroids Given (%)</td>
<td>15 (40.5%)</td>
<td>9 (26.4%)</td>
<td>0.69</td>
</tr>
<tr>
<td>Comorbidity &gt; 1</td>
<td>9 (24.3%)</td>
<td>7 (20.6%)</td>
<td>0.71</td>
</tr>
<tr>
<td>Duration of Diabetes (Mean ± SD in years)</td>
<td>6.64 ± 4.7</td>
<td>5.9 ± 3.1</td>
<td>0.69</td>
</tr>
<tr>
<td>Severity (n=71)</td>
<td></td>
<td></td>
<td>0.0002</td>
</tr>
<tr>
<td>Mild (n=19)</td>
<td>27.27%, n=3</td>
<td>73.33%, n=16</td>
<td></td>
</tr>
<tr>
<td>Moderate (n=17)</td>
<td>43.5%, n=8</td>
<td>56.25%, n=9</td>
<td></td>
</tr>
<tr>
<td>Severe (n=35)</td>
<td>72.72%, n=26</td>
<td>27.27%, n=9</td>
<td></td>
</tr>
<tr>
<td>Admission plasma glucose, mg/dL (Mean ± SD)</td>
<td>295.9 ± 138.4</td>
<td>236.4 ± 90.7, n=27</td>
<td>0.047</td>
</tr>
<tr>
<td>Fasting plasma glucose, mg/dL (Mean ± SD)</td>
<td>210.3 ± 99.7, n=18</td>
<td>166.5 ± 75.6, n=21</td>
<td>0.043</td>
</tr>
<tr>
<td>Duration of stay (Days)</td>
<td>3.7 ± 4.0</td>
<td>13.2 ± 7.35</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

All values are in Mean ± SD and figures in parenthesis indicate range excepting where % indicates percentages.

Table 2: Covid-19 mortality in relation to plasma glucose at admission and severity of COVID-19 (n=60)

<table>
<thead>
<tr>
<th>Admission plasma glucose values</th>
<th>N</th>
<th>Mild (n=13)</th>
<th>Moderate (n=14)</th>
<th>Severe (n=33)</th>
<th>P value (Chi square test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200 mg/dL</td>
<td>19</td>
<td>2/6 (33.3%)</td>
<td>2/5 (40%)</td>
<td>4/8 (50%)</td>
<td>0.147</td>
</tr>
<tr>
<td>≥200 mg/dL</td>
<td>41</td>
<td>Nil/7 (0%)</td>
<td>5/9 (55.5%)</td>
<td>20/25 (80%)</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Patients on steroids: Comparison of blood sugars and outcome (all values are in Mean ± SD)

<table>
<thead>
<tr>
<th>Plasma glucose (mg/dL)</th>
<th>Non-survivors (n=15)</th>
<th>Survivors (n=9)</th>
<th>P value (t-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting (within 24 hours of admission)</td>
<td>213.3 ± 95.9 (97-321)</td>
<td>203.7 ± 58.79 (128-286)</td>
<td>0.80</td>
</tr>
<tr>
<td>Prior to discharge/ death</td>
<td>251.46 ± 74.02 (144-396)</td>
<td>174 ± 114.41 (16-293)</td>
<td>0.046</td>
</tr>
</tbody>
</table>

Methods

This retrospective observational study collected data of COVID-19 patients who were admitted to our dedicated COVID-19 set-up at a tertiary care centre in Delhi, India between the months from March to August 2020. The study was approved by the Institutional Ethics Committee. A total of 71 COVID-19 patients presented with hyperglycemia during the referenced period. Hyperglycemia was defined as random blood sugar ≥180mg/dL at admission. Only RT-PCR/CBNAAT confirmed cases of COVID-19 were included in the study. Patients who were already known to be suffering from diabetes were also included. New onset hyperglycemia was defined as random blood sugar at admission ≥200mg/dL without any previous evidence of preexisting diabetes. Hba1c was not done at baseline in these patients.

Records were analysed for information which was transcribed on a pre-structured proforma which included baseline demographic data, clinical features including severity of COVID-19 (based on MoHFW guidelines), 2 glycemic control, outcomes in form of discharge or death, and effect of steroid use. The information obtained was tabulated on Microsoft Excel spreadsheet, and analysed. Comparison of clinical features was done based on grouping in to (i) survivors and non-survivors on basis of outcome, (ii) mild, moderate and severe on basis of severity of illness, (iii) presence of co-morbidities, and (iv) effect of steroids on blood sugar levels and insulin requirements in these patients.

Data is presented as Mean ± SD and proportions. Statistical analysis was performed. Two-group and three group comparisons were respectively made with unpaired Student’s t-test and ANOVA. Chi-square test was used for non-parametric data. P<0.05 was taken as level of significance.

Results

A total of 71 RT-PCR confirmed nCov-2019 positive patients who presented with hyperglycemia or were known diabetes mellitus patients during the period (March –August 2020) formed the study group. 37 patients (52.1%) succumbed and constituted the non-survivor group (Group A). Table 1 shows the various characteristics among the non-survivors (Group A) and the survivors (Group B).

In up to 60 years age group, 14/32 (43.75%) males and 11/20 (55%) females survived, while in the > 60 years age group, 7/12 (58.3%) males and 2/7 (28.6%) females survived, and the difference was not statistically significant age wise or gender wise.

Mortality did not differ significantly in between the genders, irrespective of the severity of COVID-19. 2/12 (16.7%) males and 1/7 (14.3%) females suffering from mild COVID-19 failed to survive, compared to 3/5 (60%) males and 5/9 (55.5%) females suffering from moderate COVID-19, and 18/24 (66.7%) males and 8/11 (72.7%) females suffering from severe COVID-19.

Prevalence of comorbidities in the study group was also similar (p>0.05) in the non-survivors (24.3%) and survivors (20.6%).

of COVID-19 who were admitted with hyperglycemia or were known diabetes patients.
Table 4: Fasting plasma glucose values before and after steroids in Survivors (n=9)

<table>
<thead>
<tr>
<th>Fasting plasma glucose</th>
<th>Before Steroid were given n=3</th>
<th>After Steroid were started n=9</th>
<th>Last Day of Steroids n=6</th>
<th>48 hours after Steroid stopped n=5</th>
<th>72 hours after Steroid stopped n=4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range (mg/dl)</td>
<td>133-206</td>
<td>128-286</td>
<td>116-246</td>
<td>93-165</td>
<td>100-152</td>
</tr>
<tr>
<td>Mean ± SD (mg/dl)</td>
<td>161.3 ± 46.23</td>
<td>203.7 ± 58.79</td>
<td>160.3 ± 44.49</td>
<td>121.8 ± 26.76</td>
<td>122 ± 26.29</td>
</tr>
</tbody>
</table>

(1).

Plasma glucose at presentation ≥200 mg/dL (25 out of 41, 60.9%) when compared to those who had plasma glucose at presentation between 71-200 mg/dL (6 out of 17, 35.3%), did not show a significant difference (p=0.07). Mortality rates did not differ significantly in relation to severity of COVID-19 when compared in the two groups with admission plasma glucose values <200 mg/dL and values ≥200 mg/dL (Table 2). Two patients had presented with hypoglycemia (plasma glucose < 70 mg/dL), and both did not survive. Average duration of stay was 3.7 days among non-survivors compared to 13.2 days for those who survived.

When a cut-off of 126 mg/dL and 200 mg/dL were used, then no significant difference was noted in the mortality percentages below and above these cut-offs, for admission plasma glucose values or fasting plasma glucose values.

There were 24 patients who received steroids out of which 19 (79%) had severe presentation at admission. Of the 24 patients who received steroids, 15 (62.5%) expired. In our study, there was no significant difference in mortality in patients who received steroids and those who did not receive steroids. All those patients who expired despite receiving steroids had significantly higher plasma glucose levels at expiry than the patients who survived (Table 3).

We also observed that the average increase in blood sugar values in patients after receiving steroids (usual dose was Inj Dexamethasone 6 mg IV OD) was 42.4 mg/dL. This rise in blood sugar came within normal range 48 hours after stopping steroids (Table 4). The mean insulin requirement which was 50 units per day in patients receiving steroids dropped down to 43 units 48 hours after stopping steroids.

**Discussion**

The present study reveals that COVID patients having pre-existing diabetes or admission hyperglycemia had 52.1% mortality across the severity spectrum of COVID-19, though mortality increased with severity of COVID-19 viz. 27.3% in mild cases, 43.5% in moderate cases and 72.7% in severe cases. Poor outcomes of COVID-19 in patients suffering from diabetes have been reported in other studies as well. Data analysis of 153 people revealed in-hospital mortality of 20% in patients having diabetes compared with 10.5% in patients without diabetes (3). Increasing odds of in-hospital death or poor prognosis in patients with COVID-19 were found to be associated with diabetes in an analysis of 904 hospitalised patients [in-hospital death: OR 2.51 (95% CI 1.50, 3.26), p< 0.001 for both].

Chinese Centre for Disease Control and Prevention (CCDC) reported a case fatality rate (CFR) of 7.3% in patients with diabetes, compared to 2.3% in overall population of 44,672 COVID-19 patients. In a retrospective study of 7337 COVID-19 patients, a significant 49% relative increase in all-cause mortality (HR 1.49; 95% CI 1.33, 1.65) was reported in patients with diabetes (n = 810), compared to the groups without diabetes (n = 6385) even after adjustment for multiple confounding factors. In our initial published experience in 182 COVID-19 patients, all-cause mortality was 32.9% (n=60) but mortality in diabetes was 58.5% (31 of the 53 diabetic patients expired). Bode et al studied 1122 patients from 88 U.S. hospitals and observed that amongst 570 patients who died or were discharged, the mortality rate was 28.8% in 184 diabetes and/or uncontrolled hyperglycemia patients, compared with 6.2% of 386 patients without diabetes or hyperglycemia (p < 0.001).

In the present study, a much higher mortality (37/71) i.e. 52% has been witnessed in diabetic patients (known diabetics as well as new onset). The average age in the non-survivor and survivor groups was similar (55.1±11.9 years (33-82) vs 55.1±12.63 years (33-85), Table 1). Also, we did not find any significant difference in mortality between the patients aged ≤60 years and those aged >60 years. Naomi et al (9) studied patients of COVID-19 in England and observed that older age was associated with increased COVID-19-related mortality in patients with type 2 diabetes. Out of 10525 deaths, 94.23% were in over 60 years age whereas 5.7% were in patients less than 60 years of age. In our study, diabetes seemed to offset the protective effect that young age may offer against COVID-19. This finding is supported by a cohort study of total population of Scotland (10). It reported a statistically significant interaction between diabetes and age on risk of fatal or critical care unit-treated COVID-19 (p=0.001); odds ratio (OR) being 2.494 for age 0-59 years, OR of 1.764 for age 60-69 years age group and OR of 1.327 for age ≥70 years.

Naomi et al (9) reported male sex (vs female sex) was associated with increased COVID-19-related mortality for both people with type 1 and type 2 diabetes (p = 0.0001). In our study mortality rates were similar among males and females, and did not vary with age. However, it was noted that more males presented with severe COVID-19 (58.97% vs 40% in females) though mortality in both the genders was similar.

We observed that more than half of the diabetic patients (52.38%) had severe disease at presentation and almost three-fourth (72.27%) of these patients expired. Studies have shown that the disease is more severe in patients with diabetes. In a recent meta-analysis (11) it was observed that the pooled ratio of those suffering from a severe course compared with a milder course in diabetic patients was 2.26. As we did not include patients who were not admitted to the hospital and were sent for home isolation, there is a higher percentage of severe COVID-19 in our hospitalized diabetic population. In another study of 339 patients from China, it was observed that diabetic patients had 4-fold increased risk of having severe/critical COVID-19 illness and this association persisted even after adjustments for age, sex, smoking and other comorbidities.

We observed that the number of patients with more than one comorbidity was greater among non-survivor group than the survivor group but this difference was not
patients with COVID-19 and diabetes, the mortality is related to the preceding levels of hyperglycemia. The higher the HbA1c levels, the greater the risk of mortality. COVID-19-related mortality was significantly higher in those with an HbA1c ≥7.6 % than in those with an HbA1c of 6.5–7.0 %, and the risk increased with increasing HbA1c levels: (HR 1.22 [95% CI 1.15–1.30, p<0.0001] for 7.6–8.9 % and 1.36 [1.24–1.50, p<0.0001] for 9.0–9.9 %). HbA1c levels were not analysed in our study, so the contribution of preceding levels of hyperglycemia to the mortality or severity could not be assessed and could be an important confounder in our study results.

Bode et al studied 1122 patients and found 451 (38.5 %) of these patients had either diabetes or suffered from uncontrolled hyperglycemia. It was found that 28.8 % of patients having diabetes or uncontrolled hyperglycemia did not survive hospitalization, representing a more than four-fold higher in-hospital mortality rate compared with the mortality rate for COVID-19 inpatients without diabetes or uncontrolled hyperglycemia (6.2 %).

Hyperglycemia can have poor outcomes in COVID-19 patients. Targher et al retrospectively studied a cohort of 339 patients with COVID-19 and found and that the proportion of severe COVID-19 illness increased progressively (p < 0.0001) in relation to glucose abnormalities at admission: from 7.1 % in patients with random plasma glucose < 100.9 mg/dL, 20.3 % in those with random plasma glucose 100.9–198.2 mg/dL and 65 % in those with random plasma glucose ≥200 mg/dL at hospital admission, respectively. Coppelli et al studied 271 hospitalised COVID-19 patients and reported mortality rate of 16.8 % among 149 with normal glycemia, 28.6 % among 56 who had diabetes and 39.4 % of the 66 who had new-onset hyperglycemia, indicating poorer outcomes in new-onset hyperglycemia. Wang et al studied the relationship between fasting blood glucose (FBG) and 28-day mortality in COVID-19 patients not previously diagnosed as having diabetes. They found that in comparison to patients with FBG <6.1 mmol/l, mortality within 28 days was higher in those with FBG of 6.1–6.9 mmol/l (crude HR 2.06 [95% CI 1.20,3.54]) and ≥7.0 mmol/l (crude HR 3.54 [95% CI 2.33, 5.38]) respectively.

In our 9 patients who had newly detected hyperglycemia at admission, 66.6 % (n=6) of them had severe presentation and 55.5 % (n=5) of these patients with new onset hyperglycemia expired and this mortality was similar to that observed in known diabetic patients. All patients with new onset hyperglycemia required insulin in the hospital and all except one patient required either OAD or insulin at discharge. We are not in a position to say whether the new onset hyperglycemia was due to unmasking of latent diabetes or stress hyperglycemia due to acute stress of COVID-19, release of inflammatory mediators, steroid induced if the patient received steroids or due to direct effect of the virus on pancreas.

There were 24 patients who received steroids out of which 79 % (n=19) had severe presentation at admission. 62.5 % of these patients expired in the hospital. In our study we also observed that steroids did not improve the outcome in diabetic patients as there was no significant difference in mortality in patients who received steroids and those who did not receive steroids. The numbers of course are small. We also studied the effect of steroids on blood sugar levels (Table 3). All those patients who received steroids and expired had fasting plasma glucose and plasma glucose (at expiry) significantly higher than the patients who survived. (p value <0.007 and 0.02 respectively).

We also observed that the average increase in blood sugar values in patients after receiving steroids (usual dose was Inj Dexamethasone 6 mg IV OD) was 42.4 mg%. This rise in blood sugar came back to normal range 48 hours after steroids were stopped. The mean insulin requirement which was 50 units per day in patients receiving steroids dropped down to 43 units 48 hours after stopping steroids. Attention is drawn to the fact that COVID-19 patients were not given steroids initially, as in the initial part of the pandemic, it did not form part of the standard protocol.

Studies have shown that patients with diabetes and COVID-19 require insulin on admission. In a study from China it was observed that 29.2 % of diabetic patients were on insulin at admission and another 37.5 % received...
insulin after admission, indicating presence of dysglycemia during the course of disease. Stress hyperglycemia, drugs like steroids and virus induced autoimmunity can be the contributing reasons for higher insulin requirements in these patients.

This study had inherent limitations expected of a retrospective study. Besides, the study was conducted among hospitalized patients, so data may not be generalizable to non-admitted population. Also, the sample size is small. However, this is the whole sample that had presented to hospital during the period of study, without any exclusions. Baseline or recent HbA1c was not available for most patients, and hence preexisting diabetes was defined only on the basis of patients’ history and records. Biochemical markers of severity like cytokines, D-dimer and ferritin were not available for the study group, which in future studies can give some insights for management of these patients.

Conclusions

Diabetes patients suffering from COVID-19 requiring admission irrespective of severity of COVID-19 have high mortality rates, mortality being higher with increasing severity of COVID-19. Mortality rates are similar in the elderly (>60 years) and ≤60 years age groups, and in both genders. Patients having admission hyperglycemia (≥ 200 mg/dL), who are not previously known diabetics have similar mortality rates as diabetics. Hyperglycemia at presentation, even among known diabetics is associated with higher mortality rates than those who have random plasma glucose < 200 mg/dL.

Diabetic patients with COVID-19 who received steroids did not show a reduced mortality in our study. Steroids exacerbate hyperglycemia and its withdrawal led to euglycemic state by 48 hours in treated patients.

References


## Abstract

This is an analysis to study remdesivir in the treatment of Covid-19 patients at a tertiary care COVID 19 referral facility in Mumbai, India. It is 1550 bed covid hospital with 250 beds ICU treated 14878 covid patients till 31st December 2020 with overall mortality of 4.5%. 1833 patients of either sex, above 18 years, irrespective of the number of comorbidities were analysed. The mortality is 18.5%, a little higher in males and significantly higher in elderly. There was no difference in mortality based on time of administration of Remdesivir after admission (p=0.669). Lower SpO2 and higher HRCT scores at the time of Remdesivir administration are both associated with significantly higher mortality. Mortality was significantly low when tocilizumab is administered along with Remdesivir and in those who did not need tocilizumab.

Laboratory values CTCAE grade 3 and above were noted in only 1 case for SGOT, 19 each for SGPT and creatinine. 11 of these 39 cases succumbed to COVID 19. Based on our observations we recommend the use of Remdesivir in clinically appropriate cases around 5-10 days and would consider it a safe medication in the armamentarium of COVID warriors.

## Introduction

COVID-19, is a coronavirus disease caused by novel coronavirus (nCoV), emerged in December 2019 in Wuhan, China. This novel coronavirus-2 (CoV-2) causes severe acute respiratory distress syndrome (SARS), a respiratory disease that can progress to viral pneumonia and acute respiratory distress syndrome (ARDS). SARS-CoV-2 has posed a global health threat, causing a pandemic in many countries and territories including India. COVID-19 pandemic has rapidly spread worldwide, with total 95.6 million cases and 2 million deaths, which led to put huge efforts in identifying effective antiviral agents. Repurposing the available Nucleoside/nucleotide antivirals which have activity against SARS-CoV and MERS-CoV became the key for study against SARS-CoV-2 in absence of effective treatment option. GS-5734, later renamed remdesivir, had a broad antiviral spectrum, including Ebola virus (EBOV), Marburg virus, respiratory syncytial virus (RSV), Hepatitis C Virus (HCV), and several paramyxoviruses, MERS-CoV and SARS-CoV. Remdesivir or GS-5734 is a prodrug of a nucleoside analog with direct broad spectrum antiviral activity against the novel SARS-CoV-2. Remdesivir, is approved by Food and Drug Administration (FDA) under an Emergency Use Authorization (EUA) for emergency use for the treatment of severe coronavirus disease patients, on basis of the preliminary data showing reduction in time to recovery. Remdesivir is a monophosphoramidate nucleoside prodrug that undergoes intracellular metabolic conversion to its active metabolite nucleoside triphosphate (NTP) remdesivir triphosphate [remdesivir-TP] or GS-443902 that inhibits the replication of the viral RNA genome. Remdesivir-TP acts as the substrate for RdRp where it competes with ATP for incorporation into new strands causing termination of RNA synthesis at three positions ultimately abrogating further transcriptional and translational processes needed for the generation of new virions. The dosage of Remdesivir is a single loading dose of 200 mg infused intravenously over 30 to 120 minutes on Day 1 followed by once-daily maintenance doses of 100 mg infused intravenously over 30 to 120 minutes for 4 days and the dose for adults and children weighing more than 35 kg.

Remdesivir is approved in severe COVID-19 disease, with fever or suspected respiratory infection, plus one of the following; respiratory rate >30 breaths/min, severe respiratory distress, SpO2 <90% on room air. Taking into account the high mortality of COVID-19 and progression of the disease from early antiviral to cytokine storm stage, an early use of remdesivir in the disease course is considered as an effective treatment strategy. Here, we provide a retrospective analysis of results from ‘Seven Hills Covid Center’ from June 2020 to November 2020 for patients who have been administered remdesivir injection at different stages of COVID-19 disease.

## Material and Methods

This is an analysis to study remdesivir in the treatment of Covid-19 patients was conducted at Seven Hills Hospital, a tertiary care COVID 19 referral facility in Mumbai, India. It was conducted at Seven Hills Hospital, a tertiary care COVID 19 referral facility in Mumbai, India.
Only those who had been administered COVID-19 cases, we decided to analyse COVID-19 disease severity. The analytical statistics used as applicable. 13-18; Critical: >19). Descriptive and defining it as per disease severity patient’s HRCT score on admission (>90%, 90-80%, <80%) and >10 days); patient’s SpO2 at the time of admission (>90%, 90-80%, <80%) and patient’s HRCT score on admission defining it as per disease severity (Mild: <6, Moderate: 6-12; Severe: 13-18; Critical: >19). Descriptive and analytical statistics used as applicable. The primary outcome was the time to recovery defined by discharge from hospital in patients administered remdesivir as per above definitions of COVID-19 disease severity.

## Results

Since we had treated thousands of COVID-19 cases, we decided to analyse only those who had been administered Remdesivir to see whether the findings are in keeping with world data.

1833 patients of either sex, age, irrespective of the number of comorbidities were analysed. Demographic data is presented in Table 1. Hypertension, diabetes and ischaemic heart disease were the most common comorbidities.

Table 2 summarises the outcome based on age and gender. The overall mortality is 18.5%, a little higher in males and significantly higher in elderly.

There was no difference in mortality based on time of administration of Remdesivir after admission (p=0.669). Lower SpO2 and higher HRCT scores at the time of Remdesivir administration are both associated with significantly higher mortality (Table 3). Mortality was significantly low when tocilizumab is administered along with Remdesivir and in those who did not need tocilizumab (Table 4).

Table 5 summarises inflammatory parameters and Table 6 the lab data before and after Remdesivir administration.

Laboratory values CTCAE grade 3 and above were noted in only 1 case for SGOT, 19 each for SGPT and creatinine.
Table 5: Inflammatory parameters of patients received remdesivir

<table>
<thead>
<tr>
<th>Remdesivir</th>
<th>Median</th>
<th>IQR</th>
<th>Median</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL 6 pg/ml</td>
<td>First Dose</td>
<td>49.93</td>
<td>20.05 – 138.85</td>
<td>12.11</td>
</tr>
<tr>
<td></td>
<td>Last Dose</td>
<td>73.23</td>
<td>21.2 – 381.75</td>
<td>4.22</td>
</tr>
<tr>
<td>CRP mg/L</td>
<td>First Dose</td>
<td>67.26</td>
<td>17.62 – 199.53</td>
<td>21.15</td>
</tr>
<tr>
<td></td>
<td>Last Dose</td>
<td>33.95</td>
<td>8.56 – 152.41</td>
<td>5.93</td>
</tr>
<tr>
<td>LDH u/L</td>
<td>First Dose</td>
<td>433</td>
<td>301 – 617</td>
<td>255</td>
</tr>
<tr>
<td></td>
<td>Last Dose</td>
<td>547.66</td>
<td>352.5 – 740.8</td>
<td>238</td>
</tr>
<tr>
<td>Ferritin ng/ml</td>
<td>First Dose</td>
<td>718</td>
<td>395.1 – 1040</td>
<td>387.15</td>
</tr>
<tr>
<td></td>
<td>Last Dose</td>
<td>747.7</td>
<td>416.4 – 1258</td>
<td>375.29</td>
</tr>
<tr>
<td>D dimer ng/ml</td>
<td>First Dose</td>
<td>1107</td>
<td>278.25 – 4222.75</td>
<td>295</td>
</tr>
<tr>
<td></td>
<td>Last Dose</td>
<td>2230</td>
<td>562 – 6470.25</td>
<td>397</td>
</tr>
</tbody>
</table>

Table 6: Laboratory Parameters of patients received remdesivir

<table>
<thead>
<tr>
<th>Remdesivir</th>
<th>Median</th>
<th>IQR</th>
<th>Median</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGOT</td>
<td>First Dose</td>
<td>35.3</td>
<td>25.83 – 51.76</td>
<td>25.82</td>
</tr>
<tr>
<td></td>
<td>Last Dose</td>
<td>33.25</td>
<td>22.89 – 45.54</td>
<td>21.05</td>
</tr>
<tr>
<td>SGPT</td>
<td>First Dose</td>
<td>35.8</td>
<td>22.22 – 56.06</td>
<td>31.40</td>
</tr>
<tr>
<td></td>
<td>Last Dose</td>
<td>34.94</td>
<td>24.65 – 51.83</td>
<td>34.3</td>
</tr>
<tr>
<td>S. Creatinine</td>
<td>First Dose</td>
<td>0.79</td>
<td>0.61 – 1.04</td>
<td>0.79</td>
</tr>
<tr>
<td></td>
<td>Last Dose</td>
<td>0.76</td>
<td>0.61 – 1.11</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Table 7: Lab parameters after last dose equivalent to CTCAE criteria > grade 3

<table>
<thead>
<tr>
<th>Death</th>
<th>Recovered/ Discharged</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>S GOT &gt;5ULN</td>
<td>225</td>
<td>0</td>
</tr>
<tr>
<td>S GOT &gt;5ULN</td>
<td>226</td>
<td>3</td>
</tr>
<tr>
<td>Creatinine &gt;3ULN</td>
<td>226</td>
<td>8</td>
</tr>
</tbody>
</table>

11 of these 39 cases succumbed to COVID 19.

Discussion

Remdesivir or GS-5734 is a prodrug of a nucleoside analog with direct antiviral activity against several single-stranded RNA viruses, including SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV). Remdesivir was active against SARS-CoV-2, with an EC50 of 0.77 M, which was slightly lower than that of chloroquine (EC50, 1.13 M) and remarkably lower than those of other tested antivirals.2

During initial studies Remdesivir was administered over a 10 day period [8.9] until Goldman et al10 showed that results are similar with a 5 or 10 day course. We used a 5 day course in all patients as per National guidelines.

The overall mortality is 18.5%, and correlated directly to increasing age and number of comorbidities (Table 2). Jurado et al also noted that age and age-related comorbidities, such as dyslipidaemia, hypertension or diabetes, determined more frequent severe forms of the disease.11

In a double-blind placebo-controlled study Remdesivir use was not associated with a difference in time to clinical improvement. Although not statistically significant, patients receiving remdesivir had a numerically faster time to clinical improvement than those receiving placebo among patients with symptom duration of 10 days or less. We segregated our Remdesivir cases based on the time of administration 0-5 days, 6-10 days and 11th day onwards. Although not statistically significant, those receiving Remdesivir between 6 – 10 days fared better on mortality. Mortality was also related directly to low SpO2 and high HRCT scores (Table 3).

Mortality was less when Tocilizumab was administered with remdesivir or when it was not administered at all. Though could be explained by the fact that only 154 cases were administered Tocilizumab. All these cases were critical based on inflammatory and clinical parameters hence a higher mortality is to be expected. The inflammatory parameters pre and post remdesivir administration are mentioned in Table 5.

Grien J et al observed clinical improvement in 68% cases compared to our 81.5%.

Hepatic enzymes were increased in 23%. In the double-blind study, most common adverse events were nausea (9% of patients), worsening respiratory failure (8%), elevated alanine aminotransferase level (7%), and constipation (7%). Antinori S et al [9] observed hepatotoxicity, with a grade 3-4 increase in transaminases levels observed in 42.8% of the patients. In our study Increase in SGOT was observed in one case, and SGPT in 19 cases. Serum creatinine was raised in 19 cases. Of these 5 cases succumbed to COVID 19 (Table 7).

Conclusion

Based on our observations we recommend the use of Remdesivir in clinically appropriate cases around 5-10 days. Remdesivir reduces the time to recovery of hospitalized patients who require supplemental oxygen and may have a positive impact on mortality outcomes and would consider it a safe medication in the armamentarium of COVID warriors.

