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*Preference with Evidence*
COVID-19 are we at the End of the Road in India - Pandemic to Endemic Journey

Shashank R Joshi

As we enter 2022, we reflect at the last two years of this pandemic, that has caused the largest disruption of life on planet earth after World War 2; due to a small microbe SARS-CoV2. A virus which surpassed the Human retrovirus HIV, that had propelled the AIDS epidemic as we still observe December 1st as the World AIDS day. India’s story of COVID-19 from ground zero of Mumbai and Maharashtra has a simple message from the public health standpoint - we are clearly seeing active virus in circulation and geographies like Mumbai and India will have cluster outbreaks. However, India may perhaps be the first country in the world to declare that COVID-19 has become an Endemic. The original variant of the virus was a glycosylated one, which led to the first wave in April - June 2020; where the elderly and individuals with comorbidities like hypertension, diabetes formed the vulnerable group. It has a R0 of 3.5 and was Social distancing. Masking and Sanitisising was the key. As the first wave abated across India in 2020 it clearly bore the brunt of lockdown, fear and aftermath of uncertainty. Medications used were empirical and protocols experimental as we evolved based on adaptive evidence base. The first wave ejected out many repurposed agents like hydroxychloroquine, lopinavir-ritonavir, oseltamivir etc. - many drugs that linger to this date, but are yet to generate hard evidence like Ivermectin or Favipiravir. Clearly, there was a role of steroids (we used methyl prednisolone before Recovery trial in India), prone position, oxygen therapy, low molecular weight heparins, and a limited role of agents like Tocilizumab or Itolizumab. In hospitalised moderate to severe cases due to data of faster recovery, symptoms relief and lesser length of stay in the hospital.

The key to natural history and outcomes of COVID19 from first Indian wave was - identification of the vulnerable who are likely to die, home or institutional isolation - based on the ability to access healthcare systems and affordability, optimal utilisation of 6 min walk test with pulse oxymeter for desaturation and red flagging as well as ability to ensure every Indian got care which was needed. Mortality mostly occurred in elderly, individuals with comorbidities or in those who went late to healthcare facilities. Clearly India despite of all the resource limitations did well. In the first Indian wave we did capacity building in ensuring we scaled up both private and public health infrastructure for laboratory testing for RT-PCR; to healthcare facilities with oxygen and ventilators with all medications. The key was still breaking the chain of transmission at a public health landscape. The virus remained in the circulation, people did not adhere to COVID appropriate protocols and gradually after 120 days we started seeing a new wave coming up which was brutal and dramatic. In early February we saw in central India vidarbha region dramatic test positivity rate of more than 50 percent in Amravati, Akola and other local geographies which had different phenotype. This strain was fast transmissible like chicken pox and spread across the entire country by April 2021. It clearly stretched the healthcare infrastructure of some geographies of the country but both the central and state governments with the healthcare community, in which, physicians played a vital role, rose to the occasion and made a major dent in the wave by mid may, though a thick tail lingered for a long time in Kerala, Maharashtra and northeast India. Genomic data and surveillance was in place and revealed the most dominant strain was delta or delta derivatives which replaced kappa in Mumbai or alpha in Delhi eventually. Serial serosurveys showed across India a large exposure with antibody prevalence beyond 70 percent in June and later
in some urban geographies like Delhi and Mumbai crossing 90 percent. The second India wave made us use oxygen more rationally, needed audits and had to put systems in place to ensure it's available for the future. The delta strain was faster spreading but also had rapid recovery in most. The delta strain had newer manifestations like gut or unusual features, longer time table of 2 to 3 weeks as well as lead to a surge of mucormycosis. The likely possibility of mucormycosis was due to unholo trinity of Steroid use, uncontrolled diabetes and COVID19 virus itself. Many other causes like humidifier water or micronutrients were essentially only speculative and the vigilance for Mucor was needed almost 100 days post COVID. It focussed the need to rational use of steroids in optimal dose and duration as well as tightly control the blood glucose. Long COVID19 emerged as a major complication with sudden cardiac deaths, lung fibrosis, autonomic dysfunction, new onset diabetes or thyroiditis as well as neurological syndromes of COVID19 amongst many others. The real aftermath was the mental health tsunami the two waves left not only in the affected population as well as the non affected one which ensured our mental health experts got us geared up to be resilient and strong.

Newer vaccine candidates are being rapidly discovered. The current vaccines are all early generation, possibly requiring a booster dose after 6 months, to save lives and prevent severe disease but may not prevent COVID19. The quest for sterilizing vaccines using nasal routes as well as mRNA vaccines in India is still ongoing. India is the vaccine pharmacy of the world and has innovated platforms like DNA (which is Indian equivalent of mRNA, ZyCoV-D by Zydus Cadila) or Subunit (Novavax or Covomax by Serum) or mRNA (by Genova) all made in India. Indian science and pharmaceutical industry has done incremental innovation and led from the front in this. Two other vaccines one dose Jansen adenovirus one from Biological Evans and Moderna to be marketed by Cipla have not yet been seen available despite of approval for the Drug controller general.

India has more than 130 crore population and has crossed more than 100 crore vaccination with at least one dose. It has had a significant exposure of its population to the Delta strain subclinically during the second wave. So there is a substantial seropositivity in the population due to either natural exposure or vaccine or both (hybrid immunity). The word and definition of 'Herd Immunity threshold' (HIT) in the COVID-19 space has been elusive globally and possibly India has many geographies which may have had HIT crossing 70, 80 or even 90 percent which means possibility of the potentially large third wave is now remote and possibly India may become the first country in the world where COVID-19 may become ‘Endemic’. The invisible active virus is still in circulation and is likely to circulate in the totally or partially unvaccinated population or children who have had no exposure or moderately & severely immunocompromised individuals who failed to mount an immune response. Thus the strategy will be to ensure that the current vaccination is completed and have the India booster strategy in place. Indian booster strategy will be based on Indian as well as global evidence and science. Exposure to natural SARS-COV-2 will itself be equivalent to a booster. So the strategy is likely to factor health care and front line workers after 6 months of the last dose, who never had COVID-19 as well moderately to severe immunocompromised states and elderly in an similar fashion as the initial vaccination program was launched in January 2021. Vaccination program for the children is likely to be launched in near future once there is sufficient availability and evidence in the vulnerable groups. This focus will allow India to save maximum lives and have a goal of zero COVID-19 deaths as well as minimize severe or moderate diseases.

With unlocking across India, adherence to COVID-19 appropriate behaviour has been challenging but with the winter months coming up masking even double masking is mandatory. In fact cloth mask may have challenges and such individuals in indoor or crowded spaces must wear another extra mask like surgical three ply mask as N95 masks may not be routinely available or affordable in general population. Mask mandates with distancing, sanitation as well as having well ventilated environment with less crowds is the key independent of the vaccine status. Its abundantly clear now that the SARS-COV-2 is an airborne droplet and will circulate independent of vaccine status or early exposure so just like breakthrough infection we may get reinfection also. Our public health agencies of the states and center can’t afford to let their guard down and still will need to mandate zero tolerance to non adherence to COVID-19 appropriate behavior.

Globally an important tool used in the unlocked world is “self testing” with lateral flow test which are rapid tests which are encouraged to be done everytime one goes out to a high risk exposure but the data of such strategy in India needs to be generated. Most importantly one must self test and follow it with an RT PCR but also self isolate if there is likelihood of possible symptoms or exposure to a positive individual. Self testing, isolation and repeating it after 3 to 5 days is the key to micro contain the virus and break its chain which is why the “Test, Track, Isolate and Treat” policy will stay for 2022 even if the disease become endemic. Unfortunately people have developed fatigue and rebellious, revengeful tendencies to break such protocols which needs mass education from influential personalities as well as family members who have lost their near and dear ones due to the pandemic. A small but significant population had been orphaned due to the COVID-19 pandemic and one should reach out to this group to help and aid them to rebuild their lives voluntarily. The mental health consequences of COVID-19 and their aftermath which will last for decades with the traumas, fears and anxiety will need nationwide interventions from population to individuals from domain experts.

The availability of newer medicine will there be hope or hype as we enter 2022 is a big science question ? In early treatment strategies we some new Antivirals like Molnupiravir or Ritonavir boosted Protease inhibitor which can cut mortality rates from 50 to 90 percent and significantly reduce severe disease. These agents offer promise if used early in first 5 days and will work best if used earlier but till date will still need to undergo scrutiny of global regulators like Indian Drug controller as well as US FDA and various other global agencies. The
cost, affordability, voluntary versus compulsory licensing and ability of India pharmaceutical industry to make these drugs will be the key. Also the agencies will have to generate and lay down policies for rational use of these agents as there is always a fear of incorrect use which could lead do some form of resistance. This hope if used rationally and early may significantly dent the landscape of the natural history of COVID-19 and it may become a domiciled managed infection with close monitoring saving lot of health care resources. Another treatment option is the monoclonal cocktail of antibodies which has been clearly used now in last 6 months as the second wave started declining. The antibody of Casirivimab / Imdevimab has been most impactful in the most susceptible and vulnerable population who get COVID-19. If immunocompromised or elderly or population with co morbidities get COVID-19 early use of this cocktail of antibody clearly reduces hospital stay and saves lives. New data also shows it can be used with double dose later, in hospitalised space as well has role in post exposure prophylaxis. Currently cost is the rate limiting step and many more such antibody cocktails are in the horizon even from Indian manufacturers. Indian emerging data in this space will be crucial for general use of them in the indicated subset of population used. India also has access to cytokine receptor blockers like Tocilizumab as well as its very own CD6 cytokine formation blocker like Itolizumab which still will have a role in moderate to severe COVID-19 who rapidly deteriorate and need double the amount of oxygen in 24 hours despite of steroid therapy. Also steroid sparing agents like Baricitinib in Indian setup will find a role in a carefully selected cohort in combination with Remdesivir. Low cost Remdesivir as well oral Remdesivir are other Indian innovation which may see the light of the day in the future.

Indic from COVID-19 standpoint is now at a stage where it could be the first country on planet earth to transition into an “Endemic” stage. The R factor is an index which public health experts use for understanding transmission dynamic to see the numerical variations of cases in the population. During the rising tide of the wave usually the R factor exceed one and it falls below one during low tide as the wave declines. Clearly if the R factor gets stable with miniscule fluctuations an Endemic stage can be reached as well. The distinction between epidemic and Endemic numbers is determined by many factors especially the Herd immunity threshold, based on vaccination and natural infection. The key factor in the current numbers will be the active virus in circulation versus the actual number of cases diagnosed and reported. There will always be a significant proportion of COVID-19 cases above 80 to 85 percent which will be visible and asymptomatic which will not be reported and keep the live virus in circulation while a subset of 15 to 20 percent of symptomatic population will form the visible pool which will be tested and partially reported. The focus on RT PCR as a metric to diagnose should continue due to higher sensitivity of 70 percent compared to rapid test which may be lower than even 50 percent sometimes. However rapid test if positive allow time advantage to isolate and break the chain earlier. The focus on RT PCR and serial testing on suspects is the key to transmission interruption. The standard public health strategies adoption with all available resources with active sentinel and genomic surveillance is the key now to the disease spread and containment. There is clear rapid shrinkage of the susceptible population due to large vaccine coverage and exposure of the virus either clinically or subclinically (as evidence by the very high seropositivity in serosurveys across India).

Unless Genomic surveillance does not show prevalence of a new Variant of concern or interest its unlikely any form of another wave will occur. As the current Indian data from Genomic groups show only delta or delta derivatives as the predominant Indian strain coupled with large seropositivity for the same due to exposure. However that should not lead to complacency as the active virus is still in circulation and will mutate, only the host immunity and virulence or strain will determine the future COVID-19 disruptions in India in 2022. The current pool which is susceptible is the unvaccinated (total or partial) as well as the vulnerable population which failed to mount an immune response from groups of immunocompromised states, elderly or health care or front line subsets. The pediatric subset is unvaccinated and with opening of schools can be a nidus of viral outbreaks if preventive measures and strategies including vaccination are not adopted. Full vaccination of the school working personnel as well family members is equally crucial to be done. The future will be to continue efforts to contain the invisible pool of the virus contained in the population and reservoirs don’t lead to either drug resistant strains or vaccine immune Escape or give birth to new variants of concern. So good public health policing, voluntary participation of the community to Mask and minimize high risk behavior as well as building robust host immune response will be the key. The focus will be protecting the vulnerable from deaths, severe disease and hospitalizations so that we can move towards a COVID safe world and eventually a COVID free world.

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Coronavirus Disease, Diabetes and Glucocorticoid a Terrible Trio for Invasive Mucormycosis: An Observational Study from Northwest Rajasthan

Hardeva Ram Nehara 1*, Sahdev Kumawat 2, Jigyasa Gupta 3, Gaurav Gupta 4, Parmendra Sirohi 5, Sunil IH 6, Balkishan Gupta 5

Abstract

Objective: This study aims to describe the epidemiology, predisposing factors, clinical manifestations, management, and outcome of post-COVID rhino-cerebral-orbital mucormycosis.

Methods: This is a prospective observational study of patients with post-COVID RCOM conducted tertiary care hospital during May-June 2021.

Results: The mean age of patients was 49.58±15.12 years and majority (64.80%) were male. The majority of patients were rural, Hindu and illiterate. Diabetes was present 78.10% patients, glucocorticoids were required in 66.30%, and supplemental oxygen was used in 27.60% of patients. Most of the patients developed symptoms of RCOM within 15 days of COVID-19. Majority of patients (46.67%) had stage 3 disease and orbit was involved in 60% of patients. All patients received intravenous antifungal drugs and combined antifungal drugs and surgical debridement was performed in 77.10% patients. Predictor associated with poor outcome were RCOM stage 3c or above and qSOFA score ≥2 at presentation.

Conclusion: Diabetes and glucocorticoids are the most important risk factors for post-COVID RCOM. COVID-19 patients must be followed closely for 2-4 weeks to detect mucormycosis as earlier as possible. Antifungal drugs should be started immediately if clinico-radiological feature suggest RCOM before microbiological confirmation. Combined medical and surgical treatment significantly reduces mortality.

Introduction

The COVID-19 pandemic still creating havoc all over the India. People surviving the COVID-19, now facing another catastrophic invasive fungal infection, mucormycosis. Mucormycosis is not unusual, as India contributes to 40% of the global burden, with an estimated prevalence of 140 cases per million in pre-COVID era. Presently post-COVID mucormycosis is rising unprecedented. As on June 28, 2021 more than 40,000 cases and more than 3000 deaths have been reported in Indian government portal. More than two times increase in mucormycosis cases compared to previous year was reported during first wave of COVID-19 infection.

The four major predisposing factors have been purposed for post-COVID mucormycosis: environment, COVID-19, diabetes, and steroid. Mucormycosis is ubiquitous fungus, exuberantly present in decomposing organic matter. A heavy mould spore counts in hospital air was reported in India due to hot and humid conditions in tropical climate. Post-COVID mucormycosis has been reported even in patients with mild to moderate COVID-19 infections. Hyperglycemia is one of the major predisposing factors for mucormycosis. The COVID-19 infection itself deteriorate glucose metabolism by destroying beta cell of pancreas and alters iron metabolism. Diabetic ketoacidosis further increases serum free iron. Iron is essential host factor for growth of Mucorales and excess iron is efficiently taken up through siderophores of Mucorales. COVID-19 infection also causes vascular endothelial damage allowing entry of Mucorales in the vascular circulation.

Hyperglycaemia and acidosis induce up regulation of endothelial receptor glucose regulated protein (GRP78), leading to impaired chemotaxis, polymorphonuclear dysfunction, and impaired phagocytosis. Steroids further impair migration of neutrophil and fusion of phagolysosome. Finally, COVID 19 patient with diabetes receiving steroids is susceptible for development of mucormycosis. Rhino-cerebral-orbital mucormycosis (RCOM) is an opportunistic infection of the paranasal sinuses and brain. In developing countries including India, mucormycosis is associated with a high mortality (45-90%). The probable reasons include a delay in diagnosis and high cost of managing mucormycosis. Many single center studies suggest that the epidemiology of mucormycosis is different in India as compared to the developed world.

As rapid surge of rhino-cerebral-orbital mucormycosis (RCOM) is seen in post-COVID patients in India, we planned this study to describe the epidemiology, predisposing factors, clinical manifestations, management, and outcome of post-COVID rhino-cerebral-orbital mucormycosis.
This study included 105 consecutive patients of rhino-cerebral-orbital mucormycosis. The mean age of the patients was 49.58±15.12, and 68 (64.80%) were male. The majority of patients belonged to rural area (76.20%), were Hindu (78.10%) by religion, and were illiterate (61.00%) (Table 1).

**COVID-19 illness**

Out of 105 patients 101 (96.20%) had COVID-19 illness. Diagnosis of COVID-19 was established by RT-PCR, radiology and serology (IgG antibody) in 72 (71.29%), 20 (19.80%) and 9 (8.91%) patients respectively. Out of 101 patients with COVID-19 illness 8 (7.92%) patients were asymptomatic, 36 (35.64%) had mild illness, 41 (40.60%) had moderate illness and 16 (15.80%) had severe illness. Median CT severity score was 10.00 (IQR: 4.00-14.00) (Table 1).

**Risk factors for RCOM**

Besides, COVID-19 which was found in 101 (96.20%) patients, most common underlying risk factor was diabetes followed by use of glucocorticoids for COVID-19 illness. Diabetes was present in 82 (78.10%) patients with 64 (61.00%) patients had uncontrolled diabetes and 8 (7.60%) patients having diabetic ketoacidosis at presentation. Glucocorticoid for COVID-19 treatment was considered inappropriate if it was given in patients without hypoxia (oxygen saturation <94%), dose more than 0.1 mg/kg dexamethasone or equivalent or duration more than 10 days. RCOM cases were categorised into 4 stages. Clinical severity of COVID-19 was defined as per the Indian Ministry of Health and Family Welfare guideline. Quick sequential organ failure assessment (qSOFA) score was defined as per Sepsis-3.

**Statistical analysis**

The data were analyzed using the commercial statistical package SPSS 16.0. The descriptive statistics are presented as frequencies, mean with standard deviation, or median and interquartile range, as appropriate. The categorical variables were compared using chi-square test while the differences between continuous data were analyzed using Mann-Whitney test or t-test as appropriate. A binary logistic regression analysis was performed for identifying factors predicting mortality, by including variables that were significant (p<0.05) on univariate analysis. A p-value <0.05 was considered significant.
patients (67.70%) developed symptoms of RCOM within 15 days and 32.30% patients developed symptoms after 15 days. Frequencies of the symptoms of RCOM are shown in Figure 1b.

Common symptoms of RCOM at presentation were headache (17.94%), facial pain (16.17%), periorbital pain (13.71%), nasal stiffness (12.66%), facial numbness (11.39%), nasal discharge (10.34%), loss of vision (5.90%), diplopia (3.38%), and loss of teeth (0.42%). Frequencies of signs of RCOM are shown in Figure 1c. Common signs of RCOM at presentation were lid edema (22.97%), black nasal crust (20.73%),

Table 2: Clinico-radiological features of rhino-cerebral-orbital mucormycosis patients (n=105)

<table>
<thead>
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<th>Characteristics</th>
<th>Frequency (%)</th>
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</thead>
<tbody>
<tr>
<td>RCOM Stage 1</td>
<td>0</td>
</tr>
<tr>
<td>RCOM Stage 2 (n=41(39.04%))</td>
<td></td>
</tr>
<tr>
<td>Stage 2a</td>
<td>1 (0.95%)</td>
</tr>
<tr>
<td>Stage 2b</td>
<td>1 (0.95%)</td>
</tr>
<tr>
<td>Stage 2c</td>
<td>5 (4.76%)</td>
</tr>
<tr>
<td>Stage 2d</td>
<td>34 (32.38%)</td>
</tr>
<tr>
<td>RCOM Stage 3 (n=49(46.67%))</td>
<td></td>
</tr>
<tr>
<td>Stage 3a</td>
<td>9 (8.57%)</td>
</tr>
<tr>
<td>Stage 3b</td>
<td>16 (15.24%)</td>
</tr>
<tr>
<td>Stage 3c</td>
<td>22 (20.95%)</td>
</tr>
<tr>
<td>Stage 3d</td>
<td>2 (1.91%)</td>
</tr>
<tr>
<td>RCOM Stage 4 (n=15(14.29%))</td>
<td></td>
</tr>
<tr>
<td>Stage 4a</td>
<td>1 (0.95%)</td>
</tr>
<tr>
<td>Stage 4b</td>
<td>7 (6.67%)</td>
</tr>
<tr>
<td>Stage 4c</td>
<td>5 (4.76%)</td>
</tr>
<tr>
<td>Stage 4d</td>
<td>2 (1.91%)</td>
</tr>
<tr>
<td>Paranasal sinus involvement (n=105)</td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>61 (58.10%)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>2 (1.91%)</td>
</tr>
<tr>
<td>Ethmoid</td>
<td>176* (28.34%)</td>
</tr>
<tr>
<td>Maxillary</td>
<td>160* (25.76%)</td>
</tr>
<tr>
<td>Sphenoid</td>
<td>154* (24.80%)</td>
</tr>
<tr>
<td>Frontal</td>
<td>131* (21.10%)</td>
</tr>
<tr>
<td>Orbital involvement</td>
<td></td>
</tr>
<tr>
<td>[n=63 (60%)]</td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>61 (58.10%)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>2 (1.90%)</td>
</tr>
<tr>
<td>CNS involvement</td>
<td></td>
</tr>
<tr>
<td>Palatalal involvement</td>
<td>18 (17.1%)</td>
</tr>
<tr>
<td>Facial cellulitis</td>
<td>61 (58.1%)</td>
</tr>
</tbody>
</table>

RCOM: rhino-cerebral-orbital mucormycosis; *: number is greater than 105 as many patients had more than one paranasal sinus involvement; CNS: central nervous system.
Table 3: Comparison of demographic and clinical parameters in survivor and non-survivor rhino-cerebral-orbital mucormycosis patients (n=105)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Survivors (n=76)</th>
<th>Non-survivors (n=29)</th>
<th>t/X/U</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) [Mean±SD]</td>
<td>47.40±16.14</td>
<td>55.27±10.24</td>
<td>2.96</td>
<td>0.004*</td>
</tr>
<tr>
<td>Male</td>
<td>50 (65.78%)</td>
<td>18 (62.06%)</td>
<td>0.12</td>
<td>0.72</td>
</tr>
<tr>
<td>Residence</td>
<td>Rural</td>
<td>56 (73.68%)</td>
<td>0.95</td>
<td>0.32</td>
</tr>
<tr>
<td>Religion</td>
<td>Hindu</td>
<td>58 (76.32%)</td>
<td>2.67</td>
<td>0.26</td>
</tr>
<tr>
<td>Education</td>
<td>Illiterate</td>
<td>41 (53.95%)</td>
<td>8.78</td>
<td>0.03*</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Total</td>
<td>57 (75.00%)</td>
<td>1.54</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>DKA</td>
<td>5 (8.77%)</td>
<td>0.20</td>
<td>0.65</td>
</tr>
<tr>
<td></td>
<td>Uncontrolled</td>
<td>42 (73.68%)</td>
<td>2.07</td>
<td>0.14</td>
</tr>
<tr>
<td>Glucocorticoid for COVID-19</td>
<td>Total</td>
<td>50 (75.78%)</td>
<td>0.46</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>Inappropriate</td>
<td>40 (80.00%)</td>
<td>0.09</td>
<td>0.75</td>
</tr>
<tr>
<td>Hematological malignancy</td>
<td>Total</td>
<td>2 (2.63%)</td>
<td>0.77</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supplemental oxygen</td>
<td>Total</td>
<td>18 (25.68%)</td>
<td>2.13</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steam inhalation</td>
<td>Total</td>
<td>14 (18.42%)</td>
<td>0.07</td>
<td>0.79</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COVID-19 vaccine</td>
<td>Total</td>
<td>8 (10.52%)</td>
<td>3.17</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COVID Category (n=101)</td>
<td>Asymptomatic</td>
<td>8 (10.96%)</td>
<td>0</td>
<td>0.04*</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>28 (38.35%)</td>
<td>7.87</td>
<td>0.04*</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>29 (39.73%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>8 (10.96%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCOM Stage</td>
<td>Stage 2</td>
<td>39 (51.32%)</td>
<td>44.73</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td></td>
<td>Stage 3</td>
<td>33 (43.41%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stage 4</td>
<td>4 (5.27%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>qSOFA=2</td>
<td>2 (2.63%)</td>
<td>17 (38.62%)</td>
<td>44.4</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Combined antifungal and surgery</td>
<td>69 (90.78%)</td>
<td>12 (41.37%)</td>
<td>29.1</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

SD: standard deviation; DKA: diabetic ketoacidosis; RCOM: rhino-cerebral-orbital mucormycosis; qSOFA: quick sequential organ failure assessment score; *: significant

Table 4: Comparison of laboratory parameters in survivor and non-survivor rhino-cerebral-orbital mucormycosis patients (n=105)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Total (n=105)</th>
<th>Survivors (n=76)</th>
<th>Non-survivors (n=29)</th>
<th>U</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (gm/dl) [median (IQR)]</td>
<td>10.70 (9.45-12.05)</td>
<td>11.30 (9.30-12.70)</td>
<td>10.00 (9.20-11.65)</td>
<td>966.00</td>
<td>0.33</td>
</tr>
<tr>
<td>NLR [median (IQR)]</td>
<td>4.60 (2.66-8.30)</td>
<td>4.20 (1.87-7.00)</td>
<td>8.30 (5.01-12.06)</td>
<td>453.50</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>CD4 count ((cells/μL) [median (IQR), n=73]</td>
<td>587 (495-685)</td>
<td>572.00 (416.00-712.00)</td>
<td>557.00 (516.00-639.00)</td>
<td>402.00</td>
<td>0.47</td>
</tr>
<tr>
<td>CRP (mg/dl) [median (IQR), n=31]</td>
<td>44.00 (30.00-74.00)</td>
<td>44.00 (18.00-74.00)</td>
<td>44.00 (39.25-66.00)</td>
<td>47.00</td>
<td>0.82</td>
</tr>
<tr>
<td>RDW-CV (%) [median (IQR), n=6]</td>
<td>15.90 (15.00-17.10)</td>
<td>16.30 (15.20-17.80)</td>
<td>16.30 (14.75-17.80)</td>
<td>1.01</td>
<td>0.51</td>
</tr>
<tr>
<td>Platelet count (cells/μL) [median (IQR)]</td>
<td>245 (200-321)</td>
<td>255.00 (217.00-321.00)</td>
<td>298.00 (206.00-351.00)</td>
<td>900.50</td>
<td>0.14</td>
</tr>
<tr>
<td>Creatinine (mg/dl) [median (IQR)]</td>
<td>0.70 (0.90-1.21)</td>
<td>0.70 (0.90-1.06)</td>
<td>1.17 (0.80-1.60)</td>
<td>666.00</td>
<td>0.04</td>
</tr>
<tr>
<td>Plasma glucose (mg/dl) [median (IQR)]</td>
<td>221 (96-286)</td>
<td>221 (96-286)</td>
<td>251 (108.00-362.00)</td>
<td>918.00</td>
<td>0.18</td>
</tr>
<tr>
<td>HbA1c % [median (IQR), n=30]</td>
<td>10.10 (8.25-12.20)</td>
<td>5.80 (4.20-13.30)</td>
<td>5.80 (4.20-13.30)</td>
<td>91.50</td>
<td>0.48</td>
</tr>
<tr>
<td>CTSS [median (IQR)]</td>
<td>10.00 (4.00-14.00)</td>
<td>10.00 (2.00-13.75)</td>
<td>10.00 (6.00-17.00)</td>
<td>909.00</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Hb: hemoglobin; NLR: neutrophil lymphocyte ratio; CRP: C-reactive protein; RDW: red cell distribution width; HbA1c: glycated hemoglobin; CTSS: computerised tomography severity score; IQR: interquartile range.

The most common PNS involved was maxillary (28.34%), followed by ethmoid (25.76%), sphenoid (24.80%), and frontal (21.10%). Orbital involvement was found in 63 (60.00%) with unilateral involvement in 61 (58.10%) and bilateral involvement in 2 (1.90%) patients. CNS involvement was found in 18 (17.10%) patients. Palatal involvement was seen in 18 (17.10%) patients and 61 (58.10%) patients had evidence of facial cellulitis at presentation. Categorization of the patients was done as per the proposed staging system and found that most patients 49 (46.67%) had stage 3 disease.

Management and outcome of RCOM

Management performed for RCOM is shown in Table 1. Liposomal amphotericin B was given in 96 (91.43%) patients and intravenous posaconazole was given in 9 (8.57%) patients. Functional endoscopic sinus surgery (FESS) was performed in 63 (60.00%) patients, FESS and orbital exenteration were performed in 11 (10.48%) patients, and FESS and maxillectomy were performed in 7 (6.67%) patients. Combined antifungal treatment and surgical debridement were performed in 81 (77.10%) patients.

Out of 105 patients 70 (66.67%) improved and discharged, 6 (5.71%) patients are still hospitalized and improving, 9 (8.57%) patients left against medical advice, and 20 (19.05%) patients died. For analysis of outcome, patients were divided in two groups [n=76 (72.38%)] and non-survivors [n=29 (27.62%)]. Median duration of hospital stay was 25.00; IQR: 15.00-30.00 days.

Comparison of demographic, clinical and laboratory parameters between survivor and non-survivor groups are shown in Table 3 and 4. Mean age of non-survivors was significantly more than survivors (55.27±10.24 vs 47.40±16.14; p=0.004). Poor outcome was significantly more in illiterate patients (0.03). Moderate to severe COVID was associated with poor outcome (0.04). Similarly severe RCOM (stage 3 or above) was also associated with poor outcome (<0.001). Patients having qSOFA score ≥2 were associated with poor outcome (<0.001). Combined antifungal treatment and surgical debridement were associated with better outcome (<0.001). On binary logistic regression predictor associated
Discussion

Mucormycosis is a catastrophic and angioinvasive fungal infection caused by Mucorales, which belongs Zygomycetes class. Mucorales inhabit the nasal mucosa of humans as a commensal structure like paranasal sinuses, palate, orbits and brain. Hypoxia, hyperglycemia and hyperferritennemia produced by COVID-19, and impaired phagocytosis of leukocytes due to immunosuppression caused by SARS-CoV-2 itself and glucocorticoids used for hypoxia is sufficient for germination and proliferation of the fungal spores. This study was conducted to explore epidemiology, risk factors, clinical manifestations and predictors of outcome of post-COVID RCOM to improve management and outcome of RCOM patients.

Mean age of the patients in this study was 49.58±15.12 years and 65.78% were male. Sen M et al. in their study from India reported a mean age of 51.9 years with male (71%) predominance. Male preponderance was also reported in other studies, which may be attributable to greater outdoor activity and exposure to fungal spores. The majority of patients belonged to rural area, were Hindu by religion, and were illiterate. This may be attributable to high environmental exposure to fungal spores in rural and illiterate people involved in agricultural activities.

COVID-19 was a major risk factor in this cohort of patients and was found in 96.2% patients. Majority of patients (56.4%) had moderate to severe COVID-19 illness and only 27.6% required supplemental oxygen and 19.0% had history of steam inhalation during COVID-19 illness. In studies done by John TM and Pakdel et al majority of patients had severe COVID-19 illness. In Sen M et al.’s study 57% of patients required oxygen supplementation. So, contaminated oxygen supplementation and steam inhalation didn’t appear to be a major risk factor for post-COVID RCOM. Median CT severity score was 10.00 (IQR: 4.00-14.00), which is similar to previous study.

Diabetes was found in 78.1% of RCOM patients, with 61% had uncontrolled diabetes and 7.6% had diabetic ketoacidosis at presentation. Sen M et al. reported diabetes in 78%, uncontrolled diabetes in 41%, and diabetic ketoacidosis in 3.6% of patient in a large cohort of 2836 RCOM patients. In recent studies from India, Sharma S et al. and Ravani SA et al. reported 91.3% (52.17% uncontrolled) and 96.3% (54.17% DKA) prevalence of diabetes in COVID-19-associated RCOM patients respectively. Singh et al. found 83.3 % patients of diabetes with 14.9% having DKA. Similarly John TM et al. reported prevalence of diabetes of 80.4% with 19.5% having DKA. Diabetes has been found to be independent risk factor for mucormycosis. Hyperglycemia and acidosis increase free iron which allows germination and proliferation of mucor. Systemic glucocorticoid for COVID-19 illness was used in 66.3% of RCOM patients and it was used inappropriately in 52.5% patients. In patients without diabetes glucocorticoid was used in 39.13% patients. According to previous studies from India, 61-100% of the patients with COVID-19 associated RCOM had history of intake of systemic glucocorticoids for COVID-19 illness. Singh et al. found history of glucocorticoids in 76.3% patients. Inappropriate use of glucocorticoids may be a possible factor in causation of RCOM. Glucocorticoids itself and glucocorticoid induced hyperglycemia impair neutrophil migration and phagocytosis and predispose to mucormycosis. Other underlying risk factor was haematological malignancies in 1.9% patients. In previous studies haematological malignancies was found in 3-13% patients. No underlying risk factor was found in 10.47% patients except COVID-19. Sen M et al. reported COVID-19 as only risk factor in 18% of patients. So, multifactorial etiolo is a likely explanation for post-COVID mucormycosis including COVID-19, hyperglycemia, glucocorticoids and environmental factors eg. tropical climate.

Median duration of onset of symptoms of RCOM from the diagnosis of COVID-19 was 12 days. Most of the patients (67.7%) developed symptoms of RCOM within 15 days and 32.3% patients developed symptoms after 15 days. The median time for diagnosis of mucormycosis from COVID-19 was 13 days with 56% of the patients developed symptoms within 14 days in study done Sen M et al. In study done by Singh et al. 60% and 40% of the cases seen in active and recovered COVID-19 patients respectively. Most common symptoms of RCOM were headache, facial/periorbital pain, nasal stiffness/discharge and facial numbness. Most common signs of RCOM were lid edema, black nasal crust, ptosis, proptosis and ophthalmoplegia. The most common signs and symptoms in study done by Sen M et al. were loss of vision, orbital/facial pain, periorcular/facial swelling, ptosis, and nasal discharge. In most of the patients (75.2%) PNS involvement was bilateral, this is contradictory to study done by

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>SE</th>
<th>OR (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥50 years</td>
<td>0.86</td>
<td>1.00</td>
<td>2.38 (0.33-17.01)</td>
<td>0.38</td>
</tr>
<tr>
<td>&lt;50 years (reference)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>COVID Category Severe</td>
<td>0.34</td>
<td>1.03</td>
<td>1.40 (0.18-10.71)</td>
<td>0.74</td>
</tr>
<tr>
<td>Asymptomatic, Mild, Moderate</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Education</td>
<td>1.29</td>
<td>1.18</td>
<td>3.65 (0.35-37.07)</td>
<td>0.27</td>
</tr>
<tr>
<td>Literate (reference)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>RCOM stage</td>
<td>1.89</td>
<td>0.74</td>
<td>6.67 (1.54-28.95)</td>
<td>0.01*</td>
</tr>
<tr>
<td>Stage 3c and above</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Stage 3b and below (reference)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>qSOFA ≥2</td>
<td>2.97</td>
<td>1.34</td>
<td>19.59 (1.41-271.02)</td>
<td>0.02*</td>
</tr>
<tr>
<td>&lt;2 (reference)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NLR ≥4.6</td>
<td>0.97</td>
<td>0.75</td>
<td>2.65 (0.61-11.55)</td>
<td>0.19</td>
</tr>
<tr>
<td>&lt;4.6 (reference)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Treatment</td>
<td>0.70</td>
<td>1.09</td>
<td>2.03 (0.23-17.51)</td>
<td>0.51</td>
</tr>
<tr>
<td>Only antifungal</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Antifungal + surgery (reference)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

B: unstandardized coefficient; SE: standard error; OR: odd ratio; CI: confidence interval; *: significant; RCOM: rhino-cerebral-orbital mucormycosis; qSOFA: quick sequential organ failure assessment score; NLR: neutrophil lymphocyte ratio.
Sen M et al. in which only 40% patients had bilateral PNS involvement. The most common PNS involved was maxillary, followed by ethmoid, sphenoid, and frontal. While ethmoid sinus was most commonly affected in study done by Sharma S et al. Orbital involvement was found in 60% with predominant unilateral involvement. Similarly, orbital involvement is seen in 72% patients in study done by Sen M et al. with predominant unilateral involvement. While orbital involvement is seen 43.47% and 30% patients in study done by Sharma S et al. and John TM et al. respectively.16,20 CNS involvement was found in 17.1% patients. CNS involvement is seen 21-40% patients in previous studies [16-20]. Palatal involvement was seen in 17.1% patients. Palatal involvement is seen 39.13% patients in study done by Sharma S et al. Most patients (62.86%) had RCOM stage 3b or less and 37.14% patients had stage 3c or above disease. While in study done by Sen M et al. 51% patients had RCOM stage 3b or less and 49% patients had stage 3c or above disease.17

Liposomal amphotericin B was given in 91.43% patients and intravenous posaconazole was given in 8.57% patients. FESS, FESS with orbital exenteration, and FESS with maxillectomy were performed in 60%, 10.48%, and 6.67% patients respectively. Combined antifungal treatment and surgical debridement were done 77.10% patients. In study done by Sen M et al. FESS was done in 67% patients and both FESS orbital exenteration were done in 17% patients.17 The management of mucormycosis consist of strict glycemic control, control of other risk factors, timely surgical debridement, and medical treatment with antifungal drugs.24

A total of 72.38% patients survived and 27.62% patients had poor outcome. In study done by Singh et al. similar mortality rate (31%) was found in COVID-19 associated mucormycosis.16 Median duration of hospital stay was 25 days. Non-survivors were older, more illiterate, had qSOFA score ≥2, had more severe COVID illness, and had more severe RCOM stage. Patients undergoing combined antifungal treatment and surgical debridement had more chance of survival, similar to previous study.23 On binary logistic regression predictor associated with poor outcome were RCOM stage 3c or above and qSOFA score ≥2. According to a large review survival rate was 3%, 57%, 61% and 70% with no intervention, with surgery alone, with amphotericin deoxycholate, and combined antifungal and surgical debridement respectively. In study done by Patel A et al. predictors associated with increased mortality were age, site of involvement, and ICU admission.2 Few limitation of this study need to be mentioned, first this is a single center study, so data may not be representative of whole population. Second, we do not have data regarding environmental risk factors of mucormycosis eg. burden of fungal spores in the hospital environment. Third, there is no data of COVID-19 patients without RCOM as a control to determine risk factors. The strength of our study is sufficiently large number of patients to make the observations credible.

In conclusion, post-COVID RCOM mainly occurs in middle aged males with majority of the patients developing RCOM within 15 days of diagnosis COVID-19. Besides COVID-19, diabetes and glucocorticoids appears to be most important risk factors for post-COVID RCOM. To prevent post-COVID mucormycosis strict control of glycemia is of paramount importance. Beside this, glucocorticoids should be used judiciously in COVID-19 patients with hypoxia as per recommendation. Medical treatment with antifungal drugs should be started immediately if clinical suspicion is high even before microbiological confirmation. Combined treatment with antifungal drugs and surgical debridement improve survival and should be considered in each patient. Mortality is higher in patients with severe RCOM stage and should be managed aggressively.

References:
For risk reduction of Major adverse cardiac events (MACE) in CAD/PAD

Rivaroxaban 2.5 mg Tablets

The Vascular Dose for Polyvascular disease

an Expanded PAD indication for the Rivaroxaban Vascular Dose

turalization-for-due-to-symptomatic-pad (Oct 11, 2021, 11:15)

# To reduce risk of major thrombotic vascular events in patients with PAD, including patients after recent lower extremity revascularization due to symptomatic PAD

CAD - Coronary Artery Disease      PAD - Peripheral Artery Disease
Follow-up Study of Pulmonary Function, Exercise Capacity and Radiological Changes after Recovery from Moderate to Severe COVID Pneumonia without Mechanical Ventilation

Ritu Karoli 1*, Nikhil Gupta 2, Shobhit Shakya 2

Abstract

Background: The long-term effects of COVID on the lungs remain unclear, but, given the extent of the pandemic, it has the potential to become a significant chronic global health problem. Aim of our study was to ascertain the proportion of patients with moderate to severe pneumonia but without mechanical ventilation who have compromised exercise capacity, pulmonary function test and presence of radiological abnormalities and to study any correlation between clinical features with radiological abnormalities.

Methods: In a hospital-based study, COVID-19 patients with moderate and severe pneumonia were followed 3 months after discharge and assessed with chest computed tomography (CT) imaging, 6 minute walk test and pulmonary function tests.

Results: A total of 102 participants were enrolled, including 64 patients who had recovered from moderate disease and 38 patients from severe COVID-19. The patients with critical disease and who required mechanical ventilation or who had previously known chronic lung disease were excluded. High proportion of patients of both groups showed radiological abnormalities and deranged pulmonary function tests 3 months after recovery from acute illness which had significant correlation with severity of disease.

Conclusions: Pulmonary function and radiological abnormalities remained in significant proportion of patients 3 months after recovery from COVID-19 that needs more attention on pulmonary rehabilitation and long term follow up of these patients.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first reported in late December 2019, originating from Wuhan in Hubei Province, China, has infected millions of people worldwide and caused a pandemic that is still ongoing. COVID-19 caused by SARS-CoV-2 comprises of multi system involvement with respiratory system predominance. The long-term effects of COVID on the lungs remain unclear, but, given the extent of the pandemic, it has the potential to become a significant chronic global health problem. Follow-up data from previous coronavirus outbreaks, SARS-CoV and MERS-CoV, have shown that approximately one third of survivors continue to have abnormalities of pulmonary function and radiographic changes consistent with pulmonary fibrosis. Since the lungs are the most involved organs in COVID 19 it is crucial to define and predict the outcome and to determine the risk factors that can lead to fibrosis and loss of function of lungs. There are variable reports of persistent radiographic changes and abnormalities of pulmonary function tests (PFTs) in a proportion of their patients, with prevalence ranging from 18 to 90% for computerised tomography (CT) changes and PFT abnormalities.

During this pandemic, there has been availability of substantial data regarding epidemiology, clinical manifestations and risk factors associated with morbidity and mortality but there is paucity of literature on long term follow up and sequelae in survivors of COVID 19, particularly in our country. Therefore, we present this retrospective analysis of patients who were admitted in our tertiary care facility during the second wave and were followed up prospectively in medical outpatient departments with objectives to ascertain the proportion of patients with moderate to severe pneumonia but without mechanical ventilation who have compromised exercise capacity, pulmonary function test and presence of radiological abnormalities and to study any correlation between clinical features with radiological abnormalities.

Methods

This was a retrospective hospital-based cohort study, conducted on patients admitted between 1st April-15th May 2021 in Department of Medicine, Dr Ram Manohar Lohia Institute of Medical Sciences, Lucknow, a tertiary care teaching institute situated in North India.

The study included patients of moderate to severe COVID 19 who had real-time reverse transcriptase polymerase chain-reaction (RT-PCR) test-confirmed SARS-CoV-2 infection required hospitalization.

The data was collected on demographic profile, anthropometry, clinical characteristics, co morbid status, medications, history of smoking.
Table 1: Baseline characteristics of study participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Moderate (n=64)</th>
<th>Severe (n=38)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>55±11</td>
<td>57±13</td>
<td>0.12</td>
</tr>
<tr>
<td>Male Gender</td>
<td>29(45%)</td>
<td>25(66%)</td>
<td>0.04</td>
</tr>
<tr>
<td>BMI</td>
<td>22.7±1.8</td>
<td>25.2±1.92</td>
<td>0.01</td>
</tr>
<tr>
<td>Presence of comorbidity</td>
<td>33(52%)</td>
<td>24(63%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Use of oxygen therapy</td>
<td>60(94%)</td>
<td>38(100%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Use of anticoagulants</td>
<td>60(94%)</td>
<td>38(100%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Use of supplemental oxygen therapy</td>
<td>60(94%)</td>
<td>38(100%)</td>
<td>0.8</td>
</tr>
<tr>
<td>PaO2/FIO2 &lt;200</td>
<td>22(34%)</td>
<td>23(61%)</td>
<td>0.01</td>
</tr>
<tr>
<td>CT score</td>
<td>12±6.5</td>
<td>17±7</td>
<td>0.54</td>
</tr>
</tbody>
</table>

The pulmonary function tests were performed using spirometry in PFT lab Master screen PFT, Hoechberg, Germany. The following parameters were measured: forced vital capacity (FVC), forced expiratory capacity at the first second of exhalation (FEV1), FVC/FEV1 ratio, total lung capacity (TLC), vital capacity (VC), residual volume (RV), diffusion capacity of the lung for carbon monoxide (DLCO).

Pulmonary function tests were analyzed based on the ATS-ERS guidelines. All parameters were expressed as percentages of the predicted normal value. Impaired or reduced diffusion was considered as DLCO < 80% of predicted value.

At the time of admission, all patients with suspected COVID-19 pneumonia underwent posterior–anterior and lateral chest X-rays and or high resolution CT thorax were performed. The initial X-rays and CT scans were followed-up by CT scans 3 months later for all patients. For the portion of our cohort who did not undergo a CT scan at the initial stage of disease, posterior–anterior and lateral chest X-rays were used for the assessment of disease extent for every patient. All CT images were acquired at the end of inhalation using a 64-row CT scanner (Somatom Definition AS 128, Siemens Health System, Forcheim, Germany).

CT features such as ground-glass opacities (GGO), consolidation, parenchymal bands and architectural distortion, air bronchograms, bronchiectasis, as well as their distribution were noted. The findings were classified into two groups as either inflammatory changes, being GGO and consolidation, or fibrotic/reticular changes (parenchymal bands, architectural distortion, traction bronchiectasis). Involvement of each lobe was quantified using method previously used in other studies for evaluating pulmonary fibrosis caused by SARS. Each of the 5 lung lobes were given a score of 0–5 points for inflammatory and fibrotic/reticular changes. Points were given as follows: 0 for a lobe without perceptible changes, 1 for lesions involving up to 5% of a lobe, 2 for lesions involving 6–25% of a lobe, 3 for lesions involving 26–50% of a lobe, 4 for lesions involving 51–75% of a lobe, 5 for lesions involving more than 75% of a lobe. In baseline studies, points of each lobe were added together, with a maximum summed score of 25, and one score was attributed for the extent of lesions, not taking into account the type of CT features; in contrast, in follow-up studies not only the scores but CT findings were recorded to analyse the inflammatory and fibrotic changes.

Radiological findings suggestive of fibrosis will be defined as evidence of traction bronchiectasis, architectural distortion, or honey combing with reticulation.

Laboratory parameters included total leukocyte and lymphocyte counts and C-reactive protein, D-dimers, interleukin-6 (IL-6), ferritin lactate dehydrogenase (LDH); liver enzymes AST; asparagine aminotransferase; ALT, alanine aminotransferase) and renal profile were analysed to evaluate the kidney and liver injury.

Statistical Analysis

All statistical analyses were conducted with Statistical package for Social Sciences (SPSS version 23.0 IBM, Armonk, NY, USA) statistical software. Statistical analysis was performed using Descriptive statistics such as frequency tables and mean (standard deviation) were used to describe quantitative and qualitative data, respectively. Normality of quantitative variables was assessed by the Kolmogorov–Smirnov test. Differences between two independent quantitative and qualitative groups were evaluated by the Student’s t-test and Fisher exact test, respectively. Bonferroni correction was used for pairwise comparisons. Correlation was tested using Spearman’s correlation coefficient. Univariate analysis and logistic regression analysis to study the risk factors related to fibrosis will be performed. A p value of <0.05 is denoted as statistically significant.

Results

Baseline characteristics have been shown in Table 1. The study included 102 patients, out of them 64(63%) had moderate and 38 (37%) had severe covid pneumonia. The mean age of the patients was 58±12 years. Sixty three patients (62%) were between 40-60 years. There was slight male 54(53%) predominance in study population. More than half (n=57,56%) had one or more comorbid condition. Most common coexisting illness was hypertension(n=57,56%).
At the time of acute disease, there was no difference in the different levels of abnormality in the lungs were still present in 88 patients, a mean radiological score of 14.8±9.5. In both lungs in all the patients, with radiological abnormalities were noted in 70% patients compared with moderate pneumonia patients (68% vs. 32%; p = 0.03).

A restrictive pattern [forced vital capacity (FVC)<80% predicted and forced expiratory volume in one second/forced vital capacity (FEV1/FVC) ratio [70%] was seen in 35 patients (32%), and was not significantly different in two groups of patients.

The more severe the disease, the greater the impairment detected in lung function as reduction of DLCO showed statistically significant difference in two groups of patients. The impairment of other lung function parameters, i.e., reduced lung volumes, FVC (p = 0.02), TLC (p = 0.01), and FEV1/FVC (p = 0.02) were also significantly different in two groups.

Table 4 is showing correlation analysis with reduced DLCO and pulmonary functions with reduced DLCO. The impairment of DLCO showed significant negative correlation with severity of disease, peak concentrations of inflammatory markers hsCRP (p = 0.012) and ferritin during acute illness and longer duration of hospital stay age >50, DM and leucopenia, as depicted in Table 5. In Multi variate analysis (Table 6). It was noted that PaO2/FIO2 <200, higher peak inflammatory markers, and longer duration of hospital stay were significantly associated with presence of fibrotic changes at 12 weeks.

**Discussion**

The present study reports that survivors of moderate and severe covid pneumonia do not show complete recovery even 3 months after the acute illness. Although patients with critical pneumonia who required mechanical ventilation were excluded from our study. The residual abnormalities and the long-term effects on changes in both pulmonary function and chest imaging were still observed in three quarters of the cohort at 3 months after discharge.

There have been several risk factors at admission that are associated with pulmonary sequelae. They are severity of disease; higher peak levels...
of inflammatory markers and longer duration of hospital stay.

Male gender, higher BMI and presence of comorbidities were associated with the severity of COVID-19 and a prolonged recovery period as shown by previous studies.\textsuperscript{15,16} Presence of residual symptoms at the follow-up visit: fatigue, reduction of physical activity, dyspnea, asthenia were similar to those reported in the literature.\textsuperscript{17,18} We observed impaired lung function at follow-up as revealed by at least one abnormal parameter in PFT in 75% of patients and poor exercise capacity in 6MWT in 34% patients. We noted reduced DLCO in 54% patients in the whole cohort. The similar rates of DLCO impairment were found in the studies of other researchers.\textsuperscript{19–21}

At 12 weeks follow-up visit, significant radiological findings in the lungs were still discernible in the majority of our study cohort. Ground-glass opacity (GGO) was the most common radiological feature, found in 70% of the patients. It was noted that pure GGO, GGO with consolidation, interstitial thickening, crazy paving, irregular interface and parenchymal band located mainly in bilateral lower lobes with peripheral distribution were the most common CT features in COVID-19.

Radiological findings suggestive of fibrosis were found in 54(53%) patients.

Fibrosis was more likely to develop in patients with severe clinical conditions, especially patients with high inflammatory markers higher level of CRP and ferritin in patients with fibrosis an increased inflammatory reaction might lead to the formation of pulmonary fibrosis. Patients with fibrosis had a longer period of hospital stay than those without fibrosis. The results in the literature are variable with some studies reporting completely recovered lungs in most of the patients\textsuperscript{22} and others report different levels of residual abnormality.\textsuperscript{23–25}

Our study is one of very few studies performed in our population that provides objective results for survivors of moderate to severe COVID-19 who did not require mechanical ventilation and without influence of previously existing chronic lung damage. The main limitation of this study is that it was conducted at single centre with small number of patients and the limited follow-up period; a longitudinal study will be needed to supplement and substantiate these data.

In conclusion, present study demonstrates that residual radiological and functional changes in the lungs, reduced physical activity are found in a significant number of COVID-19 survivors 3 months after discharge from hospital who had moderate to severe pneumonia but did not require mechanical ventilation. It is necessary to follow-up these patients to detect and appropriately manage any persistent long-term sequelae in lungs caused due to SARS-CoV-2.

### References


COVID-19 with Early Neurological and Cardiac Thromboembolic Phenomena—Timeline of Incidence and Clinical Features

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Abstract
Background and Purpose: We documented patients with cardiac and neurological thromboembolic phenomena as a primary presentation of COVID-19 at a tertiary care hospital, and compared a subset of COVID associated strokes against COVID-19 patients without thrombotic manifestations.

Methods: We included cases with ischemic arterial stroke/ Acute Coronary Syndrome (ACS) presenting prior to/within 72 hours of systemic/ respiratory COVID manifestations and studied differences between COVID- strokes and non-thrombotic COVID controls in a nested case control analysis.