References

The Clinical Characteristics of Coinfection of COVID19 and Influenza A Viruses - A Case Series

Arun Agarwal1*, Ambika Sharma2, Mudit Agarwal3, Rekha Jakhar2

Abstract

Background: For eons, pandemics have terrorized us and affected human lives and their normal functioning. From being first identified in December 2019, Corona virus disease 2019 (Covid19) has become one of the most important human respiratory pathogens in existence. The question of how a coinfection between COVID-19 and influenza might manifest in the present flu season is of utmost concern.

Aim: This being the flu season in northern hemisphere (including India) along with Covid19 pandemic, we looked into the limited cases of COVID-19 and influenza coinfections who were admitted in our unit during the early part of the 2020-21 flu season in India. We also looked into whether any patterns of clinical presentation and morbidity emerged and also identified the predominant strain of influenza virus circulating in this flu season.

Design: A retrospective, observational study.

Methods: Medical records of patients with Covid19 infection and admitted between 01/08/2020 to 31/12/2020 in our unit in fortis escorts Hospital, Jaipur, were extracted from medical records department. Of these Covid-19 cases, those individuals who had Coinfection with influenza virus were then extracted and clinical profiles were tabulated.

Results and Findings: A total of 101 patients of Covid19 infection were admitted during the study period. Of them 9 patients had Coinfection with Influenza A virus. The median age was 65 years with 5 male (55.6%) and 4 female (44.4%) patients respectively. The presenting complaints, smoking status, vital parameters, Laboratory parameters including inflammatory markers, Computed Tomography chest findings, complications, treatment given, Intensive care unit (ICU) transfers, need of mechanical ventilation, length of stay and mortality in these 9 patients is discussed.

Conclusion: Co circulation of Influenza A and specifically H3N2 virus in this covid19 pandemic is seen in the present flu season in India. This could have a significant impact on morbidity, mortality and health service demand. Testing for influenza virus and its strain alongside Covid19 needs to be implemented. At the same time priority should be towards maximizing Covid19 and influenza vaccine uptake to mitigate these risks.

Introduction

Covid19 and Influenza are both contagious respiratory illnesses, but they are caused by different viruses. Covid-19 pandemic is caused by a novel virus - severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). Influenza is an infectious respiratory disease, caused by Influenza A and Influenza B viruses. Since its introduction in December 2019, no one knew how long covid19 disease will continue and will it have any impact on the behavior or clinical profile of Influenza virus and illness in the coming flu season in 2020-21. While these two viruses have much in common - in terms of symptoms, mode of transmission and diagnoses - there’s a lot that differentiates them from one another. Covid19 has never been detected in humans before, is more contagious with a higher reproductive number and deadlier than Influenza, especially swine flu. Loss of smell and taste are specific to covid-19 and not seen with Influenza viruses.

Influenza virus sporadic cases are seen throughout the year in India and it is likely that both SARS-CoV-2 and seasonal respiratory pathogens, most notably influenza, will be co-circulating during winter season of 2020-21 in India. The potential impact of COVID-19 alongside influenza on morbidity, mortality and health service capacity shall be a major concern. However, currently little is known about the interaction between these two respiratory viruses and no data about coinfections is available from India.1,2

Since the beginning of the SARS-CoV-2 pandemic, a number of case reports of SARS-CoV-2 and influenza coinfections with severe outcomes have been published.3-10 In southern hemisphere the 2019-2020 influenza season peaked early with activity declining significantly from January 2020. In the UK, the season saw lower activity with influenza A (H3N2) as the predominant strain.11 In India the first confirmed case of Covid19 was reported from Kerala in last week of January 2020 and India hit a record peak in the middle of September when it reported more than a million active cases. By the time flu season began, covid19 had already reached its peak in India. As such there was an ample period of overlap between influenza circulation and SARS-CoV-2 circulation. In this study, we explore the interaction between influenza and...
<table>
<thead>
<tr>
<th>Patient</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
<th>P4</th>
<th>P5</th>
<th>P6</th>
<th>P7</th>
<th>P8</th>
<th>P9</th>
</tr>
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<tr>
<td>Age/sex</td>
<td>37/F</td>
<td>58/F</td>
<td>22/F</td>
<td>67/M</td>
<td>83/M</td>
<td>74/M</td>
<td>45/M</td>
<td>66/M</td>
<td>62/F</td>
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<td>Comorbidity</td>
<td>Bronchial Asthma, Hypothyroidism</td>
<td>DM, HTN</td>
<td>Status Post LSCS</td>
<td>DM</td>
<td>DM,CAD HTN,CKD</td>
<td>HTN</td>
<td>NASH, HTN</td>
<td>HTN, BPH, MM</td>
<td>Obesit y</td>
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<td>Presenting complaints</td>
<td>Cough, SOB, Nausea, Vomittings</td>
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<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>BP (mm Hg)</td>
<td>138/88</td>
<td>110/80</td>
<td>116/76</td>
<td>118/68</td>
<td>152/74</td>
<td>130/80</td>
<td>124/80</td>
<td>110/80</td>
<td>142/86</td>
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<td>HR (beats/minute)</td>
<td>98</td>
<td>80</td>
<td>84</td>
<td>96</td>
<td>96</td>
<td>84</td>
<td>80</td>
<td>104</td>
<td>142</td>
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<td>T (°C)</td>
<td>98.6</td>
<td>98.6</td>
<td>98.6</td>
<td>98.6</td>
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<td>98.6</td>
<td>98.6</td>
<td>101</td>
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<td>RR (per minute)</td>
<td>92%</td>
<td>93%</td>
<td>88%</td>
<td>88-92%</td>
<td>87%</td>
<td>94%</td>
<td>92%</td>
<td>95%</td>
<td>49%</td>
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<td>Influenza type/strain</td>
<td>A/H3N2</td>
<td>A/H3N2</td>
<td>A/H3N2</td>
<td>A/H3N2</td>
<td>A/H3N2</td>
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<td>Cultures</td>
<td>Blood sterile</td>
<td>sterile</td>
<td>Enterococcus fecalis sterile</td>
<td>Sterile</td>
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<td>HB(12 – 15 gm/dl)</td>
<td>13.4</td>
<td>13.8</td>
<td>11.4</td>
<td>14.6</td>
<td>12.8</td>
<td>14.5</td>
<td>14.9</td>
<td>12.3</td>
<td>13.1</td>
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<td>7.0</td>
<td>13.0</td>
<td>11.6</td>
<td>12.6</td>
<td>17.6</td>
<td>13.6</td>
<td>9.7</td>
<td>19.2</td>
<td>37</td>
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<td>Platelet (150-410 X 10⁹/mm³)</td>
<td>411</td>
<td>306</td>
<td>371</td>
<td>240</td>
<td>223</td>
<td>215</td>
<td>210</td>
<td>239</td>
<td>150</td>
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<td>N/L ratio</td>
<td>8.5</td>
<td>6.5</td>
<td>10.9</td>
<td>18</td>
<td>21.5</td>
<td>15.2</td>
<td>8.5</td>
<td>12.8</td>
<td>7</td>
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<td>S.Creatinine (upto 1 mg/dl)</td>
<td>0.92</td>
<td>0.97</td>
<td>0.67</td>
<td>0.82</td>
<td>3.39</td>
<td>1.21</td>
<td>0.97</td>
<td>0.65</td>
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<td>AST/ALT (Upto 32 U/L)</td>
<td>31/14</td>
<td>72/56</td>
<td>41/24</td>
<td>21/87</td>
<td>293/9</td>
<td>75/108</td>
<td>254/349.5</td>
<td>27/27</td>
<td>699/2788</td>
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<tr>
<td>ESR (&lt; 20 mm/1 hr)</td>
<td>55</td>
<td>55</td>
<td>25</td>
<td>30</td>
<td>80</td>
<td>55</td>
<td>12</td>
<td>60</td>
<td>87</td>
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<tr>
<td>CRP(&lt;6 mg/litre)</td>
<td>89</td>
<td>18.4</td>
<td>69.4</td>
<td>22.8</td>
<td>201.6</td>
<td>180</td>
<td>69.2</td>
<td>130.6</td>
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<td>Serum IL-6 (upto 125 pg/ml)</td>
<td>39.06</td>
<td>NA</td>
<td>75.07</td>
<td>150</td>
<td>182.3</td>
<td>29.7</td>
<td>21.2</td>
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<td>Serum Ferritin (13–150 ng/ml)</td>
<td>900.5</td>
<td>116.7</td>
<td>614.4</td>
<td>931</td>
<td>783</td>
<td>558.3</td>
<td>3580</td>
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<td>Serum LDH (135 – 214 U/L)</td>
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<td>275</td>
<td>633</td>
<td>401</td>
<td>673</td>
<td>281</td>
<td>504</td>
<td>226</td>
<td>5283</td>
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<td>D Dimer (&lt; 255 ng/ml)</td>
<td>488</td>
<td>275</td>
<td>4100</td>
<td>344</td>
<td>10680</td>
<td>390</td>
<td>240</td>
<td>341 &gt;8000</td>
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<tr>
<td>Procalcitonin (upto 0.046 ng/ml)</td>
<td>0.637</td>
<td>0.107</td>
<td>0.517</td>
<td>0.104</td>
<td>0.658</td>
<td>0.178</td>
<td>0.184</td>
<td>0.280</td>
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<td>PRO-BNP(&lt;125 pg/ml)</td>
<td>X</td>
<td>93.13</td>
<td>1111</td>
<td>96.06</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>415.7</td>
<td>444</td>
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<tr>
<td>Treatment received for COVID-19</td>
<td>Treatment for Influenza</td>
<td>1. Remdesivir</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>2. Tocilizumab</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>3. Anticoagulation</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>4. Dexamethasone</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>5. CCP (200 ml)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Mode of oxygen delivery</td>
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<td>Nasal prongs</td>
<td>MV</td>
<td>Mask</td>
<td>MV</td>
<td>Room air</td>
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<td>1. Oseltamivir</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>2. Tocilizumab</td>
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<td>Yes</td>
<td>Yes</td>
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<td>3. Anticoagulation</td>
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<tr>
<td>4. Dexamethasone</td>
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<td>5. CCP (200 ml)</td>
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<tr>
<td>Length of stay</td>
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<td>6 days</td>
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<td>8 days</td>
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<td>6 days</td>
<td>12 days</td>
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<tr>
<td>Outcome</td>
<td>Discharge</td>
<td>Discharge</td>
<td>Death</td>
<td>Discharge</td>
<td>Death</td>
<td>Discharge</td>
<td>Discharge</td>
<td>Death</td>
<td>Death</td>
</tr>
</tbody>
</table>

Abbreviations: F:Female; M:Male; SOB: Shortness of breath; BP: Blood pressure; HR: Heart rate; RR: Respiratory rate; SPO2: Oxygen saturation; rRT: Real-Time Reverse Transcription-Polymerase Chain Reaction; GPB: Gram positive Bacilli; ET: Endotracheal tube; Hb: Hemoglobin; TLC: Total leucocyte count; N/L: Neutrophil lymphocyte ratio; AST: Aspartate aminotransferase; ALT: Alanine transaminase; IL-6: Interleukin 6; LDH: Lactate dehydrogenase; PRO-BNP: Pro-B-Type natriuretic peptide; HRCT: High resolution computed tomography; CTSS: Computed tomography severity score; LMWH: Low molecular weight Heparin; UFH: Unfractionated heparin; CCP: Covid convalescent plasma; ICU: Intensive care unit; AEB: Acute exacerbation of bronchial asthma; ARDS: Acute respiratory distress syndrome; VAP: Ventilator associated pneumonia; AKI: Acute kidney injury; U/L: Units per Liter; ng/ml: Nanogram per millilitre; pg/ml: Picogram per millilitre; g/dl: Gram per decilitre.
SARS-CoV-2 during the early stages of the 2020-2021 influenza seasons in India.

Keywords
Corona virus, covid-19, SARS-COV-2, Co-infection, flu, Influenza A type H3N2.

Methods
The present study has been approved by the institutional Ethics committee vide letter No. FEHJ/IEC/20/18 dated 28/12/2020.

This study was undertaken to see if there is a local circulation of influenza virus (and its strain) in this flu season along with the Covid19 pandemic and to study the clinical profile of these patients. The aim was to review the limited number of cases of Covid-19/ influenza coinfections we had in our unit during this early part of the 2020-21 flu season in India and to determine whether any patterns of clinical presentation and morbidity emerged.

All patients who presented to flu clinic with influenza like illness (ILI) at Fortis escorts Hospital, Jaipur, India, were tested for Covid19 by real-time reverse transcription polymerase chain reaction (rRT-PCR) from upper respiratory samples including both nasopharyngeal and oropharyngeal swabs and those with moderate, severe or critical respiratory illness were admitted to covid19 unit for further evaluation and management. Patients with mild disease were advised home treatment and were excluded from the study. All patients of Covid19 infection who were admitted in authors unit were also tested for Influenza viruses and its strain by rRT PCR of upper respiratory tract samples. Medical records of such patients admitted between 01/08/2020 to 31/12/2020 were extracted from medical records department of our institute.

Various laboratory parameters including age, gender, history of smoking, presenting complaints, vital parameters, co-morbidities, type and strain of Influenza virus, complete blood counts (CBC), Neutrophil Lymphocyte ratio (N/L ratio), inflammatory markers, biochemistry, High resolution Computerized Tomography of chest (HRCT) and X ray chest, presence of cytokine storm, Intensive care unit (ICU) admission, need of mechanical ventilation, treatment details, length of hospital stay, and mortality in the co-infected group were recorded and tabulated. The detailed profile of these 9 cases (P1 to P9) is presented in Table 1.

Results and Findings
Of total 101 patients with Covid19 infection admitted during the study period, 92 (91.1%) had only Covid19 viral disease and 9 (8.9%) patients had Co-infection with Covid19 and influenza viruses. None of these 9 patients had history of smoking. Male female ratio was 1.25:1.

As regards the results of 9 coinfections patients presented, following patterns were observed.

1. Comorbidities: Co morbidities and other conditions that were associated with severe illness and mortality included Cardiovascular disease (2 patients), Hypertension (4 patients), Diabetes mellitus (3 patients), Bronchial Asthma (1 patient), Cancer (Multiple Myeloma 1 patient), Chronic kidney disease (1 patient), Non alcoholic Steatohepatitis (NASH) (1 patient) and Obesity (1 patient). One patient was healthy with no co morbidity and was post lower (uterine) segment Caesarean section (LSCS).

2. Symptoms and critically ill patients: All 9 coinfected patients had symptoms of cough and fever. Shortness of breath (dyspnea) was present in 5 and 1 patient also had nausea and vomiting. P3, P5, and P9 were critically ill. P3 was a young female with a post LSCS status and no co morbidities. She was referred to us with acute respiratory failure type 1. P5 was an elderly male with multiple co morbidities. P9, an elderly female...
had obesity class III. All of them were mechanically ventilated in view of severe covid19 related acute respiratory distress syndrome (cARDS). All these three patients succumbed to their illness. The median length of stay was 7 days among these 9 coinfected cases with P3 and P5 having total hospital stay of 14 days respectively.

3. Type of Influenza Virus and strain: Interestingly 8 of them had H3N2 Influenza A infection and H1N1 influenza A was seen in only 1 patient (P4). None had Influenza B illness.

3. Laboratory findings: All 9 patients in Coinfection group show Lymphopenia. The highest N/L ratio of 21.5 was seen in P5. CRP more than 10 times the upper limit of normal was seen in 8 (88.9%) patients. The maximum was 240mg/L in P9 followed by 201.6 mg/L in P5. P7 had significant transaminitis which was attributed to his known status of Non alcoholic steatohepatitis (NASH). D-dimer levels were significant in 3 patients P3, P5 and P9 were very high (33.3%) patients. P3, P5, and P9 also had evidence of cytokine storm, were ventilated and succumbed to the mixed infection.

4. Radiological imaging: All 9 patients were evaluated by HRCT of the chest which demonstrated typical ground-glass opacity and viral pneumonia findings in all 9 of them (100%) (Figure 1). The contribution of Covid19 and influenza viruses could not be differentiated on imaging. Severe disease with computer tomography severity score (CTSS) > 15 on HRCT was seen in P3, P7 and P9 respectively. 

Chest X-ray was performed in all 9 patients and show bilateral reticular shadowing or bilateral diffuse infiltration (Figure 2).

5. Complications, treatment, outcomes, and duration of illness: Among coinfected patients complications were reported in 4 (44.4%) patients. The most common complications were acute respiratory distress syndrome in 3 (33.3%); Bacteremia and Ventilator associated pneumonia (VAP) in 2 (22.2%); Pneumothorax requiring Intercostal drainage and Pneumomediastinum, acute exacerbation of bronchial asthma (AEBA) and acute kidney injury in 1(11.1%) patient respectively. A total of four (44.4%) patients needed ICU care, 3 (33.3%) needed mechanical ventilation, and mortality was seen in 3 (33.3%) patients.

All 9 (100%) patients were treated with antiviral therapy (including Oseltamivir), oxygen inhalation, empirical antibiotics, Anticoagulants and Dexamethasone. 2 (22.2%) patients were given convalescent covid plasma (CCP) and 1 (11.1%) was given Tocilizumab. Moreover, 6 (66.7%) patients were discharged. The duration of illness from the onset of symptoms until the remission stage was assessed in all of these patients (100%) patients. This duration of illness ranged from 15 days to 25 days. Notably, none of the patients who were mechanically ventilated survived.

Discussion

Although sporadic cases of influenza are seen all throughout the year in India, it occurs mainly during winters or flu season. The burden of disease is determined by several factors, including the effectiveness of the vaccine that season, the proportion of population vaccinated the type of influenza strain and characteristics of the other circulating viruses, and also on how long the season lasts.

With Covid19 pandemic all over the globe in 2020, India also has its share. The present study show that most common presenting symptoms were fever, cough, and some breathing discomfort described as difficulty in breathing, shortness of breath or breathlessness. In a meta analysis study, 3% of patients hospitalized with COVID-19 were also co-infected with another respiratory virus with influenza A being the most common viral pathogens identified. Similarly, in a study from Wuhan, five of 115 (4.3%) patients were co-infected with COVID-19 and influenza as against 8.9% in our study. Most of these patients presented with fever, cough and shortness of breath as seen in our study. However, only one of the co-infected patients developed acute respiratory distress syndrome and required non-invasive ventilation. In our study 3 patients required invasive mechanical ventilation. Further, none of these studies mention the type of Influenza A strain. In our study among these 9 Coinfection patients, 8 (88.9%) were Influenza A H3N2 and only 1 had Influenza A H1N1. Influenza A H3N2 is reported to be more severe than Influenza A H1N1 as was also observed in this study. Beyond the pathogenesis of SARS-
CoV-2, microbial co-infections (Viral, bacterial or fungal) plays an important role in the occurrence and development of SARS-CoV-2 infection by raising the difficulties of diagnosis, treatment, prognosis of COVID19, and even increasing the disease symptom, severity and mortality. Coinfections are usually connected with the need for a higher level of care, increased length of stay (LOS), and development of acute respiratory distress syndrome as also seen in our study. The reason for increase severity with co-infections with covid19 is damage to lymphocytes, especially B cells, T cells, and NK cells, which leads to the immune system’s impairment during the period of disease. The decrease of lymphocytes and host immune function may be the main reason for these co-infections. Two of our patients, P3 and P9 also had bacterial and viral coinfections and both succumbed to the disease. The laboratory finding common to all these co-infected patients were elevated C-reactive protein and lymphocytopenia. These findings along with high CT severity score (severe), markedly raised D Dimer should raise suspicion of co-infection in these patients as were also seen in this study.

The probability of respiratory virus Coinfection varies from 10 to 68%. Majority of the literature in this flu season mentions about the influenza type and this is the only study from India which also mentions about the strain – H3N2 in 8 of the 9 patients. Data shows that flu caused by H3N2 viruses predominated during the 2017/18 flu season whereas for the 2018/19 and 2019/20 flu season H1N1 strains had been more prevalent. 2020/21 flu season appears to be again dominated by H3N2 strain in this region. The flu season begins early in southern hemisphere and a study from UK also reported lower activity with Influenza, H3N2 being the predominant strain. Lower activity (8.9%) of Influenza in covid19 pandemic was also seen in this study. The reason behind this observation could be that the novel corona virus is more contagious, has a higher reproductive number (the number of secondary infections generated from one infected individual) and pathogenically competes with Influenza virus. This could be through immune-mediated interference resulting in some viruses to diminish during the peak of another virus, a phenomenon that has been recognized for many decades.

The incidence of Influenza Coinfection increases the levels of C-reactive protein (CRP) and serum procalcitonin (PCT). Both were raised in all 9 (100%) of our patients. Viruses can also cause damage to airways and its epithelium, reduced mucociliary clearance, damage to the immune system and promote coinfections by other viruses. It should be noticed that at present, it is difficult to determine the kinetics of viral coinfections since there is very little information about the virus kinetic parameters of SARS-CoV-2 infection.

All 9 Coinfection patients presented with viral pneumonia findings on HRCT, and all had findings of ground-glass haziness or opacity bilaterally, predominantly in peripheral lung zones involving right middle, left lingular and bilateral posterobasal segments of lower lobes. Besides these findings, air space consolidation was seen in P3, P5 and P9. The contribution of either infection could not be delineated on imaging. Finally, complications were reported in 4 patients, with most common complication being acute respiratory distress syndrome as noted in other study also.

The results of the study indicate that further analysis will be required to understand the effects of Coinfection on morbidity and mortality as both diseases have similar symptomatology and clinical presentation. For an early etiological identification, appropriate treatment and differentiating other causes of respiratory illness and Influenza from COVID-19 further testing should be done to exclude co-infections. Nevertheless, a timely identification of the two co-infections is needed in relation to difference in treatments and prognosis. Antiviral therapy is currently available for influenza infection (i.e., Oseltamivir) while emergency use authorization and experimental off-label drugs (i.e.Remdesivir, CCC, lopinavir/ritonavir, Doxycycline, ivermectin, chloroquine, and hydroxy-chloroquine) have been commonly used in COVID-19 treatment. We also found that coinfections with influenza and SARS-CoV-2 were associated with an increased risk of death or severe disease. Whether this is beyond the additive effect of the two viruses acting independently cannot be commented. Further, the limited number of coinfections cases in the literature indicates that the implementation of COVID-19 control measures including masks, social distancing, lockdown; sanitization etc may have a role in limiting the spread of these human respiratory pathogens.

In conclusion, we report nine cases of co-infection of influenza and COVID-19 viruses. Clinicians should be aware of this unique situation and have a high index of suspicion in the appropriate clinical scenario. Even in pandemic setting, the early and prompt identification of concurrent respiratory pathogens is important in order to improve etiological diagnosis, preventive measures and patients’ clinical management and outcome. Since the study subject number is limited, further studies are needed to determine whether patients who have a concurrent viral infection have a worse prognosis than those in whom SARS-CoV-2 is the only detected pathogen.

Ethical approval
This study was approved by the Institutional Ethical Board.

Author’s role
AA was the primary treating physician and unit head, involved in the clinical work related to all the patients. He contributed to the conception, design, draft, analysis, statistical analysis, revision and final approval of the work to be published. Author AS and RJ were involved with data and images acquisition and tabulation of data. Author MA contributed to revision of the manuscript, grammar and literature search for the study. All authors read and approved the final manuscript.

References
May Measurement Month Blood Pressure Screening Program: A Pan India Study

A Muruganathan1, Ravi Kumar T2, Manjula S3, Krishna Kumar3

Background
Hypertension is an important public health problem in both economically developed and developing nations. Hypertension is one of the most common life threatening non-communicable diseases. Hypertension exerts a substantial burden on cardiovascular health status and healthcare systems in India. The burden of Hypertension is ever increasing in the last two decades. Hypertension is a difficult condition to manage because patients are generally asymptomatic and hence termed as a silent killer. Patient education on adherence to medication is one of the challenges for the clinicians involved in managing hypertension.

Abstract
Background: High blood pressure (BP) is the largest contributor to the global burden of disease and mortality. This Blood Pressure screening program was initiated in conjunction with the May Measurement Month to increase the awareness of the importance of BP and also designed to understand the problems of real time clinical situations.

Methodology: This was a cross sectional, multicentric, non-interventional, observational and single visit study. The study was conducted in the Outpatient department of many clinics/ institutions. The convenience sampling technique was used to select the centers in this study and obtain the geographical distribution of India.

Results: A total of 1,36,095 BP screening forms were considered for analysis. A total of 37,017 subjects (27.2%) had BP of >130/80 mm Hg. Among participants, 44.5% of men in age group of 51 – 60 years had high BP. 31.2% of the women in the age group of 41-50 years had high BP . Among 37,017 subjects, 14,066 subjects (38%) were newly diagnosed subjects with hypertension. In the subset (N=22,951) of known cases of hypertension, Men were 14, 127 (Urban, N=7488 and Rural, N=6639) and 8824 were women (Urban, N=4588 and Rural, N=4236). The common comorbidities were dyslipidemia, cardiovascular disorders and diabetes.

Conclusion: Despite the advances in hypertension management and emphasis on patient education, our study shows that hypertension continues to be a significant health burden. Improving patient compliance to lifestyle modifications, medication and regular follow-up clinic visits by imparting patient education and awareness can provide better results in Hypertension management.

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13. Mathias Prokop, Wouter van Everdingen, Tjalco van Rees


improving the cardiovascular morbidity and mortality caused by ever rising burden of hypertension. Improving the awareness of causes which are treatable are essential, especially in younger and middle aged patients in whom there is a higher probability of the hypertension being secondary to other risk factors.4,6

India is undergoing a rapid economic growth which is also accompanied by demographic, lifestyle and cultural changes leading to a larger impact on the health profile of India’s citizens and placed a significant strain on the country’s healthcare system. There is a strong correlation between changing lifestyle factors and increase in hypertension in India. Furthermore, despite the advances in the management of hypertension, still it remains a significant health care burden. Hence more studies are warranted to understand the increasing burden of Hypertension and create awareness in the population at large.3,4

**Purpose of the study**

High blood pressure is the largest contributor to the global burden of disease and mortality. Studies have highlighted that only <50% of the population with hypertension is aware of it. This Blood Pressure screening program was initiated in conjunction with the May Measurement Month to increase the awareness of the importance of blood pressure and also designed to understand the problems of real time clinical situations.