Results: We admitted 68 stroke (49 ischemic strokes) and 122 acute coronary syndrome (ACS) cases associated with COVID-19 during April–November 2020, with the proportion of Strokes being 1.67%, and that of ACS being 2.99%, of 4069 total COVID cases. We compared a subset of COVID associated strokes (Cases: n=43; mean age 51.5 years;12 women) against COVID-19 patients without thromboembolic manifestations (Controls: n=50; mean age 51.6 years; 9 women). Cases had significantly higher D-Dimer values than controls (32.59 vs 16.47 nmol/L; p=0.035). Mortality was significantly higher in cases (51.2% vs. 26.0%; p = 0.018; OR 2.98, 95CI OR 1.25–7.11). Even within the patient subset needing minimal oxygen support, cases had 7.5 times higher mortality than controls.

Conclusions: Respiratory distress in COVID-strokes could have been due to COVID-19 lung infection or aspiration pneumonia resulting from obtunded sensorium. Death probably occurred before progression to intense respiratory support, due to severe central nervous system insult.

Introduction

There are numerous reports of patients with COVID-19 presenting with both arterial (stroke, myocardial infarction) and venous thrombosis (deep vein thrombosis, pulmonary thromboembolism, cerebral venous sinus thrombosis).1–10 Accelerated thrombogenesis in COVID-19 is postulated to be due to Virchow’s triad, resulting in endothelial dysfunction, abnormal flow and a hypercoagulable state.11–15 At our tertiary care public hospital, we saw COVID-19 presenting with thromboembolic phenomena, where the respiratory involvement was either very mild and simultaneous, or occurred only later during hospitalization, indicating a possible early thrombo-inflammatory pathology, in a subsection of patients. Hence, we documented patients with cardiac and neurological thromboembolic phenomena as a primary presentation of COVID-19. Further, we compared clinical and inflammatory markers in a subset of these patients with markers in patients without thrombotic manifestations of the disease during hospitalization.

Aims

We aimed to document the incidence of acute thromboembolism, namely, ischemic stroke and acute coronary syndrome (ACS) as a presentation of COVID-19. We also aimed to compare clinical and inflammatory markers in a subgroup of patients of COVID-19 with acute ischemic stroke at presentation or within the first 72 hours of other signs and symptoms of COVID-19, with the parameters in patients presenting with respiratory onset disease.

Materials and Methods

Our study center is a 1400 bedded, tertiary care, municipal public hospital in Mumbai, India. We did a retrospective observational serial recruitment of all cases satisfying the inclusion criteria, followed by a nested case control analysis of a subset of the larger cohort of COVID-19 patients.

Operational definitions

Ischemic stroke: Patients who presented to the hospital with ischemic arterial stroke, without systemic or respiratory signs and symptoms of COVID-19 at admission, or stroke developing within 72 hours of systemic or respiratory signs and symptoms of COVID-19, were included during the study period of April to November 2020. Any of the symptoms comprising fever, myalgia, throat pain, dry cough, tachypnoea, loose motions, and an oxygen saturation under 95% on room air at admission were considered as indicative of presence of systemic and respiratory signs of COVID-19.
Acute coronary syndrome: Patients who presented to the hospital with ACS (ST segment elevation myocardial infarction (STEMI) or Non-ST segment elevation myocardial infarction (NSTEMI), or Unstable angina, diagnosed as per standard criteria) without systemic or respiratory signs and symptoms of COVID-19 at admission, or ACS developing within 72 hours of systemic or respiratory signs and symptoms of COVID-19, were included in a similar manner. Patients with pulmonary or other systemic and peripheral thromboembolism and patients with cerebral venous sinus thrombosis (CVST) were not included in the detailed analysis in this study, unless associated with stroke or ACS, as a separate registry is being maintained for them.

Inclusion in case group and control group

We compared clinical and inflammatory markers in patients of COVID-19 with thromboembolic phenomena (acute ischemic stroke) at presentation or within the first 72 hours of other signs and symptoms of COVID-19, with the parameters in patients presenting with respiratory onset disease. The latter group continued to be free of cardiac and neurological ischemic pathology till discharge. We selected the group with acute ischemic stroke as the case group, as complete data was available for the patients with COVID-19 associated stroke. Thus, we analyzed detailed data for 43 COVID-19 cases with associated stroke, and 50 controls with COVID-19 and no associated thromboembolic events.

Controls were included similar proportion to cases. The selection of controls from any given month of the study duration (April to November 2020), corresponded to the proportion of COVID strokes to total COVID-19 cases, for that month. As strokes were highest in proportion to total COVID-19 cases in September and October 2020, the maximum number of controls were taken from that period. Individual cases were selected using random computer-generated numbers.

We evaluated and compared demographic features (age, gender), clinical features (comorbidities, oxygen saturation at admission and modality of maximum oxygen support required during hospitalization), laboratory parameters (inflammatory markers such as C Reactive Protein (CRP) and D-Dimer, creatinine level, platelet count), mortality and predictors of mortality in the case group versus the control group. Modalities of respiratory support included, in order of increasing intensity, nasal cannula, venturi mask, non-rebreathing bag and mask (NRBM), high flow nasal cannula (HFNC), non-invasive ventilation (NIV), and intubation and mechanical ventilation. In the correlation of inhospital mortality with requirement for respiratory support, we divided the patients into two groups. The low flow oxygen support subgroup included patients on room air, nasal cannula and venturi mask, and the high flow oxygen support subgroup included patients on NRBM, HFNC, NIV and intubation with mechanical ventilation.

We used the unpaired samples T-test and chi-square test to study differences in key variables. We assumed unequal variances in reporting T tests. We calculated 95% confidence intervals for mean differences and odds ratios, and considered a p value below 0.05 to be statistically significant only if the confidence intervals for the concerned statistic were congruent. We performed binary logistic regression to determine key predictors of in-hospital mortality. We entered the following variables as independent predictors for both cases and controls: age, sex, number of comorbidities and respiratory distress level (the last coded on an ascending scale reflecting the intensity of mode of supplementary oxygen delivery, where 0 represented no support required, and 6 represented invasive ventilation). CRP and D-Dimer were not added as predictors to this model, as laboratory reports for both markers were available for only 20 cases. In the initial days of the pandemic, logistic pressures on the hospital made it difficult to procure reports for all patients.

Ethical considerations: The study was approved by the Human Research Institutional Ethics Committee of the institute.

Results

During the period April-November 2020, 4,069 COVID-19 cases were admitted in our hospital (Figure 1). There were 68 cases of stroke associated with COVID-19 and 122 cases of ACS associated with COVID-19. Total COVID-19 cases and cardiac cases peaked in May and June 2020. Stroke cases peaked in September and October 2020.

Among 68 patients with stroke, 49 had ischemic stroke. Of these 49 patients, 43 satisfied inclusion criteria for early presentation as ischemic stroke (case group) as per operational definitions. Half of these 43 cases (21; 48.9%) belonged to the 41-60 years age group. Among them, 11 were aged 51-60 years, and 10 were 41-50 years of age. Whereas out of 50 controls, 13 patients (26.0%) were aged 61-70 years, followed by 11 each (22.0%) in the 31-40 years and 51-60 years age groups, respectively.

The sex distribution of cases and controls was as follows: 12 (27.9%) women and 31 (72.1%) men in the case group, versus 9 (18.0%) women and 41 (82.0%) men in the control group.

Cases and controls did not differ significantly in age or sex distribution. Among the cases, 14 of 43 patients (32.6%) were free of comorbidities,
Among the 43 stroke cases, we noted 28 (65.1%) had a CT angiography or MRI angiography done. Large vessel occlusion (LVO) was present in 19/28 (67.8%) patients.

Cases had significantly lower average levels of respiratory support requirement and significantly higher D-Dimer values than controls (Table 1).

We observed that 16 of the 43 stroke cases (37.2%) had an isolated neurological presentation, i.e., they presented with only stroke and no respiratory signs and symptoms of COVID-19. Comparing maximum respiratory support requirement in cases versus controls, we noted that 32/50 (64.0%) of the controls required intensive modes of respiratory support (NRBM, HFNC, NIV, Intubation) as compared to 10/43 (23.26%) of the cases. This difference was statistically significant ($\chi^2 = 22.02$, df 6, $p = 0.001$).

Mortality was 51.2% in the case group compared with 26.0% in the control group, being significantly higher in cases compared to controls ($\chi^2 = 6.237$, df 1, $p = 0.018$; OR 2.98, 95CI 1.25–7.11).

Patients requiring higher modalities of oxygen support (NRBM, HFNC, NIV, invasive ventilation) had higher mortality in both cases and controls (Table 2). In both low flow and high flow oxygen subgroups, cases had significantly higher mortality than controls. However, the differences in mortality between cases and controls was striking in the low flow subgroup. In the latter, despite maintaining satisfactory oxygen saturation on room air or with minimal oxygen support, the mortality was 7.5 times higher in COVID stroke patients as compared to controls (Low flow: 42.4% vs 5.6%, $\chi^2 = 7.626$, df 1, $p = 0.006$; OR 12.53, 95CI 4.90–36.74).

Accurate dates of admission and discharge/death were available for 26 of 43 cases, and all 50 controls. Mean duration of hospitalization for cases was 13.25 days for those who survived and 9.36 days for those who died. For controls it was 12.57 days for those who survived and 11.54 days for those who died.

Table 3 shows the results of binary logistic regression analysis. Respiratory support requirement level was the sole independent predictor of mortality in cases. In controls, mortality was

Table 1: Comparison of means for selected variables in the case and control groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Case mean</th>
<th>Control mean</th>
<th>Mean Difference</th>
<th>% 95% CI of the Difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>43 51.51</td>
<td>50 51.62</td>
<td>-0.11</td>
<td>-6.29–6.08</td>
<td>0.972</td>
</tr>
<tr>
<td>Distress Level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SpO2 on Admission mg/dL</td>
<td>43 89.12</td>
<td>50 86.42</td>
<td>2.70</td>
<td>-3.05–8.45</td>
<td>0.354</td>
</tr>
<tr>
<td>CRP μg/L</td>
<td>20 59.63</td>
<td>50 80.36</td>
<td>-20.73</td>
<td>-53.77–12.30</td>
<td>0.212</td>
</tr>
<tr>
<td>D-dimer ng/mL</td>
<td>20 2975.44</td>
<td>50 1503.42</td>
<td>1472.02</td>
<td>110.72–2833.32</td>
<td>0.035</td>
</tr>
<tr>
<td>D-dimer mmol/L</td>
<td>20 32.59</td>
<td>50 16.47</td>
<td>16.12</td>
<td>1.21–36.74</td>
<td></td>
</tr>
</tbody>
</table>

CRP: C-Reactive protein; SpO2: percentage saturation of oxygen

Table 2: Maximum respiratory support requirement versus mortality in case and control groups

<table>
<thead>
<tr>
<th>Respiratory Support Requirement</th>
<th>Case Died</th>
<th>Case Survived</th>
<th>Control Died</th>
<th>Control Survived</th>
</tr>
</thead>
<tbody>
<tr>
<td>Room air</td>
<td>5 25.0%</td>
<td>15 75.0%</td>
<td>8 100.0%</td>
<td></td>
</tr>
<tr>
<td>Nasal cannula</td>
<td>7 70.0%</td>
<td>3 30.0%</td>
<td>9 90.0%</td>
<td></td>
</tr>
<tr>
<td>Venturi</td>
<td>2 66.7%</td>
<td>1 33.3%</td>
<td>0 0.0%</td>
<td></td>
</tr>
<tr>
<td>NRBM</td>
<td>6 75.0%</td>
<td>2 25.0%</td>
<td>17 85.0%</td>
<td></td>
</tr>
<tr>
<td>HFNC</td>
<td>1 100.0%</td>
<td>0 0.0%</td>
<td>2 100.0%</td>
<td></td>
</tr>
<tr>
<td>NIV</td>
<td>1 100.0%</td>
<td>0 0.0%</td>
<td>1 100.0%</td>
<td></td>
</tr>
<tr>
<td>Intubation</td>
<td>0 0.0%</td>
<td>8 100.0%</td>
<td>0 0.0%</td>
<td></td>
</tr>
<tr>
<td>Low flow group</td>
<td>14 42.4%</td>
<td>19 57.6%</td>
<td>17 94.4%</td>
<td></td>
</tr>
<tr>
<td>High flow group</td>
<td>8 80.0%</td>
<td>2 20.0%</td>
<td>20 62.5%</td>
<td></td>
</tr>
</tbody>
</table>

Low flow: Room air, Nasal cannula and Venturi modes; High flow: NRBM, HFNC, NIV and Intubation modes

Compared to 22 of 50 controls (44.0%). The case group had 9 patients with hypertension (HTN), 4 with diabetes mellitus (DM), and 12 who had both comorbidities. Among the controls, 6 patients had HTN, 11 had DM, and 9 had both. These differences were not statistically significant.

Among the 43 stroke cases, we noted 40 patients with pure arterial infarcts, one with arterial infarct associated with CVST, and two patients with bithalamic infarcts, possibly due to blockage of artery of Percheron or vein of Galen. As CT angiography and venography were not available for these two patients, they were classified as of indeterminate (arterial/venous) etiology. CT scans pinpointed the vascular territory affected in 37 of 41 patients (40 pure arterial infarcts and one infarct+CVST) with arterial infarcts. Of these, 26 (70.3% of 37) had infarcts in the carotid territory, four (10.8% of 37) in the vertebrobasilar territory, and seven patients (18.9% of 37) had infarcts in both territories. Additionally, four patients were clinically diagnosed as carotid territory infarct, although their initial CT scans revealed no acute changes (repeat CTs were not done either due to logistic constraints or clinical deterioration). Among the 33 carotid ischemic strokes with CT scans available (comprising carotid territory strokes and carotid component of mixed territory strokes), 15 were classified as large hemispherical, 10 were subcortical and 8 were pure cortical infarcts.

Among the 43 stroke patients, 28 (65.1%) had a CT angiography or MRI angiography done. Large vessel occlusion (LVO) was present in 19/28 (67.8%) patients.

Cases had significantly lower average levels of respiratory support requirement and significantly higher D-Dimer values than controls (Table 1).

We observed that 16 of the 43 stroke cases (37.2%) had an isolated neurological presentation, i.e., they presented with only stroke and no respiratory signs and symptoms of COVID-19. Comparing maximum respiratory support requirement in cases versus controls, we noted that 32/50 (64.0%) of the controls required intensive modes of respiratory support (NRBM, HFNC, NIV, Intubation) as compared to 10/43 (23.26%) of the cases. This difference was statistically significant ($\chi^2 = 22.02$, df 6, $p = 0.001$).

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Patients requiring higher modalities of oxygen support (NRBM, HFNC, NIV, invasive ventilation) had higher mortality in both cases and controls (Table 2). In both low flow and high flow oxygen subgroups, cases had significantly higher mortality than controls. However, the differences in mortality between cases and controls was striking in the low flow subgroup. In the latter, despite maintaining satisfactory oxygen saturation on room air or with minimal oxygen support, the mortality was 7.5 times higher in COVID stroke patients as compared to controls (Low flow: 42.4% vs 5.6%, $\chi^2 = 7.626$, df 1, $p = 0.006$; OR 12.53, 95CI 4.90–36.74).

Accurate dates of admission and discharge/death were available for 26 of 43 cases, and all 50 controls. Mean duration of hospitalization for cases was 13.25 days for those who survived and 9.36 days for those who died. For controls it was 12.57 days for those who survived and 11.54 days for those who died.

Table 3 shows the results of binary logistic regression analysis. Respiratory support requirement level was the sole independent predictor of mortality in cases. In controls, mortality was
predicted by increasing age and female sex in addition to respiratory support requirement.

Discussion

During the COVID-19 pandemic, it was recognized early on that the presence of thrombosis in multiple organ systems points to thromboembolism being an integral component in the pathogenesis of this novel disease.\(^{10,11,14,15}\)

During May and June 2020, we noted many patients presenting with thromboembolic phenomena as an early manifestation of COVID-19, or developing these complications during admission. Hence, the first part of our study comprised documentation of acute cerebral and cardiac thromboembolic events during admission for COVID-19 infection. Acute neurovascular and cardiac events associated with COVID-19 at our centre included 68 cases of stroke and 122 cases of ACS during the period of April-November 2020. Among these 68 strokes, 22 (37.9%) had presented with only stroke and no respiratory signs and symptoms of COVID-19. Of these 68 strokes, 49 had ischemic strokes of whom 43 were selected for the present study. We noted a similar proportion of isolated neurological presentation (16/43; 37.2%) in this subset too. This possible early thromboembolic effect of COVID-19 on the neurovascular system, prompted us to investigate patients with ischemic stroke as a primary presentation of COVID-19, in the second part of our study. The occurrence of thromboembolic phenomenon early in the course of COVID-19 disease has also been observed in other studies by Pillai et al.,\(^{12}\) Stefanini et al.\(^{16}\) and Mao et al.\(^{17}\)

43 patients satisfied our inclusion criteria for this study viz., ischemic stroke within 72 hours of onset of first symptoms of COVID-19. As complete data was available for the patients with stroke, we compared characteristics of stroke patients with corresponding findings in patients without thromboembolic manifestations of the disease. A detailed similar analysis of the patients with ACS was not possible, due to lack of complete data.

Figure 1 shows the timeline of admission of all COVID-19 cases, COVID-19 with ACS, and COVID-19 with stroke, under medicine and cardiology departments. Whereas cardiac cases peaked in May and June 2020, the peak of stroke cases was in September and October 2020, at which time stroke and ACS incidence were approximately the same. As both ACS and stroke are thrombo-inflammatory manifestations of the virus, it is surprising that these two events have shown different peaks. ACS incidence declined gradually after June whereas stroke incidence gradually rose to peak in September-October. In September and October 2020, the number of COVID-19 admissions (only patients with higher category oxygen requirement, beyond nasal cannula at 4 litres/minute, or those with systemic complications, are admitted at our centre) had fallen steeply, with ACS cases also showing a gradual decline. It is possible that patients with severe strokes may have expired at home due to difficulties of travel in a severely disabled state during the lockdown in peak months. Hence, the rise in stroke admissions later may have been due to better facilities of transportation, as the lockdown eased in the city.

Among the 43 stroke cases, CT confirmation of infarct and arterial territory could be made in 37 patients. Four patients were diagnosed clinically as carotid territory stroke, and the lack of hemorrhage on the CT classified them as possible early infarcts. Due to the difficulties inherent in and peculiar to the COVID-19 situation in a large public hospital, repeat imaging could not be done in these patients. However, it was clear that in those with imaging confirmation, the infarcts were either large or multiple, or in eloquent areas; 18.9% being in both anterior and posterior circulation territories, 10.8% in vertebrobasilar territory, and even among the carotid territory strokes, almost half being large hemispherical strokes. Additionally, evidence of LVO in 67.8% of those who had a CT angiography, portended the possibility of enlargement of infarct area.

CRP levels, while being over 10 times the upper limit of normal level in both groups, showed no significant difference between the two groups (Table 1). This was not surprising as both the groups fell into the moderate to severe infection categories, in terms of respiratory and other systemic involvement. While both cases and controls had high levels of D-Dimer (more than thrice the upper limit of normal value), the case group had a significantly higher D-Dimer level than the control group. A deranged coagulation function, including elevated D-Dimer, has been demonstrated to lead to disease progression of COVID-19.\(^{16,19}\) Several studies have reported elevated CRP and D-Dimer in COVID-19 patients.\(^{14,17,20,21}\) COVID-19 associated inflammation resulting in a hypercoagulable state has been well documented.\(^{20,22}\)

In our study, controls required higher respiratory support than cases. The number of patients requiring NRBM, HFNC or intubation being 32 (64%) in the control group, as against 10 (23.26%) in the case group. This could be related to two factors: the higher survival rate in controls (mortality in case and control groups being 51.2% and 26.0% respectively), and longer mean duration of survival in controls (the patients in the case group who died in hospital, survived for an average of 9.3 days as against 11.5 days in the patients who expired in the control group).

In the overall ‘low flow oxygen support group,’ the 7 times higher death rate in cases compared to controls, was striking. Death in cases probably occurred before progression to higher levels of respiratory support,
due to severe central nervous system insult, without severe respiratory involvement. The phenomenon of increased risk of thrombus formation leading to stroke (postulated to be due to viral involvement of the endothelium), in the absence of severe respiratory disease, has been previously documented.\textsuperscript{17,21} Contrarily, other authors have posited that the incidence of stroke in COVID-19 may be related to severity of infection.\textsuperscript{17,21}

In this study, although higher modes of respiratory support were less frequent in the case group, respiratory distress level requiring higher modality of support predicted mortality within the group. The respiratory distress could have been due to COVID-19 lung infection or due to aspiration pneumonia resulting from obtunded sensorium in stroke.

The prediction of mortality by increasing age, as seen in the control group in our study, has been well documented by various authors.\textsuperscript{23,25} However, most studies have shown that men have a higher risk of COVID-19 related death than women,\textsuperscript{23,25} contrary to our findings in the control group. Our sample size for the control group was small, and this limitation could have led to this finding.

A major limitation of our study is the lack of documentation of clinical and subclinical pulmonary thromboembolic phenomena in the case and control groups. This was highly probable, given the thrombo-inflammatory milieu, and the concomitantly existing cerebral thrombosis. It is possible that this was more common in the case group and could have contributed to the mortality. We did not take pulmonary thromboembolism into account in our analysis, as complete data on CT pulmonary angiography was not available in many patients.

In conclusion, our comparison of a thromboembolic cerebral presentation of COVID-19 with a clinically non-thromboembolic presentation of COVID-19, demonstrated higher D-Dimer levels, and a higher mortality in the absence of prominent respiratory compromise, in the former group. The higher mortality was possibly due to the severity of stroke and presence of proximal LVOs. We could not compare mortality in COVID-19 associated strokes with a cohort of non-COVID associated strokes in the same period, as our regular admissions were severely limited during the pandemic. A meta-analysis of stroke in COVID-19 has highlighted that the mean mortality rate among stroke patients with COVID-19 infection was 46.7% compared to only 8.7% among those without COVID-19 infection.\textsuperscript{26}

The study was approved by the Human Research Institutional Ethics Committee, Lokmanya Tilak Municipal Medical College and General Hospital, Sion, Mumbai.

References

In Management of Asthma and COPD Patients

Consider

Esiflo
Salmeterol and Fluticasone Propionate

The Synonym of Trust

COPD - Chronic Obstructive Pulmonary Disease

Abridged prescribing information: Dosage form: Esiflo inhaler is available in 125 & 250 Transhaler (Metered Dose Inhaler) and 100, 250 & 500 Transcap (Dry Powder Inhaler). Indications and usage: Esiflo inhaler is indicated in the regular treatment of asthma, where use of combination (long-acting beta-2 agonist and inhaled corticosteroid) has been found to be appropriate and in patients with severe COPD. Dosage and administration: Dosage in individual is adjusted according to disease severity. Asthma: Adult and adolescents (12 years and older) - Esiflo 125/500 transhaler 2 inhalation twice daily or Esiflo 200/500 transcap 1 inhalation twice daily. Children (4 yrs and above) - Esiflo 50 Inhaler 2 inhalations twice daily or Esiflo 100 transcap 1 inhalation twice daily (not recommended for children below 4 years of age). COPD: Esiflo 125/500 transhaler 2 inhalations twice daily or Esiflo 250/500 transcap 1 inhalation twice daily. Contraindications: Patients with a history of hypersensitivity to any components of the drug product. Warnings and precautions: Not to be used to treat acute asthma symptoms. Esiflo inhaler should be administered with caution in patients with pulmonary tuberculosis, severe cardiovascular diseases, diabetes mellitus, untreated hyperkalaemia or hypokalaemia, Pregnancy: Should only be considered if the expected benefit to the expectant mother is greater than any possible risk to the foetus. Lactation: Should only be considered if the expected benefit to the nursing mother is greater than any possible risk to the child. Adverse effects: Tachycardia, nasal congestion/loosenage, dryness of mouth, weight gain. Full prescribing information is available on request.

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Real-world Experience with Favipiravir for Treatment of COVID-19 among Indian Healthcare Professionals

Mangesh Tiwaskar¹, Raja Dhar², Deepak Talwar³, Abdul Ansari⁴, Mahesh Lakhe⁵, Sagar Panchal⁶*, Sagar Bhagat⁷, Saiprasad Patil⁸, Hanmant Barkate⁹

Abstract

Introduction: Favipiravir has shown promising results for COVID-19 globally. Though many Indian patients have received favipiravir, there is a lack of real-world data for its clinical use by the practicing physicians. Hence, a qualitative survey was conducted to understand real-world use of favipiravir in management of COVID-19.

Methods: A cross-sectional, web-based, qualitative survey was conducted between September 2020 to October 2020, among Indian physicians from various specialties involved in COVID-19 care and using favipiravir in their practice. Physicians were provided survey link having a structured questionnaire with 32 questions. They were enquired on-1) demographics, practice information, 2) place of favipiravir in clinical practice, 3) treatment protocol for mild to moderate COVID-19, 4) dosage and duration of favipiravir, 5) effectiveness of favipiravir, 6) tolerability of favipiravir 7) global efficacy and safety assessment of favipiravir.

Results: A total of 500 physicians were contacted, of which 50 physicians completed the questionnaire. 25(50.0%) were from south zone followed by 12(24.0%) from west. Majority physicians (47, 97.9%) stated that favipiravir was used for COVID-19 in outpatient setting. Favipiravir was considered as the current drug of choice for mild COVID-19 with fever (86.6%). All physicians agreed that favipiravir was being used as per the recommended dose. A total of 75% & 62.5% physicians agreed to observed clinical improvement by around 3-5 days & 5-7 days in symptomatic mild & moderate COVID-19 respectively.

Conclusion: Majority of the physicians considered favipiravir to be safe and effective in treatment of mild to moderate COVID-19.