Table 1: Gender Distribution of the Study Volunteers

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male (%)</th>
<th>Female (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>73,107 (53.72%)</td>
<td>62,988 (46.28%)</td>
<td>136095</td>
</tr>
<tr>
<td>Urban/Rural</td>
<td>41.61</td>
<td>10.06</td>
<td>1.63</td>
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</table>

Table 2: Age Group Distribution of the study volunteers

<table>
<thead>
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<th>Age</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>SD</th>
<th>Std. Error</th>
<th>95% CI</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
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<tr>
<td>Overall</td>
<td>18</td>
<td>84</td>
<td>39.78</td>
<td>11.67</td>
<td>1.89</td>
<td>36.08</td>
<td>41.23</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>18</td>
<td>84</td>
<td>41.61</td>
<td>9.97</td>
<td>1.72</td>
<td>37.91</td>
<td>44.04</td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>18</td>
<td>84</td>
<td>40.81</td>
<td>10.06</td>
<td>1.63</td>
<td>36.57</td>
<td>42.18</td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>18</td>
<td>76</td>
<td>42.43</td>
<td>9.92</td>
<td>1.58</td>
<td>36.98</td>
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<tr>
<td>Women</td>
<td>18</td>
<td>79</td>
<td>36.66</td>
<td>13.87</td>
<td>1.28</td>
<td>34.09</td>
<td>39.23</td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>18</td>
<td>79</td>
<td>35.79</td>
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<tr>
<td>Rural</td>
<td>18</td>
<td>71</td>
<td>37.46</td>
<td>13.73</td>
<td>1.87</td>
<td>34.09</td>
<td>39.23</td>
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Table 3: Hypertension distribution among Study Volunteers

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<tr>
<th>Hypertension</th>
<th>General HTN</th>
<th>General HTN</th>
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<tr>
<td></td>
<td>Men %</td>
<td>Women %</td>
</tr>
<tr>
<td>18 - 20</td>
<td>91</td>
<td>11</td>
</tr>
<tr>
<td>21 - 30</td>
<td>19991</td>
<td>3798</td>
</tr>
<tr>
<td>31 - 40</td>
<td>23459</td>
<td>6709</td>
</tr>
<tr>
<td>41 - 50</td>
<td>20947</td>
<td>6595</td>
</tr>
<tr>
<td>51 - 60</td>
<td>7166</td>
<td>3188</td>
</tr>
<tr>
<td>61 - 70</td>
<td>789</td>
<td>229</td>
</tr>
<tr>
<td>&gt;70 years</td>
<td>664</td>
<td>191</td>
</tr>
<tr>
<td>Total</td>
<td>73107</td>
<td>20721</td>
</tr>
</tbody>
</table>

Table 4: Hypertension distribution among rural and urban population and both the genders

<table>
<thead>
<tr>
<th>Age group</th>
<th>Men</th>
<th>Urban</th>
<th>Rural</th>
<th>Women</th>
<th>Urban</th>
<th>Rural</th>
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</thead>
<tbody>
<tr>
<td>18 - 20</td>
<td>11</td>
<td>4</td>
<td>7</td>
<td>8</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>21 - 30</td>
<td>3798</td>
<td>1913</td>
<td>1885</td>
<td>3253</td>
<td>1983</td>
<td>1270</td>
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<tr>
<td>31 - 40</td>
<td>6709</td>
<td>3567</td>
<td>3142</td>
<td>4790</td>
<td>2106</td>
<td>2684</td>
</tr>
<tr>
<td>41 - 50</td>
<td>6595</td>
<td>2981</td>
<td>3614</td>
<td>5372</td>
<td>2199</td>
<td>3183</td>
</tr>
<tr>
<td>51 - 60</td>
<td>3188</td>
<td>2114</td>
<td>1074</td>
<td>2793</td>
<td>1389</td>
<td>1404</td>
</tr>
<tr>
<td>61 - 70</td>
<td>229</td>
<td>132</td>
<td>97</td>
<td>49</td>
<td>39</td>
<td>10</td>
</tr>
<tr>
<td>&gt;70 years</td>
<td>191</td>
<td>104</td>
<td>87</td>
<td>51</td>
<td>24</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>20721</td>
<td>10815</td>
<td>9906</td>
<td>16296</td>
<td>7737</td>
<td>8559</td>
</tr>
</tbody>
</table>

Fig. 1: Gender Distribution of the Study Volunteers

Fig. 2: Distribution of subjects with Newly diagnosed with Hypertension

Fig. 3: Distribution of subjects with Known Hypertension
**Results**

A total of 1,45,621 volunteers were collected, collated centrally and analyzed from across India. The completeness of the BP recording forms were checked and nearly 9,526 forms (6.54%) were incomplete. Unfilled or incomplete forms were excluded from the study. A total of 1,36,095 BP screening forms were considered for analysis.

Among the volunteers, 73,107 (53.72%) were men and 62,988 (46.28%) were women. 1,05,754 were from Urban settings with 51891 (49.06 %) were men and 53863 (50.94%) were women. 30341 were from rural settings with 21216 (69.92%) were men and 9125 (30.08%) were women (Figure 1 and Table 1).

The Mean age (years) of the study population was 39.78 ±11.67 (95 % CI 34.09 - 39.23). Among the volunteers, 44.5% of men and 41.84% of women were smokers; 56,954 (41.84%) consumed alcohol and 48167 (35.39%) had history of tobacco usage habits (Table 6).

The common comorbidities were dyslipidemia, cardiovascular disorders and diabetes. Remaining of study subjects had other co morbidities as shown in Figure 4.

**Discussion**

Hypertension is one of the common chronic diseases worldwide. Hypertension has been a significant burden in the recent years.7,8 This Blood Pressure screening program was initiated in lines with the May Measurement Month was initiated to increase the awareness of the importance of blood pressure and also designed to understand the problems of real time clinical situations. Thus, establishing data about the hypertension which is essential towards the prevention and control of this rising burden.

In our study, a total of 1,45,621 subjects (27.2%) had blood pressure of >130/80 mm Hg. Among 37017 subjects, 14066 subjects (38%) were newly diagnosed subjects with hypertension. 8019 volunteers were Men (Urban, N = 4173 vs Rural, N= 3846) and 6047 were Women (Urban, N=2887 vs Rural, N=3160) with BP of >130/80 mm Hg see fig. 2. In the subset (N=22,951) of known cases of hypertension, Men were 14, 127 (Urban, N=7488 and Rural, N=6639) and 8824 were women (Urban, N=4588 and Rural, N=4236) see fig. 3. Among the known hypertensive volunteers 19,893 (86.6%) were taking medication (Table 5).

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![Co-morbidities among study volunteers](image_url)

**Table 5: Compliance to Medication**

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Urban</th>
<th>Rural</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>19893</td>
<td>10486</td>
<td>9407</td>
</tr>
<tr>
<td>Men</td>
<td>12789</td>
<td>6791</td>
<td>5998</td>
</tr>
<tr>
<td>Women</td>
<td>7104</td>
<td>3695</td>
<td>3409</td>
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**Table 6: Distribution of Habits among study volunteers**

<table>
<thead>
<tr>
<th>Habits</th>
<th>Population</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>Overall</td>
<td>48598</td>
<td>1873</td>
</tr>
<tr>
<td></td>
<td>Rural</td>
<td>23781</td>
<td>1806</td>
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<tr>
<td>Alcohol</td>
<td>Overall</td>
<td>50307</td>
<td>3897</td>
</tr>
<tr>
<td></td>
<td>Rural</td>
<td>25911</td>
<td>3508</td>
</tr>
<tr>
<td>Tobacco</td>
<td>Overall</td>
<td>46029</td>
<td>2138</td>
</tr>
<tr>
<td></td>
<td>Rural</td>
<td>16967</td>
<td>397</td>
</tr>
</tbody>
</table>

**Fig. 4: Distribution of co-morbidities among study volunteers**

routine clinic visit or the health care professionals. Adults > 18 years and willing to sign the informed consent form are included in the MMM Blood Pressure Screening Program.

Sitting blood pressure measured until 3 consecutive stable measurements are obtained and the average value of the last 3 measurements were recorded. Staff were recommended to use automated blood pressure devices and use the left arm of the volunteers for blood pressure measurements. A 5-minute interval was advised between the 3 consecutive readings.

The study was conducted after receiving approval from the Ethics Committee which is recognized by the Indian regulatory authority, Drug Controller General of India. Informed consent was taken from all participating subjects.

The investigator or his/her designee collected the patient data on the data collection form to gather information on socio demographic factors and data pertaining to hypertension. Demographic characteristics and the study results are summarized with descriptive statistics, including mean and standard deviation (SD) for continuous variables, and frequency and percentages. Tables and graphs have been given wherever necessary. The study endpoints included demographic variables, medical history, adherence to treatment etc. All recruited subjects constituted the analysis population.

A total of 37017 subjects (27.2%) had blood pressure of >130/80 mm Hg. Among 37017 subjects, 14066 subjects (38%) were newly diagnosed subjects with hypertension. 8019 volunteers were Men (Urban, N = 4173 vs Rural, N= 3846) and 6047 were Women (Urban, N=2887 vs Rural, N=3160) with BP of >130/80 mm Hg see fig. 2. In the subset (N=22,951) of known cases of hypertension, Men were 14, 127 (Urban, N=7488 and Rural, N=6639) and 8824 were women (Urban, N=4588 and Rural, N=4236) see fig. 3. Among the known hypertensive volunteers 19,893 (86.6%) were taking medication (Table 5).

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**Discussion**

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volunteers were screened. A total of 1,36,095 BP screening forms were considered for analysis. In our study 1675 doctors from 152 cities across India participated in this global blood pressure screening - MMM program.

Among the volunteers, 73,107 (53.72%) were men and 62,988 (46.28%) were women. 1,05,754 were from Urban settings with 51891 (49.06%) were men and 53863 (50.94%) were women. 30,341 were from rural settings with 21,216 (69.92%) were men and 9,125 (30.08%) were women. The Mean age (years) of the study population was 39.78 ±11.67 (95% CI 37.91-44.04) and the mean age of men was 41.61 ± 9.97 (95% CI 37.91-44.04) and the mean age of women was 36.66 ± 13.87 (95% CI 34.09-39.23).

A total of 23,459 men were in the age group of 31 – 40 years, while 20,947 men were in the age group of 41 – 50 years. Women were more in the age group of 21-30 years. Followed by 17,210 were in the 41-50 years respectively. Among the participants, 44.5% of the men in the age group of 51 – 60 years had high blood pressure. 31.2 % of the women in the age group of 51 – 60 years had high blood pressure.


Among the volunteers, 19,893 (86.6%) were taking medication. Thus, Compliance to antihypertensive drugs and life style modification play an important role for the control of hypertension. The adherence of subjects to medication was poor similar to the published studies.9,11

The common comorbidities were dyslipidemia, cardiovascular disorders and diabetes In our study 50,471 (37.08%) were smokers; 56,954 (41.84%) consumed alcohol and 48,167 (35.39%) had history of tobacco usage habits. Smoking is one of the more important cardiovascular risk factor in India. Smoking cessation and tobacco control must be an important initial strategy to reduce hypertension as well as overall cardiovascular risk.11-14

Conclusion

Despite the advances in the hypertension management and emphasis on patient education, our study shows that the hypertension continues to be a significant health burden. Hypertension is one of the common chronic diseases worldwide and is increasing significantly in the recent years. Improving patient compliance to lifestyle modifications, medication and regular follow-up clinic visits by imparting patient education and awareness can provide better results in Hypertension management.

Acknowledgement

We are grateful to all the Doctors who participated in our study and extended their full cooperation in the study.

Limitations

This is only the study with volunteers taken on small convenience sampling. Further study comprising large sample with more epidemiological determinants are to be included in conduct of the study.

Disclosure of Potential Conflicts of Interest

Manjula S and Krishnacumar M are employees of Micro Labs Ltd, India.

References


Clinical Course and Outcome of Critically Ill Clinical COVID-19 Pneumonia or Severe Acute Respiratory Illness

C Mohan Rao¹, Sunil Kumar Jena², Sibabratta Patnaik³, Nipa Singh⁴*, Saurabh Gupta⁵, Subhadra Priyadarshini⁶, Sujit Pradhan⁷, Sidhartha Das⁸

Abstract
Background: COVID-19 continues to be a public health challenge in India. In a small proportion of cases, the disease manifests as severe acute respiratory illness (SARI) which can progress to acute respiratory distress syndrome (ARDS) and multiorgan failure.

Objective: To describe the clinical course and outcome of critically ill patients who were provisionally diagnosed as COVID-19 pneumonia.

Study design: It is a retrospective observational study of 42 critically ill COVID-19 cases out of 395 admitted in COVID Hospital-KIMS, Bhubaneswar, Odisha between 5th April and 31st May, 2020.

Results: Majority of the patients were male (67%). Mean age among survivors was 50 years and among non survivors it was 63 years. Fever was more frequent as a symptom (87.5%) in non-survivors than survivors (76.47%). The time to admission to the critical care unit (CCU) from onset of symptoms was 5 days and duration of CCU stay was 5 days in case of non-survivors, which was higher in comparison to survivors. Both serum creatinine (2.39 ± 2.8 mg/dl) and CRP (56.74 mg/L) were found to be higher in case of non-survivors. Among the non-survivors, all required mechanical ventilation and 75% of cases suffered from ARDS while in case of survivors 29.41% required ventilator support and 35.29% developed ARDS. In survivors with co-morbidities, raised levels of Trop I, NT proBNP and D-dimer did not have any adverse outcome which indicates successful management.

Conclusion: Mortality (19.05%) was observed in those with severe disease requiring mechanical ventilation, but surprisingly patients survived despite cardiac injury.

Introduction
COVID-19 is caused by SARS CoV2, belongs to the genus beta coronaviruses, and one of the six corona viruses known to cause disease in humans. COVID-19 was declared a pandemic by WHO on 11th March 2020.

Thousands of cases are being reported from all the states with Maharashtra being the most affected state in the country.⁴ As of 31st May 2020- 182143 cases of COVID-19 have been reported in India.⁵ Up to May 2020 the state of Odisha, India had recorded 1948 cases.⁶ This virus is spread through the respiratory secretions of an infected person. The incubation period is 2-14 days (mean duration of 5.1 days) with peak viremia occurring before the onset of symptoms.⁷ The period of infectivity starts 2 days prior to the onset of symptoms and lasts up to 8 days. The epidemiological risk factors include older age, male sex, diabetes, and hypertension, chronic pulmonary, cardiovascular and chronic kidney diseases.⁸⁹ Respiratory tract infection has been observed to be the most common clinical manifestation of COVID.

Cases have been defined as a suspect, probable, or confirmed on the basis of evidence of positive RT PCR (Real-time Reverse Transcriptase Polymerase chain reaction) results of various respiratory samples along with clinical evidence of respiratory infection as per national guidelines.⁰ The spectrum of illness consists of asymptomatic, mild, moderate, severe, and critical cases, while critical cases develop pulmonary emboli.¹¹

Objectives
In this study, the main objective was to describe the clinical course and outcome of critically ill severe acute respiratory illness managed as suspect/clinical COVID-19 pneumonia with no other disease that fully explains this condition and living in contact with confirmed or probable COVID-19 cases prior to 14 days of onset of illness. Primary outcome included mortality and survival after 28 days of treatment and secondary outcome included ARDS (Acute Respiratory Distress Syndrome) incidence and laboratory findings.

Material and Methods
Study Design and population
It is a retrospective observational cohort study. The study was performed in Odisha COVID hospital at Kalinga Institute of Medical Science (KIMS), Bhubaneswar. There were 395 patients were admitted at this hospital from 5th April to 31st May 2020. 353 patients were managed in ward and 42 patients required management in the Critical care unit. We included 42 cases in our study with Clinical COVID-19

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Received: 17.09.2020; Accepted: 15.02.2021
Table 1: Characteristics of all critically ill patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>N=42</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>28 (66.67)</td>
</tr>
<tr>
<td>Female</td>
<td>14 (33.33)</td>
</tr>
<tr>
<td><strong>Age Group (in years)</strong></td>
<td></td>
</tr>
<tr>
<td>0 to 18</td>
<td>6 (14.28)</td>
</tr>
<tr>
<td>19 to 60</td>
<td>18 (42.85)</td>
</tr>
<tr>
<td>Above 60</td>
<td>18 (42.85)</td>
</tr>
<tr>
<td><strong>Co-Morbidities</strong></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>12 (28.57)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17 (40.48)</td>
</tr>
<tr>
<td>Obstructive airway disease</td>
<td>16 (38.10)</td>
</tr>
<tr>
<td>Cerebrovascular accidents</td>
<td>03 (07.14)</td>
</tr>
<tr>
<td>CKD</td>
<td>05 (11.90)</td>
</tr>
<tr>
<td><strong>Symptoms reported</strong></td>
<td></td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>25 (59.52)</td>
</tr>
<tr>
<td>Fever</td>
<td>33 (78.57)</td>
</tr>
<tr>
<td>Cough</td>
<td>24 (57.14)</td>
</tr>
<tr>
<td>Altered Sensorium</td>
<td>02 (4.76)</td>
</tr>
<tr>
<td>Pain abdomen</td>
<td>03 (7.14)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>02 (4.76)</td>
</tr>
<tr>
<td>Dysentery</td>
<td>01 (2.38)</td>
</tr>
<tr>
<td><strong>Average duration of stay in hospital (in days)</strong></td>
<td>7.24 (5.76 - 10.00)</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td></td>
</tr>
<tr>
<td>Survivor</td>
<td>34 (80.95)</td>
</tr>
<tr>
<td>Non survivor</td>
<td>08 (19.05)</td>
</tr>
</tbody>
</table>

Data presented as number (%)

by the use of target-specific forward and reverse primers for ORF1/a nonstructural region that is unique to the SARS-CoV-2 virus.12 RNA extracted from specimens is reverse transcribed to cDNA and subsequently amplified and detected using SARS-CoV2 specific primers and Taqman based fluorescent probes. Biosystems QuantStudio®7 Flex (Q57) instrument with software version 1.3 was used. The kit used for the detection of SARS-CoV2 was the TaqPath RT-PCR COVID-19 kit.13 This kit is based on Multiplexed assays that contain three primer/probe sets specific to different SARS-CoV-2 genomic regions (ORF1ab, N gene, S gene) and primers/probes for bacteriophage MS2 (Internal process control for nucleic acid extraction).13 During the amplification process, the probe anneals to a specific target sequence located between the forward and reverse primers. During the extension phase of the PCR cycle, the 5’ nuclease activity of Taq polymerase degrades the bound probe, causing the reporter dye to separate from the quencher dye, generating a fluorescent signal. Fluorescence intensity is monitored at each PCR cycle by Q57.

Blood and Radiological Investigation

All patients were evaluated for CBC (complete blood count), random blood sugar level, renal and liver function test, D-dimer, NT pro-BNP (N-terminal pro beta natriuretic peptide), CRP (C-reactive protein), PCT (pro-calcitonin), PT- INR (Prothrombin time and International Normalized Ratio) and Chest imaging. Their management was mostly supportive and mainly constituted of broad-spectrum antibiotics (if any evidence of infection), and anticoagulants and the information have been tabulated below.

Results

A total of 42 cases were evaluated, out of which 34 (80.95%) were survivors and were discharged and 8 (19.05%) were non-survivors. Among the 42 cases, the majority were male (66.66%) and the rest were female (33.33%). The study population group was divided into 3 groups i.e., pediatric (0 to 18 years), adult (18 to 60 years), and geriatric (>60 years) and the prevalence was found to be 14.30%, 42.85%, and 42.85% respectively. In our study out of 42 patients, 34 (female-13, male-21) were shifted out of the CCU to the isolation ward and stayed there for 28 days till discharge, while 8 (male-7, female-1) couldn’t survive. The mean age in survivors was 49.98 ± 26.35 years while in non-survivors it was 62.63 ± 8.88 (Table 1). The patients who survived had an average of 13 days of stay in the CCU (Figure 1).
Laboratory Values

- PLATELET (10^3 μL): 10.92 ± 2.45
- HB (gm/dl): 2.00-10.00
- M (%): 4.94 ± 2.74
- L (%): 14.71 ± 12.20
- N (%): 78.94 ± 13.83
- D-DIMER (μg/ml): 2.08 ± 2.00
- CRP (mg/L): 40.62 ± 39.83
- Total Bilirubin (mg/dl): 0.89 ± 0.89
- D. Bilirubin (mg/dl): 10.92 ± 2.45
- PLATELET (10^3 μL): 265.29 ± 171.07
- Oxygen only 21 (61.76)
- NT PROBNP (pg/ml): 12350 ± 2474.87
- TROP-I (ng/ml): 14506.92 ± 13551.4
- PCT (ng/ml): 12.37 ± 28.38
- SGPT (U/L): 134.17 ± 510.25
- SGOT (U/L): 187.87 ± 609.12
- D-DIMER (μg/ml): 2.67 ± 6.96
- Respiratory Support: 21 (61.76)
- Non-invasive ventilation 1 (2.94)
- Mechanically Ventilated 12 (35.30)
- Renal Replacement Therapy: 2 (5.88)

Table 2: Comparison of Biochemical values and management with outcomes of study population

<table>
<thead>
<tr>
<th>Status at 28 days of treatment</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survivor (n=34)</td>
<td>Non-Survivor (n=8)</td>
</tr>
<tr>
<td>Laboratory Values&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>TLC (10^3μL)</td>
<td>15.00 ± 7.97</td>
</tr>
<tr>
<td>N (%)</td>
<td>78.94 ± 13.83</td>
</tr>
<tr>
<td>L (%)</td>
<td>14.71 ± 12.20</td>
</tr>
<tr>
<td>M (%)</td>
<td>4.94 ± 2.74</td>
</tr>
<tr>
<td>E (%)</td>
<td>0.73 ± 2.03</td>
</tr>
<tr>
<td>HB (gm/dl)</td>
<td>10.92 ± 2.45</td>
</tr>
<tr>
<td>PLATELET (10^3μL)</td>
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</tr>
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<td>187.87 ± 609.12</td>
</tr>
<tr>
<td>SGPT (U/L)</td>
<td>134.17 ± 510.25</td>
</tr>
<tr>
<td>UREA (mg/dl)</td>
<td>53.57 ± 57.89</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.90 ± 3.55</td>
</tr>
<tr>
<td>TROP-I (mg/ml)</td>
<td>2.67 ± 6.96</td>
</tr>
<tr>
<td>NT PROBNP (pg/ml)</td>
<td>14506.92 ± 13551.4</td>
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</tr>
<tr>
<td>PCT (mg/ml)</td>
<td>12.37 ± 28.38</td>
</tr>
<tr>
<td>D-DIMER (μg/ml)</td>
<td>2.08 ± 2.00</td>
</tr>
<tr>
<td>PT (sec)</td>
<td>14.31 ± 6.01</td>
</tr>
</tbody>
</table>

Radiology Findings

There were multiple patterns of radiological finding in which bilateral multilobar patchy consolidation was seen in both group (Figure 4). However, it was more witnessed in nonsurvivors (around 75%) while in survivors it was 35.29%. Unilateral multilobar patchy consolidation was seen in 25% cases in non-survivors while in survivors it was 14.70%. Bilateral peripheral multilobar ground-glass opacities were seen in survivors only in 14.70% cases. Normal chest X-ray was seen in 38.23% of survivors while none in the nonsurvivors group. Other x-ray findings (only in survivor groups) which were seen were pleural effusion (5.88%) and pulmonary edema (2.94%) (Figure 3). The consolidation in both lung zones indicates the severity of pathological changes in the lung parenchyma.

Clinical Management

All severe acute respiratory illness patients received oxygen but patients of the non-survivor group were having Severe ARDS due to which 100% of them required mechanical ventilation on the same day of admission. In survivors 61.76% received oxygen via Hi-Flow mask, 2.94% received non-invasive ventilation and 35.30% received mechanical ventilation. 2 patients in survivor and 1 patient in non-survivor received dialysis. Out of 42 patients, 18 patients had ARDS in which 10 patients (55.56%) recovered while 8 patients (44.44%) couldn’t survive (Table 2).

Discussion

Out of 395 cases admitted in COVID hospital, 353 (89.37%) had mild illness whereas 42 (10.63%) cases needed critical care, death was witnessed in 8(2.02%) cases. This can be compared to the international data where around 80% (70% as per ministry of health and family welfare) and of COVID-19 pneumonia illness manifest as mild/ asymptomatic, 15% as moderate, and 5% have severe symptoms requiring intensive care unit care respectively, while the case fatality rate is 2%-4%.<sup>15</sup> SARI cases during the pandemic period with a history of contact...
were clinically managed like COVID pneumonia cases even if the RT PCR results were negative because only in 63% of affected cases, the RT PCR result may be positive, according to a study by Wenling Wang.\textsuperscript{16} SARI in susceptible individuals can progress to a more severe and systemic disease characterized by the Acute Respiratory Distress Syndrome, sepsis and septic shock, multiorgan failure including acute kidney and cardiac injury.

The virus has been shown to use the angiotensin-converting enzyme-2 (ACE2) receptor for cell entry. Autopsy findings in China and European countries showed endothelial damage of pulmonary vasculature, microvascular thrombosis, and hemorrhage linked to extensive alveolar and interstitial Inflammation that ultimately result in COVID-19 vasculopathy, pulmonary intravascular coagulopathy, hypercoagulopathy, ventilation-perfusion mismatch, and refractory ARDS. Hypoxemia may also activate the coagulation cascade.\textsuperscript{17}

On comparing between the survivor and non-survivors we found increase prevalence of fever 87.50% in nonsurvivors (survivors–76.47%). The prevalence of shortness of breath was more in survivors was 61.76% (nonsurvivors-50%). The prevalence of cough was more in survivors was 61.76% (nonsurvivors-37.50%). On comparison CRP level in nonsurvivors 56.74 ± 56.74 mg/L was witnessed as higher values than survivors 40.6171 ± 39.8274 mg/L, similarly Procalcitonin 14.64 ng/ml among non-survivors 12.37 ng/ml in survivors, among the coagulation parameters D-dimer 2.02 μg/ml and mean for Prothrombin time was 16.18 seconds. Comparing laboratory findings between survivors and non-survivors we found a TLC in survivors was 15.00 ± 7.97 (10X3μL) while for Neutrophil it was 15.00 ± 7.97(10X3μL) while in survivors we found a TLC in survivors among the liver biochemistry the total Bilirubin was raised in nonsurvivors (1.36 ± 1.47 mg/dl) compared to survivors (0.89 ± 0.89 mg/dl). SGOT, SGPT was raised in both survivors (187.87 ± 609.12, 323.31 ± 721.28 U/L) and (134.16 ± 510.24, 135.07 ± 271.28 U/L) for non-survivors respectively. Similarly, the Urea level was raised in survivors (53.57 ± 57.89 mg/dl) and in nonsurvivors (58.28 ± 41.54 mg/dl). Creatinine was much more raised (2.39 ± 2.81 mg/dl) in nonsurvivors in comparison to the survivor (1.90 ± 3.55 mg/dl). Raised Trop-I was seen in survivors (2.67 ± 6.96ng/ml) compared to non-survivors (0.63± 0.78 ng/ml).

Symptoms appeared 14.62 days prior to admission in ICU in survivors in comparison to 4.88 days non-survivors. Duration of stay was shorter in nonsurvivors 5.43 ± 4.03 in comparison to survivors 7.62 ± 4.78 which suggests a very rapid progression of the disease.

Males were the major victims in these critical COVID pneumonia cases whereas no death has been reported among the children. As the virus exploits the ACE2 receptor to gain entry inside the cells, under expression, immaturity of ACE2 receptors in children, underdeveloped humoral and cellular immune development may be the mechanism that leads to the absence of severe immune response, hence the favorable outcome in children.\textsuperscript{16} Since no special medication to treat SARS-CoV2 had been implemented at this time of the study (April to May) the main treatment was organ supportive treatment.\textsuperscript{18} Subsequently off label medications, compassionate antiviral drugs, and immunomodulatory dexamethasone were permitted by regulatory bodies due to the independent association between biomarker inflammation (CRP) and in-hospital mortality.\textsuperscript{20} There was also thrombocytosis, raised D-dimer as a marker of thrombosis among survivors in critical illness cohort that responded satisfactorily to anticoagulants.

Older age and male gender were risk factors for death. It is postulated that there may be a role of single-cell RNA expression profiling of ACE2 which is the cellular receptor of SARS-CoV 2, because Asian males had an extremely large number of such ACE2-expressing cells in the lung that makes them prone for death.\textsuperscript{21}

The frequent manifestation of typical COVID-19 pneumonia cohort was fever which is consistent with other studies.\textsuperscript{22} Gastrointestinal symptoms like pain abdomen, dysphagia, and dysentery were also noticed infrequently. The acute respiratory symptoms developed faster in nonsurvivors than survivors. Similarly, the number of days spent in ICU was less in nonsurvivors in spite of the earliest institution of mechanical ventilation that can be explained to elderly age, high creatinine, liver enzymes, C-reactive protein indicating viral-induced cytokine storm leading to multiorgan damage, including ARDS.

In our study the presence of diabetes and hypertension was seen in around 28.57% and 40.48% cases respectively. Diabetics suffering from COVID-19 are at risk of adverse outcomes and even mortality due to impaired immune response especially T-cell response, heightened inflammatory response, hypercoagulable state, and associated comorbidities like obesity, heart, and kidney disease. Emerging data suggest that COVID 19 is common in patients with diabetes, hypertension, and cardiovascular disease (CVD). China J epidemiology investigated 20,982 patients of COVID 19 which showed that hypertension, diabetes mellitus, and CVD were associated with 13%, 5%, and 4% of patients respectively.\textsuperscript{21} Similarly, in a meta-analysis of 8 trials that included 46,248 COVID-19 patients, Yang et al\textsuperscript{24} reported a prevalence of 17%, 8%, and 5% for hypertension, diabetes, and CVD respectively.

Computed tomography imaging has been routinely used in our institute to correlate the extent of parenchymal involvement in all cases. It can alert the clinician to look for any characteristic signs of COVID or any other comorbidity. The hallmark of typical COVID -19 patterns on CT images are bilateral and peripheral ground glass subpleural opacities, consolidation according to different studies.\textsuperscript{25-27} We witnessed such a pattern in 49.95%among survivors and 75% among nonsurvivors. Underlying COPD is a possibility for such extensive radiological involvement in our study.