Introduction

COVID-19 is an infectious disease of respiratory system caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2).¹,² COVID-19 pandemic still continues to adversely impact the socio-economic framework globally.³ COVID-19 has a spectrum of manifestations including early stage of mild illness dominated by virological response while late phase of severe illness dominated by dysregulated inflammatory response.⁴ Viral shedding is observed 1-2 days before symptoms and may continue for 1-2 weeks in mild-moderate cases and for more than 2 weeks in severe cases.⁵,⁶ There is a higher risk of infection and disease progression in elderly and patients with comorbidities.⁷

RdRp inhibitors as remdesivir and favipiravir have emerged as potential treatment options: Rapid viral clearance, higher clinical recovery rate, oral administration with proven safety profile makes oral RdRp inhibitor, favipiravir a promising repurposed drug to treat mild to moderate COVID-19.⁸⁻¹¹

Treatment guidelines from many countries and some states from India have included favipiravir in the COVID-19 treatment protocol.¹¹

Drug Controller General of India (DCGI) granted 1st manufacturing and marketing approval to Glenmark for FabiFlu® (favipiravir) on 19th June-2020 through accelerated approval process.¹² Recently published Phase III Indian trial (CTRI/2020/05/025114) of favipiravir in mild to moderate COVID-19 showed faster time to clinical cure with favipiravir (3 days) compared to standard supportive care (5 days), p = 0.030. Adverse events (AEs) were mild to moderate in severity and transient in nature.¹³

Though many patients have received favipiravir during ongoing pandemic, there is a lack of real-world insights on its clinical use. Hence, to understand real-world use of favipiravir in management of COVID-19 a qualitative survey was conducted among Indian physicians involved in COVID-19 patient care.

Methods

Study design

A cross-sectional, web-based, voluntary, qualitative survey was conducted among physicians from various specialties (general physician, consultant physician, pulmonologist, intensive care specialist, ear nose throat [ENT] specialist, and infectious diseases specialist) involved in COVID-19 care. Survey was conducted across all four regions of India (North, South, East and West), between 01 September 2020 to 31 October 2020. Inclusion criteria comprised of physicians who provided COVID-19 care and prescribed favipiravir. Convenience sampling method was used for survey.

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Physicians were identified from IQVIA OneKey® database lists according to their speciality and favipiravir prescriptions.

Invitations to participate in the survey were sent via e-mail and WhatsApp. Physicians accessed the survey through a distinct link. All physicians who expressed willingness to participate in web-based survey were requested to give their consent. No compensation was offered for their participation in survey to avoid bias. Further, to ensure good response rate, targeted physicians were sent e-mail reminders.

**Methodology**

A web-based, anonymous, structured qualitative questionnaire was developed and distributed using SurveyMonkey® an online questionnaire generator. Questionnaire consisted of 32 close-ended questions related to 1) Physicians’ demographics, practice information, 2) place of favipiravir in clinical practice, 3) treatment protocol for mild to moderate COVID-19, 4) dosage and duration of favipiravir 5) effectiveness of favipiravir, 6) tolerability of favipiravir and 7) global efficacy and safety assessment of favipiravir. The survey questionnaire is present in supplementary material 1. The survey was compliant with Checklist for Reporting Results of Internet Surveys (CHERRIES). Responses to questions were captured either on a five point Likert scale (1 = Strongly disagree to 5 = Strongly agree) or Yes/No format. Survey questionnaire was in English and was validated for its consistency, comprehensibility and appropriateness by a multidisciplinary physicians' panel. Participating physicians were free to opt out of survey at any point. Confidentiality of information was preserved by keeping it anonymous and participants were requested to provide their honest responses. Once the responses were submitted physicians could not undertake survey again. Total time for completion of survey was estimated up to 10 minutes.

All analyses were descriptive in nature and carried out using data provided by SurveyMonkey®. No statistical comparison was planned since, no hypothesis testing was performed. Response data was presented as percentages. Categorical variables were described as the relative percentage per category. For the responses on Likert scale weighted average were also obtained.

**Results**

**Surveyed Physicians demographics**

Of total 500 physicians who were contacted, 50 physicians participated in survey. Among 50 with completed and analysable questionnaire, 25 (50.0%) were from south zone followed by 24(48.0%) from west and 1 (2.0%) from north. Overall, most of participants were consultant physicians (25, 50.0%) followed by pulmonologist (10, 20.0%) and general physicians (5, 10.0%).

**Place of favipiravir in clinical practice**

Majority of the physicians (97.9%) reported to use favipiravir for patients with COVID-19 in outpatient setting while 65.9% physicians stated its use in hospitalised patients.

**COVID-19 patient profile and favipiravir usage**

Among wide range of clinical spectrum of COVID-19, maximum (percentage, weighted average) (86.6%, 4.04) agreement was for favipiravir use in 'mild COVID-19 with fever'. Next (80%, 3.96) agreement was for favipiravir use in 'very mild COVID-19 with symptoms other than fever'. 34.0% (2.27) and 43.1% (3.23) physicians agreed for favipiravir use in 'mild COVID-19 with fever'. 2.2% (1.1) and 11.3% (6.67) physicians agreed for favipiravir use in 'very mild COVID-19 patients with symptoms other than fever'. 34.0% (2.27) and 43.1% (3.23) physicians agreed for favipiravir use in 'very mild COVID-19 patients awaiting emergency surgery, is required for specific reasons (e.g. Liver disease (CLD), Chronic kidney disease (CKD) (eGFR <30 mL/min) and chronic liver disease (CLD).'

### Table 1: Use of favipiravir as per patient profile

<table>
<thead>
<tr>
<th>Clinical statements</th>
<th>Strongly Disagree (1)</th>
<th>Disagree (2)</th>
<th>Neutral (3)</th>
<th>Agree (4)</th>
<th>Strongly Agree (5)</th>
<th>Weighted Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favipiravir is the current drug of choice for mild COVID-19 with symptoms other than fever. (Very mild) (N=45)</td>
<td>2.2%</td>
<td>0.0%</td>
<td>17.7%</td>
<td>60.00%</td>
<td>20.00%</td>
<td>3.96</td>
</tr>
<tr>
<td>Favipiravir is the current drug of choice for mild COVID-19 with fever. (Mild) (N=45)</td>
<td>0</td>
<td>6.67%</td>
<td>6.67%</td>
<td>62.22%</td>
<td>24.44%</td>
<td>4.04</td>
</tr>
<tr>
<td>Favipiravir is the current drug of choice for high-risk (e.g. Elderly, Comorbidities) mild COVID-19 patients. (N=44)</td>
<td>2.2%</td>
<td>9.09%</td>
<td>18.18%</td>
<td>61.36%</td>
<td>9.09%</td>
<td>3.66</td>
</tr>
<tr>
<td>Favipiravir is the current drug of choice for moderate COVID-19, not requiring oxygen support. (N=44)</td>
<td>2.27%</td>
<td>6.82%</td>
<td>38.64%</td>
<td>43.18%</td>
<td>9.09%</td>
<td>3.50</td>
</tr>
<tr>
<td>Favipiravir can be initiated in suspected clinical case of COVID-19 (empirically) while awaiting RT-PCR report (N=44)</td>
<td>2.22%</td>
<td>8.89%</td>
<td>26.67%</td>
<td>51.11%</td>
<td>11.11%</td>
<td>3.60</td>
</tr>
</tbody>
</table>

N=total number of physicians responding to the question; RT-PCR: Reverse transcription polymerase chain reaction; IL: Interleukin; CRP: C reactive protein; LDH: Lactate dehydrogenase.
HCQ ± LMWH ± Steroids’ in moderate COVID19 patients. (N=40)

Favipiravir is prescribed as 1st line treatment along with ‘supportive treatment + antibiotic ± LMWH ± Steroids’ in moderate COVID19 patients. (N=40)

Favipiravir is the 1st line treatment along with ‘supportive treatment + antibiotic + HCQ’ in symptomatic mild COVID-19 patients. (N=40)

Clinical statements Strongly Disagree (1) Disagree (2) Neutral (3) Agree (4) Strongly Agree (5) Weighted average

Favipiravir treatment to be continued upto 2-3 days beyond symptom resolution (N=40)

2.50% 25.00% 52.50% 20.00% 3.9

Favipiravir treatment duration to be continued till RT-PCR negativity is reached (N=40)

75.00% 17.50% 7.50% 3.3

Favipiravir treatment to be continued for 14 days irrespective of clinical cure or RT-PCR negativity (N=40)

5.00% 35.00% 47.50% 10.00% 3.60

Clinical improvement is generally observed in symptomatic mild COVID-19 patients within 3-5 days with favipiravir (N=40)

5.00% 20.00% 62.50% 12.50% 3.83

Clinical improvement is generally observed in moderate COVID-19 patients within 5-7 days with favipiravir (N=40)

7.50% 30.00% 55.00% 7.50% 3.63

N=total number of physicians responding to the question; RT-PCR: Reverse transcription polymerase chain reaction

Clinical statements Strongly Disagree (1) Disagree (2) Neutral (3) Agree (4) Strongly Agree (5) Weighted average

With favipiravir, there is a trend towards lesser progression of disease in mild COVID-19 cases (N=40)

5.00% 35.00% 52.50% 7.50% 3.63

With favipiravir, there is a trend towards lesser progression of disease in moderate COVID-19 cases (N=40)

10.00% 45.00% 40.00% 5.00% 3.40

With favipiravir, there is a trend towards lesser requirement of oxygen support in mild to moderate COVID-19 (N=40)

16.22% 43.24% 35.14% 5.4% 3.30

N=total number of physicians responding to the question

Table 2: Treatment protocol in mild to moderate COVID-19

Treatment protocol in mild to moderate COVID-19

Maximum agreement (92.5%, 4.08) was seen for favipiravir 1st line treatment along with ‘supportive treatment and antibiotic combination’ in symptomatic mild COVID-19. High agreement (77.5%, 3.95) was also seen for favipiravir 1st line treatment along with ‘supportive treatment’ in symptomatic mild COVID-19. However favipiravir use as 1st line treatment along with ‘supportive treatment, antibiotic, HCQ with and without low-molecular-weight heparin (LMWH) and Steroids’ in moderate COVID-19 (25.5%, 3.08) was least agreed (Table 2).

Dosage and duration of favipiravir in practice

All physicians agreed that favipiravir was being used as per recommended dose of 1800 mg BID on Day 1 followed by 800 mg BID from Day 2 onwards.

Major agreement (72.5%, 3.90) was on favipiravir treatment continuation up to 2-3 days beyond symptom resolution rather than waiting till RT-PCR negativity or 14 days (Table 3).

Clinical response with favipiravir

75% (3.83) agreed upon observation of clinical improvement within 3-5 days in symptomatic mild COVID-19. Furthermore, 62.5% (3.63) agreed that clinical improvement was observed by 5-7 days in moderate COVID-19 (Table 3).

70.0% (3.83) agreed on observing trend towards lesser progression of disease in mild COVID-19 cases treated with favipiravir, while 60% (3.63) admitted observing such trend in moderate COVID-19. No agreement was obtained among the physicians on requirement of oxygen or hospital discharge in patients treated with favipiravir (<50%) (Table 4).

Safety and Tolerability of favipiravir

Majority physicians (95.0%) tracks liver function test (LFT) and uric acid as a routine practice in patients on favipiravir. However only 57.8% agreed to Electrocardiogram (ECG) checking before and after favipiravir. Gastrointestinal disturbance as the Commonest AE has been agreed by half of the surveyed physicians. 73% physicians acknowledged good tolerability of favipiravir in mild to moderate COVID-19 (Table 5). Upon being enquired about overall experience with favipiravir, 62.0% physicians rated favipiravir as safe and effective in treatment of mild to moderate COVID-19, while 38.0% physician had a neutral view for safety and effectiveness.
Discussion

In a first of its kind attempt to present real-world evidence for use of favipiravir from an Indian physician’s perspective, this survey was conducted. Overall, surveyed physicians across various specialities from various regions of country agreed that favipiravir was a safe and effective treatment option for mild to moderate COVID-19 especially in OPD setting. Physicians unanimously followed the recommended dose for favipiravir -1800 mg BID on Day 1 followed by 800 mg BID from Day 2 onwards which was in line with the approved posology.

Survey revealed that favipiravir is being used most commonly in mild COVID-19. Mild COVID-19 represents biggest pie of disease spectrum and agreement on using favipiravir in this subset appears to be in line with Maharashtra and other state guidelines that have recommended use of favipiravir for mild symptomatic patients with or without comorbidities or having red flag signs, along with moderate COVID-19. Favipiravir use was reported to be in combination of supportive treatment and antibiotics in mild cases by majority of the physicians.

Also favipiravir use to reduce viral shedding in specific population (e.g. undergoing surgery) of asymptomatic COVID-19 has been favoured by respondents which underlines probable benefit of higher viral clearance with favipiravir (62.5%) as compared to SOC (30%) (P = 0.018) from Russian RCT and numerically faster (5 days vs 7 days, p=0.129) viral clearance observed in Indian RCT.

Less than half of the physicians start favipiravir in very mild and mild COVID-19 patients irrespective of presence of elderly, comorbidities and raised inflammatory markers (red flag signs) while one third would initiate it based on the red flag signs. This highlights the still evolving understanding of precise therapeutic window of intervention.

Use of favipiravir in CKD and CLD population was restricted by majority of physicians which is in line with current prescribing information.

Majority physicians agreed observing early clinical improvement within 7 days of favipiravir use in mild to moderate COVID-19. Findings were consistent with results from Japanese registry study, where clinical improvement at 7 days was 73.8% and 66.6% for mild and moderate COVID-19, respectively. Also our findings were in line with interim results of phase II/III Russian RCT where median time to body temperature normalisation (<37°C) was 2 days (IQR 1–3) in favipiravir groups and 4 days (IQR 1–8) in SOC group(p =0.007). Similarly in prospective, RCT from Japan of early versus late favipiravir in hospitalised COVID-19 patients, a faster defervescence (2.1 days versus 3.2 days) in early treatment group was reported (aHR, 1.88; 95% CI, 0.81–4.35, and p = 0.048).

When asked about safety profile of favipiravir, majority agreed asymptomatic, transient rise in uric acid and LFT as common AEs observed. Its documented that hyperuricemia and LFT abnormalities were the most common AEs in real-world setting. It is in line with the established and well-characterised safety profile of favipiravir.

Physicians were inquired on safety monitoring measures taken while using favipiravir. More than 90% responded to keeping a track of LFT and uric acid as a routine practice in patients prescribed with favipiravir. Majority agreed favipiravir to be safe and well tolerated in clinical practice, however 38% opted to stay neutral on its use. This responses seems to be due to limited experience and emergency authorization of the drug in the country.

This is the first of its kind real-world assessment on the use of favipiravir. However, we do acknowledge certain limitations to our survey. A response rate of 10% was observed for the survey. This lower participation from physicians can be attributed to COVID-19 pandemic reaching its peak in India when our survey was rolled out and voluntary participation without any compensation. Further, due to continued outbreak of the pandemic and physicians’ involvement in its prevention and control, we were unable to conduct focus group interviews to get further insights on the use of favipiravir. In addition, data presented in this survey was dependent on the physicians’ honesty and recall ability; thus, they may be subject to recall bias.

Nevertheless, this survey provides first-hand experience from the frontline warriors of COVID-19 about antiviral drug favipiravir. Participation from diverse specialities provided comprehensive insights about use of favipiravir in India. We believe more such studies on large scale will not only add to real-world data on the repurposed drugs for the scientific community but will also help in understanding the clinical practice preferences of physicians related to management of COVID-19 in India. More such real-world evidence from other repurposed drugs will surely help in streamlining the treatment protocols for COVID-19. Furthermore, long-term experience of the participating physicians would be valuable to explore in the future.

Conclusion

Majority of the Indian physicians acknowledged favipiravir to be safe as well as effective drug in the treatment of mild to moderate COVID-19. Favipiravir emerged to be the current drug of choice for mild COVID-19 with fever and as the 1st line treatment along with ‘supportive treatment and antibiotic combination’ in symptomatic mild COVID-19.
Effectiveness of Framingham and ASCVD Risk Scores in Predicting Coronary Artery Disease – A Comparative Study with Syntax Score

Sucharita Duttagupta1*, Rajesh Thachathodyil2, Anjana Rameshan1, Akshaya Venkatachalam1, Sneha Georgy3, Dipu TS4, Jaideep Menon2

Abstract

Objectives: Primary objective was to determine an association between Atherosclerotic Cardiovascular Disease (ASCVD) and Framingham (FRS) risk scores with Syntax score (SS).

Secondary objective was to determine sensitivity, specificity and discriminative ability of FRS and ASCVD risk scores in detecting Coronary Artery Disease (CAD) and predicting its severity.

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References


17. Favipiravir Prescribing Information.


Materials and Methods: This is a cross-sectional study carried out in the Comprehensive Health Clinic of Amrita Institute of Medical Sciences, Kochi, Kerala. Patients voluntarily visiting the clinic for a health check-up were referred to Cardiology based on a positive treadmill test result where they underwent a coronary angiogram. Secondary data on patients’ demographics, prior history of cardiovascular diseases, investigations and interventional procedures was collected from the hospital registry. The risk scores were calculated using the data through online calculators. Analysis was carried out using SPSS.

Results: Chi-square analysis showed significant association between FRS and SS. Both FRS and ASCVD risk scores have good sensitivity for CAD while having good specificity for patients with high Syntax score (SS≥33). ROC curve showed that ASCVD risk score has a higher positive likelihood ratio than FRS for predicting CAD and high Syntax Score Patients.

Conclusion: The study concludes that FRS and ASCVD risk scores are effective risk predicting models for CAD. FRS is a more sensitive risk score than ASCVD risk score in predicting CAD whereas ASCVD risk score has a higher ability to differentiate patients with CAD and high Syntax Score than FRS.

Introduction

Cardiovascular diseases are the leading causes of death globally, accounting for nearly 17.9 million deaths annually.1 Atherosclerotic cardiovascular disease (ASCVD) is characterized by a long gestation period progressing from fatty streaks to atheromatous plaques and further to obstructive lesions. If individuals at risk are identified and necessary steps towards lifestyle change and risk factor modification are achieved, progression of disease would be decelerated greatly. Therefore, risk assessment of developing a cardiovascular disease is crucial in the current scenario where there is an increase in prevalence of non-communicable diseases due to changes in lifestyle along with other factors. Coronary artery disease contributes to more than 9 million deaths in a year globally.2 According to a Global burden study, cardiovascular diseases contributed to 28.1% of total deaths and 14.1% of total DALYs in India in 2016 compared to 15.2% and 6.9%, respectively, in 1990.3 Coronary artery disease was the leading cause of DALYs in India, contributing to 17.8% of total deaths and 8.7% of total DALYs in 2016.4

Cardiovascular risk scores like Framingham and ASCVD risk score are useful tools that enable clinicians to estimate the risk of developing cardiovascular diseases and also to decide on treatment measures. Framingham Risk Score is a risk score developed from the Framingham Heart Study, a cohort study which was primarily done among Caucasians. The study brought out major risk factors for cardiovascular diseases.4 The risk score is calculated based on variables like age, sex, blood pressure, smoking habits, chewing tobacco, total cholesterol (TC) and high density lipoprotein (HDL) levels. Patients with scores (<10%) are classified as low risk, (10-20%) as moderate risk and (20%) as high risk.5 The score though useful in estimating cardiovascular risk in the western population, is inaccurate in estimating the risk in Indian population due to the difference in the racial, ethnic and behavioral variation of risk factors in both of the populations. Another score, the Atherosclerotic Cardiovascular Disease, risk score, was published in 2013 by the American Heart Association.6 Unlike the FRS, ASCVD risk score was created by pooling in data from diverse racial populations. This algorithm evaluates the cardiovascular risk based on variables like age, sex, race, total cholesterol levels, HDL levels, blood pressure, history of diabetes and hypertension, habits like smoking and chewing tobacco and use of medications like aspirin and statin. Patients are categorized as high (>20%), intermediate (7.5-20%), borderline (5-7.5%) or low (< 5%) risk score category depending on the score calculated.6

Syntax score

This score is a calculated prerequisite to percutaneous coronary intervention/Coronary Artery Bypass Graft along with the angiogram report. It is calculated using the following variables: arterial dominance, lesion number, coronary tree segments involved and adverse variables of the lesion like total occlusion, bifurcations or trifurcation lesions, aortic ostial lesion, severe tortuosity, thrombus, calcification, length of stenosis (>20 mm), and diffuse disease (>75% length of segment with a diameter of <2 mm).7 Occlusion ≥50 % in a vessel and of ≥1.5 mm of diameter should be scored.8 Patients can either have a Syntax Score (SS=0) or (no CAD).9 Patients with (SS>0) are categorized as those with low (1-22), intermediate (23-32) or high score (≥33).10

Though separate studies on comparison of different cardiovascular risk scores and usage of SS to determine the therapeutic intervention in a patient exist, only a few studies have been done to compare risk scores with the severity of coronary artery lesions calculated using SS.11,12 In this study, we have focussed on two important established risk scores, Framingham and ASCVD, to assess the relationship of each score with Syntax score. This will help us to assess the ability of each score to accurately predict cardiovascular risk and mortality, and determine whether better risk predicting scores have to be made.

Methodology

Study design

This is a retrospective observational study, carried out in the comprehensive health clinic of Amrita Institute of Medical Sciences, a tertiary care centre in Kochi, Kerala.

Sample size calculation

The sample size was calculated based on the results of a study by Jean-Michel Paradis et al. where 44.03% of people had moderate and high Syntax score (≥23).10 On calculation, the estimated sample size was 122 with 95% CI and 20% relative precision.

Inclusion criteria

Any patient more than 20 years of age who visited the Comprehensive Health Clinic between January (2016) and December (2017), and were referred to Adult Cardiology Department based on positive treadmill test results.
Patients were categorised based on Syntax score as SS=0 (without CAD) and SS>0 (with CAD). A second categorisation was SS<33 (without high Syntax Score) and SS≥33 (with high Syntax Score) to separate patients with severe coronary artery lesions from those with mild or no lesions. Categorical variables were expressed as percentages (%) and compared using chi-square test. Sensitivity and specificity of both risk scores were calculated. The receiver operating characteristic (ROC) curves were made based on the presence of CAD (SS>0) and high Syntax Score (SS≥33). The discriminative ability (area under the curve) and positive likelihood ratio of each score was calculated from ROC curves. p-value (<0.05) was considered statistically significant. All statistical studies were conducted with SPSS program version 21.0. Ethical committee approval was taken prior to data collection.

**Results**

The study population had 125 patients having a mean age of 56.2±7.68 years with a range of 38–71 years, among which 114 were males and 11 were females. The characteristics of the population are described in Table 1. The study population was categorised into low, intermediate and high risk category based on Framingham and ASCVD risk scores as shown in the same Table. On calculating Syntax Score, 95 (76%), 20 (16%) and 10 (8%) were of low, intermediate and high risk score category respectively. Among the low score category, 22(17.6%) had Syntax Score=0.

Risk predicting variables of the patients were compared between SS=0 (without CAD) and SS>0 (with CAD) (Table 2). The baseline characteristics of the patients are well matched as shown in Table 2.

As given in Table 3, both FRS and ASCVD risk scores have good sensitivity [(91.3%), (88.6%)] respectively in identifying the presence of CAD in a patient. Both have good specificity [(94.6%), (94.4%)] in identifying patients with high Syntax Score.

On doing chi-square analysis between high FRS score (>20%) and high ASCVD risk score (>20%) with categories (SS=0) and SS>0, FRS showed significant association (Pearson’s coefficient=8.42, p-value = 0.004), whereas ASCVD risk score shows a positive association but of no statistical significance (Pearson’s coefficient=2.83, p-value = 0.09). The study population had 125 patients having a mean age of 56.2±7.68 years with a range of 38–71 years, among which 114 were males and 11 were females. The characteristics of the population are described in Table 1. The study population was categorised into low, intermediate and high risk category based on Framingham and ASCVD risk scores as shown in the same Table. On calculating Syntax Score, 95 (76%), 20 (16%) and 10 (8%) were of low, intermediate and high risk score category respectively. Among the low score category, 22(17.6%) had Syntax Score=0.

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On doing chi-square analysis between high FRS score (>20%) and high ASCVD risk score (>20%) with categories (SS=0) and SS>0, FRS showed significant association (Pearson’s coefficient=8.42, p-value = 0.004), whereas ASCVD risk score shows a positive association but of no statistical significance (Pearson’s coefficient=2.83, p-value = 0.09).

**Table 2: Distribution of patients based on parameters of CVD risk scores and calculated CVD risk scores**

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<thead>
<tr>
<th>Age group</th>
<th>Frequency</th>
<th>Percentage (%)</th>
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<td>&lt; 40</td>
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<td>40 – 49</td>
<td>23</td>
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<td>50 – 59</td>
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<td>60 – 69</td>
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<td>35.2</td>
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<td>&gt; 70</td>
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<td>1.6</td>
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<table>
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<th>Gender</th>
<th>Frequency</th>
<th>Percentage (%)</th>
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<tr>
<td>Male</td>
<td>114</td>
<td>91.2</td>
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<tr>
<td>Female</td>
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<td>8.8</td>
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<table>
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<tr>
<th>Blood Pressure</th>
<th>Frequency</th>
<th>Percentage (%)</th>
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<td>Normal</td>
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<td>7.2</td>
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<td>Elevated</td>
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<td>14.4</td>
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<th>Percentage (%)</th>
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<td>41</td>
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<table>
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<th>Stage II Hypertension</th>
<th>Frequency</th>
<th>Percentage (%)</th>
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<td>57</td>
<td>45.6</td>
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<thead>
<tr>
<th>Treatment for Blood Pressure</th>
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<th>Percentage (%)</th>
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<td>45.6</td>
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<tr>
<td>Yes</td>
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<td>Yes</td>
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<td>60.0</td>
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<td>Borderline High</td>
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<td>High</td>
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<td>9.6</td>
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<th>Percentage (%)</th>
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<td>49.6</td>
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<tr>
<td>Optimal</td>
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<td>43.2</td>
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<td>High</td>
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<td>7.2</td>
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<th>LDL**</th>
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<td>Near Optimal/Above Optimal</td>
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<td>28.0</td>
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<tr>
<td>Borderline High</td>
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<td>26.4</td>
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<tr>
<td>High</td>
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<td>9.6</td>
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<tr>
<td>Very High</td>
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<td>4.0</td>
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<td>Yes</td>
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<tr>
<td>Yes</td>
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<td>56.0</td>
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<th>Percentage (%)</th>
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<td>No</td>
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<td>76.0</td>
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<td>Yes</td>
<td>21</td>
<td>16.8</td>
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<table>
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<th>Frequency</th>
<th>Percentage (%)</th>
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<td>No</td>
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<td>69.6</td>
</tr>
<tr>
<td>Yes</td>
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<td>30.4</td>
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<td>96.0</td>
</tr>
<tr>
<td>Yes</td>
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<td>4.0</td>
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<th>Frequency</th>
<th>Percentage (%)</th>
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<td>69.6</td>
</tr>
<tr>
<td>Yes</td>
<td>38</td>
<td>30.4</td>
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<table>
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<th>Frequency</th>
<th>Percentage (%)</th>
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<td>17.6</td>
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<tr>
<td>Abnormal</td>
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<th>Angioplasty</th>
<th>Frequency</th>
<th>Percentage (%)</th>
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</thead>
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<tr>
<td>No</td>
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<td>61.6</td>
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<tr>
<td>Yes</td>
<td>46</td>
<td>36.8</td>
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<table>
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<th>Emergency Angioplasty</th>
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<th>Percentage (%)</th>
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<tbody>
<tr>
<td>No</td>
<td>113</td>
<td>90.4</td>
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<tr>
<td>Acute Coronary Syndrome</td>
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<table>
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<th>Angina Incidence</th>
<th>Frequency</th>
<th>Percentage (%)</th>
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</thead>
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<tr>
<td>No</td>
<td>35</td>
<td>28.0</td>
</tr>
<tr>
<td>Yes</td>
<td>35</td>
<td>28.0</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>MI</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>5</td>
<td>4.0</td>
</tr>
<tr>
<td>Yes</td>
<td>4</td>
<td>3.2</td>
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<table>
<thead>
<tr>
<th>&gt;1 Interventional Procedure</th>
<th>Frequency</th>
<th>Percentage (%)</th>
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<tr>
<td>No</td>
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<td>96.8</td>
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<tr>
<td>Yes</td>
<td>4</td>
<td>3.2</td>
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<table>
<thead>
<tr>
<th>Framingham Risk Score</th>
<th>Frequency</th>
<th>Percentage (%)</th>
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<tbody>
<tr>
<td>Low Risk</td>
<td>19</td>
<td>15.2</td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td>37</td>
<td>29.6</td>
</tr>
<tr>
<td>High Risk</td>
<td>69</td>
<td>55.2</td>
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<table>
<thead>
<tr>
<th>ASCVD Risk Score</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>36</td>
<td>28.8</td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td>54</td>
<td>43.2</td>
</tr>
<tr>
<td>High Risk</td>
<td>35</td>
<td>28.0</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Syntax Score</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Score</td>
<td>95</td>
<td>76.0</td>
</tr>
<tr>
<td>Intermediate Score</td>
<td>20</td>
<td>16.0</td>
</tr>
<tr>
<td>High Score</td>
<td>10</td>
<td>8.0</td>
</tr>
</tbody>
</table>

*WHO classification**, **ATP III Guidelines (NCEP)**

**Data Collection**

Secondary data was collected from hospital information system on age, gender, lipid profile like total cholesterol, high density lipoprotein and low density lipoprotein, history of prophylactic use of aspirin and statin therapy, prior history of cardiac diseases, interventional procedures and their outcomes. Anthropometric measures like height and weight, blood pressure and habits like smoking and alcohol intake were found out by personally contacting the patients.

Those who were referred to Cardiology department underwent an angiogram procedure and their syntax score was calculated and recorded. Data was entered into MS-Excel and the scores were calculated using online Framingham Risk Score Calculator (2008), ASCVD calculator (ASCVD+), and Syntax Score Calculator.13

**Data Analysis**

Patients were categorised based on Syntax score as SS=0 (without CAD) and SS>0 (with CAD). A second categorisation was SS<33 (without high Syntax Score) and SS≥33 (with high Syntax Score) to separate patients with severe coronary artery lesions from those with mild or no lesions. Categorical variables were expressed as percentages (%) and compared using chi-square test. Sensitivity and specificity of both risk scores were calculated. The receiver operating characteristic (ROC) curves were made based on the presence of CAD (SS>0) and high Syntax Score (SS≥33). The discriminative ability (area under the curve) and positive likelihood ratio of each score was calculated from ROC curves. p-value (<0.05) was considered statistically significant. All statistical studies were conducted with SPSS program version 21.0. Ethical committee approval was taken prior to data collection.
Table 2: Comparison of Patients without CAD (SS=0) and Patients with CAD (SS>0) with Individual Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No CAD (SS=0)</th>
<th>CAD (SS&gt;0)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>1(4.5)</td>
<td>0</td>
<td>0.042</td>
</tr>
<tr>
<td>40 – 49</td>
<td>7(31.8)</td>
<td>16(15.5)</td>
<td></td>
</tr>
<tr>
<td>50 – 59</td>
<td>10(45.5)</td>
<td>45(43.7)</td>
<td></td>
</tr>
<tr>
<td>60 – 69</td>
<td>4(18.2)</td>
<td>40(38.8)</td>
<td></td>
</tr>
<tr>
<td>&gt;70</td>
<td>0</td>
<td>2(1.9)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
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<td></td>
<td>0.801</td>
</tr>
<tr>
<td>&gt;18.5</td>
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<td>2(2)</td>
<td></td>
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<tr>
<td>18.5 – 24.9</td>
<td>9(40.9)</td>
<td>36(35.3)</td>
<td></td>
</tr>
<tr>
<td>25 – 29.9</td>
<td>12(54.5)</td>
<td>55(53.9)</td>
<td></td>
</tr>
<tr>
<td>&gt;30</td>
<td>1(4.5)</td>
<td>9(8.8)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
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<td>0.958</td>
</tr>
<tr>
<td>Male</td>
<td>20(90.9)</td>
<td>94(91.3)</td>
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<td>Female</td>
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<td>9(8.7)</td>
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<tr>
<td>Blood Pressure</td>
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<td>Yes</td>
<td>9(40.9)</td>
<td>61(59.2)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>13(59.1)</td>
<td>42(40.8)</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Sensitivity and Specificity of each Score

<table>
<thead>
<tr>
<th>Score</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRS</td>
<td>91.3</td>
<td>28.6</td>
<td>0.005</td>
</tr>
<tr>
<td>ASCVD</td>
<td>88.6</td>
<td>20.0</td>
<td>0.307</td>
</tr>
<tr>
<td>Moderate and high Syntax Score (SS≥23) patients</td>
<td>72.4</td>
<td>50</td>
<td>0.034</td>
</tr>
<tr>
<td>FRS</td>
<td>34.5</td>
<td>74</td>
<td>0.375</td>
</tr>
<tr>
<td>ASCVD</td>
<td>10.1</td>
<td>94.6</td>
<td>0.51</td>
</tr>
<tr>
<td>Identifying severe CAD patients (SS≥33)</td>
<td>14.3</td>
<td>94.4</td>
<td>1.41</td>
</tr>
</tbody>
</table>

*Each score was categorised as (high score ≥20%) and (low score ≤ 20%). **Chi–square test was used coefficient=1.277, p-value = 0.307) (Table 3). Chi-square analysis between categories (SS≥23) and (SS≤23) with high FRS and ASCVD risk score showed significant association between FRS and SS (Pearson’s coefficient=4.525, p-value=0.033) but no significant association was found between ASCVD risk score and SS (Pearson’s coefficient=0.787, p-value = 0.375) (Table 3).

ROC curve showed that ASCVD risk score (AUC=0.677, p=0.009) had a higher discriminative ability than FRS (AUC=0.663, p=0.017) for CAD (Figure 1). ASCVD risk score (AUC=0.617, p=0.221) again had a higher discriminative ability than FRS (AUC=0.540, p=0.675) when identifying patients with high Syntax Score from those without it (Figure 2).

The positive likelihood ratio (PLR) is higher for ASCVD (PLR=1.8) than FRS (PLR=1.5) in detecting patients with high Syntax Score. There was significant association between FRS and Syntax Score when patients were categorised as (SS=0) and (SS>0) based on the presence of CAD, and (SS<23) and (SS≥23) based on having moderate or high Syntax Score. No association was found when patients were categorised based on the presence of high Syntax Score as (SS<33) and (SS≥33) (Table 3). FRS is a better risk score for screening patients with CAD compared to ASCVD risk score. As seen in the ROC curve (Figures 1 and 2) the discriminative ability of both the risk scores was low in identifying patients...
with CAD and those with high Syntax Score. ASCVD risk score showed a higher discriminative ability than FRS in both conditions.

In a study done among the Asian population by Z. Günaydin et al., the ability of the FRS to differentiate among patients without CAD (SS<0) and patients with CAD (SS<0) was more significant compared to the ability to differentiate low Syntax Score patients (SS<23) from patients with moderate and high Syntax Score (SS≥23). This is similar to the results obtained in our study which may indicate FRS is a good tool to screen patients with CAD but not accurate enough to identify patients with severe lesions (high Syntax Score) from patients with mild or no lesions.

In our study, significant association was found between FRS and Syntax Score by doing chi-square analysis. In a study done by H. Tolunay and O. Kurmus, correlation of FRS Score with Syntax Score was done and found to be statistically significant (p=0.029). This shows FRS is a reliable score in predicting cardiovascular risk in patients.

In a study among the Indian population done by M. Bansal, no significant correlation (p-value=0.10) between FRS and ASCVD risk scores was found when the risk categories were dichotomously categorised (<20% and ≥20%). In our study, the scores were compared on their sensitivity, specificity and discriminative ability instead of searching for an association between them. Similar limitations such as lack of sufficient prospective studies regarding usage of western developed risk assessment models in the Indian population are seen in both of the studies.

**Limitations**

The limitations of our study were a small sample size, retrospective nature of the study and a possible bias arising due to the study population consisting of patients who voluntarily came to the Comprehensive Health Clinic. Similar to a study done by M. Yalcin et al. we had limitations of choosing a selective population and a possibility of patients with low risk not being adequately represented. The gender distribution in the sample population is skewed by the fact that there were only 11 females assessed out of the 125 individuals studied. As we know, age is one of the most important determinants of CVD, and in our study population, 101 out of 125 patients were above the age of 50, which by itself would generate a higher CVD risk score. A single centred study and the possibility of previous medical treatment confounding the actual risk of CAD are other limitations.

**Recommendations**

FRS and ASCVD are good risk stratification models for predicting cardiovascular risk in the general population. More number of studies in the Indian population validating the reliability of risk prediction scores in detecting coronary artery disease should be done using a greater sample size and representative population which would reduce the cardiovascular morbidity and mortality by effective screening and timely therapeutic interventions.

**Conclusion**

FRS and ASCVD risk score are effective risk predicting tools for cardiovascular diseases in an Indian study population despite being western developed risk scores. FRS has a better risk predicting ability than ASCVD risk score and shows a significant association with Syntax Score, a score which defines the pattern and severity of coronary artery lesions. Both scores have high sensitivity for CAD and high specificity for patients with high Syntax Score (severe coronary artery lesions) which are qualities of well-developed risk scores.

**Acknowledgements**

We express our gratitude to the patients for participating in this study and the ethical committee of Amrita Institute of Medical Sciences to permit us to conduct the study and access data. There is no conflict of interest.

**Abbreviations**

ASCVD, Atherosclerotic Cardiovascular Disease; FRS, Framingham Risk Score; SS, SyntaxScore; CAD, Coronary Artery Disease; TC, TotalCholesterol; HDL, High Density Lipoprotein; LDL, Low Density Lipoprotein

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4. https://framinghamheartstudy.org/fsb/about/history/
10. Jean-Michel Paradis et al. Impact of Coronary Artery Disease Severity Assessed With the SYNTAX Score on Outcomes Following Transcatheter Aortic Valve Replacement.
12. Tolunay H, Kurmus O. Comparison of coronary risk scoring effective systems to predict the severity of coronary artery disease using the SYNTAX score.
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Unmet need of current antifungal therapy: Isavuconazole, a new molecule

Almost 1.2 billion people are globally affected by invasive fungal infections, and the prevalence of these infections has increased dramatically in recent years.¹

When compared to the therapeutic options available for the treatment of bacterial infections, the number of choices available for the treatment of invasive fungal infections is quite restricted.²

The major pathophysiological factors of Invasive fungal infection³

- Long term steroid treatment
- Damaged respiratory tract
- Hyperglycaemia in the diabetic patient
- Impaired phagocytosis in cirrhosis patients
- Compromised innate and acquired immunity
- Multiorgan dysfunction
- Extended use of antibiotics
- Ill maintained equipment
- Unsanitary conditions

The following characteristics of isavuconazole make it a better choice for the treatment of invasive fungal infections⁴

- Excellent bioavailability
- Predictable pharmacokinetics
- Lower side effects
- Few drug-drug interactions
- Well tolerated safety profile
- Extended-spectrum triazole
Novel antifungal drug, isavuconazole, can be used as a potential therapeutic option to improve the patient care scenario in the future by providing better strategies to tackle the problems associated with existing available medications.

SUMMARY OF PRESCRIBING INFORMATION FOR ISAVUCONAZOLE (Cresemba) (SPI_LPDCRE052021)

Composition: Each hard capsule contains 100 mg isavuconazole (as 186.3 mg isavuconazonium sulfate). Each vial contains 200 mg isavuconazole (as 372.6 mg isavuconazonium sulfate). Indications: Isavuconazole is an azole antifungal indicated for patients 18 years of age and older for the treatment of Invasive Aspergillosis and Invasive Mucormycosis. Dosage: Loading dose (Vial) The recommended loading dose is one iv injection after reconstitution and dilution (equivalent to 200 mg of isavuconazole) every 8 hours for the first 48 hours (6 administrations in total). Maintenance dose The recommended maintenance dose is one vial after reconstitution and dilution (equivalent to 200 mg of isavuconazole) once daily, starting 12 to 24 hours after the last loading dose. Method of administration (Vial) Intravenous use. Isavuconazole must be reconstituted and then further diluted to a concentration corresponding to approximately 0.8 mg/mL isavuconazole prior to administration by intravenous infusion over a minimum of 1 hour to reduce the risk of infusion-related reactions. The infusion must be administered via an infusion set with an in-line filter with a microporous membrane made of polyethersulfone (PES) and with a pore size of 0.2 μm to 1.2 μm. Isavuconazole must only be given as an intravenous infusion. Loading dose (Hard capsule) The recommended loading dose is two capsules (equivalent to 200 mg of isavuconazole) every 8 hours for the first 48 hours (6 administrations in total). Maintenance dose The recommended maintenance dose is two capsules (equivalent to 200 mg of isavuconazole) once daily, starting 12 to 24 hours after the last loading dose. Method of administration (Capsule) Isavuconazole capsules can be taken with or without food. Isavuconazole capsules should be swallowed whole. Do not chew, crush, dissolve or open the capsule. Contraindications: Hyper-sensitivity to the active substance or to any of the excipients; co-administration with ketoconazole; co-administration with high-dose ritonavir (>200 mg every 12 hours); co-administration with strong CYP3A4/5 inducers such as rifampicin, rifabutin, carbamazepine, long-acting barbiturates (e.g., phenobarbital), phenytoin and St. John's wort; patients with familial short QT syndrome. Warning and Precautions: Caution should be used in prescribing isavuconazole to patients with hypersensitivity to other azole antifungal agents. Severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, have been reported during treatment with azole antifungal agents. If a patient develops a severe cutaneous adverse reaction, Isavuconazole should be discontinued. Isavuconazole is contraindicated in patients with familial short QT syndrome. Isavuconazole has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). Use in these patients is not recommended unless the potential benefit is considered to outweigh the risks. Isavuconazole must not be used during pregnancy except in patients with severe or potentially life-threatening fungal infections, in whom isavuconazole may be used if the anticipated benefits outweigh the possible risks to the foetus. Isavuconazole is not recommended for women of childbearing potential who are not using contraception. Breast-feeding should be discontinued during treatment with Isavuconazole. Adverse Reactions: The frequency of adverse reactions is based on data from 403 patients with invasive fungal infections treated with isavuconazole in phase 3 studies. The most common treatment-related adverse reactions were elevated liver chemistry tests (7.9%), nausea (6.4%), vomiting (5.5%), dyspnoea (3.2%), abdominal pain (2.7%), diarrhoea (2.7%), injection site reaction (2.7%), headache (2.0%), hypokalaemia (1.7%) and rash (1.7%). The adverse reactions which most often led to permanent discontinuation of isavuconazole treatment were: confusion (4.7%), headache (1.7%), convulsion (1.7%), and respiratory failure (0.5%). Drug Interactions: Co-administration of Isavuconazole with the strong CYP3A4/5 inhibitor ketoconazole is contraindicated, since this medicinal product can significantly increase plasma concentrations of isavuconazole; co-administration of Isavuconazole with potent CYP3A4/5 inducers such as rifampicin, rifabutin, carbamazepine, long-acting barbiturates (e.g., phenobarbital), phenytoin and St. John’s wort, or with moderate CYP3A4/5 inducers such as efavirenz, nelfinavir and etravirine, is contraindicated, since these medicinal products can significantly decrease plasma concentrations of isavuconazole; Co-administration with high-dose ritonavir (>200 mg twice daily) is contraindicated, as at high doses ritonavir may induce CYP3A4/5 and decrease isavuconazole plasma concentrations. Overdose: Symptoms - Symptoms reported more frequently at supratherapeutic doses of Isavuconazole (equivalent to isavuconazole 600 mg/day) evaluated in a QT study than in the therapeutic dose group (equivalent to isavuconazole 200 mg/day dose) included: headache, dizziness, paraesthesia, somnolence, disturbance in attention, dysgeusia, dry mouth, diarrhoea, oral hypoesthesia, vomiting, hot flush, anxiety, restlessness, palpitations, tachycardia, photophobia and arthralgia. Management of overdose Isavuconazole is not removed by haemodialysis. There is no specific antidote for isavuconazole. In the event of an overdose, supportive treatment should be instituted. Storage Condition: Vial: Store in a refrigerator (2°C to 8°C). Hard Capsule: Store below 30°C. Adapted from Local product document for Cresemba version LPDCRE052021.

References:

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Clinical and Laboratory Profile of Dengue in Kashmir Valley

Muzafar Naik1, Tariq Bhat1, Abdul Ahad Wani2*, Abid Amin3, Ummer Jalaalie3

Abstract

Background: As majority of cases of dengue are associated with thrombocytopenia, it is indispensable to study clinical presentation, biochemical parameters and outcome of dengue fever in a population known with low platelet count.

Methodology: A prospective observational study was conducted from September 2016 to August 2017 that included forty NS-1 antigen (IgM) Dengue positive patients. Clinical features, laboratory parameters and outcome of dengue patients were noted.

Results: All the patients had travel history outside the valley into the neighbouring state. Most patients (70%) had duration of stay between 21-30 days in dengue prevalent areas before catching the illness. Duration of symptoms was between 4-9 days in majority of patients (92.5%). Most patients (85%) presented in months of September to November. The three most common symptoms were fever (100%), chills (92.5%) and headache (80%). The most common laboratory features were thrombocytopenia (97.5%), leukopenia (87.5%), transaminitis (87.5%) and raised LDH (32.5%). One patient developed Dengue Hemorrhagic Fever (DHF). All patients recovered completely.

Conclusion: DF in Kashmir is seen exclusively in travellers to other states especially in the monsoon season. DF in Kashmiri patients has a favourable outcome despite low baseline platelet count. DHF is uncommon in Kashmiri population.

Introduction

In recent decades the incidence of dengue has grown dramatically around the world and it has emerged as a major public health problem due the morbidity and mortality associated with it. The actual numbers of dengue cases reported are the tip of the iceberg because many cases go unreported because of varied clinical presentation of dengue which ranges from asymptomatic infection to dengue shock syndrome (DSS).1 One recent estimate indicates only one-fourth of cases manifest clinically i.e. 96 million (67–136 million) out of 390 million dengue infections per year (95% credible interval 284–528 million).2 It is estimated that 3.9 billion people among 128 countries are at risk of infection with dengue viruses.3 Dengue is now endemic in more than 100 countries in the WHO regions of Africa, the Americas, the Eastern Mediterranean, South-East Asia and the Western Pacific. Among the changing trends of dengue fever is the increasing number of cases, disease spreading to new areas and more unexpectedly occurring explosive outbreaks.

In India dengue was endemic in Maharashtra, Karnataka, Tamil Nadu and Pondicherry, Delhi, Rajasthan, Haryana, Punjab and Chandigarh in the early 2000s. However recently dengue has spread to many other states such as Orissa, Arunachal Pradesh and Mizoram, where dengue was historically non-existent and also the union territories.4 Increased incidence of dengue, disease severity and major shift in the geographical range of disease are the other problems in the health sector. The various factors responsible for expansion of dengue in India are related to migration from non-endemic states to endemic states, unplanned urbanization, changing environmental factors, host–pathogen interactions and population immunological factors. Inadequate vector control measures have also created favourable conditions for dengue virus transmission and its mosquito vectors. However dengue is also seen in those areas which do not have favourable atmosphere for Aedes survival and the reason can be explained ranging from the globalization of travel and trade, which favours the propagation of pathogens and vectors, to unfavourable climatic zones. There has been reports of dengue fever in Kashmiri population too despite the fact that the valley of Kashmir has unfavourable climate for Aedes mosquito survival owing to the low mean temperature due to its geographical location. This study was conducted to elucidate risk factors, clinical presentation and outcome of serologically confirmed dengue fever in Kashmiri population.

Material and Methods

This prospective observational study was carried out in the department of General Medicine SKIMS Medical College and Hospital, Srinagar over a period of 2 years from September 2016 to August 2017. All patients above 14 years with confirmed dengue, who were either hospitalized or managed as outdoor patients with detection of viral antigen NS1 (non-structural protein 1) and/or IgM dengue antibody positivity were included in the study. The patients with concomitant malaria, typhoid, leptospirosis etc. were excluded from the study. Detailed history including travel history and careful clinical examination was performed on each patient. Laboratory investigations done were haemoglobin, total and differential leucocyte counts, platelet count, haematuria, liver function tests, blood urea and serum creatinine, chest radiograph and ultrasound scan of abdomen. Blood counts and liver function tests were monitored

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periodically as and when required till resolution. Other differential diagnoses were excluded by appropriate tests.

## Results

A total of 40 patients who reported from September 2016 to August 2017 were studied and analysed. Majority of patients (24/40, 60%) were in age group of 21-30 yrs. 12 patients (30 %) were in 15-20 years of age group. Three patients (7.5 %) were in age group of 31-40 years. One patient was in the age group of 41-50 years. Majority of patients 95% were males. Most of the patients (30/40, 75 %) were students. Five patients (5/40, 12.5 %) were businessmen and on business trip to the neighbouring state.

All the patients (100%) had a history of travel to neighbouring states of north India (Table 1). None of the dengue patient was without history of travel.

Majority of patients (28/40, 70%) had stay of 21-30 days in dengue endemic areas before developing symptoms of dengue fever. Seven patients (17.5%) developed symptoms within 10 days of stay. Four patients (10%) manifested symptoms within 11-20 days and 1 patient (2.5%) developed symptoms within 21-30 days of stay in endemic area.

Time from onset of symptoms to diagnosis of dengue was 7-9 days in 47.5%, 4-6 days in 45% and 7.5 % within 1-3 days (Table 2).

Most of the cases were detected in September (10), October (16) and November (8) (85%) as compared to June, July and August 2 each.

The virus detected in all the 40 cases was dengue virus 1. Only one patient had 2nd attack of dengue while rest had first attack of dengue. Fever was a universal symptom (100%) while chills (92.5%), headache (80%), lymphadenopathy and rash occurred in 7.5% of patients (Table 3).

In laboratory findings thrombocytopenia was seen in (97.5%), leukopenia (87%) transaminitis (87.5%) azotemia was seen in only in one case (Table 4).

Platelet count was reduced (<50,000) in 22.5% and was in the range of 50000-100000 in 67.5% (Table 5).

Only one patient (2.5 %) had dengue haemorrhagic fever. There was no reported mortality and all cases recovered spontaneously.

## Discussion

Our study revealed that dengue was exclusively seen in patients with a history of recent travel to outside valley with three fourth cases with travel history to Punjab and Delhi only and none of the case was reported without travel history, signifying the fact that dengue in Kashmir valley is an imported one. The two most important climatic factors in disease manifestation and transmission of dengue virus through its vector Aedes mosquito are temperature and precipitation. Life cycle of Aedes mosquito and incubation period of dengue virus within Aedes mosquito is significantly influenced by temperature, wherein warm temperature increases the life span of Aedes mosquito, the incubation period of dengue virus in Aedes is shortened. The net result is faster virus replication and heightened transmission.

Data compiled from National and regional distribution of dengue in India from National Vector Borne Disease Control Program (NVBDCP) in between 1997-2009 were reported in 27 of the 35 states and UTs during 1997–2009, and these 27 states and Union territories (UTs) accounted for >90% of the Indian population. In this comprehensive report less than 50 cases were reported in any given year from Bihar, Orissa, Jammu and Kashmir, Madhya Pradesh and Nagpur. These 27 states and Union territories (UTs) accounted for >90% of the following major species of mosquitos especially Aedes aegypti, Aedes albopictus, Anopheles

## Table 1: Distribution of cases according to destination of travel

<table>
<thead>
<tr>
<th>State</th>
<th>Punjab</th>
<th>Delhi</th>
<th>Others</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>17</td>
<td>13</td>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>Percentage</td>
<td>42.5</td>
<td>32.5</td>
<td>25</td>
<td>100</td>
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</table>

## Table 2: Duration of symptoms prior to diagnosis

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<tr>
<th>Days</th>
<th>1-3</th>
<th>4-6</th>
<th>7-9</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>3</td>
<td>18</td>
<td>19</td>
<td>40</td>
</tr>
<tr>
<td>Percentage</td>
<td>7.5</td>
<td>45</td>
<td>47.5</td>
<td>100</td>
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</tbody>
</table>

## Table 3: Clinical symptoms and signs of dengue cases

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>40</td>
<td>100</td>
</tr>
<tr>
<td>Rigors</td>
<td>29</td>
<td>72.5</td>
</tr>
<tr>
<td>Chills</td>
<td>37</td>
<td>92.5</td>
</tr>
<tr>
<td>Headache</td>
<td>32</td>
<td>80</td>
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<td>Nausea</td>
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<td>32.5</td>
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<tr>
<td>Myalgia</td>
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<td>67.5</td>
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<tr>
<td>Arthralgia</td>
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<td>30</td>
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<tr>
<td>Cough</td>
<td>3</td>
<td>7.5</td>
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<tr>
<td>Abdominal pain</td>
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<td>2.5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4</td>
<td>10</td>
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<tr>
<td>Diarrhoea</td>
<td>1</td>
<td>2.5</td>
</tr>
<tr>
<td>Anorexia</td>
<td>10</td>
<td>25</td>
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<tr>
<td>Malaise</td>
<td>26</td>
<td>65</td>
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<tr>
<td>Sweating</td>
<td>18</td>
<td>45</td>
</tr>
<tr>
<td>Seizures</td>
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<td>0</td>
</tr>
<tr>
<td>Altered sensorium</td>
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<tr>
<td>Retro orbital pain</td>
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<td>10</td>
</tr>
<tr>
<td>Bony pain</td>
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<td>5</td>
</tr>
<tr>
<td>Rash</td>
<td>3</td>
<td>7.5</td>
</tr>
<tr>
<td>LAP</td>
<td>3</td>
<td>7.5</td>
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</tbody>
</table>

## Table 4: Laboratory abnormalities of dengue cases

<table>
<thead>
<tr>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>35</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>39</td>
</tr>
<tr>
<td>Azotemia</td>
<td>1</td>
</tr>
<tr>
<td>Transaminitis</td>
<td>35</td>
</tr>
<tr>
<td>Raised LDH</td>
<td>13</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>3</td>
</tr>
</tbody>
</table>

## Table 5: Characterization of thrombocytopenia in dengue cases

<table>
<thead>
<tr>
<th>Platelet count</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50,000</td>
<td>9</td>
<td>22.5</td>
</tr>
<tr>
<td>50,000-150000</td>
<td>27</td>
<td>67.5</td>
</tr>
<tr>
<td>&gt;150000</td>
<td>3</td>
<td>7.5</td>
</tr>
</tbody>
</table>

The first reported case of a mosquito borne disease in Kashmir Valley dates back to 1912 when in Mission hospital Dr Neve reported 3 cases of Malaria one in a Kashmiri who had been to Delhi Durbar, the second one who had been to Jammu and the third one who had been to Karna a low-lying area of Valley. A diligent search for the prevalence of various mosquitos was made in the Srinagar and Ganderbal district from April 1912 to October 1912 and it revealed Culicine and Neo Willmori as prevalent mosquitos without any mention of Aedes mosquito. However recently a study from Kashmir valley has reported the presence of Aedes mosquitos from various areas of Kashmir valley but it needs to be substantiated with further studies because this is a single study that showed presence of all the three major species of mosquitos especially Aedes aegypti, Aedes albopictus, Anopheles
been reported lower owing to the count in Kashmiri population has had normal platelet count. Platelet % of patients and only one patient thrombocytopenia was seen in 97.5 with and without rash in our study. Interestingly leucopenia was seen in 87.5 % of patientsat presentation which is in accordance to studies conducted in Singapore and Puerto Rico. The incidence of neutropenia in DF is reported much lower from South India and Bangkok. The possible explanation to this discrepancy may be the presentation of our patients during the febrile phase or else could be explained by the geographical distribution. Nonetheless none of our patient developed severe neutropenia (absolute neutrophil count < 500) and leucopenia resolved completely at the time of discharge. Transaminitis was also seen in 87.5 % of patients, Serum glutamic oxaloacetic transaminase (SGOT) being higher than Serum glutamic pyruvic transaminase (SGPT), these results are in accordance to a study conducted in south India.