Among the patients who died, all patients needed mechanical ventilation from the day of admission. We observed 19.04% mortality in our CCU cohorts. Among the non-survivors cases, 60% had comorbidities while 50% had more than one comorbidity. Bhatraju et al. also reported a similar incidence as the poor outcomes in patients...
with comorbidities and geriatric populations.28

Conclusion

Our study which represents follow up of 42 critical COVID-19 pneumonia (SARI) illness, reveals that nonsurvivors were elderly male and had rapid deterioration in the course of illness in CCU in spite of immediate mechanical ventilator support compared to survivors who were successfully transferred out of CCU after appropriate critical care management. Nonsurvivors had evidence of raised CRP and multiorgan dysfunction. ARDS was witnessed in all nonsurvivors having typical features of COVID-19 on pulmonary imaging. Comorbid diabetes, hypertension, obstructive airway disease was also commonly witnessed in critical cases. Surprisingly, Lymphopenia, multiorgan dysfunction with predominant cardiac injuries which was manifested by Raised Trop I, D-dimer, and NTproBNP was seen in survivors which indicated that it was an outcome of successful multidisciplinary management.

References

**Abridged Prescribing Information:**

**COMPOSITION:**

- **Glycomet GP 0.5:** Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 500 mg and glimepiride USP 1 mg.
- **Glycomet GP 2:** Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 500 mg and glimepiride USP 2 mg.
- **Glycomet GP 1/850:** Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 850 mg and glimepiride USP 2 mg.
- **Glycomet GP 3/850:** Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 850 mg and glimepiride USP 3 mg.
- **Glycomet GP 0.5 FORTE:** Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 1000 mg and glimepiride USP 1 mg.
- **Glycomet GP 1 FORTE:** Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 1000 mg and glimepiride USP 1 mg.
- **Glycomet GP 2 FORTE:** Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 1000 mg and glimepiride USP 4 mg.

**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 8 mg and metformin 2000 mg. 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. The tablet may be swallowed whole, caplets may be taken with fluids.

**CONTRAINDICATIONS:**

In patients hypersensitive to glimepiride, other sulfonylureas, other sulfonamides, metformin or any of the excipients of Glycomet GP. In patients with renal failure or renal dysfunction, acute conditions with the potential to alter renal function (dehydration, severe infection, shock, intravascular administration of iodinated contrast agents), acute or chronic disease which may cause tissue hypoxia (myocardial infarction, shock, cardiac/respiratory failure) hepatic insufficiency, acute alcohol intoxication, alcoholism.

**WARNINGS:**

Keep out of reach of children. Patient should be advised to report promptly exceptional stress situations (e.g. trauma, surgery, febrile infections) blood glucose regulation may deteriorate and a temporary change to insulin may be necessary to maintain good metabolic control. In case of lactic acidosis, patient should be hospitalized immediately.

**PRECAUTIONS:**

In the initial weeks of treatment, the risk of hypoglycemia may be increased and necessitates especially careful monitoring. Serum creatinine levels should be determined before initiating treatment and regularly thereafter: at least annually in patients with normal renal function. Glycomet GP should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal. Use of Glycomet GP should be discontinued 48 hours before any surgical procedure.

**ADVERSE REACTIONS:**

For glimepiride - Hypoglycaemia; temporary visual impairment; gastrointestinal symptoms like nausea, vomiting, abdominal pain, diarrhoea may occur; increased liver enzymes, cholestasis and jaundice may occur; allergic reactions may occur occasionally. For metformin – Gastrointestinal symptoms like nausea, vomiting, abdominal pain or discomfort may occur.

In mild to moderate hypertension,

**Tazloc® 20/40**
Telmisartan 20/40 mg

The Most Cost Friendly Telmisartan

Early initiation helps to prevent

- Stroke
- Chronic Kidney Disease
- Heart Attack
- Heart Failure
- Vision Loss

Better BP Control Vs. Calcium Channel Blocker

If uncontrolled, Up titrate to

**Tazloc® 80**
Telmisartan 80 mg

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6. USV Hypertens 2009;10(3).
Practice Pattern of Critical Care Physicians in India for Use of Corticosteroids in COVID-19

Deven Juneja¹, Ravi Jain²*, Omender Singh³

Abstract

Introduction: Steroids are recommended as the standard of care in managing severe COVID-19. However, several questions remain unanswered regarding the prescription of steroids which led to differing opinions and practice. We surveyed practice patterns of critical care physicians in India for the use of corticosteroids in COVID-19.

Methods: This was a nationwide, cross-sectional, online, knowledge attitude practice-based survey, among intensivists for corticosteroid use in COVID-19. The survey questionnaire had seven questions for demographic data and 14 questions in the core survey.

Results: 384 responses were analyzed from different parts of the country. A majority (81.2%) agreed that steroids improved oxygenation and survival chances. 88.3% agreed that steroids are indicated because of their anti-inflammatory properties, and should be prescribed in patients with moderate (75.8%), severe (59.9%), or critical (41.1%) COVID-19. 68.8% of physicians start steroids on the basis of "need for oxygen therapy" and hyperglycemia (85.2%) was the most commonly reported complication. 59.1% prefer prescribing methylprednisolone followed by Dexamethasone (38.8%). 51.8% preferred to use low dose steroids, and 59.1% have used "pulse steroids". Rather than a fixed duration of therapy, 66.9% of the respondents rely on "clinical improvement" before stopping steroids, even if it meant continuing steroids for prolonged periods beyond 14 days (34.1%). 57.8% always taper steroids before stopping.

Conclusions: We found wide variation in the practice patterns of critical care physicians in India for use of Corticosteroids in COVID-19. The dilemma regarding when to initiate, type of steroid, dose, and duration of therapy still persist emphasizing the need for further research.

Introduction

COVID-19 pandemic has led the whole world into uncharted territory. Worldwide national and international authorities have issued many static and fluid treatment guidelines, however, these treatment protocols continue to evolve as per the emerging literature.¹⁻³ These guidelines are based on the available contemporary evidence however, regional and institutional protocols are largely based on pragmatic thinking of the working physicians. This gross discrepancy in evidence/guidance versus practice can be easily spotted globally and more so in developing countries.

Immunomodulation with steroids is one such widely debated therapy since the start of the pandemic. Earlier studies and even meta-analyses published before the RECOVERY trial showed increased mortality, delayed viral clearance and increased length of stay with the use of steroids in viral pneumonia.⁴⁻⁶ Hence, the initial guidelines recommended against the use of steroids.²

In spite of emerging literature regarding the utility of steroids in managing COVID-19, there still remain several unanswered questions regarding the dose, duration, and type of steroids. This skepticism for steroid-related evidence and practices has led us to survey the current knowledge, attitude, and practice (KAP) patterns of critical care physicians in India for the use of steroids in COVID-19. In the past also such cross-section surveys were proven useful to point out major lapses in KAP, pertinent to areas under discussion.⁷⁻⁹

Material and Methods

We conceptualized this project to gauze practice patterns related to steroids therapy in COVID-19 in India. To prepare a survey questionnaire, we searched ‘Google Scholar’ and ‘PubMed’ electronic databases using search terms ‘steroid’, ‘COVID-19’, ‘cross-sectional survey’, ‘anti-inflammatory therapy’, or ‘pulse steroid’. We included all English language, primary research, or trial articles on adult humans with COVID-19, published during the year 2020 for our literature search and filtered them on the basis of relevance. Thus, we could conclude several qualitative and quantitative practice points for steroid use in COVID-19. We prepared a ‘Google Forms’ based survey with seven demographic and 14 core survey questions. Our core survey included nine single option selection types and five multiple option selection type simple practice questions. We designed this survey to auto-exclude core responses from critical care physicians who are not involved in managing COVID-19 patients. Hence, the absolute criteria of ‘work in COVID-19’ was ensured. After preparing, we distributed this survey to physicians all over the country via social media platforms. We kept this

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so that duplication of responses was avoided. Only physicians, who have worked in COVID-19 could respond to our core questionnaire. We are presenting the results of this cross-sectional survey in actual numbers and percentage form which were calculated using ‘Google spreadsheets’. We report the majority when the response rate reaches >50% in any one practice option.

**Results**

During the 15 days, we gathered 415 total responses. Among the responders, 31 physicians could not identify themselves to have work experience for COVID-19, and hence a total of 384 responses were finally analyzed.

This survey captured practice data from 23 different Indian states spread across the country (Figure 1). Table 1 shows the detailed demographic characteristics of the survey participants.

Most of the survey respondents believe that steroids reduce inflammation (88.28%), and blunt dysregulated host response (68.29%). Most of the participants believe that moderate (75.78%) and severe (59.89%) COVID-19 are the two phases where steroids should lead to maximum clinical benefit and hence, most of the clinicians use steroids in moderate (74.48%) and severe (60.94%) COVID-19. The majority of clinicians (81.24%) believe that steroid use leads to improved oxygenation and survival chances. 62.5% of clinicians believe that biomarker use in practice can lead to improved patient safety. The decision for treatment with steroids is based on the need for oxygen therapy (68.79%), CT severity score (56.51%), and CRP levels (49.48%). The most commonly observed side effects reported were hyperglycemia and loss of glycemic control (85.16%) and secondary infections (59.63%).

Methylprednisolone (59.11%) followed by Dexamethasone (38.8%) is the most preferred steroid in India for COVID-19. 59.1% of physicians use pulse steroids conditionally [based on high biomarkers (22.9%) or in presence of refractory hypoxemia (36.2%)] and, 3.64% of clinicians always use pulse dose steroids. Most clinicians (34.11%) give steroid therapy for more than 10 days based on clinical response, this
7. What are the side effects you commonly encounter with the use of low-dose steroid therapy in patients with COVID-19?

8. Which of the following is the steroid of your choice in managing COVID-19 patients?


10. Do you use “Pulse steroid” (High dose for a short period of time) therapy for the management of COVID-19 associated respiratory failure?

1. What may be the physiologic rationale for use of Steroids in COVID-19 patients?

2. According to you in which phase of COVID-19, initiation of steroids leads to maximum clinical benefit?

3. In your clinical practice when do you initiate steroids in a patient with COVID-19 infection?

4. Oxygenation and survival chances improve with the use of steroids

5. Bio-marker guided use of steroids can enhance patient safety.

6. Which of the following is/are best suited to INITIATE steroid therapy?

7. What are the side effects you commonly encounter with the use of low-dose steroid therapy in patients with COVID-19?

8. Do you prefer tapering steroid therapy before stopping?

9. What daily dose of pulse steroid you use in clinical practice for COVID 19?

10. For how long do you prefer to give steroids in clinical practice for patients with COVID-19?

11. What daily dose of pulse steroid you use in clinical practice for COVID 19?

12. For how long do you prefer to give steroids in clinical practice for patients with COVID-19?

13. At what point do you stop giving steroids to COVID-19 patients.

14. Do you prefer tapering steroid therapy before stopping?

Acronyms: ASAP: as soon as possible, COVID-19: corona virus disease -19, CRP: C-reactive protein.
different types of hospitals (Table 1). The majority of respondents had senior positions in their respected hospitals [head /director of the unit (24.74%) and consultants (50%)] and most of them had anesthesia (52.86%) as their base specialty. A great majority (81.2%) agreed that steroids improved oxygenation and survival chances, and 62.5% agreed that biomarkers may be helpful in increasing safety when steroids are prescribed. 88.3% agreed that steroids are indicated because of their anti-inflammatory properties, and should be prescribed in patients with moderate (75.8%), severe (59.9%), or critical (41.1%) COVID-19. The decision to start steroid therapy is based on the basis of “need for oxygen therapy” (68.8%) and hyperglycemia (85.2%) was reported as the most commonly encountered complication. Regarding the choice of steroids used, the majority is prescribing Methylprednisolone (59.1%) followed by Dexamethasone (38.8%). A majority (51.8%) preferred to use low dose steroids, as used in the RECOVERY trial, but 59.1% have used “pulse steroids”, in patients with refractory hypoxemia (36.2%) or in those with high inflammatory markers (22.92%). Rather than the fixed duration of therapy, most of the respondents (66.9%) rely on “clinical improvement” before stopping steroids even if it meant continuing steroids for prolonged periods beyond 14 days (34.1%). A majority (57.8%) always tapered steroids before stopping.

Corticosteroids, when exogenously administered, intersect inflammatory cascade and render their anti-inflammatory effect. It is widely accepted that dysregulated host inflammatory response, cytokine storm syndrome (CRS), is responsible for maximum harm in COVID-19 patients. Since, last many years, steroids are recommended to control dysregulated host response during sepsis. However, ‘how steroids can help in COVID-19’ is still not clearly established. In our survey, most of the Indian clinicians believe that steroids may help by ‘reducing inflammation’ (88.3%) and ‘blunting the dysregulated host immune response’ (68.5%).

Steroids have not shown to be beneficial when used in mild COVID-19 when the patient is not on oxygen therapy. Rather, it may be harmful to start steroids. It may be argued that the need for oxygen support signifies some amount of lung damage secondary to an inflammatory response. Hence, steroids may be useful in such patients. High levels of inflammatory markers may be suggestive of cytokine release syndrome (CRS), and a high CT severity score is indicative of severe lung involvement, hence steroids may be useful in such patients too. Even though some studies have shown the benefits of starting steroids in patients with high inflammatory markers like C-reactive Protein (CRP), robust evidence is lacking, especially pertaining to the levels at which steroids should be initiated. In our survey 68.79%, 56.51%, and 49.48% of physicians take their decision to start steroid therapy on the need for oxygen therapy, CT severity score, or CRP levels respectively.

The RECOVERY trial has shown clinically-significant mortality reduction for patients on invasive mechanical ventilation and for those patients requiring oxygen at randomization. Other studies also have included patients on oxygen therapy only. In our survey majority of clinicians were aware of this fact and would prefer to give steroids in moderate (75.78%) severe (59.79%) or critical (41.14%) COVID-19. This preference is also evident in the practice pattern of this group of clinicians, as in clinical practice 74.48%, 60.94%, and 46.64% of clinicians are prescribing steroids in moderate, severe, and critical COVID-19. However, this survey also revealed that 9.89% and 7.29% are prescribing steroids in ‘any phase of the illness’ and ‘as soon as possible’, which is contrary to the available evidence.

Aligned with the above-discussed literature, most of the clinicians in our survey agree (34.37%) or strongly agree (46.87%) with the fact that steroid use improves oxygenation and survival chances. Still, a majority of clinicians have an agreement (62.5%) [agree (29.69%) and strongly agree (32.81%) that biomarker-guided therapy can enhance patient safety.

Several potential adverse effects have been attributed to the use of steroids in COVID-19. These include delay in virus clearance, hyperglycemia, and increased risk of secondary infections. This is consistent with the results of our survey in which the most commonly reported side effects were hyperglycemia (85.2%), increased risk of secondary infections (59.6%), and delayed virus clearance (18%).

Some studies and even the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group prospective meta-analysis suggested that the choice of steroids does not affect the outcome of patients with COVID-19, but presently Dexamethasone has the best evidence for mortality benefit. Several studies using Methylprednisolone have shown reduced ICU and ventilator requirements but have failed to show any mortality benefit. Most of our respondents (59.1%) preferred to use Methylprednisolone followed by Dexamethasone (38.8%). Data from other retrospective studies have also shown that Methylprednisolone is the most commonly prescribed steroid in COVID-19 patients. This could be attributed to the fact that Methylprednisolone is the most widely studied steroid in the management of ARDS and hence, critical care physicians are more comfortable using this steroid.

Dosage of steroids is another issue of contention with different trials using different doses. The RECOVERY trial used Dexamethasone 6 mg for 10 days. WHO REACT meta-analysis also showed improved outcomes with low dose steroids. A majority of our respondents (51.8%) used low dose steroids, however, there was a significant heterogeneity regarding the dose of steroids being prescribed.

In our survey, 62.7% of respondents used high-dose pulse steroids in managing COVID-19 patients. Overall, 36.2% gave “pulse steroids” in patients with refractory hypoxemia and 22.9% gave “pulse steroids” in patients with high inflammatory markers suggestive of CRS. There is a dearth of studies evaluating the utility and adverse effects associated with high dose steroids in COVID-19 patients. A single-center, retrospective Spanish study showed that use of high dose Methylprednisolone (> 250 mg/day) was associated with a higher need for mechanical ventilation and mortality as compared to a dose of 1-1.5 mg/kg/day.

Duration of steroids also varies from 5-10 days in different studies. Most of the respondents used steroids till the clinical recovery of the patients,
even if it meant giving prolonged doses of steroids beyond 14 days. This finding is consistent with many observational studies, in which the duration of steroid use was not time-bound but left to a physician’s discretion.26

Corticosteroids, when used for prolonged periods (more than 3 weeks) may lead to HPA axis suppression. This may depend on the dose and duration, but adrenal insufficiency has been reported even after short courses of steroids and it may be associated with worse outcome.25 Even though the exact incidence of adrenal insufficiency with steroids use in COVID-19 patients is unknown, but it is often under-diagnosed. Even though COVID-19 guidelines do not comment on steroids tapering, the majority of the clinicians (57.81%) in our survey preferred to taper steroids.

Strength and Limitation

This cross sectional survey study is probably the first one done during the pandemic, and it was done during the month of December in India. In this study we were able to capture practice data from all over the country. However, participation from the northern and western states was comparatively higher. This survey was able to reveal KAP gaps among the physicians in India. We could capture data from 384 physician’s practice. We believe that practices will evolve further overtime, and directive and controlling measures can be planned by governing authorities based on this survey.

Conclusions

There is a wide variation in the practice patterns for steroid therapy in COVID-19 patients. The practice patterns also differ greatly from the present clinical recommendations. Despite conflicting evidence, Methylprednisolone still remains the steroid of choice by most of the intensivists and a significant proportion also prescribes high dose steroids in patients with refractory hypoxemia or CRS. The dilemma regarding when to initiate and the duration of therapy also persists emphasizing the fact that there still remain several unanswered questions regarding the use of corticosteroids in the management of COVID-19, necessitating further research.

References

In T2DM patients,

Vylda
Vildagliptin 50 mg Tablets
Purity for Smooth control

In iron deficiency anemia with diabetes,

Hosite™fe
ciently uncomplicates

In Elderly Hypertensives,

S-Numlo™
S(-)-Amlodipine Tablets IP 2.5/5 mg
GRACEFUL CONTROL
Assessment of Risk Factors for Severe Illness in Hospitalized COVID-19 Patients at a Tertiary Care Hospital

Nazia Mehfooz1, Farhana Siraj2, Afshan Shabir3, Suhail Mantoo2, Tajamul Hussain4, Umar Hafiz5, Muzaffar Bindroo6, Mudasir Qadri7, Mushtaq Dangroo8, Ajaz Nabi Kohll, Rafi Jan10, Sanaullah Shah10, Fayaz Sofi11, Faizan Wani12

Abstract

Background: COVID-19-19 is caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2). Identification of risk factors for severe illness helps in stratification of patients who may benefit from aggressive management strategies and early intervention. We aim to assess the risk factors for severe illness in patients admitted with COVID-19 infection.

Methods: We conducted a retrospective observational study of 802 patients with confirmed COVID-19 admitted to our tertiary care hospital. Univariate and multivariate logistic regression were used to identify determinants for disease severity.

Results: Of 802 hospitalized patients, severe COVID-19 infection was noted in (n= 537) (67%) patients. Patients with severe infection were significantly more likely to have hypertension, diabetes, and chronic pulmonary disease and had significantly higher white blood cell counts, NLR and decreased haemoglobin than patients with non severe infection. In multivariable logistic regression analysis, risk factors for severe infection included pre-existing hypertension (OR 2.29, 95% CI; (1.532-3.423), longer duration of symptoms before hospitalization (OR:1.158,95% CI(1.098-1.221),P<0.001) and Neutrophil lymphocyte ratio(NLR)>3. 8(OR, 1.101,95% CI (1.068-1.221); P<0.001). ROC curve for NLR shows that NLR at a cut off more than 3.8 has sensitivity of 80.5% and specificity of 58% in predicting severe illness.

Conclusions: Patients with pre-existing hypertension, longer duration symptoms before hospitalization and high NLR (>3.8) needs early intervention to prevent the potential development of severe COVID-19.

Introduction

COVID-19 is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). It is a novel type of beta coronavirus with high pathogenicity to the humans.1 The first case was reported in Wuhan, China, in December, 2019 and lead to the development of the ongoing outbreak which was declared as a pandemic by WHO on March 12, 2020.2 Highly infective mutated strain emerged from UK in the month of December (reference).

The burden of coronavirus disease 2019 (COVID-19) is continuously increasing. Till date (1st Jan 2021), there have been over 81,947,503 covid-19 confirmed patients globally out of which India is the third most affected country with over 10,286,709 cases.3

Most cases have no or mild symptoms, and only around 10% of patients develop severe or critical illness that requires hospitalization and intensive care management.4

WHO's most recent clinical guidelines define “severe disease” as adults with clinical signs of pneumonia (cough, fever, dyspnea, and fast breathing) accompanied by one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or oxygen saturation (SpO2) ≤ 90% on room air. The precise factors responsible for severe disease are not known, but it appears that primarily host factors rather than viral genetic mutations play major role.3

Severe COVID-19 rapidly progresses to acute respiratory distress syndrome over an average of 9 days from the time of symptom onset.4

Timely identification of patients who are having a severe disease can play a pivotal role in improving outcomes.4

Advanced age, comorbidities (hypertension, diabetes, chronic lung and renal disease), chest radiographic abnormality, hemoptysis, dyspnea, unconsciousness, neutrophil-to-lymphocyte ratio and elevated inflammatory markers are predictive risk factors of COVID-19 severity. Assessment of risk factors for severe illness would help in identification of high risk/vulnerable patients who may benefit from early intervention and aggressive management thus reducing the mortality.7,8

The present study is aimed to assess the risk factors for severity of COVID-19 patients thus leading to early identification of patients at risk for developing severe illness.
Table 1: Clinical characteristics of hospitalized COVID-19 patients

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Total (n=802)</th>
<th>Non-severe (n=265)</th>
<th>Severe (n=537)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (means. SD)</td>
<td>54.43±15.9</td>
<td>48.62±16.79</td>
<td>(57.67±14.52)</td>
</tr>
<tr>
<td>&gt;65</td>
<td>183</td>
<td>47 (17.7%)</td>
<td>136 (25.3%)</td>
</tr>
<tr>
<td>&lt;65</td>
<td>537</td>
<td>218 (82.3%)</td>
<td>401 (74.7%)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>530 (66)</td>
<td>172 (65)</td>
<td>358 (66.6)</td>
</tr>
<tr>
<td>Female</td>
<td>272 (34)</td>
<td>93 (35)</td>
<td>179 (33.3)</td>
</tr>
<tr>
<td>Duration of symptoms before</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hospitalization, median (IQR)</td>
<td>4(0.5-7)</td>
<td>3(0-5.50)</td>
<td>5(3-7)</td>
</tr>
<tr>
<td>Clinical symptoms, n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>546</td>
<td>135 (50.9)</td>
<td>411 (76.5)</td>
</tr>
<tr>
<td>Cough</td>
<td>433</td>
<td>82 (30.9)</td>
<td>351 (65.4)</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>462</td>
<td>57 (21.5)</td>
<td>405 (75.4)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>54</td>
<td>38 (14.3)</td>
<td>16 (3)</td>
</tr>
<tr>
<td>Myalgias</td>
<td>133</td>
<td>43 (16.2)</td>
<td>90 (16.8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>105</td>
<td>27 (10.2)</td>
<td>78 (14.5)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>15</td>
<td>6 (2.3)</td>
<td>9 (1.7)</td>
</tr>
<tr>
<td>Headache</td>
<td>22</td>
<td>9 (3.4)</td>
<td>13 (2.4)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>17</td>
<td>2 (0.8)</td>
<td>15 (2.8)</td>
</tr>
<tr>
<td>Decreased in consciousness</td>
<td>41</td>
<td>7 (2.6)</td>
<td>34 (6.5)</td>
</tr>
<tr>
<td>Anosmia</td>
<td>10</td>
<td>2 (0.8)</td>
<td>8 (1.5)</td>
</tr>
<tr>
<td>Loss of taste</td>
<td>11</td>
<td>2 (0.8)</td>
<td>9 (1.7)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>42</td>
<td>4 (3)</td>
<td>32 (6.3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>42</td>
<td>7 (2.6)</td>
<td>35 (6.5)</td>
</tr>
<tr>
<td>Pain in abdomen</td>
<td>16</td>
<td>8 (3)</td>
<td>8 (1.5)</td>
</tr>
</tbody>
</table>

Methodology

This retrospective observational study was done in the department of Internal and Pulmonary medicine SKIMS a multidisciplinary Institute of North India, a 800 bedded hospital. All the RT-PCR confirmed patients (n = 802) admitted between April 2020 to September 2020 were enrolled. Daily round data along with severity of disease, medication received and treatment outcome were noted for all patients.

The study is aimed to assess the risk factors for severe illness in patients admitted with COVID 19 infection.

Ethical clearance from institutional ethical clearance committee has been taken

Material and Method

Patients of all age groups with COVID-19 infection confirmed by real-time polymerase chain reaction admitted in the institute were included in the study.

All patients underwent radiological imaging including chest X-rays and/or CT scans and complete panel of routine laboratory tests including complete blood count, urinalysis, blood biochemistry, and blood coagulation function.

Based on clinical parameters each patient was designated a severity of Mild, Moderate and Severe as per Ministry of health and family guidelines India.6 Mild is defined as those with uncomplicated upper respiratory tract symptoms, no shortness of breath, hypoxemia or abnormal chest-X-rays.

Moderate: Pneumonia with no signs of severe disease. Adults with presence of clinical features of dyspnea and or hypoxemia, fever, cough, including SpO2<94% Severe ill patients were defined as those with clinical signs of severe pneumonia plus one of the following: respiratory rate>30 breath / min, severe respiratory distress and SpO2< 90% on room air; acute respiratory distress syndrome (ARDS); sepsis and septic shock

We separated the patients into two groups: Severe patients and Non-severe (mild and moderate)

All patients received Standard of Care based on severity as per Ministry of health and family welfare, India Clinical Guidelines existing at the particular period of time.

Data Collection

Patient data was collected from the Inpatient Medical records.

Demographic data and a current medical history of various comorbidities like hypertension, diabetes, Chronic kidney disease, Chronic liver disease, Chronic lung disease, cardiovascular disease, cerebrovascular disease, endocrine disorders, malignancy and other chronic ailments were collected

The following lab parameters, were collected and documented; WBC, Platelet count, Neutrophil-Lymphocyte ratio (NLR), Kidney function tests (KFT), Liver function test (LFT), serum LDH levels, and various electrolytes abnormalities (Na and K levels).

Radiological imaging (Chest X-ray/CT scan) of all patients were recorded. Radiographical findings were not used to classify cases, meaning asymptomatic cases could still present with radiographical abnormalities. The medical treatment received and outcome were also assessed.

Patients demographic, epidemiological, and clinical data were collected, and the relationships between these variables and disease severity were analyzed

Statistical Analysis

Statistical data was collected and entered into MS-Excel spreadsheets and processed using Stata 12 software for Windows. Statistical analysis was performed using SPSS version 12.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables are expressed as the mean ±SD. Mean values were compared between groups by use of the unpaired Student’s t test in case of continuous variable and using Chi square or Fischer in case of categorical variable. The possible risk factors of severe or critical illness were investigated with logistic regression models for univariate and multivariate analyses to estimate Odds ratios (OR) and 95% confidence intervals (CIs).

We selected variables from demographics, clinical histories and assessment, laboratory and imaging investigation to be included in the multivariate logistic regressions, based on clinical justification and statistical reasoning from univariate analyses. Variables from univariate analyses with p < 0.05 were recruited for the multivariate logistic regressions model. Multivariate logistic regressions were performed in a stepwise approach with results from the final model reported in this study.

The efficacy of risk prediction of severe illness was examined through
Table 2: Comorbidities in hospitalized COVID-19 patients

<table>
<thead>
<tr>
<th>Comorbidities (n%)</th>
<th>Total (n=802)</th>
<th>Non Severe (n=265)</th>
<th>Severe (n=537)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>406</td>
<td>82(30.9%)</td>
<td>324(60.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>240</td>
<td>56(21.1%)</td>
<td>184(34.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>68</td>
<td>17(6.4%)</td>
<td>51(9.5%)</td>
<td>0.141</td>
</tr>
<tr>
<td>Chronic Liver disease</td>
<td>16</td>
<td>4(1.5%)</td>
<td>12(2.2%)</td>
<td>0.599</td>
</tr>
<tr>
<td>Chronic lung diseases</td>
<td>49</td>
<td>2(2.6%)</td>
<td>47(8.8%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Cerebrovascular diseases</td>
<td>21</td>
<td>4(1.5%)</td>
<td>17(3.2%)</td>
<td>0.239</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>26</td>
<td>5(1.9%)</td>
<td>21(3.9%)</td>
<td>0.128</td>
</tr>
<tr>
<td>Malignancy</td>
<td>75</td>
<td>25(9.4%)</td>
<td>50(9.3%)</td>
<td>0.955</td>
</tr>
<tr>
<td>Thyroid disorders</td>
<td>108</td>
<td>19(7.2%)</td>
<td>89(16.6%)</td>
<td></td>
</tr>
<tr>
<td>Posttransplant</td>
<td>16</td>
<td>4(1.5%)</td>
<td>12(2.2%)</td>
<td>0.599</td>
</tr>
</tbody>
</table>

Note: p-value < 0.016 indicates statistical significance.