There was no reported mortality in our study and similar results with no deaths were reported from Jammu and Kashmir in year 2016 as compared to 227 (0.202 %) deaths from all over India with 42 (0.55%) in Uttar Pradesh, 34 (0.19%) in West Bengal and 32 (0.47%) in Maharashtra in the same year. However, mortality rates of up to 17 % have been reported from a study. The reason being the absence of DSS in our study, an important risk factor leading to mortality in dengue fever.

In conclusion dengue in the valley of Kashmir is an imported one and manifesting in dengue fever (mild form) predominantly and mortality as well as morbidity due to dengue fever is low despite low platelet counts of Kashmiri population. There is a definite need of studies elucidating distribution of mosquitos in Kashmir valley.

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Mutheneni SR, Morse AP, Caminade C, Upadhyayula SM. Dengue burden in India: recent trends and importance of climatic parameters. Emerging Microbes and Infections 2017; 6, 670. doi:10.1038/s41396-017-0004.
A Randomized Open-Label Parallel-Group Study Comparing the Efficacy and Safety of Cilnidipine and Amlodipine in Hypertensive Adults

Napolean Kagoo JJ1, Darling Chellathai D2, R Kavitha*

Abstract

Background: Cilnidipine, an upcoming anti-hypertensive drug, is a combined L- and N-type calcium channel blocker. It is proposed to be more efficacious and safer due to its two-pronged approach in treating hypertension.

Methods: The study was a randomized open-label parallel-group study, conducted in the Department of General Medicine, Sri Ramachandra Medical College Hospital, Chennai, during the period September 2014 to May 2015. 50 patients were randomized to the amlodipine group and 50 to the cilnidipine group. The blood pressure, pulse rate and adverse effects were monitored in each patient over 12 weeks. The difference in the Systolic Blood Pressure(SBP), Diastolic Blood Pressure(DBP) and Heart Rate(HR) before and after treatment within each group, and between the two groups were analyzed using paired and unpaired t tests respectively. The adverse effects reported in each group were analyzed using Chi-square test.

Results: There was no statistically significant difference in the reduction of SBP and DBP between the two groups (p>0.05). The HR however, showed an increase of 1.07/min in the amlodipine group and decreased by 1.16/min in the cilnidipine group. The patients in the cilnidipine group experienced significantly less adverse effects such as pedal edema and palpitations when compared to those in the amlodipine group (p<0.05).

Conclusions: Cilnidipine therapy is an effective and safe alternative in the treatment of essential hypertension. It can be used as a first line antihypertensive drug since its efficacy is comparable to that of amlodipine with a better safety profile than amlodipine.

Introduction

In the modern era of changing lifestyles and globalization, non-communicable diseases have usurped the position of infectious diseases from the leading cause of morbidity and mortality world-wide. The common non-communicable diseases are cardiovascular disease, diabetes, cancer and chronic lung disease.1

In the primary care setting, the commonest cardiovascular disease encountered is hypertension, and the implications of effective treatment of this seemingly simple disorder are tremendous. Early damage at the target-organ level like left-ventricular hypertrophy, micro albuminuria and cognitive dysfunction are often seen before hypertension is detected.2 It is a silent killer that can produce devastating effects like stroke, myocardial infarction, renal failure and death if left undetected and untreated in due course of time.

The implications of treatment can be seen in the difference in costs between the therapy of hypertension and the interventions used to manage the complications like coronary artery bypass surgery, carotid artery surgery and dialysis.1

The results of the Global Burden of disease study (2010) showed that hypertension was the leading factor contributing to disease burden.3 It is estimated that hypertension is the direct cause for 57% of mortality due to stroke and 24% of mortality due to coronary heart disease in India.4 The prevalence of hypertension in India was found to be 29.8%, as reported by a systematic review and meta-analysis done in 2014, with the prevalence varying from 27.6% in rural areas and 33.8% in urban areas. Nevertheless, in various studies, the awareness and control of hypertension remain abysmally low, ranging from 20 to 54% and 7.5 to 25%, respectively.5 The common risk factors for hypertension were found to be smoking, increasing age and body mass index, diabetes, dietary fat and salt intake.

Primary prevention and lifestyle modification include curtailing the risk factors like alcohol and tobacco use, physical exercise and weight reduction, restricting salt and fat intake and promoting healthy diet including vegetables and fruits.1 Both pharmacological as well as non-pharmacological measures must go hand in hand for the proper control of blood pressure in hypertensive patients.6

The mainstay of pharmacotherapy of hypertension includes Angiotensin Converting Enzyme inhibitors (ACE-Is), Angiotensin Receptor Blockers (ARBs), Calcium Channel Blockers (CCBs), thiazide type diuretics, beta-blockers and aldosterone antagonists.7

The most commonly used calcium channel blocker in clinical practice as monotherapy of hypertension is...
Amlodipine, and newer drugs are emerging in this category with better efficacy and safety profiles. These include Cilnidipine, Lacidipine, Felodipine, Lercanidipine, Isradipine, Nisoldipine, Nicardipine and Benidipine.8-9

Cilnidipine is a newer member of the calcium channel blocker family, which blocks N-type calcium channels as well as L-type calcium channels. This N-type channel blockade can be used as a fresh approach to treat cardiovascular disease. Widespread pre-clinical and clinical studies have been done and protective effects of cilnidipine on the kidneys, heart and the nervous system have been demonstrated.

Cilnidipine blocks both N- and L-type calcium channels, to lower the blood pressure. Blockade of N-type channels inhibits the release of norepinephrine from the sympathetic nerve endings, while L-type channel blockade causes vasodilation. Thus, this two-pronged approach in the anti-hypertensive effect of cilnidipine is the uniqueness of the drug. This sympathetic blockade may also help in treating the comorbidities of hypertension.10,11

Amlodipine is the most commonly used CCB to treat hypertension, hence this drug was chosen to compare the efficacy and safety of the new drug Cilnidipine. The unique properties of Cilnidipine in terms of N-type Calcium channel blockade can be demonstrated by comparing its effect with that of Amlodipine, which is a pure L-type calcium channel blocker. The properties thus brought out can be used to reduce sympathetic over-activity that is inherent as well as induced as a reflex by CCBs in patients with hypertension.

Objectives

Primary Objective: To compare the efficacy of Cilnidipine with Amlodipine in lowering the Diastolic & Systolic blood pressure in patients with mild to moderate essential hypertension.

Secondary Objective: To compare the effect of Cilnidipine with Amlodipine on the resting heart rate of the patients. To assess the safety of Cilnidipine with Amlodipine in terms of adverse effects reported as well as physical findings.

Materials and Methods

Study design: A randomized controlled parallel-arm two-group open-label study with active comparator that was conducted in the Department of General Medicine, Sri Ramachandra Medical College Hospital, Chennai, during the period September 2014 to May 2015, according to the Helsinki declaration and ICH-GCP guidelines. Institutional Ethics Committee approval was granted and informed consent obtained from all study participants.

Inclusion Criteria

• Sex- both
• Age-18 years to 60 years
• Newly diagnosed patients with mean sitting diastolic blood pressure of ≥90 and ≤109 mmHg measured at 2 or more office visits
• Patients with mean sitting Systolic blood pressure of ≥140 and ≤179 mmHg measured at 2 or more office visits

Exclusion Criteria

• Patients with mean sitting diastolic blood pressure of ≥110mmHg or mean sitting systolic blood pressure of ≥180mmHg
• Cardiovascular complications (angina pectoris, myocardial infarction, arrhythmia in the previous 6 months, cerebrovascular disease)
• Patients with Chronic renal disease, type 2 diabetes mellitus, type 1 diabetes mellitus, Secondary hypertension, Pregnant and lactating women
• Patients with any comorbid conditions and clinical emergencies during the trial.

Study Procedure

Patients fulfilling the eligibility criteria were randomized using computer-aided randomization into two parallel groups in 1:1 ratio in blocks of 10. Study group 1 – A dose of 2.5mg of Amlodipine is given orally in the morning, once daily (O.D) for 12 weeks, taken with a cup of water after food. Study group 2 – A dose of 5mg Cilnidipine is given orally in the morning once daily (O.D.) for 12 weeks, with a cup of water after meals. Cilnidipine is twice as potent as amlodipine, i.e. 2.5mg of amlodipine = 5mg of cilnidipine.12

The duration of treatment in both the groups was 12 weeks. The baseline mean sitting diastolic blood pressure (MSDBP), mean sitting systolic blood pressure (MSSBP) and heart rate (HR) were measured. Baseline investigations like complete hemogram, renal and liver function tests, ECG, lipid profile and serum electrolytes were done before prescribing either drug. These were repeated during any study visit or at the end of the study if necessary.

Then the patients were given one of the 2 drugs as per protocol and reviewed every two weeks for a total period of 12 weeks. Cilnidipine was given once daily at an initial dose of 5 mg orally for 4 weeks. If the SBP remained ≥140mmHg or DBP ≥90mmHg, or the absolute reduction in BP was insufficient (SBP decreased by <20mmHg or DBP decreased by <10 mmHg), the dose of Cilnidipine was raised to 10 mg O.D. for another 4 weeks. Amlodipine was given once daily at an oral dose of 2.5mg initially for 4 weeks. If the BP was not adequately controlled with this dose, the dosage of amlodipine was raised to 5mg O.D.

Procedure at Each Visit

Patients were asked to come for follow-up every 2 weeks for a total period of 12 weeks during which replenishment of the drugs was done if required. At every visit, the patient’s Mean sitting Systolic and Diastolic Blood pressure and pulse rate were recorded and systemic examination done. Blood pressure was recorded using a mercury sphygmomanometer in the right upper limb in the sitting position after 15 minutes of rest. Pulse rate was recorded by palpation of the radial artery at the extended wrist in the sitting position after 15 minutes of rest.

The patients were asked to report any side-effects like dizziness, flushing, headache, peripheral edema, palpitations and GI disturbances due to the drug. The patients were also examined for ankle edema at each visit. Ankle edema was assessed by sustained pressure over the medial malleolus for 30 seconds using the ball of the thumb. At each scheduled visit, a 2 week pill pack along with compliance card are given to study subjects and assessed periodically. There were seven scheduled visits during the study.

Adverse event reporting during the study

Adverse events observed in or
reported by the study participants were recorded in the Case Report Form and reported along with the classification of severity as mild, moderate or severe and possible relation to the medication used in the study.

**Study endpoints**

**Efficacy endpoints**

- Mean change in mean sitting diastolic blood pressure ≥ 10 mmHg after 12 weeks of therapy
- Mean change in mean sitting systolic blood pressure ≥ 20 mmHg after 12 weeks of therapy
- Mean change in resting heart rate in patients on Cilnidipine after 12 weeks of therapy

**Safety endpoint**

Mean change in resting heart rate in patients after 12 weeks of therapy.

**Incidence of adverse effects within 12 weeks of therapy.**

**Statistical analysis**

The statistical analysis was done using Statistical Package for the Social Sciences for Windows (SPSS) version 17. The patient demographic data like age and sex and baseline patient characteristics were analyzed in each group using descriptive statistics to evaluate the statistical significance of the difference, if any, between them. Mean and standard deviation were calculated for continuous variables, while frequencies and percentage were calculated for categorical variables. The mean diastolic and systolic blood pressures and heart rate in each group before and after treatment were compared using paired ‘t’ test. The mean diastolic and systolic blood pressures and heart rate from baseline to 12 weeks between both the groups were compared using unpaired ‘t’ test.

**Results**

Out of 174 patients screened, 74 patients were excluded based on the exclusion criteria and the rest of the 100 patients were randomized into 2 groups- Cilnidipine group (50) and Amlodipine group (50).

The adverse events in each group were compared using Chi Square test. P value <0.05 was taken to be statistically significant. All the analyses were based on Intention to treat (ITT) principle. All the study participants who had come for at least one follow-up visit were included in the Intention-to-treat analysis.

**Efficacy profile**

The reduction in systolic blood pressure and diastolic blood pressure after 12 weeks of therapy was highly significant when compared to baseline measurements in both the groups. In amloidipine group, the baseline DBP and SBP were 99.84±2.73 and 152.65±2.01 mmHg, which at the end of 12 weeks showed a reduction to 87.88±1.41 and 134.98±2.04 mmHg and the patients in the cilnidipine group...
showed a change from baseline DBP and SBP 99.70±2.82 and 153.01±2.09 mmHg to 88.26±1.16 and 135.26±2.11 mmHg respectively at the end of 12 weeks. This is shown in [Figure 2]. In the amlodipine group, it was found that the systolic blood pressure decreased by 11.57% (p<0.001) and the diastolic blood pressure decreased by 11.97% (p<0.001). In the cilnidipine group, the systolic blood pressure was proven to reduce by 11.97% (p<0.001) and the diastolic pressure reduced by 11.47% (p<0.001).

It was found that there was no statistically significant difference in the reduction of systolic and diastolic blood pressures between the groups treated with amlodipine and cilnidipine after 12 weeks of therapy (p>0.05).

The heart rate in the amlodipine group showed a change from a baseline value of 88.04±6.31 bpm to 89.11±4.21 bpm at the end of 12 weeks and that in the cilnidipine group showed a change from baseline 90.09±6.10 bpm to 88.93±3.31 bpm at the end of 12 weeks. This is shown in (Figure 3). The heart rate however, showed an increase by 1.07 bpm in the mean value after treatment with amlodipine and decreased by 1.16 bpm on an average after treatment with cilnidipine.

**Tolerability profile**

The study drugs were well-tolerated in both the groups. All adverse events encountered by the participants during the treatment period were captured and assessed for causality.

Among the patients treated with amlodipine, 8(16%) of them reported pedal edema, 5(10%) had palpitations and 1(2%) had giddiness. Among those in the cilnidipine group, the incidence of giddiness was 1(2%), mild gastric irritation was found in 2(4%) of them, which was well-managed with oral antacid and 1(2%) complained of headache, which was managed with paracetamol. It was significant to note that the side-effects common to calcium channel blockers as a group, like pedal edema and palpitations, were not seen in the patients treated with cilnidipine. This is shown in (Table 2).

No discontinuation of treatment due to adverse effects was seen in either of the groups. No serious or life-threatening adverse events were seen in either group during the 12 weeks study period.

**Discussion**

The present study evaluated the efficacy and safety of cilnidipine and amlodipine in reducing the diastolic and systolic blood pressure in patients with mild to moderate essential hypertension.

No statistically significant difference was observed in the baseline characteristics in both the groups with respect to age, body mass index, weight, height, smoking and alcoholism.

In the study Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),13 it was demonstrated that the lowering of BP was associated with a significant decrease in cardiovascular events.

The increase in peripheral vascular resistance and vascular smooth muscle contraction seen in hypertension is dependent on the free intracellular calcium concentration.14 Calcium channel blockers act to reduce the blood pressure by causing arteriolar smooth muscle relaxation and thus a reduction in the peripheral vascular resistance.15 Calcium channel blockers are effective both as monotherapy and in combination therapy in the treatment of hypertension; this view has been confirmed by a number of recent large clinical trials.16,17 It has been reported in a study that short-acting calcium channel blockers, by virtue of their baroreceptor-mediated reflex sympathetic stimulation, may not entirely reduce the risk of cardiovascular disease.18,19 According to JNC-7 guidelines, long-acting calcium channel antagonists with lesser sympathetic stimulation are now recommended in the treatment of hypertension.20

In the present study there is reduction in the systolic blood pressure and diastolic pressure after 12 weeks of therapy of amlodipine and cilnidipine. The reduction in the systolic and diastolic blood pressure is due to long half-life of amlodipine which causes gradual relaxation of smooth vascular muscle through L-type channels and decreased peripheral resistance and less baroreceptor-mediated sympathetic discharge. On the other hand, cilnidipine causes smooth vascular muscle relaxation through L-type calcium channels and it has the added advantage of causing lesser sympathetic discharge through N-type channel blockade.

In the present study, in the amlodipine group, it was found that the DBP was reduced by 11.97% and SBP decreased by 11.57%. In the cilnidipine group, the DBP was reduced by 11.47% and the SBP was reduced by 11.97%.

In the study done by Hoshide et al21 it is found that the reduction of DBP was 12.37% and that of SBP was...
15.29% in the amlodipine group. In the cilnidipine group, the reduction of DBP was 12.63% and that of SBP was 16.37%. This shows that the anti-hypertensive efficacy in reducing SBP and DBP in amlodipine and cilnidipine groups in the present study are similar to that done by Hoshide et al. The study duration in the present study was 12 weeks, whereas in the above study, it was 16 weeks. The dose used was similar in both the studies, amlodipine (2.5 to 5mg) and cilnidipine (5 to 10 mg), to achieve the desired therapeutic effect.

In the study done by Zaman et al and Adake et al, it was found that the reduction in DBP was 8.1%, 13.4%, and SBP 8.4%, 14.2%, with amlodipine and DBP 8.0%, 11.1% and SBP 7.2%, 12.8% with cilnidipine respectively. The dose used in the above study was 5-10mg of amlodipine and 10-20mg of cilnidipine, in contrast to the present study in which we used 2.5-5mg of amlodipine and 5-10mg of cilnidipine to achieve the desired anti-hypertensive effect. This may be due to a combination of environmental, lifestyle and pharmacogenomic differences in the respective study populations.

In a meta-analysis of 11 clinical trials on the efficacy and safety profile of cilnidipine, Xu Guo-Liang et al in Chinese patients with mild to moderate essential hypertension, it was concluded that amlodipine is comparable to cilnidipine both in terms of safety and efficacy. In our study, the anti-hypertensive efficacy in reducing both SBP and DBP was noted to be similar in the use of amlodipine and cilnidipine in essential hypertension.

The study results demonstrate a comparable efficacy of amlodipine and cilnidipine in reducing the diastolic and systolic blood pressure of patients. This is a momentous finding in itself because cilnidipine is demonstrated to be equally efficacious to amlodipine, which is the currently preferred choice among calcium channel blockers as a first line monotherapy for essential hypertension. This finding in Tamil Nadu, India, is similar to those demonstrated in other studies done by Hoshide S et al, Zaman ZA et al, Adake et al, Xu Guo-Liang et al from all around the world and in India too.

In the present study, it was found that patients treated with amlodipine, 61.2% of them achieved the desired reduction of blood pressure at a dose of 2.5mg once-daily dosage and the rest (38.8%) of the patients required a dose of 5 mg to attain the target BP. And among the cilnidipine group, 63% of the patients required a dose of 5mg once-daily dosage to decrease the BP to the desired level and the remaining patients (37%) needed a dose of 10mg once-daily to reach the desired therapeutic response. The mean reductions in the systolic and diastolic blood pressure was gradual in the present study may be due to other confounding factors which can influence the blood pressure like overweight, smoking and alcoholism.

In the present study, the heart rate however, showed an increase by 1.07 bpm in the mean value after treatment with amlodipine and decreased by 1.16 bpm in the mean value after treatment with cilnidipine.

In the studies done by Hoshide et al and Zaman et al, there is a change in the mean heart rate in the amlodipine group from baseline to post-treatment. The heart rate showed an increase by 2 and 1.5 (mean value) after treatment with amlodipine and decreased by 1 and 1.5 (mean value) after treatment with cilnidipine.

Studies have demonstrated that amlodipine increased the resting heart rate, sympathetic stimulation and reflex tachycardia due to its vasodilatory effect, which are adverse effects common to all conventional dihydropyridine calcium channel blockers.

When the heart rate of patients treated with amlodipine was compared with those on cilnidipine, it was noted that amlodipine is associated with reflex tachycardia which is expected with all calcium channel blockers due to its vasodilatory effect. But this effect is overcome with a decrease in heart rate observed among those treated with cilnidipine, because of its N-channel blocking effect in addition to the L-channel blocking property common to all CCBs. Additionally, cilnidipine has been proven to suppress the cardiac sympathetic over activity to a greater extent than amlodipine.

The decrease in heart rate in patients with hypertension is an added benefit because a higher resting heart rate is proven as an independent risk factor causing cardiovascular mortality. It is seen that Cilnidipine caused a significant reduction in BP without increasing the PR, but not Amlodipine. The JNC-7 guidelines have recommended that calcium channels that have a lesser sympathetic stimulatory effect are preferred the treatment of hypertension. Thus cilnidipine can be used safely used in patients with cardiovascular disease like coronary heart diseases.

The study drugs were well-tolerated in both the groups. All adverse events encountered by the participants during the treatment period were recorded. It was found that 8 (16%) patients treated with amlodipine had pedal edema whereas none of the patients treated with cilnidipine had pedal edema.

Ankle edema is an adverse effect that is commonly seen with amlodipine, an L-type calcium channel blocker that is commonly used in treating hypertension, with incidence rates approaching 15%. Amlodipine-induced edema is mostly self-limited and minor, but can become severe and reach proportions like anasarca in some patients. But even mild edema can result in poor drug compliance and discontinuing therapy by causing cosmetically undesirable effect. An otherwise highly effective anti-hypertensive drug is hindered by this seemingly minor adverse effect.

The study done by Adake et al showed 19 persons complained of pedal edema in amlodipine and 2 persons affected with pedal edema in cilnidipine. In normal individuals, venous congestion on standing results in pre-capillary vasoconstriction which restricts filtration of fluid into the interstitium. L-channel blockade by calcium channel blockers like amlodipine produces dilatation only on pre-capillary vessels sparing post capillary vessels, by its arteriolar dilation and this results in pedal edema. In cilnidipine, the dual N- and L- channel blockade produces dilatation of both pre- and post-capillary vessels, which restricts fluid filtration, thus producing less pedal edema. Cilnidipine has been found to be effective to treat the pedal edema produced by Amlodipine.

In the Amlodipine group seven patients had palpitations, which was not seen with cilnidipine, probably
because of the lack of the reflex tachycardia in the use of cilnidipine. One person reported to have giddiness.

Among those in the cilnidipine group, 1(2%) of the patients reported to have giddiness, 2(4%) of them reported to have mild gastric irritation, which was well-managed with oral antacid and 1(2%) of them reported headache, which was managed with paracetamol. It was significant to note that the side-effects common to calcium channel blockers as a group like pedal edema and palpitations, are not seen in cilnidipine treated group of patients in the present study.

No discontinuation of treatment was seen in either study group as a result of adverse effects. No serious or life-threatening adverse events were reported in either group during the 12 weeks study period.

Both the groups exhibited a good patient compliance (>80%) to drug therapy and there was no statistically significant difference in the drug compliance between the two groups. This is probably attributable to the weekly reminders sent to the study participants during the study period and shorter duration of the study (12 weeks).

The limitations of the study are as follows. This study was done on a relatively small sample size. A similar study with larger population would increase the power of the study. The study was done over a relatively short duration of 12 weeks. If the population were followed up for a longer period, the anti-hypertensive effect could be studied whether it is sustained and long-term safety profile could be better characterized. The open labelling of the two groups is a potential cause for bias, with respect to reporting of adverse events. Double-blinding can be considered to resolve this bias.

Conclusion

The study concludes that cilnidipine therapy is comparable to amlodipine therapy in reducing 24 hour systolic and diastolic blood pressure in mild to moderate essential hypertension. Despite similar blood pressure reduction, cilnidipine therapy causes no increase in the heart rate since it causes sympathetic blockade through its action on the N-type calcium channel. And when compared to amlodipine there is a lower incidence of pedal edema because of dilation of pre- and post-capillary vessels and no palpitations since it suppresses sympathetic activity through N-type calcium channel.

To conclude, cilnidipine therapy is an effective and safe alternative in the treatment of essential hypertension. Better patient compliance and less treatment discontinuation rates are expected in the cilnidipine group. It can be used as a first line antihypertensive drug since its efficacy is comparable to that of amlodipine with a better safety profile than amlodipine.

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Author contributions

Dr. Napoleon Kagoo JJ was the principal investigator of the study, who prepared the study design case proforma, collected the data, tabulated and analysed data and prepared the manuscript. Dr. Darling Chellathai was instrumental in reviewing the study protocol, case proforma, data analysis and Dr. R. Kavitha had contributed in careful reviewing and editing the manuscript.

Disclaimer

This article is based on the author’s personal views as a researcher and not as an employee of Novartis. This study was conducted when the author was a student of Sri Ramachandra Medical College & Research Institute and has no bearing with the author’s employment in Novartis.

References

25. Lefrandt JD, Heitmann J, Servé K, et al: The effects of
Is Hyperuricemia a Marker of Severity of Disease in Scrub Typhus?

Sanyam K Mahajan¹, Ritin Sharma¹, Balraj Singh², Sanjay K Mahajan³*

Abstract

Aims: To study association of hyperuricemia with severity of scrub typhus.

Methods: We studied clinical features, laboratory profile, in hospital course and outcome of 92 patients of scrub typhus and association of hyperuricemia with severity of disease.

Results: Of total 92 patients in study group, 66 (71.7%) were females and 26 (28.3%) were males. Fever (100%), cough (37%), headache (33%), vomiting (31%), altered sensorium (23%), diarrhea (18%), abdominal pain (16%), myalgia (14%), and seizures (3%) were common clinical features. Eschar was present in 23%. Of total 92 patients 34 (37%) patients had hyperuricemia (HU) and 58 patients had normal serum uric acid levels. The patients of scrub typhus with HU had significantly higher presentation with altered sensorium (35.3%). In HU group, mean TLC, mean serum urea and serum creatinine were higher and mean serum albumin and mean HDL cholesterol were lower than patients of scrub typhus without hyperuricemia. These differences between two groups were statistically significant. Neurological dysfunction, severe sepsis, serum creatinine >3.5mg/dL and involvement of at least single organ was significantly higher in HU group. Total 4 patients (4.3%) died and all had HU.

Conclusion: Hyperuricemia in patients of scrub typhus was associated with severe scrub typhus. The serum uric acid levels should be done in early course of all patients suffering from scrub typhus. The patients showing hyperuricemia should be monitored closely for early recognition of complications and management aggressively.

Introduction

Scrub typhus is caused by Orientia tsutsugamushi and is an acute febrile illness. The organism multiplies at the skin site after inoculation leading to necrotic eschar. It actually proliferates in endothelial cells of blood vessels supplying brain, pancreas, lung, kidney and skin leading to release of inflammatory mediators such as cytokines, prostaglandins and leukotrienes. On histopathology perivasculitis is the hallmark of scrub typhus leading to of multiple organs dysfunction Syndrome.¹²

Uric acid is the final oxidative product of purine metabolism in humans and majority is excreted by the kidney some part is excreted by the gastrointestinal tract.³ The increased levels of uric acid have been associated with atherosclerosis, hypertension, hyperinsulinemia and chronic kidney disease. Uric acid has also been shown to be elevated in hypoxic states such as chronic heart failure and obstructive pulmonary disease.⁵⁶

Sepsis is characterized by a systemic inflammatory response syndrome and in the presence of a known or suspected infection and can have severe consequences. The majority of patients admitted to intensive care unit patients undergo ischemic-reperfusion injury and inflammation. In patients with sepsis, high levels of oxyradicals and lower antioxidant levels are believed to be a cause of multiorgan failure. Uric acid has both oxidant and antioxidant properties and may play a role in these processes. Thus the measurement of uric acid levels could be possibly used as a marker of oxidative stress in patients with sepsis.⁹¹⁰

We conducted the present study to find association of hyperuricemia with severity of disease and outcome in patients of scrub typhus.

Methods

The study was conducted on patients diagnosed as scrub typhus with indirect fluorescence immunoassay (IFA) and admitted to wards of a tertiary care centre from July 1st 2015 through June 30th 2016.

Inclusion Criteria

We conducted the study among patients aged ≥ 18 yrs, diagnosed as scrub typhus with indirect fluorescence immunoassay (IFA)
The harmful host response to infection; systemic response to proven or suspected infection plus some degree of organ hypofunction i.e.

Table 1: Clinical characteristics among study participants

<table>
<thead>
<tr>
<th>Symptoms and signs</th>
<th>All (n=92)</th>
<th>Hyperuricemia (n=34)</th>
<th>No hyperuricemia (n=58)</th>
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<td>High grade fever</td>
<td>25 (27.2)</td>
<td>9 (26.5)</td>
<td>16 (27.6)</td>
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<td>Chills/Rigors</td>
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<td>29 (85.3)</td>
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<td>Duration of presenting complaint</td>
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<td>&lt;7 days</td>
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<td>8 (23.5)</td>
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<td>7 – 14 days</td>
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<td>23 (67.6)</td>
<td>29 (50.0)</td>
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<td>&gt;14 days</td>
<td>11 (12.0)</td>
<td>4 (11.8)</td>
<td>7 (12.1)</td>
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<td>Cough</td>
<td>34 (37.0)</td>
<td>16 (47.1)</td>
<td>18 (31.0)</td>
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<td>8 (23.5)</td>
<td>22 (37.9)</td>
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<td>10 (29.4)</td>
<td>19 (32.8)</td>
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<td>Altered sensorium</td>
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<td>12 (35.3)</td>
<td>9 (15.5)</td>
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<tr>
<td>Rash</td>
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<td>2 (3.4)</td>
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<tr>
<td>Seizures</td>
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<td>1 (2.9)</td>
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<td>Lymphadenopathy</td>
<td>13 (14.1)</td>
<td>2 (5.9)</td>
<td>11 (18.9)</td>
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</tr>
</tbody>
</table>

**Organomegaly**

- Splenomegaly
- Hepatomegaly
- Hepato-splenomegaly
- Ascites
- Tenderness epigastrum
- Crepitations
- Pallor

Exclusion Criteria

Patients with known preexisting chronic kidney disease, history of malignancy and those on diuretics and low dose aspirin were excluded.

Operational Definitions

**Hyperuricemia**

Serum uric acid 7.2 mg/dL in males and 6.0 mg/dL in females was defined as hyperuricemia. (Beckman Coulter Diagnostics).11

**Scrub typhus**

A patient with features suggestive of scrub typhus (fever, rash, eschar etc.) and positive IgM antibodies with IFA

Severe Disease

A case of scrub typhus with criteria fulfilling severe sepsis or septic shock or evidence of organ system failure was defined as severe disease and a case of scrub typhus leading to mortality was defined as a poor outcome.

Septic (or severe sepsis)27

The harmful host response to infection; systemic response to proven or suspected infection plus some degree of organ hypofunction i.e.

1. Cardiovascular: Arterial systolic blood pressure ≥90 mm Hg or mean arterial pressure ≥70 mm Hg that responds to administration of IV fluid.
2. Renal: Urine output <0.5 ml/kg per hour for 1 h despite adequate fluid resuscitation.
3. Respiratory: Pao2/Fio2 ≤250 or, if lung is the only dysfunctional organ, ≤200.
4. Hematologic: Platelet count <20,000 platelets/mm3 or white blood count <1,000 cells/μL.
5. Organ system failure

Hematologic

- Hemoglobin 11.2 ± 2.1 11.6 ± 2.0 0.368
- TLC (thou/μl) 12.5 ± 5.6 9.2 ± 5.7 0.008
- Platelets (thou/μl) 99.8 ± 87.9 125.1 ± 87.8 0.185
- Neutrophils (%) 69.7 ± 40.7 36.5 ± 40.6 <0.001
- Sodium 136.2 ± 6.5 137.2 ± 6.5 0.478
- Potassium 3.8 ± 0.5 >0.999
- Cholesterol (mg/dl) 121.5 ± 38.7 133.1 ± 39.1 0.171
- HDL (mg/dl) 23.9 ± 14.8 30.7 ± 14.7 0.035
- Hb (g/dl) 127.2 ± 40.5 102.8 ± 40.5 0.006

Organ system failure

Neurologic: - Glasgow Coma Score < 6 (in absence of sedation) (Glasgow Coma Score: Sum of best eye opening, verbal, and motor response)

Cardiovascular:
- Heart rate < 54 beats per min
- Mean arterial blood pressure < 49 mm Hg (systolic blood pressure < 60 mm Hg)

Pulmonary
- PaCO2 > 50 mm Hg (acutely)
- (A-a)DO2 > 350 mm Hg (A-a)DO2 = [713 x FiO2 - (PaCO2/RQ) - PaO2] - PaO2
- Ventilator or continuous positive airway pressure dependence on the second day of organ dysfunction

Hepatic
- Jaundice (bilirubin > 6 mg/100 dL)
- Coagulopathy (prothrombin time, 4 sec greater than control, in the absence of anticoagulation)

Renal
- Urine output < 479 mL/24 hr or < 159 mL/8 hr
- Serum BUN > 100 mg/100 dL
- Serum creatinine > 3.5 mg/100 dL

Hematologic
- White blood count < 1,000 cells/μL
- Platelets < 20,000 platelets/mm3

Table 2: Comparison of haemotologic and biochemical findings

<table>
<thead>
<tr>
<th></th>
<th>Hyperuricemia (n=34)</th>
<th>No hyperuricemia (n=58)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>11.2 ± 2.1</td>
<td>11.6 ± 2.0</td>
<td>0.368</td>
</tr>
<tr>
<td>TLC (thou/μl)</td>
<td>12.5 ± 5.6</td>
<td>9.2 ± 5.7</td>
<td>0.008</td>
</tr>
<tr>
<td>Platelets (thou/μl)</td>
<td>99.8 ± 87.9</td>
<td>125.1 ± 87.8</td>
<td>0.185</td>
</tr>
<tr>
<td>Leukocytes (%)</td>
<td>69.7 ± 40.7</td>
<td>36.5 ± 40.6</td>
<td>&lt;0.001</td>
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<tr>
<td>Sodium</td>
<td>136.2 ± 6.5</td>
<td>137.2 ± 6.5</td>
<td>0.478</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.8 ± 0.5</td>
<td>&gt;0.999</td>
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</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>121.5 ± 38.7</td>
<td>133.1 ± 39.1</td>
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</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>23.9 ± 14.8</td>
<td>30.7 ± 14.7</td>
<td>0.035</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>127.2 ± 40.5</td>
<td>102.8 ± 40.5</td>
<td>0.006</td>
</tr>
<tr>
<td>Severity criteria</td>
<td>All (n=92) n (%)</td>
<td>Hyperuricemia (n=34) n (%)</td>
<td>Nohyperuricemia (n=58) n (%)</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----------------</td>
<td>---------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Sepsis</td>
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<tr>
<td>SIRS6</td>
<td>70 (76.1)</td>
<td>28 (82.4)</td>
<td>42 (72.4)</td>
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<td>Severe Sepsis1</td>
<td>30 (32.6)</td>
<td>16 (47.1)</td>
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<td>Septic Shock</td>
<td>4 (4.3)</td>
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<td>1 (1.7)</td>
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<td>Organ system failure</td>
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<tr>
<td>Renal</td>
<td></td>
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<tr>
<td>BUN &gt;100 mg/dL</td>
<td>2 (2.2)</td>
<td>2 (5.9)</td>
<td>0</td>
</tr>
<tr>
<td>Creatinine&gt;3.5mg/dL</td>
<td>8 (8.7)</td>
<td>7 (20.5)</td>
<td>1 (1.72)</td>
</tr>
<tr>
<td>Hepatic</td>
<td>6 (6.5)</td>
<td>1 (2.9)</td>
<td>5 (8.6)</td>
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<tr>
<td>Neurologic</td>
<td>21 (22.8)</td>
<td>12 (35.3)</td>
<td>9 (15.5)</td>
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<td>2 (2.2)</td>
<td>2 (5.8)</td>
<td>0</td>
</tr>
<tr>
<td>Anyone of above3</td>
<td>31 (33.7)</td>
<td>18 (52.9)</td>
<td>13 (22.4)</td>
</tr>
<tr>
<td>MODS3</td>
<td>5 (5.4)</td>
<td>3 (8.8)</td>
<td>2 (3.4)</td>
</tr>
</tbody>
</table>

1p-value calculated by chi-square test or Fisher’s exact test as admissible based on the data distribution; 2SIRS: Severe Inflammatory Response Syndrome; 3SIRS with any one or more of the Severe Sepsis components; 4Serum bilirubin >6.0 mg/dl; 5Altered sensorium; 6Platelet count <20,000/μl; 7Organ system failure; 8Two or more organ system failure

• Hematocrit < 20%. The study was cleared by Institutional Ethics Committee.

Indirect Immunofluorescence Assay (IFA)
Five ml of venous blood (3ml serum tube+ 2ml EDTA tube) was collected under all aseptic conditions. The sera were processed for IgM IFA for the detection and semi quantitative determination of IgM class antibody against Orientia tsutsugamushi in human serum or plasma was done using kit manufactured by Fuller Laboratories.

The data was entered on Microsoft excel spreadsheet and was analyzed using Epi Info 7.1.5 for windows. We analyzed the demographic, clinical, laboratory data, ventilator support and outcome in hyperuricemia group (HU) and no-hyperuricemia (NHU) group. The p-values ≤ 0.05 was considered as statistically significant.

Results
Total 92 admitted patients of scrub typhus aged from 18 years to 80 years were included in the study. Seventy eight (85%) patients were in age group of 18-60 years. Out of 92 patients, 72% were females and 28% were males with the ratio of female to male 2.5:1. Fever was present in all cases, however high grade fever was present in 27% patients. Thirty four (36.9%) patients were in hyperuricemia (HU) group and 58 (63.1%) were in No-hyperuricemia (NHU) group.

The clinical features at presentation in two groups are given in Table 1 and difference in presentation in altered sensorium was statistically significant. The findings in various laboratory investigations in two groups are given in Table 2. Mean total leucocytes count (TLC), mean random blood sugar level, mean serum urea and serum creatinine were significantly higher in HU group. The difference in mean random blood sugar level was also statistically significant. However mean serum albumin levels and mean serum HDL cholesterol were significantly lower in HU group.

Table 3 depicts the distribution of patients by severity of disease (SIRS, Severe Sepsis/Septic shock, organ failure). The number of patients with criteria of serum creatinine > 3.5 mg/dl and any organ dysfunction were significantly higher in HU group. In HU group 52.9% patients had at least single organ involvement and 8.8% had more than one organ involvement in comparison to 22.4% and 3.4% in NHU group. In HU group significantly higher number of patients had severe sepsis (p=0.023). Three of 34 (8.8%) patients in HU group and 5 of 58(8.6%) in NHU group required ventilator support and difference was not statistically significant however 4 of 34 (11.7%) in HU group died and there was no death in NHU group (p=0.007).

Discussion
In this study the patients of scrub typhus with hyperuricemia, more patients presented in altered sensorium with higher mean TLC, significantly higher renal dysfunction, hypoalbuminemia and significantly lower HDL cholesterol. The presence of severe sepsis, serum creatinine >3.5mg/dl and involvement of at least single organ was also significantly higher in HU group.

The higher incidence in female can be attributed to working of females in the fields or cutting grass with bare hands in sitting position which exposes them to infected mites. Sharma et al also reported higher incidence among females.14

There is limited data available in on association of hyperuricemia with severity of scrub typhus. In our study, altered sensorium was higher in HU group which was statistically (p=0.029).

The mean total leucocytes count TLC in HU group was significantly higher than in NHU group (p=0.008). The difference in mean serum albumin levels in HU group (2.6 g/dl) and NHU group (2.9g/dl) was also statistically significant (p=0.50). Lee et al concluded that hypoalbuminemia in scrub typhus was closely related to the frequency of various complications.15

In our study in HU group mean serum urea was significantly higher (p<0.001) and serum mean creatinine levels were significantly higher (p=0.007) than in NHU group. The distribution of patients as per severity of disease with serum creatinine levels > 3.5 mg/dL was significantly higher in HU group (Table 3).

Akber et al concluded that though uric acid has both oxidative and antioxidative properties but that during significant degrees of stress such as sepsis, protective antioxidative properties of uric acid get overwhelmed and that despite higher levels of uric acid levels during oxidative stress it is more injurious to the human body. Thus uric acid levels can be an early marker of impending acute kidney injury in patients with sepsis and can predict the risk of acute kidney injury in sepsis.9

In our study, severe sepsis (p=0.023), neurological involvement (p=0.029) and involvement of at least single organ (p=0.002) was significantly higher in HU group when compared with NHU group.

Uric acid crystals have been implicated for acute inflammation of the renal epithelial cells via uric acid but it can also impact the human body by its non-crystal effects also.
The endothelial dysfunction, an afferent renal arteriopathy and tubulointerstitial fibrosis in the kidney by activating the renin-angiotensin-aldosterone system,\textsuperscript{16} activation of various inflammatory transcription factors, and induction of systemic cytokine production such as tumor necrosis factor alpha\textsuperscript{17} and local expression of chemokines such as monocyte chemotactic protein 1 in the kidney and cyclooxygenase 2 (COX-2) in blood vessels\textsuperscript{18} have been postulated in kidney and cyclooxygenase 2 (COX-2) in blood vessels\textsuperscript{18} have been postulated as various mechanism. Experimentally induced hyperuricemia lead to systemic and glomerular hypertension in animal models.\textsuperscript{19,20} Some in vitro experimental studies showed decreased production and depletion of nitric oxide by that uric acid.\textsuperscript{21,22}

The non-crystal effects of uric acid remain contentious because, under physiologic concentrations, urate is a powerful antioxidant that can scavenge superoxide, hydroxyl radicals, and singlet oxygen.\textsuperscript{23} In a study findings by Akber SA et al demonstrated that hyperuricemia was associated with poorer clinical outcomes in patients admitted to the Medical ICU with sepsis and levels of serum uric acid can be potentially used as a marker of severity of illness as well as a predictor of morbidity in patients presenting to the MICU with sepsis.\textsuperscript{9}

Conclusions

In this study, presence of hyperuricemia in patients of scrub typhus was associated with severe scrub typhus. The serum uric acid levels should be done in early course of all patients suffering from scrub typhus. The patients showing hyperuricemia should be monitored closely for early recognition of complications and management aggressively.

Limitations

The possibility of preexisting elevated uric acid level and non-availability of asymptomatic baseline renal function prior to acquiring infection are main limitations of this study. Present study sets the stage for further randomized control trials that are multicenter and encompass a greater sample size and population diversity to help better elucidate and confirm our findings.

Financial Assistance: IFA was done as a part of Project No. GIA/32/2014-DHR Dated 22-10-2014, funded by Indian Council of Medical Research.

References

Neutrophil Gelatinase-associated Lipocalin (NGAL) as a Marker of Renal Tubular Injury in Metabolic Syndrome Patients with Hyperuricemia

Ritu Karoli¹, Nikhil Gupta², Yogesh Karoli³, Manish Raj Kulshreshtha⁴, Vandana Tiwari⁵

Abstract

Background: Hyperuricemia has been associated with chronic kidney disease, evidence suggests that hyperuricemia might play a role in progression of renal damage. Whether hyperuricemia can lead to renal tubular injury remains unclear. In this study we aimed to determine serum NGAL and urinary NGAL/creatinine ratio as markers of renal tubular injury in metabolic syndrome patients with hyper or normouricemia.

Material and Methods: In this hospital based cross-sectional study, 180 participants with metabolic syndrome were included, 90 patients had hyperuricemia and 90 were with normouricemia. Clinical biochemical parameters of serum NGAL and urinary NGAL were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit. Receiver operating characteristic (ROC) curve was analysis employed to assess the sensitivity and specificity of serum NGAL and urine NGAL/creatinine ratio.

Results: Out of all, 96 were males and 84 were females. The mean age of participants was 45 ± 7 years. Serum NGAL levels and Urinary NGAL/creatinine ratio were higher in metabolic syndrome patients with hyperuricemia. High Serum NGAL was positively correlated with presence of hypertension; HbA1c and waist-hip ratio and negatively correlated with HDL.

Conclusion: Serum NGAL levels and urinary NGAL/creatinine ratio were higher in metabolic syndrome patients with hyperuricemia that indicates presence of renal tubular injury in these patients. High Serum NGAL was positively correlated with presence of hypertension; HbA1c and waist-hip ratio.

Introduction

In recent years there has been a renewed interest in hyperuricemia and its association with a number of clinical disorders other than gout, including hypertension, atherosclerosis, cardiovascular disease, and chronic kidney disease.1,2 Indeed, hyperuricemia is commonly part of the cluster of metabolic and hemodynamic abnormalities including obesity, glucose intolerance, dyslipidemia, and hypertension often subsumed under the term “metabolic syndrome”.2 Metabolic syndrome is highly prevalent in patients of CKD and its components are associated with progression of CKD.3 Recent data suggest that uric acid may be an important factor in the pathogenesis of chronic kidney disease (CKD) rather than just a marker of decreased renal uric acid excretion.4 The debate remains ongoing on whether renal impairment is due to a direct nephrotoxic effect of uric acid or due to other pathologic mechanisms caused by hyperuricemia.3 Most studies have focused on uric acid-induced endothelial dysfunction, oxidative stress and inflammation in the kidney.5,7 Neutrophil gelatinase-associated lipocalin (NGAL) protein originally purified from human neutrophils, is a promising biomarker for early detection of renal tubular injury.8 Whether chronic asymptomatic hyperuricemia can be related to renal tubular injury in presence of metabolic abnormalities is not clear. Therefore, the aim of this study was to test the hypothesis that serum and urinary levels of NGAL are elevated in patients with hyperuricemia.

Material and Methods

A hospital based cross sectional, observational study was conducted at department of medicine, Dr RMLIMS, Lucknow.

Participant selection- The study included 180 patients who had an age of >20 years with normal renal functions had metabolic syndrome. The metabolic syndrome (MS) was defined according to International Diabetes Federation (IDF) criteria.8 MS by IDF is defined as Central obesity (defined as waist circumference ≥94 cm (male), ≥80 cm (female)) and any two of the following:

1. BP Systolic ≥ 130 mmHg or BP diastolic ≥ 85 mmHg
2. TG ≥ 150 mg/dl
3. HDL ≤ 40 mg/dl in men and ≤50 mg/dl in women.
4. FBS ≥100 mg/dl

Hyperuricaemia was defined as serum uric acid levels >6.8 mg/dL in both males and females.10 Estimated glomerular filtration rate (eGFR) was calculated using Equation from the Modification of Diet in Renal Disease study- Estimated GFR (mL/min per 1.73 m²) = 1.86 x (Pcr)⁻¹.154 x (age)⁻⁰.²⁰³ Multiply by 0.742 for women.

Exclusion criteria comprised of

¹Professor (Sr Gr), ²Associate Professor, Department of Medicine, ³Senior Consultant, Department of Orthopedics, ⁴Associate Professor, ⁵Professor (Sr Gr), Department of Biochemistry, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh; ¹Corresponding Author

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patients with diabetes mellitus, Heart failure, acute or chronic kidney disease, hepatic disorders, lymphoproliferative or myeloproliferative disorders, haemolytic disorders, using drugs like salicylates, diuretics like thiazides, levodopa, ethambutol, cyclosporine, nicotinic acid, pyrazinamide, antihypertensives, oral hypoglycemics or statin therapy and who consumed alcohol ≥10 grams per day. The patients with systemic inflammatory conditions and autoimmune diseases were also excluded from the study.

These patients were divided in divided in two groups, 45 patients had hyperuricemia and 45 patients had normal uric acid levels. Detailed history was taken and examination was done including anthropometric parameters. Blood pressure, weight, height, body mass index (BMI) by formula [Weight (kg)/Height(m)²], abdominal and waist circumference was measured using standard methods in each participant. After 12 h of fasting, blood samples was taken in the morning for glucose, serum creatinine, urea, uric acid and lipid profile. The concentration of serum NGAL and urinary NGAL were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer’s instructions. All specimens were diluted to obtain the concentration for the optimal density according to the instructions for the ELISA kit.

Statistical analysis

The statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) software for Windows version 17.0 (SPSS, Inc., Chicago, IL USA). Continuous variables were expressed as mean ± SD, median and inter quartile range and categorical variables were presented as percentages. To ensure the normal distribution of variables, Kolmogorov-Smirnov test was applied. Comparison between groups was performed using Student’s unpaired t test and chi square analysis. We used Pearson’s correlation coefficient to assess the relationships. Receiver operating characteristic (ROC) curve was analysis was employed and area under the curve (AUC) was calculated to assess the sensitivity and specificity of serum NGAL and urine NGAL/creatinine ratio to discriminate hyperuricemia from normouricemia. 95% Confidence interval was calculated as needed. P < 0.05 was considered statistically significant.

Results

In this hospital based cross-sectional study, 180 participants with metabolic syndrome were included, 90 patients had hyperuricemia and 95 were with normal uricemia. Out of all, 96 were males and 84 were females. The mean age of participants was 45 ±7 years. Table 1 shows that there were no significant differences across the groups in age, gender, BMI, waist circumference and waist hip ratio. Prevalence of hypertension and glucose intolerance was more in subgroup of patients with hyperuricemia.

As far as biochemical parameters were concerned as depicted in Table 2, it was observed that HbA1c, serum creatinine and serum NGAL were significantly higher in patients with hyperuricemia. Urinary NGAL/creatinine ratio was also found to be significantly higher in metabolic syndrome patients with hyperuricemia. Serum NGAL in hyperuricemia group was higher than normouricemia (median 458 ng/ml, IQR: 268-698ng/ml. of serum NGAL was positively correlated with systolic and diastolic

| Table 1: Clinical and Anthropometric data of study Participants |
|-------------------|-------------------|-------------------|----------|
| Variable          | Metabolic syndrome patients with hyperuricemia (n=90) | Metabolic syndrome patients with normouricemia (n=90) | P value  |
| Age (years)       | 46 ± 12.6         | 45±14             | 0.57     |
| Male sex, n (%)   | 24(53)            | 23(51)            |          |
| BMI (kg/m²)       | 26.1 ±4.36        | 25.7 ±4.33        | 0.23     |
| WC(cm)            | 89.62 ±8.73       | 88±8.68           | 0.12     |
| Waist/hip ratio   | 1.2 ±0.45         | 1.08 ±0.45        | 0.8      |
| Systolic BP (mm Hg) | 162.62±7.49     | 148.25±7.56       | 0.02*    |
| Diastolic BP (mm Hg) | 96 ±6.4         | 82±4              | 0.003*   |

Data is shown as Means(SD(Standard deviation); *statistically significant

| Table 2: Biochemical parameters of study participants |
|-------------------|-------------------|-------------------|----------|
| Variable          | Metabolic syndrome patients with hyperuricemia (n=90) | Metabolic syndrome patients with normouricemia (n=90) | P value  |
| HbA1C(%)          | 6.2±1.6           | 5.7±0.85          | 0.04*    |
| Total cholesterol (mg/dl) | 192±24       | 188.98±18         | 0.07     |
| HDL-cholesterol (mg/dl) | 36.85±8      | 34.85±6           | 0.6      |
| Triglycerides (mg/dl) | 178.4±34      | 180.6±30          | 0.12     |
| LDL-cholesterol (mg/dl) | 112.8±16     | 108±12.2          | 0.2      |
| Uric acid (mg/dl)  | 7.8±1.6          | 3.2±1.56          | 0.01*    |
| Creatinine (mg/dl) | 1.3±0.2         | 0.8±0.3           | 0.01*    |
| Fasting glucose(mg/dl) | 109.2±10.09  | 106±12            | 0.12     |
| Serum NGAL(ng/ml) | 352.6±34         | 214±27.8          | 0.01*    |
| Urinary NGAL/ creatinine ratio | 25.2±8       | 16.2±5.6          | 0.02*    |

Data is shown as Means SD(Standard deviation); *statistically significant

| Table 3: Correlation analysis with high NGAL |
|-------------------|-------------------|-------------------|----------|
| Parameter         | rho value         | P value           |
| Systolic blood pressure | 0.42            | 0.001            |
| diastolic blood pressure | 0.56            | 0.01             |
| HbA1c             | 0.36              | 0.002            |
| Waist/hip ratio   | 0.48              | 0.01             |
| HDL               | -0.32             | 0.04             |
blood pressure, HbA1c and waist-hip ratio and negatively correlated with HDL as shown in Table 3.