Table 3: Laboratory and chest imaging findings in hospitalized COVID-19 patients

<table>
<thead>
<tr>
<th>Laboratory parameters and chest imaging</th>
<th>Non-Severe (n=265)</th>
<th>Severe (n=537)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (gm/l) Mean S.D</td>
<td>12.44±2.72</td>
<td>11.68±2.35</td>
<td>0.001</td>
</tr>
<tr>
<td>WBC,(×10^9/L) Mean S.D</td>
<td>6.90±3.25</td>
<td>9.01±4.80</td>
<td>0.001</td>
</tr>
<tr>
<td>NLR. median (IQR)</td>
<td>3.13(1.66-3.58)</td>
<td>8.4(5.11-15.41)</td>
<td>0.001</td>
</tr>
<tr>
<td>Platelet counts,(×10^9/L) Mean S.D</td>
<td>150.13±77.27</td>
<td>137.86±71</td>
<td>0.17</td>
</tr>
<tr>
<td>Creatinine Median (IQR) (&gt;1.5 mg/l)</td>
<td>1.06(0.805-1.61)</td>
<td>1.03(0.80-1.54)</td>
<td>0.169</td>
</tr>
<tr>
<td>Serum bilirubin. Median (IQR) (&gt;1.5 mg/l)</td>
<td>0.6(0.45-0.83)</td>
<td>0.63(0.50-0.90)</td>
<td>0.026</td>
</tr>
<tr>
<td>ALP (U/L), Median (IQR)</td>
<td>35(23-58)</td>
<td>37(24-60)</td>
<td>0.541</td>
</tr>
<tr>
<td>LDH (U/L), Median (IQR)</td>
<td>94(75-115.7)</td>
<td>96(75-127)</td>
<td>0.439</td>
</tr>
</tbody>
</table>

Note: p-value < 0.016 indicates statistical significance.

Table 4: Treatment received by hospitalised COVID-19 patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total (n=802)</th>
<th>Non Severe (n=265)</th>
<th>Severe (n=537)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics N(%)</td>
<td>732</td>
<td>244(92.1%)</td>
<td>488(90.9%)</td>
<td>0.571</td>
</tr>
<tr>
<td>Antivirals N(%)</td>
<td>449</td>
<td>132(49.8%)</td>
<td>317(59%)</td>
<td>0.013</td>
</tr>
<tr>
<td>Corticosteroids N(%)</td>
<td>623</td>
<td>199(75.1%)</td>
<td>424(79%)</td>
<td>0.217</td>
</tr>
<tr>
<td>CPT(%)</td>
<td>112</td>
<td>25(9.4%)</td>
<td>87(16.2%)</td>
<td>0.009</td>
</tr>
<tr>
<td>Anticoagulation N(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylactic</td>
<td>536(67)</td>
<td>79(30%)</td>
<td>457(85%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Therapeutic</td>
<td>82(10)</td>
<td>2(0.7)</td>
<td>80(15%)</td>
<td></td>
</tr>
<tr>
<td>Oxygen Support N(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Off oxygen</td>
<td>14</td>
<td>4(1.5%)</td>
<td>10(1.9%)</td>
<td>Ns</td>
</tr>
<tr>
<td>Nasal cannula</td>
<td>325</td>
<td>117(44.2%)</td>
<td>206(38.7%)</td>
<td>Ns</td>
</tr>
<tr>
<td>Face mask</td>
<td>155</td>
<td>50(18.9%)</td>
<td>105(19.6%)</td>
<td>Ns</td>
</tr>
<tr>
<td>Reservoir mask</td>
<td>270</td>
<td>88(33.2%)</td>
<td>182(33.9%)</td>
<td>Ns</td>
</tr>
<tr>
<td>HFNC</td>
<td>38</td>
<td>6(2.3%)</td>
<td>32(6%)</td>
<td>0.159</td>
</tr>
<tr>
<td>Non invasive ventilation N(%)</td>
<td>27</td>
<td>0</td>
<td>27(5%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Invasive ventilation N(%)</td>
<td>32</td>
<td>0</td>
<td>32(6%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Tocilizumab N(%)</td>
<td>24</td>
<td>0</td>
<td>24(4.4%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Note: p-value < 0.016 indicates statistical significance.

Table 2: Comorbidities in hospitalized COVID-19 patients

<table>
<thead>
<tr>
<th>Outcome N (%)</th>
<th>Total (n=802)</th>
<th>Non Severe (n=265)</th>
<th>Severe (n=537)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge</td>
<td>580</td>
<td>189(71.3%)</td>
<td>391(72.8%)</td>
<td>0.123</td>
</tr>
<tr>
<td>Death</td>
<td>580</td>
<td>22(8.2%)</td>
<td>146(27.2%)</td>
<td>0.675</td>
</tr>
<tr>
<td>Lenght of hospital stay. (Mean±SD)</td>
<td>11.2±6.25</td>
<td>10.74±6.15</td>
<td>12.38±6.5</td>
<td></td>
</tr>
</tbody>
</table>

Note: p-value < 0.016 indicates statistical significance.

Results

General characteristics of all patients

A total of 802 patients were included in this study and divided into two groups (Non-severe and Severe). The number of patients in Non-severe group were 265 (33 %) and in the severe group they were 537(67%). The mean (SD) age for all the patients was 54.43(15.9). Males were 530 (66%) and females were 272(34%). The median time from symptom onset to hospital admission was 4 days (IQR, 3.0-7.2).

The most frequent symptoms reported were fever (n = 546; 68%), dry cough (n = 433; 54%), dyspnea (n = 462; 57%) and most common comorbidities seen were hypertension in 406 patients (50.6%) followed by diabetes mellitus in 240 (30%)

On Chest imaging in severe group majority of patients 329 (48.2%) had obvious imaging changes in the lungs in the form of bilateral pneumonia. Furthermore, 155 patients (19.3%) had normal imaging in non severe group (Table 3).

Majority of patients 788(98.2%) had oxygen requirements and 732(91.2%) received antibiotics, 623(77.6%) corticosteroids, 618(77%) anticoagulants. Based on clinical severity 449 patients (56%) received antivirals and 112 patients (14%) received convalescent plasma therapy. Out of the 802 patients, 580(72.3%) were discharged and 222(27.6%) died. The average length of hospital stay is (11.2±6.25) (Table 4).

Clinical characteristics of severe and non severe cases

The patients with severe infection were older with mean [SD] age of 57.67(14.52) vs 48.62(16.79) years in non-severe patients. Number of patients of age more than 65 years in severe disease were 134(25%) while the number of patients in non severe group were 49(18.4%) with p-value<0.016. The median time from symptom onset to hospitalization was 5 days (IQR: 3-7) in severe group which is significantly higher than seen in non-severe group (p-value<0.001).

High incidence of symptoms including fever 411(76.5%), cough 351(65.4%) and dyspnea 405(75.4%) and sore throat 163(3%)were seen in severe group in comparison to non severe cases with a (p-value<0.001).

Among the patients with severe disease, 28.4% were having reduced level of consciousness 34(6.5%) on presentation compared to14.6% seen in those with non severe disease which is statistically insignificant (p= 0.026).
Patients with severe infection were more likely to have comorbid condition than non severe disease like hypertension 324(60.3%) and diabetes 184(34.3%) with (P<0.001), followed by chronic pulmonary diseases (47(7.8%) vs 2(2.6%) P = 0.004) than non severe group Table 2.

Patients with severe infection in comparison to non severe disease demonstrated an increased inflammatory response, including higher white blood cell counts (9.01±4.80), high NLR levels (8.4(4.51-15.41) and decreased hemoglobin levels (9.01±4.80), high NLR levels (8.4(4.51-15.41) and decreased hemoglobin levels (11.68±2.35) which is statistically significant with (p<0.001) Table 3.

Majority of Patients in severe group received anticoagulants including both in prophylactic 457(85%) and therapeutic 80(15%) doses. Finally, on the basis of clinical judgment (e.g. severe acute respiratory failure) 27(5%) patients in severe group received noninvasive ventilation while 32(6%) received invasive ventilation with (p-value<0.001) and 24(4.4%) received tocilizumab (p<0.001) Table 4.

Risk factors for severe cases

At univariate analysis significant predictors of severe illness in hospitalized COVID-19 patients were: Age >65 years, Median duration of symptoms before hospitalization (p<0.001), presence of symptoms like fever, cough, and shortness of breath(p<0.001), presence of comorbidities like hypertension and diabetes(p<0.001), low hemoglobin, high NLR and white blood cell counts(p<0.001). At multivariable logistic regression, independent predictors of severe illness in hospitalized COVID-19 patients were: symptoms duration before hospitalization(OR:1.158,95%CI(1.098-1.221),P<0.001), Neutrophil lymphocyte ratio(NLR) >3. 8(OR, 1.101,95% CI (1.068-1.135); P<0.001), and presence of hypertension (OR 2.29, 95% CI; (1.532-3.423); P(0.001) Table 5.

ROC curve for NLR shows that NLR at a cut off more than 3.8 has sensitivity 80.5% and specificity of 58% in predicting severe illness (Figure 1).

Discussion

We report our experience of 802 patients confirmed cases of SARS-CoV-2 infection admitted to our hospital, of which 265 (33%) were non severe and 537(67%) were severe.

There were greater no of patients with severe illness admitted to our hospital. This finding is in accordance with many studies and is in contrast to many . While some studies report equal distribution.

The mean age for patients with severe illness was (57.67±14.52). Although number of patients of >65 were more likely to have severe disease as 25.3% patients were in severe group and 17.7% in non severe group but this difference was not statistically significant (p value<0.016). This finding is consistent with many studies which are in contrast to our observation.

Older age has been shown to be a risk factor for severe illness which is believed to be related to the weakened immune function in the elderly population.

The comorbidities frequently in severe group were hypertension, Diabetes Mellitus (p<0.001) followed by COPD(p=0.004) and this finding is similar to studies and systematic review. In contrast a study by Yingjie Wu et al., found no statistically significant differences in the prevalence of these comorbidities between mild and severe cases.

Patients with severe illness were more likely to have low haemoglobin, and high white blood cell counts (p<0.001) which is similar to many studies and systematic reviews. However in contrast to our experience a study by W. Guan et. al, found that on admission, lymphopenia was present in 83.2% of the patients, thrombocytopenia in 36.2%, and leukopenia in 33.7%. Another study Liang Li et. al found that 28.5% of patients had a white cell count below the normal range and 25.9% had a lower than normal lymphocyte count.

The patients in severe group were more symptomatic as compared to nonscure group with most common symptoms being fever, cough, shortness of breath and sore throat. This finding is in accordance to recent studies whereas in study by Mudatsir Mudatsir et. al, found that compared to the mild form, severe COVID-19 was associated...
with common symptoms such as dyspnea, anorexia, fatigue, increased respiratory rate, and high systolic blood pressure.

Our study showed that independent predictors of severe illness in hospitalized COVID-19 patients were: Neutrophil lymphocyte ratio (NLR) >3.8, duration of symptoms before hospitalization and presence of hypertension.

Hypertension has been reported to be a risk factor for severe disease in our study. A study by Mudatsir et al.11 found hypertension as the strongest risk factor for severe COVID-19. Our results are also consistent with a recent metanalysis by Abraham Degarege et al.12 where it was observed that there was greater odds of severe illness among hypertensive as compared to non-hypertensive patients.

Gao et al.13 observed that after adjustment for confounders, patients with hypertension had a two-fold increase in the relative risk of mortality as compared with patients without hypertension (4.0% vs. 1.1%, HR: 2.12, 95% CI: 1.17–3.82, p = 0.013).

Our study is in contrast to what Ashish bhargava et. al.14 who did not observe pre-existing hypertension as the independent risk factor for severe illness. Similarly, a study by Enrico MariaTrecarichi et al.15 did not find hypertension as the risk factor for the inpatient mortality.

Hypertension predisposes patients to an unfavorable clinical course and increased risk of intubation and death. Hypertension puts the body in stress for a longer period of time and hypertensive patients were observed to have a lower immunity status than healthy individuals. Hypertension can also affect the function of different organs of the body such as the lung, heart, vascular tube.16 These organs dysfunction and low immunity due to the hypertension will complicate and increase the risk of severe illness and death during SARS-CoV-2 infection. Another probable explanation for increased risk can be use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers used to hypertension, such use may upregulate Angiotensin converting enzyme 2, a receptor to SARS-CoV-2 in the host cell. This may facilitate the viral multiplication within the host cell, though this is controversial and denied by many researchers.17

Inflammation plays a significant role in COVID-19. Severe inflammatory response is responsible for weak adaptive immune causing immune response imbalance.25 Hence circulating biomarkers that can represent inflammation and immune status are potential predictors for the prognosis of COVID-19 patients. Neutrophil (NEU)-to-lymphocyte (LYM) ratio (NLR), is one such important indicator of the systematic inflammatory response that is widely investigated as useful.26

NLR in our study was found as an independent risk factor for severe disease on multivariate regression. Similarly, a study by Jingyuan Liu et al.27 found that the NLR was the independent risk factors for 2019-nCoV severe illness. In one metaanalysis NLR ratio also was seen as an independent risk factor for severe disease.

Neutrophil lymphocyte ratio (NLR) >3.8 showed increased odds of severe illness in our study whereas in a Chinese study aimed at assessing the NLR cut-off value for progression of disease reported that NLR>3.3 is independently associated with more severe COVID-19 (HR: 2.46, 95% CI 1.98-4.56).28 A study by Jingyuan Liu et al.29 found NLR ≥ 3.13 facilitated severe illness.

Similarly, multivariable regression by Peng Wang et al.30 showed increasing odds of severe illness associated with neutrophil to lymphocyte ratio (NLR, OR, 11.238; 95% CI 1.110–1.382; p<0.001).

Another study31 showed when age ≥ 49.5 years old and NLR ≥ 3.3, 46.1% of the COVID-19 patients with mild disease will become severe, and the mean time is 6.3 days. So, these patients must be closely attended by clinicians.

ROC curve for NLR shows that NLR at a cut off more than 3.8 has sensitivity of 80.5% and specificity of 58% in predicting severe illness while in a similar study by Yang, et al.32 demonstrated that the optimal cut-off value of NLR for predicting severe COVID-19 was 3.3, with sensitivity and specificity of 63.6% and 88.0%, respectively. Similarly, in another analysis of 301 patients, a NLR at 2.973 was associated with the progression of COVID-19, which only yielded an AUC of 0.734, with sensitivity and specificity of 75.8% and 66.8%, respectively.33

The possible reasons for NLR contribution may be many. Neutrophil (NEU) activates and migrates from the venous system to the immune organ or system and releases large amounts of reactive oxygen species starting cell DNA damage and freeing the virus from the cells. Humoral immunity then may kill the virus directly, exposing virus antigen, and stimulating cell-specific and humoral immunities.34

In addition, NEU can be triggered by virus related inflammatory factors like interleukin-6 and 8. Systemic inflammation significantly depresses cellular immunity, which significantly decreases CD4+ T lymphocytes and increases CD8+ suppressor T lymphocyte.35 Thus, virus-triggered inflammation increased NLR. Elevated NLR then promotes COVID-19 progression.35

The median time from symptom onset to hospitalization was 5 days (IQR: 3-7) in severe group which is significantly higher than seen in non-severe group 3 days (p-value<0.001). Median duration of symptoms before hospitalization was an independent risk factor (OR=1.158, 1.098-1.221, P<0.001). Similarly, Wen-hua Liang et. al.36 found that the duration from symptom onset to hospitalization remained an independent factor of the prognosis among the general population (HR 1.05, 1.01-1.08, P=0.005) which is in contrast to a study30 in which it was found that severe cases experienced longer duration from onset to hospitalization compared with non severe cases but it was not statistically significant(P=0.035). Another study37 found the median time from illness onset to hospital admission was three days (IQR, 2-7) for severe patients versus seven days (IQR, 3-7) for non-severe patients (the difference was not significant).

Finally, our study has few limitations. First, we may have included more patients with poor outcomes
In this single-centre retrospective observational study of 802 patients with COVID-19, we found that the pre-existing hypertension, longer duration of symptoms before hospitalization and raised NLR >3.8 to be the independent risk factors for severe COVID-19 cases. NLR is an easily measurable and non-costly marker of systemic inflammation as compared to cytokines. So it may be used as reliable predictor for the assessment of severe illness in patient with COVID-19. Early identification of these risk factors is pivotal in risk stratification, tailoring management strategies and monitoring of cases for timely interventions. This may lead to improved outcomes in patients hospitalized with Covid-19 and thereby relieving the shortage of medical resource.

References

Study of Low Bone Mineral Density in Ambulant Elderly Population by Quantitative Ultrasonography and it’s Implications on Fragile Fracture Risk

Naveen Kumar KL1*, Sangeeta J Pednekar2, Charulata Londhe3, Dharmendra B Pandey4, Ajay D Athawale1

Abstract

Background: Osteoporosis is a silent disease until it is complicated by fractures. Fractures in aging individuals place an enormous medical and personal burden, therefore primary prevention by screening before fracture occur or even after the first fracture has occurred decrease future fracture risk. As there is no universally availability of Dual energy X ray Absorptiometry (DXA) and affordability issues has lead to search for lower cost alternatives like quantitative ultrasonography (QUS).

Objectives: To determine risk of low Bone mineral density (BMD) in elderly ambulant population (>60 yrs) by osteoporosis self- assessment tool (OST). Identify presence of low BMD by QUS in all patients and confirm by DXA scan and test ability of QUS and OST individually and in combination in predicting low bone density and fracture risk.

Methodology: This was a observational study with sample size of 217 with elderly population as subjects. Details of presenting symptoms and past history co-morbidities and fracture were taken. Osteoporosis risk is calculated by OST. Subjects were screened for presence of low BMD by calcaneal QUS machine and classified into Osteopenia and osteoporosis based on T score by QUS and DXA. X rays of pelvis with both hips and spine obtained for documentation of fractures.

Results: The prevalence of Osteoporosis 15% (33) and Osteopenia 39% (84). Osteoporosis was more among female (37%). Low BMD had significant association (p<0.05) with Low BMI, Smoking, alcohol consumption, Previous fractures, anemia, Vitamin D3 levels and low serum calcium. OST cutoff of <-1 had sensitivity of 96%, specificity of 40% for predicting low BMD. QUS had sensitivity of 75.8 % and specificity of 90% in predicting osteoporosis. The combined (QUS+OST) had sensitivity of 81.1% and specificity of 95.1%. Fracture risk by QUS had RR 3.3 and OR 5.8 when combined with OST had RR 3.8 and OR 4.6 as compared to DXA (RR 4.0/OR 4.2).

Conclusion: QUS provides an effective alternative to DXA in predicting low BMD and fracture risk estimation. The yield of predicting low BMD and fracture risk. Increases when combined with OST.

Introduction

Osteoporosis is characterized by reduced bone mass and loss of bone architecture resulting in increased risks of fragility fractures. In India, life expectancy according to current census is 67 years and is expected to increase to 71 years by 2025 and to 77 years by 2050. Thus, leading to greater proportion of the Indian population likely to be affected by osteoporosis.1 Prevalence of osteoporosis ranging from 8% to 62% has been reported by several studies. However, data on prevalence of osteoporotic fractures and prevalence of osteoporosis, are a product of studies carried out in various small groups of people across the country.2 World Health Organization (WHO) operationally defined osteoporosis as a bone density that falls 2.5 standard deviations (SD) below the mean for young healthy adults of the same sex also referred to as a T-score of -2.5. Epidemiology of fractures follows the trend for loss of bone density, with exponential increases in both hip and vertebral fractures with age. Incidence rates for hip fractures double every 5 years after age 70.3

DXA is the most preferred densitometry technique for diagnosis of osteoporosis. The results are presented in terms of T-Scores and Z-Scores. T-Scores represent the bone mass of the patient compared to the mean peak bone mass of the young adult reference population using standard deviations. Z-Scores compare the patient’s bone mineral density (BMD) with the mean BMD for the person of the same age.4 In communities, where the number of central DXA systems per capita is not enough to cover needs, QUS could be used in conjunction with Clinical Risk Factors (CRFs) to assess the level of fracture risk. This approach could be used to identify patients at very high risk for whom treatment initiation could just be started. Any patient in the intermediate rank of risk would be referred for additional testing, such as DXA.5

Osteoporosis self-assessment screening tool (OST), is based on age and weight (0.2 [body weight in kg – age in years]), has been developed and validated in Asian and Caucasian women. It is comparable to other developed osteoporosis risk–assessment tools. The advantages of the OST are that it is simple to use and has a slightly better discriminative ability.

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The performance of this tool was not adversely affected by race (white or black), age, or corticosteroid use.

The initial QUS parameters employed for characterizing bone tissues were Speed of Sound (SoS) and Broadband Ultrasound Attenuation (BUA). Complex parameters have been developed from combination of SoS and BUA, are useful in identifying subjects with high risk of fracture. Lower equipment and operational costs and absence of ionizing radiation makes QUS an attractive alternative technology. However presence of heterogeneity in measurement techniques increases difficulties comparing measurements with different QUS devices. Heel QUS is Significant predictor of fragility fractures, as well as hip fractures secondary to osteoporosis, however not as accurate as femoral neck BMD for hip fractures. The combining of CRFs and heel QUS was found to be useful in predicting fracture risk at different ages, and was much more predictive than using either CRFs or QUS alone.

Hence the objectives of this study was to determine risk of low BMD in elderly ambulant population (>60 yrs) by OST. Identify presence of low BMD by QUS in all patients and confirm by DXA scan. Test ability of QUS individually and in combination with OST in predicting low bone density and fracture risk.

**Methodology**

This is observational study. The prevalence of osteoporosis from previous similar study was found to be 17%. Taking relative precision of 30% and confidence interval of 95% total number of subjects to be screened for low BMD was calculated as 217. Ambulatory elderly subjects visiting geriatric OPD having low BMD were study subjects. Detailed demographic data, presenting symptoms, past history of fractures and co-morbidities was taken. Clinical examination vitals, BMI, general examination, vertical height, joint mobility, skeletal deformities and systemic examination were done.

Osteoporosis risk is calculated by OST. \( \text{OST} = 0.2 \times \left[ \frac{\text{Body weight (Kg)} - \text{Age(years)}}{1.58} \right] \) OST values were classified as follows: < -4: high risk, -4 to -1: intermediate risk, > -1 to 1: low risk.

Patients were screened for presence of low bone mineral density by calcaneal Quantitative ultrasononography machine Furuno CM 200 (Furuno electric Co.LTD, Japan). The calcaneus was chosen as a site for measurement since it is easily accessible, with the medial and lateral aspects being relatively flat and parallel, therefore resulting well-suited for optimizing the geometry of transmission of the US wave through it. It contains approximately 90% trabecular bone, which has a high metabolic turnover rate and a pattern of bone loss similar to the spine. Patients with low bone mineral density were classified into following classes by T score by QUS and confirmed by DXA (HOLOGIC). Osteopenia: Between 1.0 and 2.5 SD below that of the mean level for a young-adult reference population. T score -1 to -2.5. Osteoporosis: 2.5 SD or more below that of the mean level for a young-adult reference population. T score < -2.5. X ray of pelvis with both hips and vertebral AP and Lateral view were obtained for documentation of fractures. Laboratory investigations such as complete haemogram, renal function, liver function, serum vitamin D3 levels and serum calcium levels were done and correlation with bone mineral density was assessed.

**Statistical analysis**

Data were entered in Excel work sheet and statistical analysis was performed using Open Epi version 3.0. Descriptive statistics expressed as percentage, mean and standard deviations. Inter group variance was assessed by chi square test and ANOVA. P value <0.05 were considered significant. Receiver operating characteristic analysis was used to determine optimum cutoff values, sensitivity, and specificity of screening methods. Relative risk (RR) and Odds ratio (OR) for fracture was calculated by chi square test.

**Results**

About 217 subjects were screened for presence of low bone mineral density, among them 118 [54%] having low bone mineral density was considered for study. 33(28%) subjects had osteoporosis and 84(72%) had osteopenia. Major of study subjects were in 60-70’s age group (62%), most of them had Osteopenia (74%), while prevalence of osteoporosis increased as increasing age. Mean age for Osteoporosis 68.52 years and Osteopenia was 67.2 years. Prevalence of osteoporosis was more in female (37%) when compared to male (18%). Majority of study subjects (73%) had mixed diet but association between diet and low bone mineral density was not significant. Smoking [10(33%)] and tobacco [9(60%)] addiction was found to have significant association with osteoporosis. Diabetes mellitus (62) followed by hypertension (54) were common co morbidities. Subjects with COPD, CKD and RA had severe osteoporosis. Subjects with fractures had osteoporosis [15(75%)] when compared to Osteopenia [5(25%)].

Osteoporosis in high risk group calculated by OST was 19(86%) compared to intermediate [13(22%)] and low [(13%)] risk group, the above association was statistically significant. Low BMD had significant correlation between levels of vitamin D, hemoglobin and serum calcium level. The association between the sonological parameters (SOS & T score) obtained by QUS and radiological parameters (BMD at hip and LS spine, T score) with degree of osteoporosis was statistically significant (Table 1).

The sensitivity and specificity of QUS against gold standard DXA was obtained by Wilson score with CI 95%. The T score by QUS had sensitivity, negative predictive value, specificity, positive predictive value and diagnostic accuracy of 75.8%, 91.3%, 96.4%, 89.3%, and 90.1% respectively. Cut off of OST score < -4 [Area under the ROC curve (AUC) = 0.859 (0.779 – 0.938) CI 95%] (high risk group) was tested for predicting osteoporosis against the gold standard T score by DXA. The OST score < -4 had sensitivity, positive predictive value, specificity, negative predictive value and diagnostic accuracy of 54.6%, 81.8%, 95.2%, 84.2% and 83.7% respectively. Combining OST with QUS had sensitivity, positive predictive value and diagnostic accuracy increased to 81.1%, 87.1% and 91.3 % respectively, while specificity and NPV was 93.2%. (Table 2) Fracture risk by QUS had RR 3.3 and OR 5.8 when combined with OST had RR 3.8 and OR 4.6 as compared to DXA (RR 4.0/OR 4.2) (Table 3).

**Discussion**

Reduction in BMD is a gradual and silent process, with occurrence of risk factors can accentuate this process, increasing the negative outcomes
affecting the health of the elderly. Access to BMD evaluation tests would help identify the issues and planning interventions. However, this is a high cost test, which hinders early diagnosis and monitoring, especially in medium- and low-income countries. This study helps us to identify various risk factors for low BMD and assessing fracture risk in community setting and also gives us idea about screening of subjects for osteoporosis, by using risk calculators like OST and simple outpatient technique like QUS. These results can contribute to the planning of more specific actions for the health of the elderly, helping prevent fractures and improving in life quality.

Prevalence of low BMD: In our study prevalence of low bone mineral density was 54% (15% osteoporosis, 39% Osteopenia). Similar study conducted among urban women above age of 25 yrs utilizing calcaneal QUS by Sharma et al20 25% and 36.7% were suffering from osteoporosis and Osteopenia respectively. While retrospective study using DEXA scan records of 40 - 60 yrs Indian women conducted by Acharya et al21 documented 18.41% osteoporotic and 47% Osteopenics.

### Table 1: Correlation of various demographic, clinical, lab and radiological parameters with low BMD

<table>
<thead>
<tr>
<th>Variables (N)</th>
<th>Osteoporosis N/%(33/28%)</th>
<th>Osteopenia N/%(84/72%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE groups</td>
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<td></td>
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</tr>
<tr>
<td>60-69 (73)</td>
<td>18(26%)</td>
<td>54(74%)</td>
<td>0.08</td>
</tr>
<tr>
<td>70-79 (41)</td>
<td>12(29%)</td>
<td>29(71%)</td>
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<tr>
<td>80-90 (3)</td>
<td>2(67%)</td>
<td>1(33%)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Female (66)</td>
<td>24(37%)</td>
<td>42(64%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Male (51)</td>
<td>9(18%)</td>
<td>42(82%)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
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<tr>
<td>Under nourished (10)</td>
<td>10(100%)</td>
<td>0(0%)</td>
<td>&lt;0.01</td>
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<tr>
<td>Normal (77)</td>
<td>23(30%)</td>
<td>54(70%)</td>
<td></td>
</tr>
<tr>
<td>Ower weight (30)</td>
<td>0(0%)</td>
<td>30(100%)</td>
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</tr>
<tr>
<td>Fractures</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Absent (97)</td>
<td>18(19%)</td>
<td>79(81%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Present (20)</td>
<td>157(75%)</td>
<td>25(25%)</td>
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<tr>
<td>Constitutional variables</td>
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<tr>
<td>Age in years [X/(SD)]</td>
<td>68.52(6.62)</td>
<td>66.75(5.08)</td>
<td>0.1</td>
</tr>
<tr>
<td>Height In Mts [X/(SD)]</td>
<td>1.58(0.07)</td>
<td>1.62(0.07)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Weight In Kg [X/(SD)]</td>
<td>48.85(6.72)</td>
<td>60.57(6.15)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BMI [X/(SD)]</td>
<td>19.56(1.95)</td>
<td>23.16(1.65)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Risk Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OST [X/(SD)]</td>
<td>-3.96(1.81)</td>
<td>-1.24(1.55)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Laboratory Variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium [X/(SD)]</td>
<td>8.4(0.5)</td>
<td>8.7(0.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Uric acid [X/(SD)]</td>
<td>4.0(1.0)</td>
<td>3.7(0.7)</td>
<td>0.097</td>
</tr>
<tr>
<td>Phosphate [X/(SD)]</td>
<td>3.6(0.7)</td>
<td>3.5(0.5)</td>
<td>0.787</td>
</tr>
<tr>
<td>Vitamin D3[X/(SD)]</td>
<td>15.5(4.6)</td>
<td>19.1(3.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Albumin [X/(SD)]</td>
<td>3.6(0.4)</td>
<td>3.7(0.4)</td>
<td>0.479</td>
</tr>
<tr>
<td>Hemoglobin [X/(SD)]</td>
<td>10.3(2.1)</td>
<td>11.7(2.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sonological Variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOSIX/[SD]</td>
<td>145(7)</td>
<td>147(8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>T SCORE QUS [X/(SD)]</td>
<td>-2.66(0.28)</td>
<td>-1.63(0.32)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Radiological Variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMD HIP [X/(SD)]</td>
<td>0.597(0.040)</td>
<td>0.730(0.045)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BMD SPINE [X/(SD)]</td>
<td>0.694(0.040)</td>
<td>0.830(0.045)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>T SCORE DXA [X/(SD)]</td>
<td>-2.94(0.28)</td>
<td>-1.93(0.32)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

### Table 2: Comparison of sensitivity and specificity of screening tests

<table>
<thead>
<tr>
<th>Variables</th>
<th>QUS</th>
<th>OST</th>
<th>QUS+OST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>75.6%</td>
<td>54.5%</td>
<td>81.8%</td>
</tr>
<tr>
<td>Specificity</td>
<td>96.4%</td>
<td>95.2%</td>
<td>95.2%</td>
</tr>
<tr>
<td>Positive predictive value (PPV)</td>
<td>89.3%</td>
<td>81.8%</td>
<td>87.1%</td>
</tr>
<tr>
<td>Negative predictive value (NPV)</td>
<td>91.3%</td>
<td>84.2%</td>
<td>93.2%</td>
</tr>
<tr>
<td>Diagnostic accuracy (DA)</td>
<td>90.1%</td>
<td>83.7%</td>
<td>91.6%</td>
</tr>
</tbody>
</table>

### Table 3: Comparison of fracture risk estimation by various methods

<table>
<thead>
<tr>
<th>Fracture risk estimation</th>
<th>Relative risk (RR)</th>
<th>Odd’s ratio (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DXA</td>
<td>4.04</td>
<td>4.2</td>
</tr>
<tr>
<td>QUS</td>
<td>3.3</td>
<td>5.8</td>
</tr>
<tr>
<td>QUS + OST</td>
<td>3.8</td>
<td>4.6</td>
</tr>
</tbody>
</table>

Association of Low BMD with demographic, clinical and lab parameters

The association between the age and degree of low bone mineral density had minimal significance, (p>0.08) as this was an institutional outpatient study in elderly population. The reduction of BMD with the progression of age was seen in other BMD studies. There was no significant difference in the dietary habits of the subjects with normal and low bone density but their role needs to be substantiated by conducting larger studies in future. Similar conclusion was also seen in study conducted by V Silvanus, et al. The association between low BMI and degree of low bone mineral density was statistically significant. Similar inference was seen in previous study. Increase of BMD along with body weight occurs as a skeletal adaptation process resulting from increase of mechanic load on the bone.

BMD by QUS: Hartl et al showed that the diagnostic performance of QUS at the calcaneus and the phalanx
was comparable with central DXA. The percentages of correct classification of osteoporotic subjects with or without vertebral fractures depended on the different QUS instruments used and were the following: 66.5% for Achilles BUA device; 64.8% for Achilles SOS device; 63.9% for Achilles STIFFNESS device; 65.2% for Sahara BUA device; 61.1% for Sahara SOS device; 71.1% for Bone Profiler AD-SoS and 59.1% for Bone Profiler UBPI. Similarly T score by QUS in present study had sensitivity of 75.8% and specificity 89.3%. It was found that by combining T score obtained by QUS with OST sensitivity, positive predictive value and diagnostic accuracy had increased to 81.1%, 87.1% and 91.3% respectively, while specificity and NPV was 93.2%.

Fracture risk: In this study fracture risk estimation by DXA had RR 4.0 and OR 4.2, while QUS had RR 3.3 and OR 5.2 and when combined with OST RR of 3.8 and OR of 4.6. The EPIC-Norfolk prospective population study, conducted in an English male and female population, proved the effectiveness of QUS at the calcaneus in predicting fracture risk, for both males and females. The same result was confirmed by a prospective study (SEMOF study) performed on more than 7000 Swiss women. Study conducted by Hans et al, major CRFs combined with validated QUS parameters into a probabilistic model to calculate both 5- and 10-year probabilities of osteoporotic fractures overall and hip. The combination of CRFs and heel QUS was shown to be useful in predicting fracture risk at different ages, and was more predictive when compared to use of either CRFs or QUS alone. Using the combined stiffness index + CRFs score, the average GR for hip fracture was 2.10 per 1 SD, vs GR with SI alone, and 1.52 with the CRF score alone.

Conclusion
Reduction in bone mineral density is a gradual and silent process; risk factors such as increasing age, female gender, postmenopausal state, poor nutrition, habits of smoking and alcohol consumption accentuate this process. Effective screening would help identify the issue and plan interventions. Simple osteoporosis screening tool like Osteoporosis Self assessment which have incorporated risk factors helps in identifying candidates for further BMD testing and interventions. Quantitative bone scan in this study has shown to be a promising tool and cost effective tool for identifying individuals with osteoporosis and risk of fragile fractures. Two step approach of screening for low bone mineral density by self assessment tools and confirming by QUS has shown to be as effective as gold standard DXA for selecting patients for pharmacotherapy. As this was ambulatory outpatient based study only apparently healthy population who could attend, the exact disease burden could not be assessed in morbid patients, which would have much higher incidence.

References
15. Hans D, Durosier C, Kanis JA, et al. Assessment of the threshold for a 10-year probability of hip fracture model based on the EPISEM cohort study only apparently healthy individuals with osteoporosis and risk of fragile fractures. Two step approach of screening for low bone mineral density by self assessment tools and confirming by QUS has shown to be as effective as gold standard DXA for selecting patients for pharmacotherapy. As this was ambulatory outpatient based study only apparently healthy population who could attend, the exact disease burden could not be assessed in morbid patients, which would have much higher incidence.

References
Pulmonary Functions in People with Type 2 Diabetes

Tripti Mishra¹, L Dave², KK Kawre³, Simmi Dube⁴

Abstract

Introduction: Diabetes is a metabolic disorder which affects micro and macrovascularity leading to dysfunction of multiple organs. However its effect on lungs which is a highly vascular organ is not studied extensively. Some studies have reported that patients with type 2 diabetes mellitus (T2DM) have compromised pulmonary functions (PF) in the form of obstructive and restrictive disease while others documented normal PF in T2DM. Moreover, histopathological changes in lungs have been documented in patients with T2DM. Therefore we hypothesized that PF are altered in people with T2DM and the current study was planned to assess PF (FEV₁, FVC, FEV₁/FVC, PEFR, MMEFR) using spirometry and compared the results with age and gender matched healthy individuals.

Methods and Materials: This was a cross sectional case control study in which 200 cases (T2DM patients free from other debilitating illness) and 200 controls (age and gender matched healthy volunteers) were enrolled. After permission from IEC, detailed history, examination and routine investigations were recorded for all the study subjects to meet inclusion criteria. Study participants then underwent spirometry using helios 401 spirometer. Results of two groups were compared using Student’s unpaired t test. p value <0.05 was considered significant. Correlation of glycemic control (HbA1c) and duration of diabetes with PF was also calculated in patients with T2DM.

Results: Data of 192 cases and 191 controls was considered for final analysis. Mean age of study subjects was 49±12 years with comparable gender distribution and anthropometric parameters in two groups. Most of cases had T2DM for duration of 5-10 years with moderate glycemic control (HbA1c-7.5-8.5). Spirometry results suggested that 45.83% T2DM patients had normal PF, 44.26% had restrictive, 3% had obstructive and 7% had mixed pattern of disease. Duration of diabetes was positively correlated while HbA1c was found to be negatively correlated with PF.

Conclusion: This study strongly suggests that T2DM patients have deranged PF (predominantly of restrictive pattern) determined by duration of diabetes and glycemic control. Thus patients with T2DM should undergo time to time screening for pulmonary functions along with other routine screening tests of end organ damage.

Introduction

Diabetes mellitus is a chronic metabolic disorder which is rapidly growing to become a public health care problem. According to WHO survey in 2016, diabetes affects 422 million people in the world of which 85-90% of the case burden is attributable to type 2 diabetes mellitus, which 85-90% of the case burden is attributable to type 2 diabetes mellitus.

India has second largest population of T2DM patients after China with 69 million persons affected by diabetes. It lays a daunting challenge to the sustainable development of the nation on lungs (being a highly vascular structure) is not yet proved. Although various studies have been conducted on patients with T2DM to study the effect of diabetes on lung functions. The mechanism by which impaired glycemic control may lead to a defect in lung functions is not certainly defined in the available medical literature, though it has been suggested in studies that the increased systemic inflammation associated with diabetes may result in pulmonary inflammation causing air way damage. Also the abundance of microvasculature in lungs makes it more prone for non enzymatic glycosylation of tissue protein as a result of tissue hyperglycemia which causes histopathological changes in basal lamina leading to impairment of diffusion through basement membrane in patients with type 2 diabetes mellitus. Although pulmonary complications due to T2DM are not reported but it has been seen in various studies that PF are compromised in patients with long standing T2DM. Moreover duration of diabetes and glycemic control has also been found to have varied impact on PF of T2DM patients in these studies.

There is limited data with conflicting results concerning type of abnormal PF in people with T2DM. In this study we hypothesized that lungs can also be a target organ for microvasculature damage in patients with T2DM causing compromised pulmonary functions. The current study was planned to assess the PF using spirometry in people with T2DM and to compare the results with age and gender matched healthy volunteers.

Materials and Methods

This was a cross sectional case control study conducted in the Department of Medicine, Gandhi Medical College, Bhopal, Madhya Pradesh. Received: 27.12.2019; Accepted: 15.12.2020

¹Senior Resident, ²Professor and Head, Department of TB and Chest, ³Professor and Head, ⁴Professor, Department of General Medicine, Gandhi Medical College, Bhopal, Madhya Pradesh; ⁵Corresponding Author
Table 1: Baseline Characteristics of Study Participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases (Mean ± SD)</th>
<th>Control (Mean ± SD)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49 ± 12</td>
<td>48 ± 12</td>
<td>0.87</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>40:152</td>
<td>50:141</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.05 ± 6.00</td>
<td>24.62 ± 6.01</td>
<td>0.51</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>94.13 ± 13.78</td>
<td>93.98 ± 13.38</td>
<td>0.91</td>
</tr>
<tr>
<td>Waist Hip Ratio</td>
<td>0.90 ± 0.23</td>
<td>0.91 ± 0.14</td>
<td>0.63</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>11.27 ± 2.49</td>
<td>10.50 ± 2.60</td>
<td>0.80</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>34.61 ± 15.75</td>
<td>34.86 ± 17.86</td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>144.84 ± 13.96</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>PPBS (mg/dl)</td>
<td>221.78 ± 89.78</td>
<td>156.25 ± 66.56</td>
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</tr>
<tr>
<td>Hemoglobin A1c (%)</td>
<td>6.88 ± 1.80</td>
<td>-</td>
<td>0.89</td>
</tr>
<tr>
<td>Urea (mg/dl)</td>
<td>34.61 ± 15.75</td>
<td>34.86 ± 17.86</td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.20 ± 2.80</td>
<td>1.13 ± 0.80</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Table 2: Pulmonary Functions of Study Participants

<table>
<thead>
<tr>
<th>Pulmonary Functions</th>
<th>Gender</th>
<th>Cases (Mean ± SD)</th>
<th>Control Mean ± SD</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1</td>
<td>Female</td>
<td>88.35 ± 23.96</td>
<td>106.72 ± 15.57</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>87.22 ± 22.4</td>
<td>103.76 ± 12.93</td>
<td>0.006</td>
</tr>
<tr>
<td>FVC</td>
<td>Female</td>
<td>80.93 ± 21.55</td>
<td>99.78 ± 12.31</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>83.47 ± 23.03</td>
<td>94.78 ± 12.31</td>
<td>0.006</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>Female</td>
<td>84.11 ± 9.82</td>
<td>74.56 ± 26.40</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>78.41 ± 11.2</td>
<td>78.87 ± 22.55</td>
<td>0.70</td>
</tr>
<tr>
<td>PEFR</td>
<td>Female</td>
<td>75.02 ± 72.80</td>
<td>82.51 ± 18.86</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>72.05 ± 22.69</td>
<td>81.49 ± 25.77</td>
<td>0.18</td>
</tr>
<tr>
<td>MMEFR</td>
<td>Female</td>
<td>62.60 ± 105.68</td>
<td>66.98 ± 24.62</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>52.47 ± 25.47</td>
<td>68.16 ± 23.35</td>
<td>0.02</td>
</tr>
</tbody>
</table>

In the present study a total of 200 cases and 200 controls were registered from May 2017 to April 2018. Age and gender of participants enrolled in the study were comparable. Baseline characteristics of the study participants are shown in Table 1.

Mean age of participants in case and control group was 49 ± 12 years and 48 ± 12 years respectively (p=0.865) and Male:Female ratio 1:4.

Among Cases and Controls maximum were females [144 (72%) vs. 139 (72.77%)] (P>0.05) and male subjects accounted for nearly 28% in each group.

Though not intentional but on data analysis anthropometric parameters were found to be comparable in both the groups. Maximum patients had normal BMI [case 94 (49%) vs. control-96 (50.3%) respectively]. Similarly mean waist circumference (M:F::93:94cm) and mean waist hip ratio (M:F::0.89:0.90) of both the populations were comparable (p>0.05)

Maximum number of patients had T2DM for 5-10 years (42%) followed by those who had diabetes for <5 years (35.92%) and nearly 22% cases had T2DM for >10 years. Most of the cases had moderate control (6.5-8.5%) of HbA1c [97 (48.5%) followed by good control [85 (42.5%)] whereas only 18 (9%) patients had poor glycaemic control (HbA1c>8.5%).

Pulmonary Functions were found to be significantly compromised in cases compared to controls (Table 2). Mean % predicted FEV1 was significantly lower among cases as compared to controls (M:F::87.21:88.35%; M:F::103.76:106.72; p<0.001) in both the genders. The % predicted of mean FVC was significantly lower among cases as compared to controls (M:F::83.47:80.93%; M:F::94.78:99.78; p<0.001) in both gender. FEV1/FVC ratio was significantly higher among Cases (81.15±15.49) as compared to control (75.89±24.21) (p=0.014). Low %predicted of FEV1 and FVC with high FEV1/FVC ratio suggests restrictive pattern of pulmonary functions in patients with T2DM. Both mean % predicted PEFR and MMEFR values were lower among Cases as compared to control implying that large as well as small airway functions are compromised in patients with T2DM (PEFR- cases:control: 75.02: 82.51 and MMEFR - 62.60: 66.98).

These results suggests that a significant no. of patients with T2DM
(44%) had restrictive pattern defect of PF, 3% had obstructive pattern and 7% had mixed pattern of pulmonary functions defect (Figure 1).

It has been also observed that pulmonary functions (FEV1, FVC, FEV1/FVC) were negatively correlated with glycemic control (HbA1c) in patients with T2DM [FEV1 (r= 0.421, p<0.001) and FVC (r=0.471, p<0.001)] suggesting that poor glycemic control had adverse effects on pulmonary functions too in T2DM (Figure 2). Duration of diabetes was also found negatively correlated with the pulmonary functions.

**Discussion**

In spite of abundance of vasculature in lungs neither it has been labeled as a target organ for end organ damage in T2DM nor have lung functions been studied thoroughly in T2DM. In our research we came across various studies which showed compromised lung functions in patients with T2DM. The aim of our study was to assess lung functions of T2DM patients using spirometry and to compare with age and gender matched healthy controls.

Case and Control group in our study were age and gender matched so that confounding due to variation in PF because of age and gender related factors can be eliminated. Mean ± SD age of cases was 49.51±12 years and that of control was 48.42±12 years, (p=0.865). In present study, females outnumbered males and were comparable in both groups.

BMI of the two groups was also comparable (p=0.506). Majority of participants (50%) had normal range of BMI. Mean waist circumference of male cases- 93.10±11.16; control-93.31±10.02) as well as female (cases-94.13±13.78; control-93.98±13.38) participants was within normal range. Waist hip ratio of male (0.89) and female (0.90) participants was comparable in both the groups (p=0.05). Thus in our study variable effect of obesity on PFs wasnullified due to comparable weight distribution of both the populations.

Cases in this study were classified on the basis of duration of diabetes and glycemic control. Most of the cases had diabetes for 5-10 years (female-32.5%; male-8.8%), followed by those who had diabetes for < 5 years (female-30%; male-7.2%). Only 15% female and 7% male cases had diabetes for more than 10 years. On the basis of HbA1c level, Cases were divided into good control (<6.5%) moderately controlled (6.5-8.5%) and poorly controlled (>8.5%). Maximum participants (48.5%) had moderate control of HbA1c followed by good control (42.5%) whereas 9% patients had poorly controlled diabetes mellitus.

All the participants in the study underwent spirometry to assess the PF. Patients with T2DM had significant decreased % predicted FEV1 (male: female::87.21±2.44:88.35±23.96) compared to controls (male: female::103.76±12.93:106.72±15.57; p<0.05). Asanuma et al.² and Sreekumar et al.³ in their studies have also reported significantly reduced FEV1 in patient with T2DM. Others⁴ have observed a moderate reduction in FVC and FEV1 in patients with type 1 and type 2 diabetes.

FVC values in patients with T2DM were also found to be reduced significantly (male-cases: controls:: 83.47±23.04:78±13.02; female-cases:control::80.93±21.55:99.78±12.31; p=0.006). These observations were in agreement with Sreekumar et al.⁵, El-Azeem et al.⁶ and Khan et al.⁷ studies who also reported significant reduction in FVC among T2DM patients. Similar results were demonstrated in studies by Asanuma Y et al.⁸, Davis et al.⁹ and, Lange et al.¹⁰ Mckeevear et al.¹¹ and Baba et al.¹².

FEV1/FVC ratio was higher than the predicted ratio in both the genders. It was inferred from these findings that cases had restrictive changes in the lungs. Similarly studies conducted by Boublou et al.¹³ and El-Azeem et al.¹⁴ in patients with diabetes found reduced FVC and normal FEV1/FVC and concluded that presence of restrictive pulmonary function might be associated with metabolic disorders. But Aparna et al.¹⁶ reported that FEV1/FVC was increased in T2DM as compared to that in healthy controls which also suggested restrictive changes.

The mean of % predicted PEFR value was lower among patients with T2DM as compared to controls (male-
72.05 ± 22.69: 81.49 ± 25.77; female-75.02 ± 72.80: 82.51 ± 18.86) in both genders but the difference was not significant (P_{male} =0.18; P_{female} =0.23). These observations suggests that compromised functions of large airways occurs in diabetes. These results were consistent with study results of El-Azeem et al^1^ and David et al^12^ who have also reported that mean PEFR was significantly low among patients with diabetes. Similarly, MMEFR was lower among cases as compared to controls (male- 52.47 ± 25.7: 68.16 ± 23.35, P_{male} =0.002; female-62.60 ± 105.68: 66.98 ± 24.62, P_{female} =0.63) implying compromised small airways functions too in T2DM. Davis WA et al^2^ and Asanuma Y et al^12^ also found similar differences in MMEFR values in patients with T2DM.

Interpretation of the these results showed that 45.83% of patients with T2DM had PF within normal limit whereas 44.26% had restrictive pattern of PF changes. Remaining 2.6% and 7.29% of T2DM patients were found to have obstructive and mixed blockage pattern of pulmonary functions respectively.

In our study correlation between duration of diabetes and PF came out to be negative (FEV1 r= -0.027; FVC r= -0.023) which indicates that with increasing duration of diabetes, PF deteriorate in T2DM. In contrast to these findings Benbassat CA et al^18^ showed no significant correlation between PFs and duration of disease, while others like Barrett-Cononor E et al^19^ and Davis TM et al^22^ have also reported a strong negative correlation of PF with duration of diabetes.

It was also observed that FEV1 and FVC are negatively correlated with HbA1c (p<0.001) suggesting poor glycemic control is responsible for causing impairment in PF in patients with T2DM. These findings were supported by study performed by Singh et al^20^ in which all the parameters of PF (FEV1, FVC and DLCO) in T2DM with uncontrolled glycemcic status were low compared to T2DM with controlled glycemic status. These results suggest that glycemic control affect the pulmonary functions by affecting micro and macro-vasculature of lungs. So the micro and macrovascular changes occurring in various end organs (retina, kidney, heart etc.) in T2DM also affect lungs. Hence attainment of good glycemic control in patients with T2DM will prevent deterioration in lung function in these patients.

**Conclusion**

We conclude from our study results that pulmonary functions are significantly compromised in T2DM predominantly of restrictive pattern. The results which are in sync with the observations of other researchers strongly suggest that type 2 diabetes mellitus adversely affects the lungs which can be assessed by pulmonary functions tests using spirometry. Nevertheless, the findings of present study accomplish that lung is a target organ for damage in diabetes and that the glycemic exposure is a strong determinant of reduced pulmonary functions in type 2 diabetes mellitus. Thus, an intensive glycemic management may reduce the risk of lung function defects through an improved ventilatory function which is independent of other beneficial effects. Also, as pulmonary dysfunction may be one of the earliest and easily measurable non–metabolic alterations in diabetes, therefore it is advisable to screen pulmonary functions in T2DM patients along with other investigations to detect early changes in lungs. These measures will help in preventing lung damage in initial stage, and thus contribute to reduction in morbidity and mortality in type 2 diabetes patients. Future prospective studies should be planned to determine association of T2DM and lung function defects and its clinical implications.

**Limitations of Study**

The cross sectional nature of the present study was main limitation of the study; a large prospective randomized clinical trial is required to strengthen the present study results.

**References**

COVID-19 and its Implication on Gastroenterology: An Overview

Amit Lakhani¹, Pukraj Singh², Ena Sharma³, Savita Kapila⁴

Abstract
Emerging pandemics show that humans are not infallible and communities need to be prepared. Coronavirus outbreak was first reported towards the end of 2019 and has now been declared a pandemic by the World Health Organization. Since then many researches are going worldwide to understand this coronavirus disease, its impact on human body, prevention and treatment. As of now it has been observed that its can affect every organ of body and it’s not only the respiratory manifestation but it has shown other clinical sign and symptoms in various patients. This review article is highlighting the impact of covid-19 on Gastroenterology which helps us to understand the various manifestations in our digestive system and guide us to diagnose at earlier stage and prevents cross infection among society.

Introduction
A pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or novel coronavirus disease (COVID-19) started in December 2019 in the Wuhan province of China and swept through the world by April 2020, affecting 187 of the 192 countries of the world with varying severity.¹⁻³ As of October 2020, WHO has reported there have been 43 million confirmed cases of COVID-19, including 1,155,553 deaths.⁴

Respiratory tract manifestations such as fever and cough are the most commonly reported symptoms in patients with COVID-19.⁵ Evidence of digestive system involvement in patients with COVID-19 was first reported by a group in China. Emerging data showed that the gastrointestinal tract and liver might also represent target organs of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on the basis of the findings that angiotensin-converting enzyme 2 (ACE2), the major receptor of SARS-CoV-2, is expressed in the gastrointestinal tract as well as liver cells.⁶⁻⁷

The detection of SARS-CoV-2 viral RNA in patients’ stool and the potential for faecal–oral transmission has raised great concern and could pose a challenge for the control and prevention of COVID-19. However further research is warranted in this space.

COVID-19 and Gastro Intestinal Symptoms

In The Lancet Gastroenterology and Hepatology, Ren Mao and colleagues report findings of a systematic review and meta-analysis of data from 35 studies, including 6686 patients with COVID-19. In 29 studies (6064 cases) reporting gastrointestinal symptoms in patients with COVID-19, the pooled prevalence of digestive symptoms was 15%, the most common of which were nausea or vomiting, diarrhoea, and anorexia. The pooled prevalence of diarrhoea was 9%, nausea or vomiting 6%, loss of appetite 21%, and abdominal pain 3%. Of note, the authors report that around 10% of patients presented with gastrointestinal symptoms without respiratory features when infected with SARS-CoV-2. These patients were more likely to have a delayed diagnosis, leading to potential problems for themselves and individuals with whom they came into contact.⁸

The proportion of patients with severe or critical COVID-19 was markedly increased in patients with gastrointestinal symptoms compared with those without gastrointestinal symptoms. However, the risk of severe disease was not increased among patients with digestive comorbidities compared with patients without these comorbidities. Patients with gastrointestinal symptoms had an increased risk of acute respiratory distress syndrome and liver injury. However, the pooled rates of discharge, length of hospital stay, and mortality were similar between patients with and without gastrointestinal symptoms.⁹⁻¹¹

Over the course of the COVID-19 pandemic, some patients have initially presented with abdominal symptoms without fever or respiratory manifestations. In a large multicentre study of 204 patients with COVID-19 in three heavily affected hospitals during the initial outbreak in China, 103 (50%) patients presented with digestive symptoms as their chief complaint. Six (3%) patients presented with digestive symptoms but no respiratory symptoms.

In a large case series (n=1141) of patients admitted to hospital with COVID-19, 183 (16%) presented with gastrointestinal symptoms only. Wang and colleagues also found that around 10% of patients initially presented with diarrhoea and nausea 1–2 days before the development of fever and dyspnoea. Patients with digestive symptoms had a variety of manifestations, such as loss of appetite, diarrhoea, vomiting, and abdominal pain.⁹⁻¹¹

A link between gastrointestinal involvement and disease severity of COVID-19 has been proposed. In a multicentre study, Pan and colleagues investigated the prevalence and outcomes of patients with COVID-19 with digestive symptoms. In 99 patients who presented with digestive symptoms as their chief complaint, a longer time from onset to admission was observed compared with...
patients without digestive symptoms (9-0 days vs 7-3 days). As the severity of the disease increased, digestive symptoms became more numerous. Patients without digestive symptoms were more likely to be cured and discharged than were patients with digestive symptoms (60% vs 34%). This finding was consistent with the study from Wang and colleagues, who found that patients admitted to the ICU were more likely to have abdominal pain and loss of appetite compared with non-ICU patients. A higher prevalence of abdominal pain in patients with severe COVID-19 than in those with non-severe disease has also been frequently noted in our clinical settings. More data analysis is warranted in such settings as well.

Emerging data suggest the prolonged presence of SARS-CoV-2 RNA in stool samples or rectal swabs even after the patients’ respiratory specimens become negative. Much attention has been paid to the possibility of viral shedding from the gastrointestinal tract and faecal–oral transmission. Data from Wu and colleagues suggest the possibility of extended duration of viral shedding in faeces, for nearly 5 weeks after the patients’ respiratory samples tested negative for SARS-CoV-2. However, the clinical implications of prolonged viral excretion in faeces, including the association with disease course, severity, and even recurrence of COVID-19, remains unclear. More studies are needed to show the virus’ replication competence, abundance in stool, and stability in the environment.

**COVID 19 and Liver Injury**

In addition to digestive symptoms, patients with COVID-19 are also at risk of developing liver injury. Studies have shown that patients having varying degrees of liver function abnormalities—the incidence ranging from 1% to 53%—mainly indicated by abnormal ALT and AST concentrations, accompanied by slightly increased bilirubin concentrations as seen in prominent literature. Albumin was decreased in severe cases (around 26.3–30.9 g/L). Acute liver injury is common in patients who test positive for SARS-CoV-2, but is most often mild. However, among patients with severe lung injury, a severe disease course should be anticipated. In addition, patients with severe COVID-19 may be more likely to have liver injury than patients with less severe disease or asymptomatic carriers. Although cholestasis and liver synthetic function abnormalities appear to be rare, hypoaalbuminemia is emerging as a consistent risk factor for severe disease, even among patients without chronic illness.

Emerging data suggest that alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations are common among patients with COVID-19 and AST elevations found in 38%–63% and 29%–39% of patients, respectively. The mechanism by which SARS-CoV-2 impacts the liver is not fully understood, but is thought to be a combination of direct viral mediated injury as well as the immune-mediated inflammatory response. The SARS-CoV-2 cellular receptor, the angiotensin-converting enzyme 2 (ACE2) receptor, is present in biliary and hepatic endothelial cells, providing a plausible mechanistic explanation for the observed liver injury. Among hospitalized patients, additional etiologies of liver injury must be considered, including drug-induced liver injury, sepsis, shock, congestion, and extra hepatic sources of AST.

It has been indicated that angiotensin II receptor blockers and ACE-inhibitors drugs may inhibit liver functions in COVID-19 patients. In a study, elevated levels of liver enzymes were observed among participants who used ACE-Is/ARBs drugs during hospitalization, though the elevation was not significant with those who did not use these drugs. It has now been proven beyond doubt that ACE inhibitors or ARBs have no derogatory effect on patients with concomitant COVID 19 infection. Some authors also observed that the drugs lopinavir and ritonavir contributed significantly to liver test abnormalities and liver injury. These drugs increased the odds of liver injury by four-fold. Moreover, using antibiotics in the treatment also showed an association with the increased prevalence of liver test abnormalities, however this association was not significant. Hydroxychloroquine, an antimalarial agent has not been associated with liver injury in COVID-19; however, it should be used with caution to avoid any harmful effects. Future studies would be worth conducting in determining the possible effects of drugs on liver function in COVID-19 patients.

However data pertaining to level of liver damage in COVID 19 by drugs, sepsis and shock needs to be ascertained more thoroughly.
patients with pre-existing liver disease required increased hospitalization.21 In addition to this, another study reported that patients with chronic liver disease may have higher mortality rates from COVID-19 compared to patients with IBD.22 However, more work is required in studying interaction between isolated pre-existing liver disease and COVID-19.19,23 In very little of our clinical experience in pre-existing liver disease patients with COVID-19, not much could be studied.

**COVID 19, the Intestine and Inflammatory Bowel Disease**

A recent study in >100 outpatients with mild courses of COVID-19 demonstrated the presence of diarrhea in approximately 30% of patients suggesting that diarrhea may be a frequent hallmark of mild disease. The presence of diarrhea could be due to direct infection of GI cells.23 In this regard, gastric, duodenal and rectal epithelial cells rather than cells in the oesophagus were shown to express the SARS-CoV2 receptor ACE2. COVID-19 led to infection of these cells followed by expression of the viral nucleocapsid protein indicating that SARS-CoV-2 may spread from infected to uninfected cells in the GI tract. Infection was not associated with marked macroscopic inflammation on endoscopy. However, numerous infiltrating plasma cells and lymphocytes with interstitial oedema were seen in a COVID-19 patients indicating mucosal immune cell activation. In addition to local enteric infection, viraemia following lung infection may occur in few patients (approximately 1%) and may lead to a secondary attack of SARS-CoV-2 on ACE2 target organs such as the kidney and the intestine.24-26

The COVID-19 receptor ACE2 is particularly highly expressed in intestinal epithelial cells from the terminal ileum and to a lesser extent in the colon, where mucosal inflammation in patients with IBD (Crohn’s disease - CD; Ulcerative Colitis - UC) is frequently detected. In this context, ACE may act as a co-receptor for nutrient uptake, in particular for amino acid resorption from food.25-27 Cytokines expressed in IBD, such as IFN-gamma, can potentially induce ACE2 expression by cytokine signalling events driving ACE2 promoter activity consistent with the idea that mucosal inflammation may increase expression of ACE2. Finally, the fusion of SARS-CoV2 with the host cell membrane is critical for uptake in cells and is modulated by the S protein. Activation of the S protein via proteolytic cleavage is controlled by host trypsin-like proteases, whose activity is upregulated in IBD, and this effect might facilitate infection in patients with IBD.28 Collectively, these findings suggested the possibility that patients with IBD might be particularly susceptible to COVID-19. However, there is no evidence so far that patients with IBD are highly susceptible to COVID-19.29 In contrast, a recent study from Wuhan studied 318 patients with IBD (204 UC and 114 CD) during the local outbreak of the disease and did not report any COVID-19 cases.30 The reasons for this observation are not entirely clear but might relate to the local adjustment of protective measures to prevent infection, the particular awareness of the IBD patient cohort to hygiene and infection prevention and the modulation of immunosuppressive therapy (eg, stop of treatment with immunomodulators and biologicals). Alternatively, patients with IBD might be less susceptible to COVID-19 and further studies in this regard are highly warranted.

Mesalazine (an anti-inflammatory drug) and mercaptopurine (a thiopurine) used in IBD therapy were identified as putative repurposable drugs for potential treatment of SARS-CoV-2 through genomics and proteomics analysis using bioinformatics tools. Indeed, studies have shown that thiopurines were able to inhibit in vitro the papain-like protease of SARS-CoV and Middle East respiratory syndrome coronavirus that represents an essential antiviral target essential in viral maturation and the antagonism of interferon stimulation.31,32 Additionally, another cohort study found that thiopurines were not associated with an increased risk of developing COVID-19.33 However, care must be taken in evaluating mesalazine as a potential drug for COVID-19 since clinical studies showed possible pulmonary toxicities associations.

**Thiopurine (azathioprine, 6-mercaptopurine) and JAKI3 inhibitor (tofacitinib) treatment can potentially reduce the number of activated T cells and affect T-cell activation and effector function. Although no data are currently available in this context, this might affect the course of COVID-19, as lymphopenia was associated with worse prognosis in this disease.**14 Moreover, tofacitinib has an increased risk for certain viral infections (eg, herpes zoster infection).34 Thus, treatment indication needs to be discussed in individual cases. At this point, no evidence for stopping these treatments in patients with remission exists. Similarly, there are no specific data available on MTX.35

Anti-TNF antibodies are frequently used for IBD therapy. As TNF inhibition may potentially affect antiviral immunity and has been shown to affect hepatitis B virus reactivation, TNF blockade could regulate the susceptibility to COVID-19. However, analyses of TNF levels in COVID-19 led to different results. One study showed no effect on TNF levels in severe COVID-19 cases in spite of the regulation of other proinflammatory cytokines.36 In contrast, another study reported that COVID-19 ICU patients had significantly higher serum levels of TNF than non-ICU patients.37 TNF may also exert pathogenic effects in COVID-19 by augmenting the expression of ACE2 or by augmenting lymphopenia through induction of direct leukocyte death via TNF/TNFRI signalling in T cells.38 These findings argue for a potentially protective effect of TNF inhibition in COVID-19 and further studies are needed to address this point.29

In summary, there is currently no evidence for an increased risk or aggravated outcomes in patients with IBD in the context of COVID-19. Other COVID-19 risks situation comprise older patients with IBD with comorbidities as well as patients suffering from malnutrition who may be at risk for infections and severe courses of the disease, respectively. Common drugs for COVID-19 treatment like hydroxychloroquine or remdesivir may increase the risks for drug-drug interactions with established IBD medications (potentially increased risk of combination therapy with hydroxychloroquine and adalimumab/infliximab for nerve damage). With regard to the effect of IBD on COVID-19, it should be pointed out that further studies are required in this highly dynamic situation. There is no evidence to suggest that patients with IBD should discontinue IBD-specific medications. However, older patients with IBD with comorbidities such as diabetes mellitus, obstructive lung disease, coronary heart disease and hypertension might have an increased risk for COVID-19 and further studies are urgently needed to address this point. In this context, there is an ongoing international programme initiated by the International Organization for the Study of IBD to register COVID-19 cases in patients with IBD in the context of COVID-19.
**COVID 19 and Endoscopy**

Health care workers (HCWs) are at increased risk for COVID-19 because upper GI endoscopy is a high-risk aerosol-generating procedure, and oral–fecoal transmission may be a potential route for COVID-19.

Recommendations have been changing rapidly and need to be updated, mainly because we are facing a scenario of sustained community transmission of COVID-19 worldwide. To conduct an overview of the recommendations for endoscopic procedures during the COVID-19 pandemic, a total of 21 of various national and international societies have elaborated specific recommendations for endoscopy during the COVID-19 pandemic. A total of 95% recommended temporarily postponing elective/nonurgent procedures; 86% recommended stratifying patients for risk of COVID-19 before the examination (questionnaire regarding symptoms and/or taking patient’s body temperature); 38% recommended reducing the number of people who accompany patients; 33% recommended requiring self-surveillance of signs and symptoms by HCWs; and 19% recommended contacting patients 14 days after the examination to check symptoms. All societies recommended the use of personal protective equipment (PPE) during the examination (gloves, mask, goggles or face shield, gown, and hairnet; double gloves and use of N95 or FF2P/3 masks were recommended in highly suspected or confirmed cases), and 43% recommended that the endoscopy team must be trained in wearing and removing PPE. There was not any mention of using preexposure or postexposure prophylaxis for HCW. All international societies recommended following a standardized reprocessing procedure for flexible endoscopes.

**Conclusion**

Pandemics always come up with various life-threatening issues. COVID-19 outbreak came up with the same health issues. Though respiratory manifestations always been considered majorly but gastrointestinal manifestation’s cannot be ignored and now it has also emerged as one of the important manifestations of COVID-19. The influence of COVID-19 on digestive system which can leads to various complications due to cytokine storm.

**References**

Primary Chondroblastic Osteogenic Sarcoma of the Rib in an Adult

Sweety Shinde¹, Srikant Balasubramaniam², Devendra Tyagi²

Abstract

Primary osteosarcoma of rib, especially in adults, is extremely rare in literature. We present an unusual case of a 24-year-old female with an osteolytic, infiltrative mass originating from the third rib. It showed mediastinal and paraspinal extension with consequent pleural effusion and compressive myelopathy. It was mistaken for neurofibroma and chondrosarcoma on imaging studies. Microscopy showed coexistent osteoid and chondroid elements consistent with chondroblastic osteogenic sarcoma. Thus, histomorphology remains the diagnostic gold standard.

Introduction

Primary osteogenic sarcoma (OS) shows a predilection for the metaphysis of long bones, while only 1-2% cases involve the flat bones of ribs. Pediatric population is affected more frequently than adults. We present a rare case of adult-onset chondroblastic osteogenic sarcoma of the rib presenting as unilateral pleural effusion and compressive myelopathy due to mediastinal and paraspinal infiltration respectively. Thus, unusual location, unusual age of onset and unusual clinical presentations should be borne in mind to prevent misdiagnosis.

Case History

A 24-year-old female presented with bilateral lower limb weakness for two months. She did not have fever, breathlessness or weight loss. She did not have any history of irradiation, Paget’s disease or chemotherapy. Her vital parameters were stable while complete hemogram, liver and renal function tests were within normal limits. Chest X-ray showed a calcified mass extending from left supraclavicular region to the posterior mediastinum with associated left sided pleural effusion. Magnetic Resonance Imaging (MRI) showed compressive myelopathy of T1-T5 region due to paraspinal expansion of the mass (Figures 1a and 1b). The MRI diagnosis was giant neurofibroma.

Computed Tomography (CT) of thorax showed a 10.7 cm x 10 cm x 9.5 cm, well-defined, lobulated, densely calcified mass arising from the posterior surface of the third rib. The mass was osteolytic and heterogeneously enhancing. The great vessels, lungs and abdominal organs were uninvolved by the tumor. The CT scan diagnosis was primary rib chondrosarcoma.

Partial resection of the tumor was done. Histomorphology showed an osteoid-forming malignant tumor coexistent with a prominent chondroid element, thus confirming chondroblastic osteogenic sarcoma (Figures 2 and 3). The patient was treated with adjuvant radiotherapy and chemotherapy. She is disease-free and asymptomatic for fourteen months after therapy.

Discussion

Primary osteogenic sarcoma (OS) shows a predilection for the metaphysis of long bones, these being the sites of greatest bone growth. Approximately 10% cases are situated in flat bones, especially of the pelvis while only 1-2% involve the thoracic bones such as ribs, sternum and clavicle. Osteogenic sarcoma of ribs is extremely rare. Children and adolescents are affected more frequently than adults. Rib OS can be clinically asymptomatic or may present as a thoracic mass with resultant dyspnea, as an exophytic mass of the chest wall, as an intrapulmonary mass or as hemorrhagic pleural effusion. In our patient, large size of the rib tumor along with mediastinal and paraspinal invasion resulted in unilateral pleural effusion along with compressive myelopathy.

CT scan is useful to identify the location, origin, component and extent of osteoid-forming tumors while MRI is useful to evaluate extension into

![Fig. 1: Magnetic resonance imaging shows a 11.5 x 10.5 x 10 cm paravertebral mass (arrows). It is heterogeneously hyperintense on T2 weighted images. There is intratumoral necrosis and cystic degeneration. (1a) Mass is causing compressive myelopathy of T1-T5 spine with vertebral erosion. (1b) The mass was isointense on T1 weighted images](image-url)
pleural osteosarcoma, metastatic tumor masses of the rib can be chondrosarcoma, variants.
Osteosarcoma can have osteoblastic, and for chondrosarcoma on CT scan.
Heads for neurofibroma on MRI
appearance, Codman’s triangle and periosteal reactions such as sunburst
OS is more likely to show aggressive within the bone
formation 25% cases each.
Morphological variants of OS as per their matrix production include osteoblastic OS in 50% cases while chondroblastic OS and fibroblastic OS form 25% cases each. Chondroblastic OS shows spindled or epithelioid tumor cells along with chondroid lobules and osteoid matrix. In addition, surface OS like periosteal OS and parosteal OS can show chondroid elements. The chondroid element raises the differential diagnosis of chondroasarcoma. The latter affects adults with a mean age of 56.7 years while that of chondroblastic OS is 24.7 years in appendicular skeleton. Chondrosarcoma is morphologically characterized by absence of osteoid matrix, presence of chondroid lobules and tumor cells within lacunae. The osteoid matrix is echoed on radiology as fluffy, cloudy opacity while chondroid matrix as stippled calcification. Our case showed classic chondroblastic differentiation coexisting with osteoid matrix on microscopy, thus consistent with chondroblastic OS.

Treatment of rib OS requires wide resection with adjuvant chemotherapy or radiotherapy. Disease free survival of rib OS ranges from 6 to 52 months. Invasion of rib OS into intercostal vessels can cause a fatal hemorrhagic shock. Our patient was treated with subtotal resection and neoadjuvant radiotherapy and chemotherapy. Till date, she did not show recurrence or metastases for fourteen months after therapy.

**Conclusion**

Location within the rib, symptoms of pleural effusion with compressive myelopathy and adult onset disease are extremely rare features for a primary chondroblastic OS. Histomorphological evidence of osteoid and chondroid matrix formation by tumor cells is the diagnostic gold standard, since radiology poses many diagnostic challenges. Wide excision with adjuvant chemotherapy and radiotherapy is recommended for rib OS.

**References**

The word injection is derived from Latin- *injecere*, which means- to throw in, to inject.

Injectable medication was not possible without a syringe device. Syringe Latin-*syrinx*-(a tube) was invented long before the needle. Earliest man made contraption resembling a syringe is referred to in Hippocratic writings; as a tube with a pig’s bladder attached to it. Anatomists like Eustachius, Malpighi, and Swammerdam attempted to preserve cadavers and outline blood vessel by injecting coloured fluids for demonstrating and teaching purpose.

Christopher Wren (1632–1723) and Robert Boyle, used trocars and animal bladders for intravenous injections in dogs. French physicians were forcing morphine paste down grooved trocars to treat neuralgia, but they could hardly be called syringes.

Francis Rynd (1803–61) of Dublin made subcutaneous injections, also for neuralgia in 1845 using the “syringe’ with a slender trocar and cannula”, it was inserted subcutaneously and the trocar retracted by means of a spring. Narcotic liquid descended from the hollow handle into the puncture site as the instrument was withdrawn. Rynd could be called the inventor as his device was patented in the Irish patents office (1852).

Charles Pravaz (1791-1853) of Lyon had almost simultaneously constructed a metal syringe with a hollow needle, which he used to inject aneurisms and reported the result of his method in 1853.

Credit for proper hypodermic glass syringe appears to belong to Alexander Wood (1817-1884), a Scottish practicing physician from Edinburg, who used an instrument similar to Pravaz syringe to inject a narcotic in a case of neuralgia (1853), and published findings in the Edinburg Medical & Surgical Journal (1855). Ironically, Wood’s wife got addicted to morphine injections when she used her husband’s instrument and died due to overdose.

Over the following century, the technology was refined and intravenous injections became commonplace. Initially syringes were of metal with; hollow pointed needle made of steel with hard rubber “slide” hub., Becton and Dickinson formed BD Company in 1897 and imported all glass syringes from Wulfing Luer of Paris. The first syringe was specially made for insulin injections by BD (1925). Yale luer-lock syringes were introduced in 1925. They provided a simple and secure method for attaching and removing the syringe.

Two decades later, improper sterilization started to plague clinical practice. Finally Australian inventor Charles Rothauser created the world’s first disposable hypodermic syringe made of polypropylene, which took care of sterilization issues in re-used glass syringes.
An Unusual Case of Severe Pneumocystis Jiroveci Pneumonia (PJP) presenting as “Recurrent Cytokine Storm” following COVID-19 Infection

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Sir,

There is a health emergency going on in the world with COVID-19 pandemic surging at great pace leading to rise in mortality of the aged and vulnerable patients all over the world. Reason for these deaths is suspected to be due to Cytokine storm (“Cytokine storm syndrome”). “Cytokine storm” is defined as an activation cascade of auto-amplifying cytokine production due to unregulated host immune response to the viral antigen. Usually it is noticed in the second week of COVID-19 disease.

But the incidence of “Recurrent cytokine storm” presenting weeks after the first episode is not known. In this correspondence, we wish to highlight such phenomenon observed in a patient who had survived the first episode of storm weeks before.

This is a case of 75 yr old Doctor known diabetic and hypertensive who is diagnosed as having COVID-19 based upon HRCT scan, which revealed CORADS-4 but, RT-PCR negative and clinically asymptomatic except for mild hypoxemia on pulse oximeter. Treated as per COVID 19 protocol. Saturation improved gradually. Ten days later, cytokine storm was diagnosed based upon gradual fall in the saturation along with the supporting biochemical and radiological data (Figure 1). Pulse dose steroid therapy started with Inj. Methyl prednisolone 500 mg OD for 4 days along with broad spectrum antibiotic cover. Theuraptic dose of SEPSIVAC vaccine was administered Later after two weeks of hospital stay including 1 week of ICU stay, patient was discharged on oral anticoagulants, oral steroids and oral antibiotics.

Since then he was on tapering dose of steroid from Methyl prednisolone 32 mg to 2mg over a month. Every week inflammatory panel was being done which was normal. A HRCT scan done as a part of regular followup which revealed 25 – 30% fibrosis along with GGOs (Ground glass opacities) (Figure 2). Within 48-72 hrs of withholding the steroid patient had noticed fall in saturation on exertion, followed by fall in resting saturation levels along with breathlessness. Routine blood investigations done along with inflammatory panel. Urine culture revealed multi drug resistant E.coli and blood culture turned out to be sterile. Treated with broad spectrum antibiotics along with coverage for PJP Pneumonia in view of long term steroid usage. Biochemical markers and clinical status were worsened over the next 48 hrs. (Table 1).

Differential diagnoses at this stage were thought to be:
1. Acute pyelonephritis with ARDS
2. Severe PJP pneumonia in view of long term steroid usage
3. Community aquired pneumonia
4. Acute pulmonary thromboembolism
5. Recurrent Cytokine storm

Acute pyelonephritis was ruled out with CT KUB. 2D ECHO was normal. But HRCT chest revealed progression of ground glass opacities compared to previous scan.

Differential diagnoses at this point being:
1. COVID 19 reinfection
2. Delayed cytokine storm
3. Severe PJP pneumonia

PCR for COVID 19 & other respiratory viruses was done which is negative. Serum Beta -D-Glucan was sent in suspicion of PJP pneumonia. Inj. Trimethoprim/Sulfamethaxazole 15 mg / kg, Inj. Fluconazole along with broad

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**Table 1: Timeline of parameters**

<table>
<thead>
<tr>
<th>Week</th>
<th>Steroid Dose (mg/day)</th>
<th>TLC (mm³)</th>
<th>IL-6 (pg/ml)</th>
<th>CRP (mg/L)</th>
<th>D-dimer (ng/ml)</th>
<th>Ferritin (ng/ml)</th>
<th>LDH (U/L)</th>
<th>Resting Saturation</th>
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<td>1</td>
<td>32</td>
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<td>4</td>
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<tr>
<td>5</td>
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<td>4</td>
<td>200</td>
<td>86</td>
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<td>97%</td>
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<tr>
<td>6 (Day 1)</td>
<td>0</td>
<td>13,000</td>
<td>160</td>
<td>300</td>
<td>94%</td>
<td>88%</td>
<td>93%</td>
<td>78%</td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td>0</td>
<td>13,000</td>
<td>168</td>
<td></td>
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<tr>
<td>Day 3</td>
<td>0</td>
<td>13,000</td>
<td>47</td>
<td>230</td>
<td>3000</td>
<td>194</td>
<td>91%</td>
<td>68%</td>
<td></td>
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<tr>
<td>Day 4</td>
<td>500</td>
<td>13,000</td>
<td></td>
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<td></td>
<td></td>
<td>93%</td>
<td>75%</td>
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<tr>
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<td>500</td>
<td>13,000</td>
<td>150</td>
<td>150</td>
<td>94%</td>
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<td>Day 7</td>
<td>250</td>
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<td>Day 8</td>
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<td>10,000</td>
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<td>Day 9</td>
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</table>
spectrum antibiotic cover administered. Pulse dose steroid of 500 mg given for 3 days along with regular standard of care. Meanwhile serum Beta –D-Glucan level was obtained which is 678 pg/ml (normal being < 70 pg/ml). False positive possibilities are ruled out. Gradually patient dyspnoea resolved and resting saturation improved from 91% to 96 % on room air.

There are multiple reports on secondary fungal infections like Mucormycosis, Invasive Candidiasis following COVID 19 infection.1,2 These infections are likely to be diagnosed relatively easier than PJP pneumonia based upon history, clinical examination, imaging and biomarkers. But the challenges in diagnosing PJP pneumonia are,

1. Rarely seen in Non-HIV patients who are not on long term immunosuppressive agents
2. HRCT chest findings will be similar to that of Cytokine storm
3. Bronchoalveolar lavage to demonstrate PJP cysts may not be feasible in view of ongoing pandemic and also yield is going to be low in Non-HIV patients
4. Quantitative PCR might be helpful but cutoff values for infection vs colonization are not defined
5. Induced sputum is having less yield in Non – HIV patients
6. The clinical presentation, imaging and biomarker levels of severe PJP pneumonia will be similar to that of a cytokine storm. The only helpful differentiating biomarker being Serum Beta –D-Glucan level.

In our case, the diagnosis of PJP pneumonia is based upon the following points,
1. Chronic steroid use of more than 20mg Prednisone/day for more than 4weeks following COVID 19 infection
2. Persistence of GGOs on HRCT scan beyond 8 weeks
3. Serum Beta –D-Glucan level of 678pg/ml
4. Resting PaO₂ on room air being 58mmHg

As the patient recovered, Inj. Trimethoprim / Sulfamethaxazole was changed to oral form and discharged. Ten days later repeat Serum Beta –D-Glucan level is found to be 98 pg/ml. Similar experience has been reported from various authors.3-5

The take home message from our experience is, for patients in whom GGOs are persisting beyond 6 weeks on HRCT scan, differential diagnosis of PJP pneumonia need to be considered and evaluated to prevent the hazardous consequence.

References

A Prospective Analysis of PTSD Development in Admitted COVID-19 Patients in Indian Scenario
Prakhar Gupta1, Arshi Ishteyaq2, Shahwar Khan3, Mehak Singh2
1Assistant Professor, Junior Resident, Dept. of General Medicine, 2Assistant Professor, Dept. of Dermatology, LN Medical College, Bhopal, Madhya Pradesh

Sir,

Posttraumatic stress disorder (PTSD) is a common mental disorder caused by major psychological trauma. It could result in serious distress and disability. Survivors of infectious epideimic are known to develop PTSD which may persist for a long period.1 In the current scenario of COVID-19 pandemic,2 there’s a huge burden on health care to manage the large number of patients. Apart from medical care, there’s a need for attention to early intervention and prevention of PTSD among COVID-19 survivors.

We conducted a prospective observational analysis among admitted COVID-19 patients in a dedicated COVID-19 tertiary care centre over a period of one month. They were followed up after 14 to 30 days of discharge, either telephonically or follow-up OPD visits, to evaluate development of PTSD symptoms. We used the PTSD Checklist for DSM-5 (PCL-5) (Supplement) to determine the presence or absence of PTSD symptoms and categorized them into minimal impact (score 0-10), low to moderate impact (11-30), moderate to high impact (31-50) and high to severe impact (51-80). Patients were also categorized based on the severity of their covid-19 illness as mild, moderate and severe based on minute of health and family welfare protocols.4 A total of 320 patients were followed up, out of which 200 patients completed the questionnaire and were included in the study. The results were analyzed to determine severity of impact of the illness as well as to correlate severity of covid-19 disease and severity of PTSD symptoms.

Out of 200, 139 patients were male, 61 patients were female. No significant difference was found between the two genders (mean PTSD score for both was 25) and no significant correlation was found between age and severity on impact of event scale (Pearson correlation coefficient 0.08).

Out of 200 patients, 74 were mild cases, 97 were moderate and 29 were of severe category. The average scores in each category were 21, 24, 40 respectively and medians were 21, 22 and 42 respectively (Table). 41% (n=82) patients showed moderate to severe impact on follow-up. Significant correlation was found between increasing severity of

<table>
<thead>
<tr>
<th>Covid Category</th>
<th>Minimal impact (0-10)</th>
<th>Low to moderate impact (11-30)</th>
<th>Moderate to high impact (31-50)</th>
<th>High to severe impact (51-80)</th>
<th>Range</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>4</td>
<td>65</td>
<td>5</td>
<td>0</td>
<td>9 to 45</td>
<td>21</td>
</tr>
<tr>
<td>Moderate</td>
<td>0</td>
<td>74</td>
<td>23</td>
<td>0</td>
<td>14 to 42</td>
<td>22</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>3</td>
<td>24</td>
<td>2</td>
<td>14 to 55</td>
<td>42</td>
</tr>
</tbody>
</table>

Comparison (for developing moderate to severe PTSD) | Relative Risk | p-value | 95% CI |
<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-severe vs Severe</td>
<td>5.4754</td>
<td>&lt;0.0001</td>
<td>3.8178 to 7.8526</td>
</tr>
<tr>
<td>Mild vs Moderate</td>
<td>3.5093</td>
<td>0.0074</td>
<td>1.4005 to 8.7935</td>
</tr>
<tr>
<td>Mild vs Severe</td>
<td>13.269</td>
<td>&lt;0.0001</td>
<td>1.4462 to 9.0679</td>
</tr>
<tr>
<td>Moderate vs Severe</td>
<td>3.7811</td>
<td>&lt;0.0001</td>
<td>2.5915 to 5.5167</td>
</tr>
</tbody>
</table>
Human to Animal Transmission of COVID-19: A Two-Way Road

Prerna Garg1, Umang Arora3, Shreya Garg2, Manish Soneja3

1 Junior Resident, Department of Medicine, 2 Junior Resident, Department of ENT, 3 Additional Professor, Department of Medicine, All India Institute of Medical Sciences, Delhi

Sir,

The origin of the novel Coronavirus, the SARS-CoV-2, that resulted in the ongoing COVID-19 pandemic with over eleven million confirmed cases as of July 2020 has been traced to the Huanan Seafood Wholesale Market in Wuhan, China. Genomic evolutionary analysis suggests that homologous recombination may have occurred between a bat coronavirus and an origin-unknown coronavirus within the viral spike glycoprotein gene.1 A similar CoV with an 85–92% nucleotide homology with the SARS-CoV-2 has been detected in Pangolins (Scaly anteaters) during the surveillance of the wild animals sold at the market.2 However, the sequence divergence between the two makes it unlikely that this virus was the direct source of the SARS-CoV-2, which remains unknown to date.

Recently, several tigers in the Bronx Zoo of New York, one of the largest foci of the pandemic, have been infected by the SARS-CoV-2. They were housed in the same area, so it is unclear if they each got infected by a single human source, or if this was an incidence of active animal-to-animal spread. In

References


Table 1: Supplement (PCL-5 questionnaire)

<table>
<thead>
<tr>
<th>Event Scale</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Moderately</th>
<th>Quite a bit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Repeated disturbing, and unwanted memories of the stressful experience?</td>
<td>[ ]</td>
<td>[ ]</td>
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<tr>
<td>2. Repeated, disturbing dreams of the stressful experience?</td>
<td>[ ]</td>
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<tr>
<td>3. Suddenly feeling or acting as if the stressful experience were actually happening again (as if you were actually back there reliving it)?</td>
<td>[ ]</td>
<td>[ ]</td>
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<tr>
<td>4. Feeling very upset when something reminded you of the stressful experience?</td>
<td>[ ]</td>
<td>[ ]</td>
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<tr>
<td>5. Having strong physical reactions when something reminded you of the stressful experience (for example, heart pounding, trouble breathing, sweating)?</td>
<td>[ ]</td>
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<tr>
<td>6. Avoiding memories, thoughts, or feelings related to the stressful experience?</td>
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<tr>
<td>7. Avoiding external reminders of the stressful experience (for example, people, places, conversations, activities, objects, or situations)?</td>
<td>[ ]</td>
<td>[ ]</td>
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<tr>
<td>8. Trouble remembering important parts of the stressful experience?</td>
<td>[ ]</td>
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<tr>
<td>9. Having strong negative beliefs about yourself, other people, or the world (for example, having thoughts such as: I am bad, there is something seriously wrong with me, no one can be trusted, the world is completely dangerous)?</td>
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<td>[ ]</td>
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<tr>
<td>10. Blaming yourself or someone else for the stressful experience or what happened after it?</td>
<td>[ ]</td>
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<tr>
<td>11. Having strong negative feelings such as fear, horror, anger, guilt, or shame?</td>
<td>[ ]</td>
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<tr>
<td>12. Loss of interest in activities that you used to enjoy?</td>
<td>[ ]</td>
<td>[ ]</td>
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<td>[ ]</td>
</tr>
<tr>
<td>13. Feeling distant or cut off from other people?</td>
<td>[ ]</td>
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<tr>
<td>14. Trouble experiencing positive feelings (for example, being unable to feel happiness or have loving feelings for people close to you)?</td>
<td>[ ]</td>
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</tr>
<tr>
<td>15. Irritable behavior, angry outbursts, or acting aggressively?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
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<tr>
<td>16. Taking too many risks or doing things that could cause you harm?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
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<tr>
<td>17. Being “superalert” or watchful or on guard?</td>
<td>[ ]</td>
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<tr>
<td>18. Feeling jumpy or easily startled?</td>
<td>[ ]</td>
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<tr>
<td>19. Having difficulty concentrating?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
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<tr>
<td>20. Trouble falling or staying asleep?</td>
<td>[ ]</td>
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</tr>
</tbody>
</table>

ROC curve analysis between covid-19 categories (mild, moderate, severe) and severity on Impact Event Scale. Area Under Curve 0.94.

Fig.: ROC Curve

The COVID-19 pandemic has posed a significant challenge to mental health services. The prevalence of mental health disorders, particularly anxiety and depression, has increased among the general population and healthcare workers. The high demand for mental healthcare services during the pandemic has highlighted the need for effective strategies to manage mental health challenges.

Human-to-animal transmission of COVID-19 is a worrying concern, and it is essential to understand the factors that contribute to this transmission. The research on animal-to-human transmission has shown that certain species are more susceptible to COVID-19 infection, and understanding these factors can help in developing strategies to prevent further transmission.

Table 1: Summary of the Prevalence of Mental Health Disorders during the COVID-19 Pandemic

<table>
<thead>
<tr>
<th>Mental Health Disorder</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>20%</td>
</tr>
<tr>
<td>Depression</td>
<td>15%</td>
</tr>
<tr>
<td>Post-Traumatic Stress</td>
<td>12%</td>
</tr>
<tr>
<td>Obsessive-Compulsive</td>
<td>8%</td>
</tr>
</tbody>
</table>

The prevalence of mental health disorders has been estimated based on various studies conducted during the COVID-19 pandemic. These findings highlight the need for effective mental healthcare services and support systems during pandemics.

Conclusion

The COVID-19 pandemic has had a significant impact on mental health services. The high demand for mental health services and the prevalence of mental health disorders during the pandemic highlight the need for effective strategies to manage mental health challenges. Understanding the factors that contribute to human-to-animal transmission of COVID-19 is crucial in developing strategies to prevent further transmission.

References

another instance, a pet dog had been infected in Hong Kong. However, no serological response was seen, and viral culture was negative. This indicates that the dog could be contagious over many weeks without effectively clearing the virus. Goumenou et al. hypothesize that dogs may act as intermediate hosts for the virus. They further propose that dogs may have played a role in the exponential rate of infection in Northern Italy. Their findings are bolstered by the existing knowledge that the virus can infect the cells of many other mammals, including Chinese horseshoe bats, civets, and pigs in in-vitro studies.

A similar picture was seen in the SARS outbreak of 2003-05, which was traced back to masked palm civets. The infected civets were asymptomatic, despite high viral loads, consequently behaving as amplifier hosts for the virus. The near-complete homology of the civet CoV with the SARS-CoV (~99·6%) indicated that they were unlikely to be the natural hosts, later determined to be the horseshoe bats. Animal testing in other species revealed the presence of the virus in various other mammals such as raccoon dogs, red foxes, wild boars, pigs, cats, and rats. Infected chickens showed the presence of viral RNA but did not mount an antibody response. No viruses could be cultured from them. This is similar to the COVID-19 infection reported in the dog in Hong Kong. Furthermore, it was seen that experimentally infected cats and ferrets could transmit the virus to other wild animals housed with them. This might potentially provide a clue to the SARS-CoV-2 outbreak in tigers at the Bronx Zoo by indicating the possibility of animal-to-animal propagation. In addition, for another related virus, the MERS-CoV, Dromedary camels, Alpacas, and Llamas act as amplifier hosts.

The current understanding of the epidemiology of COVID-19 in animals is limited. The susceptibility, route of infection and infectivity of animals is unknown. With the nations facing a critical shortage in manufacturing and import of diagnostic tests, the capacity for ecological surveys in animals is limited. It is probable that some animals may behave as asymptomatic carriers, super-spreaders, natural reservoirs, or may suffer from symptomatic disease. Isolation of such hosts could be fundamental in curtailing the spread of the disease.

In such a situation, surveillance of pets using pooled samples from hotspots should be considered. Monitoring contacts of infected animals and genomic analysis for sequence homology between humans and animals could shed light on the direction of spread. Cautionary practices could be instated to limit animal-human contact for pet-owners, herders, zoos, and wildlife sanctuaries. Removal of pangolins and civets in particular from markets, and potentially even closing down the wet markets would prevent further zoonotic spread. In the long term, reduction of human invasion of wildlife ecological niches will be vital in reducing the emergence of new zoonotic infections. The development of an animal vaccine for reservoir hosts could prove to be instrumental in curbing infections, as was attempted with camels during the MERS outbreak.

In conclusion, the bilateral transmission of COVID-19 between humans and animals poses significant risk and needs to be interrupted to limit the spread of this deadly pandemic.

Contributions of Authors

Dr. Prema Garg: Literature search, Data Interpretation, Writing; Dr. Umang Arora: Data Interpretation, Writing; Dr. Shreya Garg: Literature search, Data Interpretation; Dr. Manish Soneja: Data Interpretation.

References


COVID-19 Crisis—Are Administrative Issues Upsurging Health Concerns

Vishak Acharya1, Unnikrishnan B1

1Professor, Kasturba Medical College, Mangalore, MAHE, Manipal, Karnataka

Sir,

A large part of disease burden with COVID is handled by containment strategies technically, an administrative exercise of mammoth proportions. Lately in many countries, this pandemic struggle is turning to be an administrative quagmire slowly veering the disease out of control.

Till recently administrative issues pertaining to health were within a set and clearly defined framework and was managed as per a structured protocol. This pandemic waves have led to breakdown of most organized health care systems. The boundaries that defined health, administration, policies, and practices have been blurred by chaos that has been unleashed.

India as a prototype, is easier to understand the gravity of this thorny issue. In India health is a state subject but crucial aspects of policy drafting vests with the center. India did fairly well in the first 10 weeks when the national lockdown was imposed, in identifying, reshoring, resource creation and controlling death and recovery rates. However, since the national lockdowns were relaxed and the onus of implementation was passed to the states. This transition came when India was experiencing its deadliest surge.

Needless to say health is best managed when in the hands of health administrators. In the setting of pandemic all major decisions were taken by civil servants (who are political appointees), bureaucrats, health officials with verifiable credentials and vetoed by politicians.

Quarantine measures imposed, were scaled down at alarming regularity ranging from needlessly stringent to lax. The concerns being, the high-handedness, inconsistencies and irrationality in policy implementation without justification or scientific
An area for improvisation projected was to develop infrastructure to reduce the burden on health care by large numbered mildly symptomatic COVID patients. Mismatches in planning and implementation led to unnecessary hospitalization of asymptomatic cases for long periods stretching healthcare resources.

Bed shortages were addressed myopically by creating temporary care facilities in stadiums and auditoriums even as 30-40% of beds lay unoccupied in major hospitals. The shortages, mainly in high dependency unit’s beds still persists. Disparity in rapid resource allocation, lack of coordinated policies on patient triaging, administrative gaffes and inaction led to avoidable treatment delays and higher mortality.

Added reason for alarm was due to interstate disparity in terms of emergency readiness, resilience capabilities, political differences, center-state incoordination coupled with lack of homogeneity and policy thrust of policies between different states adding to the confusion.

Peculiar to pandemic has been lack of precedence and dearth of quality evidence backed data on measures like lockdowns, quarantines, home care versus institutional care and many other contentious questions. The arbitrariness, lack of hindsight wisdom in handling these delicate issues have mired the decision making process. To usher in much needed uniformity, accountability, scientific credence and administrative justification it is imperative we bring in a draft policy on lockdown and travel restrictions. The broad guidelines should be formed by a broad expert committee panel of epidemiologists, health administrators, physicians, politicians and bureaucrats. The broad guidelines should be formed by a broad expert committee panel of epidemiologists, health administrators, physicians, politicians and bureaucrats. This model can work only by strong administrative and community participation.

Surveillance cells are already in place in most places, but they have been hastily constituted and lack in framework, modelling and intent.

There is a need for constituting and reinforcing a central task force with uniform representation from various concerned sectors by eminent panels to oversee and direct the functioning of each independent unit. A government response stringency index is already in place internationally wherein policies of countries across the globe are compared. This should be reinforced for better international co-ordination and similar models can be implemented at state level too for comparison of different state government policies. This should ensure the best practices being pursued with accountability driven by trust, consistency, innovations and credibility in policy making with an in-built mechanism for redressal and reviews.

In rising to the challenge posed by this pandemic it’s critical for us to realize the pivot of administrative arm in this health battle. It also is imperative that we formulate a structured administrative set-up backed by health, scientific and civil credentials for rationale, decisive and objective decision making.

References


Novel Diuretic Effect of SGLT-2 Inhibitors: A Possible Option to Relieve CCB-induced Pedal Edema?

Prakash Hazra1, Jignesh Ved2, Mansij Biswas3

1Interventional Cardiologist, Head of Department of Cardiology, AMRI Hospitals, Dhakuria, Kolkata, West Bengal; 2Team Lead, Medicine, Senior Medical Advisor, Boehringer Ingelheim India, Mumbai, Maharashtra

Sir,

We read, with keen interest, the analysis by Hallom KM and colleagues on the uniqueness of SGLT2-i mediated diuretic action. Through greater free-water clearance, these agents could exert a more specific effect on the interstitial fluid volume rather than the blood volume, thus possibly contributing to certain warranted clinical effects, and lesser hemodynamic compromise. In this regard, we could hypothesize the effect of SGLT2-i agents, on the pedal edema induced by calcium channel blockers (CCBs). Pedal edema is a well-recognized adverse reaction of the CCBs. Due to the preferential dilatation of arterioles in comparison to venules, the resultant increase in capillary hydrostatic pressure causes extravasation of the fluid into the interstitial compartment. Absolute incidence of this side effect is not exactly determined because of widely varying reported rates, which may arise from differences in the surveillance technique. Active surveillance studies documented one fourth of patients who received amiodipine 10 mg per day may experience oedema. Use of a diuretic agent may not help in managing the pedal edema, as the diuretic agents have a predominant effect on reducing blood volume, as compared to the interstitial fluid volume. However, a private insurance database-based study from the US found an excessive use of loop diuretics following initiation of high dose CCBs, not explained by regular clinical practice or hypertension progression, thus raising concerns of unnecessary prescribing cascade. The SGLT2-i agents, on the other hand, may help in addressing a CCB-induced pedal edema, through a predominant effect on the interstitial fluid volume. In this context, we report here a case of amiodipine induced...
pedal edema, which was considerably resolved following the administration of empagliflozin.

A 62-year old male patient had a prior history of hypertension, type-2 diabetes, and coronary artery bypass grafting. He was managed with metformin (1gm twice daily), glimepiride (4mg once daily), amlodipine (10mg once daily), hydrochlorothiazide (12.5mg once daily), telmisartan (80mg once daily) and rosuvastatin (20mg once daily). He had developed amlodipine-associated pedal-edema. One year later, the patient presented with severe hyponatremia and hypokalemia, for which he was hospitalized and managed with hypertonic saline, as well as potassium replacement. At discharge, he was reinstalled on amlodipine, telmisartan, rosuvastatin and metformin, at pre-event dosing regimen. Hydrochlorothiazide and glimepiride were discontinued, and replaced with metoprolol (50mg once daily) and empagliflozin (25mg once daily). The patient had persistent complaints of bilateral pedal edema in the morning, with tightening of shoes. Over the subsequent 2 months of therapy, the edema had decreased to a considerable extent; however, mild edema did persist. The patient also reported weight loss and good control of blood glucose and blood pressure.

In a patient ineligible for diuretic therapy or when use of it is inappropriate, and he is suffering from amlodipine-induced pedal edema despite receiving a high dose of angiotensin-receptor blocker, addition of empagliflozin resulted in a considerable resolution of pedal edema, apart from its known effects on cardio-metabolic outcomes. Although merely a case report, this may serve as a clinical proof of principle, for the unique diuretic mechanism of the SGLT2-i agents as described by Hallow et al. This observation, with further exploration on these lines, can have promising clinical implications for patients with comorbid hypertension as well as type-2 diabetes, who are appropriate candidates for receiving a CCB and an SGLT2-i agent.

References

Structure of COVID-19 Isolation Wards and the Use of Inpatient Telemedicine in a Corporate Hospital in Urban India

Indira Kedilaya
Consultant Physician, Columbia Asia Hospital, Whitefield, Bangalore, Karnataka
Sir,

Background
The first case of COVID-19 in India was reported on January 30, 2020 and the first in the state of Karnataka on March 9, 2020. For most healthcare providers, the COVID-19 pandemic is their first real pandemic experience. The 2009 H1N1 and SARS-1 pandemics were much less widespread than the current COVID-19 pandemic, and therefore had a less significant impact on the functioning of hospitals. In contrast, the COVID-19 pandemic has had many ramifications on hospital organization. Planning and apt utilization of resources has been and will continue to be crucial in mitigating these consequences.

Introduction
A pandemic such as COVID-19 necessitates drastic changes in hospital functioning and structure. During the peak of the pandemic, non-urgent outpatient visits and surgeries were put on hold in most countries to accommodate sick COVID patients. The rules and admission criteria during the pandemic have been vastly different in each country based on its needs and resources. In India, each state has its own guidelines, which have evolved constantly in accordance with government recommendations and the healthcare system has adapted very quickly to these changes. Telemedicine in India has been used informally for a long time following the country’s digital transformation. However, in March 2020, it was formalized by the Indian government and a framework was created for its use. Telemedicine was quickly embraced in India in the outpatient setting, however, is not being used as a primary mode of rounds in the COVID isolation wards in India. On a published review, there was only one other instance of telemedicine used in the COVID isolation wards. Stanford Health implemented inpatient telemedicine in 3 of their affiliated hospitals in March, 2020 and concluded that this is a feasible option. The following is another example of successful implementation of telemedicine in the inpatient setting.

Columbia Asia is a chain of corporate hospitals in India. The Columbia Asia Hospital in Whitefield, Bengaluru (CAHW), is a 143-bed hospital. The Internal Medicine (IM) department (which has 5 full-time and 2 part-time consultants) and the pulmonary department (which has one pulmonologist) are primarily responsible for the care of COVID-19 patients (except the ones admitted to the ICU).

Structure of COVID Isolation Wards

In the state of Karnataka, during the initial few weeks of the pandemic, all positive cases irrespective of severity or symptoms were admitted. In addition, most hospitals have also had to incorporate an exclusive fever clinic to separate suspected COVID-19 patients from other patients. The medicine and pulmonary departments initially managed the IM outpatient department (OPD), pulmonary clinic, fever clinic, and isolation/non-isolation wards. Increasing admissions in the isolation wards created a significant increase in work-load and consultants in IM and pulmonary departments started using telemedicine as the primary mode to conduct rounds in COVID isolation wards. Since then, patients admitted to the COVID isolation wards have been divided amongst 7 Internal Medicine consultants and 1 pulmonologist,
who are responsible for the complete care of COVID patients throughout the hospital stay (excluding ICU stay). Consultants in other medical specialties and junior doctors assist in conducting physical rounds in the COVID isolation wards every day on a rotating schedule. On average, each doctor conducts 2 isolation duties per month in which they obtain patient history, perform pertinent physical examination, order diagnostics and medications in coordination with the assigned doctor doing telemedicine rounds. The assigned telemedicine doctor also apprises family members of patients’ condition in the isolation wards on a daily basis and provides post-hospital care to patients in the respective OPDs. This arrangement has greatly enhanced patient and physician satisfaction and has provided good continuity of care.

Platforms of Telemedicine Used

The primary modality of contact is telephone consultation. Video consultation is also used when necessary, using platforms such as Microsoft Teams and WhatsApp. Other referral consultants also use telemedicine to manage coexisting medical conditions in the COVID isolation wards when required. The COVID isolation wards are equipped with tablets and smartphones to perform video consultations with patients and with other healthcare providers to coordinate care. Patients also use email and WhatsApp to share relevant past medical history, medications and diagnostics with the consultants.

Structure of ICU During the Pandemic

The ICU in CAHW has 2 consultants and 5 junior doctors. The ICU team is also assisted by the department of anesthesia to a limited extent. The ICU is divided into 3 pods, namely COVID, COVID-suspect and non-COVID. The ICU always has at least 2 doctors available, one of which is dedicated to the COVID pod. All patient monitors in the COVID pod are connected to central monitors, placed in the non-COVID pod for additional supervision.

Conclusion

With its first admission in June 2020, CAHW has admitted 1131 COVID-19 cases as of January 24th 2021, of which there have been 26 reported deaths. On the 10th and 12th of October 2020, the highest occupancy in the isolation wards was reported, with 80 patients on both these days. On the 16th of September, the highest occupancy in the COVID-ICU was reported, at 11 patients. I believe these numbers validate that inpatient telemedicine is an effective strategy during these trying times. The unique restructuring of ward rounds has enabled physicians in our hospital to provide optimal care to patients in the COVID isolation wards while keeping physician burnout low. The COVID-19 pandemic will have a protracted course and we need a sustainable plan. Being a small hospital, our constraints are many, but we have been able to overcome manpower shortage with this strategy and the satisfaction that it has given the doctors has been immense. This is a potential model for other hospitals to follow during the pandemic and perhaps for hospital medicine in rural areas during non-COVID times as well. Telemedicine has been a boon to outpatient medicine during the pandemic, but can be successfully implemented in the inpatient sector as demonstrated in our hospital. “The doctor is just a phone call away”.

References


The Case for Tocilizumab

Yojana Gokhale
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Sir,

I am delighted at the authors’ interest in my Editorial, ‘Tocilizumab or no Tocilizumab: To be or not to be. In the editorial, I have outlined the shortcomings in 5 published RCTs such as inclusion of mild COVID ARDS, insufficient sample size, mortality significantly lower than hospitalized patients’ mortality in respective countries. This implies inclusion of mild ARDS cases in these trials. There have been numerous observational studies, which have included moderately severe cases and these have reported Tocilizumab to be beneficial. I have concluded in my editorial the need to wait for results of REMAP-CAP and RECOVERY trials, which have included large number of (4871) moderately severe patients.

As of April, results of these two large, independent, multi-center RCTs on Tocilizumab are available and have shown favourable outcomes with use of Tocilizumab, (RR 0.71, 95% CI 0.52-0.96) in REMAP-CAP and (RR 0.86, 95% CI 0.77 – 0.96) in RECOVERY trial. Quoting the RECOVERY Trial, “In patients hospitalized with severe COVID, treatment with tocilizumab reduces mortality, increases the chances of successful hospital discharge, and reduces the chances of requiring invasive mechanical ventilation. These benefits are additional to those previously reported for dexamethasone. These findings require an update to clinical guidelines”. Tocilizumab is included in NICE guidelines for treatment of hospitalized severe COVID patients.

TOCIBRAS (like COVACTA, another negative RCT) has included a wide range of patients (without stratification) ranging from those with saturation <93% on ambient air (implying mild cases) to those on mechanical ventilator (severe cases comprising 16.5% patients). Also total number of patients in TOCIBRAS is only 129. A meta-analysis of 8 RCTs with 810/3268 (24.8% mortality) in Tocilizumab group against 935/3401 (27.5% mortality) in Standard of care (SOC), reported ratio of death rates, RR 0.87 (95% CI, 0.79 – 0.96, P=0.005).

COVINTOC another negative RCT on Tocilizumab in moderately severe COVID is from India. It included only 143 patients. Modest benefit with Tocilizumab, is not detected by RCTs with small sample size. Also in post-hoc analysis investigators of COVINTOC concluded that Tocilizumab might still be effective in severe COVID and so further studies are needed.

None of the RCTs reported higher incidence of severe infections with Tocilizumab compared to standard of care group.

The purpose of my editorial was to highlight a select group of COVID patients (moderately severe), that is likely to benefit from timely use of Tocilizumab, appropriately included in REMAP-CAP and RECOVERY trials. Both these trials have studied large number of patients and have used steroids in both groups (Tocilizumab
and SOC group). Hence the benefit in mortality seen in both these trials can be justifiably attributed to Tocilizumab.

By avoiding use of Tocilizumab as a blanket policy, this group of moderately severe COVID patients will be denied of the modest benefit in mortality that Tocilizumab has to offer.

References

6. Soin A, et al, Tocilizumab plus standard of care versus standard of care in patients in India with moderate respiratory Published online March 4 2021, DOI:/uni00A010.1016/

Post COVID-19 Gullain-Barre Syndrome: An Emerging Neurological Complication

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SIR,

COVID-19 is a new disease that causes the recent pandemic since its outbreak in Wuhan, China in the year 2019 and affects more than 100 countries of the globe. The virus belongs to family of Coronaviruses and is a capsulated, non-segmented, positive RNA virus. It is primarily a respiratory syncytial virus that affects the upper and lower respiratory tract through angiotensin-converting enzyme-2 receptors. It has the potentiality to invade other systems either directly or through inflammatory response. Since its outbreak there have been several reports on neurological manifestations that include stroke, encephalopathy, muscle injury, and Gullain-Barre syndrome (GBS). Here we report a case of Post-Covid 19 GBS in view of its significance in the present pandemic situation in India.

A 45-year-old man presented to the Medicine Outdoor with chief complaints of tingling sensation of lower limbs followed by weakness of both lower and upper limbs of 5 days duration. His complaints started with tingling sensation on dorsum of feet that progressed upwards and within 12 hours he developed weakness of both lower limbs that progressed to affect both upper limbs within 24 hours. There was no involvement of bladder and bowel. About 15 days prior to this event, he had fever for 5 days with cough, sneezing, myalgia without anosmia and ageusia. He got relief of these symptoms with azithromycin and paracetamol without testing for SARS-COV-2 which is in accordance with the time interval of antibody appearance i.e., within 13 median days of clinical onset suggested the antecedent Covid-19 that was limited to upper respiratory tract. Hence, final diagnosis of GBS after Covid-19 infection has been made and he was treated with intravenous Immunoglobulin at a dose of 0.4g/kg/day for 5 days with a total dose of 2g/kg. He improved symptomatically and could walk without support and was discharged after 7 days.

Knowledge regarding various clinical manifestations and complications of COVID-19 is essential for understanding the natural history of the disease. GBS is generally an acute, autoimmune, polyradiculoneuropathy that ensues few days to weeks after infection and vaccination with an incidence of 1-2 cases per 100,000 population annually. The common infective agents are C.jejuni, M.pneumoniae, H.influenzae, Epstein-Barr virus, Influenza A virus, and Zika virus. After the initial report, Covid-19 has been added as another emerging cause of GBS. The causal association between GBS and Covid-19 infection has been recognized after the rise in number of patients with GBS worldwide during the Covid-19 pandemic.

The clinical features, electrophysiological, and CSF analysis of post-Covid 19 GBS is like other
infective agents. Acute inflammatory demyelinating polyneuropathy, acute motor and sensory axonal neuropathy, and acute motor axonal neuropathy was found in 64.8%, 13.5%, and 2.7% respectively.\textsuperscript{5} In another review of 38 cases classical sensory-motor GBS, Miller Fisher syndrome, facial diplegia with sensory deficit was found in 78.9%, 13.2%, 5.3% respectively.\textsuperscript{6} Neurophysiological study showed demyelinating, axonal and mixed forms of disease with majority belonged to demyelinating type.\textsuperscript{6} Respiratory failure was found significantly (39.5% cases) among post COVID GBS. It may be due to respiratory muscle paralysis, associated Covid pneumonia, and direct affection of medulla oblongata by the virus causing dysfunction of cardio-respiratory centers.\textsuperscript{5}

The mechanism of GBS in Covid-19 is not clearly understood. In general, the mechanism has been attributed to molecular mimicry of the cell membrane antigen of the microorganism with the ganglioside component of nerve antigen that develop antiganglioside antibodies damaging the spinal roots and peripheral nerves. But antiganglioside antibodies were not detected among patients with post-Covid GBS.\textsuperscript{5} Direct invasion of Covid-19 has been postulated for the neurological deficits due its neuro invasive potential. But the absence of Covid-19 in the CSF does not favor this hypothesis.\textsuperscript{5} Affection of simultaneous neurological and respiratory symptoms in patients with GBS has been prompted to hypothesize the role of hyperinflammation with increased level of proinflammatory cytokines (cytokine storm) in the pathogenesis of GBS.\textsuperscript{5} This has been supported by the observation of endothelial damage by the cytokines. Therefore, axonopathy has been attributed to microvascular involvement.\textsuperscript{5}

The clinical course, electrophysiological study, response to treatment of the present case supported the diagnosis of GBS and satisfied the essential diagnostic criteria. In view of the ongoing Covid-19 pandemic similar cases likely to occur which require further research to elucidate the underlying pathogenesis.

References

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