To estimate utility of serum NGAL and urinary NGAL/creatinine ratio in differentiation of hyperuricemia and normouricemia, ROC curve was used and AUC was calculated and cut-off values for serum NGAL and urinary NGAL/creatinine ratio at various sensitivity and specificity levels studied. It was observed that at level of 502ng/ml (AUC 0.88, 95% CI, 0.80-0.95, p=0.01), sensitivity and specificity for hyperuricemia were 89% and 77%, (Figure 1). For urinary NGAL/creatinine ratio, (Figure 2), AUC was 0.88(95% CI 0.6-0.98, p=0.01) a value of 27 had 88% sensitivity and 72% specificity for detecting hyperuricemia.

**Discussion**

Uric acid, an end-product of purine metabolism is excreted via kidney. Many epidemiologic studies have suggested that hyperuricemia is associated with hypertension, cardiovascular diseases and insulin resistance, and uric acid as independent predictor of renal damage.CKD is a devastating illness which is rapidly approaching epidemic proportions globally. Patients with CKD have high uric acid levels because of reduced renal clearance. The growing evidence suggests that hyperuricemia may have role in progression of CKD but whether chronic asymptomatic hyperuricemia can cause renal tubular injury is not known. Metabolic syndrome has become an important public health problem with increasing prevalence which is often associated with hyperuricemia. This study was aimed to assess presence of renal tubular injury as reflected by serum and urinary NGAL in patients of metabolic syndrome who have hyperuricemia and to study any correlation of these markers with individual components of metabolic syndrome. We included all metabolic syndrome patients to avoid any selection bias and divided into 2 groups depending upon uric acid levels. Renal tubular injury markers serum NGAL and urinary NGAL were determined and both were significantly greater in patients with hyperuricemia than normouricemia.

It is well known that acute hyperuricemia leads to acute kidney injury by precipitation of uric acid crystals causing direct renal toxicity. Experimental studies suggest that non crystallopathic mechanisms may also act to cause indirect injury such as renal vasoconstriction, oxidative stress inflammation and endothelial dysfunction. NGAL, It is a member of the lipocalin family a 25-kDa small protein that is expressed at low levels in several human tissues and rapidly released from renal by damaged renal tubular epithelium in response to various insults to the kidney. NGAL is well known biomarker of renal tubular injury. In contrast to serum creatinine which rises when renal function is substantially decreased, serum NGAL and urinary NGAL are specifically increased in the early phase of renal damage. The studies have shown that NGAL they are not only the markers of AKI but also elevated in patients with chronic tubulointerstitial disease, and may predict of long-term decline in renal function in patients with CKD.

Similar to the results of present study, Tomczak et al have studied the relation of hyperuricemia and markers of renal tubular injury. In their study on male, obese, hypertensive adolescents with hyperuricemia, they demonstrated that patients with hyperuricemia had higher urine NGAL and KIM-1 levels relative to controls with normouricemia. This study also suggested the possibility that hyperuricemia may be linked to tubular injury. Pathogenic role of uric acid in causation of renal dysfunction is indicated by the fact that lowering uric acid levels by allopurinol retards renal damage. Experimental studies have shown that induction of hyperuricemia led to progressive glomerular injury and tubulointerstitial fibrosis. Ryu et al have also demonstrated that uric acid stimulates fibrogenic process in renal tubular epithelium.  

High Serum NGAL was positively correlated with presence of hypertension; HbA1c and waist-hip ratio and negatively correlated with HDL. This finding suggests that components of metabolic syndrome have added effects on renal tubular markers along with hyperuricemia. Our findings are in concordance with Tomczak et al who have reported similar correlations of components of metabolic syndrome with NGAL in patients of hyperuricemia. Greater urinary NGAL levels have been reported by other researchers also in conjunction with hypertension.

Our study has few limitations. It has cross sectional design so causal relationship between hyperuricemia and renal tubule-interstitial injury could not be delineated. Secondly, study had small sample size and only NGAL could be assessed.

More prospective studies with large number of patients having long-term follow-up will be needed to validate our data and determine the roles of NGAL, urine NGAL/Cr ratio and other markers in patients with hyperuricemia in predicting tubulointerstitial disease and renal outcomes.

**Conclusion**

Serum NGAL levels and urinary NGAL/creatinine ratio were higher in metabolic syndrome patients with hyperuricemia that indicates presence of renal tubular injury in these patients. High Serum NGAL was positively correlated with presence of hypertension; HbA1c and waist-hip ratio Further research is needed to determine long-term prognostic values of both hyperuricemia and NGAL for recognition of complications of hyperuricemia to prevent renal damage in the early phase.

**References**


Efficacy and Safety of Empagliflozin as Add on in Patients with Type II Diabetes Mellitus (DM) Inadequately Controlled on Triple Drug Combination

Deepak Bhosle¹, Snehal Chavan², Shraddha Kardile³

Abstract

Objectives: Diabetes mellitus (DM) refers to a group of metabolic disorders characterized by hyperglycemia resulting from insulin resistance, insulin action or both. Despite availability of various treatment modalities it is difficult to achieve the desired glycemic control in many patients. In such patients new class of anti-diabetic agent sodium-glucose co-transporter II (SGLT2) inhibitors has been approved by FDA. SGLT-2 inhibitor Empagliflozin has been associated with HbA1c reduction and weight loss in a broad range of patients with type 2 Diabetes Mellitus (T2DM).

Methods: An open label, interventional, single arm, 24 weeks study was done on 120 patients who were inadequately controlled on three oral hypoglycaemic agents and reluctant to take insulin therapy. Empagliflozin 25 mg once a day was added to ongoing triple drug therapy. Changes in glycemic parameters like fasting blood sugar levels, post-prandial blood sugar levels, HbA1C, body weight, systolic and diastolic blood pressure and safety profile were assessed at baseline, three months and sixth months. Study was conducted at MGM medical college and hospital, Aurangabad in collaboration with Department of Medicine.

Results: Our study revealed Empagliflozin 25 mg once daily when used as add on to ongoing triple drug therapy has shown 3.02 % reduction in HbA1c and 3.83 kg reduction in bodyweight.

Conclusion: Empagliflozin a SGLT 2 inhibitor is a promising drug for reduction in HbA1c value and body weight in patients with T2DM who are inadequately controlled on triple drug therapy and are reluctant to insulin therapy.

Introduction

Diabetes mellitus (DM) refers to a group of metabolic disorders characterized by hyperglycemia resulting from insulin resistance, insulin action or both. Chronic hyperglycemia in Diabetes mellitus is associated with long-term dysfunction and failure of various organs, microvascular disorders like diabetic neuropathy, diabetic nephropathy, diabetic retinopathy and macrovascular disorders like cardiovascular diseases, peripheral vascular disease and cerebrovascular accidents.¹ ² Different types of Diabetes mellitus are caused by a complex interaction of genetic and environmental factors. Predominant types of Diabetes mellitus include Type 1 Diabetes mellitus, Type 2 Diabetes mellitus and Gestational Diabetes mellitus.

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The Worldwide prevalence of Diabetes mellitus is increasing alarmingly. In 2019, the prevalence was estimated to be 9.3% (463 million people) across the globe, and this is estimated to rise to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045. India is one of the seven countries included in the International Diabetes Federation (IDF) South-east Asia (SEA) region. Currently, 88 million people suffer from diabetes in the SEA region, which is expected to rise to 153 million by 2045. As per IDF SEA estimates, Diabetes mellitus is a growing challenge among the Indian population with a prevalence of 8.9%. 4

An important role in glucose homeostasis is played by kidneys as they cause the reabsorption of glucose from the glomerular filtrate. Glucose reabsorption in the kidney is mediated by two sodium glucose co transporter (SGLT) proteins, SGLT1 and SGLT2. The majority of glucose reabsorption ~90% is mediated by SGLT2 and occurs in the first part of the proximal convoluted tubule while ~10% is reabsorbed distally in the proximal convoluted tubule by the action of SGLT1. 5,6

SGLT2-mediated glucose transport inhibition in the kidney leads to loss of glucose in the urine and a reduction in hyperglycemia. In addition SGLT-2 inhibitors action does not depend on a functioning pancreatic β-cell, thus they are effective in any degree of β-cell function and also provide additional glucose lowering when combined with other classes of antihyperglycemic agents. 7 The urinary glucose excretion results in loss of calories which causes significant weight loss and the osmotic diuretic effect reduces blood pressure. 7,8 SGLT-2 inhibitors are approved in the treatment of Type 2 Diabetes mellitus in adults. Canagliflozin, dapagliflozin, and empagliflozin have approval in the United States and European Union and also in India. 9,10

Empagliflozin is currently approved SGLT2 inhibitors for the use of Type 2 Diabetes mellitus. The drug received US FDA approval in August 2014 to reduce Type 2 Diabetes mellitus associated cardiovascular risk in adult patients. 11 In India, Central Drug Standards Control Organization has approved the drug Empagliflozin at the dose of 10mg and 25mg doses, to improve glycemic control in adults with T2DM. In addition to its glucose-lowering effects, empagliflozin has been shown to reduce body weight and blood pressure without increase in heart rate. 11,12

Empagliflozin is the first glucose-lowering agent to demonstrate cardiovascular risk reduction in patients at high risk of cardiovascular disease. In a prospective outcome trial, a 14% reduction in risk of the 3-point composite endpoint of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. 13 Recently, the EMPA-REG study showed that patients, with a high-risk for cardiovascular diseases receiving empagliflozin had a lower rate of deaths from cardiovascular diseases. 14,15 Triple drug therapy has been introduced in India following the global acceptance of two drug fixed dose combinations. Studies related to triple drug treatment for Type 2 Diabetes mellitus patients have shown that the therapy provides significant reduction in HbA1C levels. 16

This analysis evaluated changes in the glycaemia parameters such as FBS, PPBS, HbA1, body weight, systolic and diastolic blood pressure in patients who were inadequately responding to maximum dose of three oral hypoglycaemic agents and reluctant to take insulin therapy along with therapeutic safety of the patients.

Methods

24 weeks prospective, open label, single centre, single arm, interventional, clinical study was conducted at MGM medical college and hospital, Aurangabad in collaboration with Department of Medicine. Patients aged 18 to 65 years (N=120) who were inadequately controlled on triple drug therapy for Type 2 Diabetes Mellitus (T2DM). Inclusion criteria was T2DM patients of either sex (male or female) on maximum dose of three OHA with inadequate response, HbA1C > 8.5% and BMI > 25 kg/m². Newly diagnosed T2DM patients, type 1 diabetes mellitus, gestational diabetes, patients with eGFR value less than 45 ml/min/1.73 m² calculated by MDRD formula, patients on insulin therapy, patients with recurrent UTI and patients with history of diabetic ketoacidosis or other co-morbid cardiac, hepatic and renal diseases were excluded.

All the patients participating in the study were explained clearly about the purpose and nature of the study in the language they can understand. They were included in the study only after obtaining a written informed consent form (ICF)

The study was commenced following the approval of the Institutional Ethics Committee. All information pertaining to the patient visiting Out Patient Department, such as patient’s age, gender, occupation, relevant history, past history and drug therapy will be recorded in a Case Record Form (CRF).

Details of the prescribed drugs for Diabetes mellitus, and all other drugs used in the patient during treatment were recorded. They include the dose, duration, type of dosage form used, frequency of drug administration etc. and necessary information was recorded in a structured Case Record Form.

Empagliflozin 25 mg (1 tablet) once daily was administered as an add-on therapy to triple drug treatment and patients were asked to take it in the morning with ample amount of water. Study assessment was done by evaluating the study visit checklist which included informed consent, screening for inclusion criteria & exclusion criteria, general & physical examination. Blood sugar – fasting & post prandial, glycosylated haemoglobin level (HbA1C), blood pressure and body weight with safety assessment were performed at baseline and follow-up visits. Total 3 visits were planned. First visit at the baseline, Second visit at 12 weeks and third visit at 24 weeks, i.e. at the end of the study.

Primary end point was change in HbA1c (%) from baseline up to 24 weeks. Secondary end point was change in body weight from baseline up to 24 weeks. Safety assessment was performed by general and systemic examination and as per ADR reported by patients. The study was performed on 120 patients of which 76 were males and 44 were females. Data were collected at the baseline and at 12 weeks and 24 weeks for estimation of FBS, PPBS, HbA1c value and body weight and blood pressure. Paired t test was applied to this data and result was derived by using SPSS v.24

Results

The study was performed on 120
patients of which 76 were males and 44 were females. Among 120 patients recruited, 116 patients completed the study (96.67%), 3 were withdrawn due to ADR (2.5%) and there was 1 drop out (0.8%). After 24 weeks of study, 3.02% reduction in HbA1c was observed from baseline and 3.83 kg reduction in body weight was recorded, P value= 0.001. 3 out of 120 patients (2.5%) reported UTI and were withdrawn from study. All the three patients were female and treatment for UTI was provided as required. 116 patients tolerated Empagliflozin 25 mg once daily well. The mean duration of Diabetes mellitus was 7.24 ± 2.29 years. The average duration of triple drug therapy in patients was 2.87 ± 0.83 years. Most frequently prescribed triple drug combination was Metformin+Glimeperide+Teneligliptin (N=31), while Metformin+Teneligliptin+Pioglitazone was the least commonly prescribed triple drug therapy (N=2) in our study (Table 1). At week 24, Empagliflozin 25 mg provided significant reductions in glycemia parameters and body weight from baseline (p<0.001) (Table 2). Significant reduction was observed in the values of FBS with mean difference from baseline to 24 weeks of – 46.76 mg/dl (P<0.001). Reduction was recorded in baseline PPBS value by – 37.41 mg/dl at 24 weeks (P<0.001). Differences in mean changes in HbA1c were –3.02% (P<0.001) with Empagliflozin 25 mg given additionally with three drug combination therapy. Significant dose-related reductions from baseline in body weight were observed (p<0.001) with empagliflozin 25 mg resulting in mean weight loss of 3.83 kg from baseline at 24 weeks. Males have shown more reduction in values of glycemia Parameters like FBS, PPBS and HbA1C as compared to females but weight loss was observed more in females as compared to male population. Though continuous reduction was observed in values of all the parameters in both males (N=76) and females (N=44); no statistically significant difference was recorded amongst both genders (Table 3). A reduction of 3.8 mm of Hg in systolic and a reduction of 2 mm of Hg in diastolic blood pressure were observed in the patients at the end of 24 weeks of study from the baseline.

### Discussion

In healthy individuals, about 180 mg of glucose is filtered and reabsorbed daily through the kidneys and maximal transport rate (Tmax) is 300 mg/min. This rate is about 20% higher i.e. 352 mg/min (19.5 mmol/l/min) to 419 mg/min (23.3 mmol/l/min) in patients with poorly controlled T2DM. This pertains to the increased expression of SGLTs in persons with diabetes which represents a physiological response to increased glucose delivery to the nephrons that is ultimately maladaptive. Antagonizing these transporters with SGLT2 inhibitors is an insulin-independent mechanism that offers a considerable advantage of increasing urinary glucose excretion without inducing hypoglycaemia and promoting weight loss due to loss of 300-400 kcal/day. Empagliflozin is currently approved SGLT2 inhibitors for the use of Type2 Diabetes mellitus. The drug has gained US FDA approval in August 2014 to reduce T2DM associated cardiovascular risk in adult patients. CDSCO has approved the drug in India at the dose of 10mg and 25mg doses on May 2015, to improve glycemic control in adults with T2DM. In addition to its glucose-lowering effects, empagliflozin has been shown to reduce body weight and blood pressure without increase in heart rate.

According to the latest American Diabetes Association (ADA) and European Association of Study of Diabetes (EASD) joint statement released in October 2018 use of newer cardio friendly drugs for treatment of type II DM has been highly recommended. Empagliflozin is the first glucose-lowering agent to demonstrate cardiovascular risk reduction in patients with diabetes at high risk of cardiovascular disease in a prospective outcomes trial: a 14% reduction in risk of the 3-point composite endpoint of death from
cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke has been reported. Recently, the EMPA-REG study showed that patients, with a high-risk for CVD, receiving empagliflozin had a lower rate of deaths from CVD. S.R Pattnaik et al. (2018) demonstrated the long-term tolerability, glycemic efficacy and safety of empagliflozin as an add-on to triple drug treatment.12-14

In this study, at week 24, Empagliflozin 25 mg provided significant reductions in glycemia parameters from baseline (p<0.001). Significant reduction was recorded in the values of FBS with mean difference from baseline to 24 weeks of –46.76 mg/dl (P< 0.0001). Reduction was recorded in baseline PPBS value by –87.41 mg/dl at 24 weeks (P< 0.0001). Differences in mean changes in HbA1c were −3.02 % with Empagliflozin 25 mg given additionally with three drug combination therapy. In all the reduction was more from baseline to 12 weeks period than from 12 weeks to 24 weeks duration.

Significant dose-related reductions from baseline in body weight were observed at week 24 (p<0.001). Empagliflozin 25 mg provided mean changes of −3.83 kg from baseline at 24 weeks. Weight loss with Empagliflozin 25 mg occurred rapidly through week 12; a progressive decrease in weight loss over the remaining treatment period was seen. Our results correlate with studies done on T2DM patients who were administered Empagliflozin 25 mg as monotherapy, or other regimens like with metformin, other two OHA and insulin. A reduction of 3.8 mm of Hg in systolic and a reduction of 2 mm of Hg in diastolic blood pressure were observed in the patients at the end of 24 weeks of study from the baseline.

In conclusion, Empagliflozin a SGLT-2 inhibitor is a promising new drug; when administered in a dose of 25 mg (one tablet) as an add on to patients with inadequately controlled type II DM who were receiving triple drug OHAs and were reluctant for an insulin therapy, it provided a significant reduction in HbA1c and body weight over a period of 24 weeks.

References
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Reduces duration of infection
- 33% reduction in duration of infectious episodes.
- Lower rate of hospitalization.

Reduces burden of medication
- Reduces the use of antipyretic drugs, anti-inflammatory drugs and antibiotics.

Dosage

Loading Dose: 1 tablet twice daily x 8 days
Maintenance Dose: 1 tablet once daily x 52 days

*where immunity is reduced (Deepak Talwar et al)
References:

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Full prescribing information available on request.

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Website: http://www.drr.org E-mail: customer.service@drr.com

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A Menace without Specific Feature – Scrub Typhus a Reemerging Disease

Sujoy Roychowdhury¹, Shibendu Ghosh², Devjit Majumder³, Prabuddha Mukhopadhyay⁴*

Abstract

Introduction: Scrub typhus is a re-emerging infectious disease. Though considered as disease of rural areas, this disease has been urbanized and the prevalence has broadened further. Disease has been reported with increasing frequency from various parts of India and has resurgence in north east. It is a disease with multi organ involvement, with or without characteristic eschar and early detection and initial specific treatment is important.

Material: An observational hospital-based study in patients >18 years admitted to a tertiary care center in eastern India. Scrub typhus was diagnosed on basis of symptoms with or without eschar and Scrub IgM. Treated with doxycycline (azithromycin in 3 pregnant patients) & clinical course was monitored. An appropriate correlation measure, based on the natures of the variable under study, (e.g.: rank correlation / Pearson correlation/ point biserial correlation) was estimated and subsequently tested at alpha =0.05 level of significance. A p value <0.05 was taken as significant.

Observations: A total of 105 patients of scrub typhus were included in present study. It had 66% male and 39% female with the most common age group being 46-60 years. Eschar was found in 33% patients. Neurological manifestation was found in 18% of the patients. Hyponatremia and raised liver enzymes were significantly noticed. 9% patients had Acute respiratory distress syndrome. 4% patients died because of multiorgan dysfunction. Three pregnant patients included in study were treated with azithromycin showed good response and pregnancy outcome was uneventful.

Conclusions: Scrub typhus is no longer a disease of rural India. Physician should have strong suspicion and needs early attempt to diagnose and treat as mostly the disease is featureless and can be treated easily, but delay in starting treatment raises chances of severe complications like encephalitis, ARDS, Macrophage Activation Syndrome. Disease mostly responded with Azithromycin, Doxycycline.

Introduction

Scrub typhus is an acute febrile illness caused by Orientia tsutsugamushi. Orientia tsutsugamushi (from Japanese tsutsu meaning “illness”, and mushi meaning “insect”) is a mite-borne bacterium belonging to the family Rickettsiaceae. It is a natural and an obligate intracellular parasite of mites belonging to the family Trombiculidae. Human beings are infected accidentally when they encroach upon mite-infested rural and suburban areas.

It is often acquired during recreational, occupational or agricultural exposure because crop fields are an important reservoir for transmission. Pathophysiological hallmark is disseminated vasculitis with subsequent vascular injury involving organs like skin, liver, kidney, brain, meninges. The clinical symptoms are fever, headache, myalgia, malaise, rash and lymphadenopathy which are commonly seen in other acute febrile illness like malaria, enteric fever, leptospirosis, dengue etc. making the clinical diagnosis tough.

According to previous literature common symptoms are high grade fever of 7-14 days duration, nausea, vomiting, headache, myalgia, cough and breathlessness. Eschar is seen in 46% cases and the common sites are axilla, breast and groin. Liver enzymes are elevated in nearly all cases (95.9%). Multiple Organ Dysfunction Syndrome (MODS) is present in one third of patients (34%). Hypotension (16%), renal impairment (12%), ARDS (8%) and meningitis (7 patients, 14%) are some other complications. The pathognomonic clinical sign is “eschar” (cigarette burn like appearance) which is a skin lesion at the site of mite bite and is inconspicuous as it is often present in the genital region and may go unnoticed until looked closely especially in the dark skinned (Figure 1 a, b, c). Rickettsial infections have been documented from various parts of India. There have been reports of sporadic outbreaks of scrub typhus mainly in the eastern and southern Indian states with serological evidence of widespread prevalence of spotted fevers and scrub typhus particularly during the monsoon and post monsoon months.

Materials and Methods

An observational study was conducted in Vivekananda institute of medical science, Kolkata from October 2018 to July 2020. This is a multispeciality referral hospital in Kolkata.

Patients presenting to us with fever requiring admission were questioned thoroughly, evaluated to detect cause of fever. Patient who has Scrub IgM positive were considered as a case of scrub typhus. “Standard Q Tsutsugamushi IgM/IgG” kit made by SD Biosensor was used, It’s an...
The patients were followed up to look for an outcome on the basis of the duration of hospital stay and survival.

Statistical Analysis

Based on the outcome parameter different statistical analysis carried out:

1. Estimate the mortality and morbidity risk of Scrub typhus infection. After the risks are calculated the incidence rate was estimated.

2. An appropriate correlation measure, based on the natures of the variable under study, (e.g.: rank correlation / Pearson correlation/ point biserial correlation) was estimated and subsequently tested at alpha = 0.05 level of significance. A p value <0.05 taken as significant.

Observation and Result

63% of the population was male and 37% female. 50% of population was above 45yr age group, followed by 20% in (31-45) years. Out of the patients admitted 77% were managed in ward and 23% in ICU.

Table 1: Frequency Table – Deranged Laboratory Parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Levels</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>&lt;=11</td>
<td>34</td>
<td>32.38</td>
</tr>
<tr>
<td>Total count</td>
<td>&gt;=11000</td>
<td>37</td>
<td>35.24</td>
</tr>
<tr>
<td>Platelet</td>
<td>&lt;1.5Lakh or &gt;= 4.5Lakh</td>
<td>24</td>
<td>22.86</td>
</tr>
<tr>
<td>Sodium</td>
<td>&lt;135 and &gt;=150</td>
<td>47</td>
<td>44.76</td>
</tr>
<tr>
<td>Potassium</td>
<td>&lt;3.5 and &gt;=5.5</td>
<td>30</td>
<td>28.57</td>
</tr>
<tr>
<td>Urea</td>
<td>&gt;=20</td>
<td>88</td>
<td>83.81</td>
</tr>
<tr>
<td>Sr Bilirubin</td>
<td>&gt;=1.2</td>
<td>47</td>
<td>44.76</td>
</tr>
<tr>
<td>SGPT</td>
<td>&gt;=70</td>
<td>66</td>
<td>62.86</td>
</tr>
<tr>
<td>ALP</td>
<td>&gt;=150</td>
<td>62</td>
<td>59.05</td>
</tr>
<tr>
<td>SGOT</td>
<td>&gt;=70</td>
<td>77</td>
<td>73.33</td>
</tr>
<tr>
<td>PT INR</td>
<td>&gt;=1.1</td>
<td>77</td>
<td>73.33</td>
</tr>
<tr>
<td>CRP</td>
<td>&gt;=6</td>
<td>104</td>
<td>99.05</td>
</tr>
<tr>
<td>ESR</td>
<td>&gt;=25</td>
<td>102</td>
<td>97.14</td>
</tr>
<tr>
<td>Albumin</td>
<td>&lt;=3.5</td>
<td>91</td>
<td>86.67</td>
</tr>
<tr>
<td>Globulin</td>
<td>&gt;3.5</td>
<td>90</td>
<td>85.71</td>
</tr>
<tr>
<td>Creatinine</td>
<td>&gt;1.2</td>
<td>45</td>
<td>42.86</td>
</tr>
</tbody>
</table>

Table 2: Complications and outcome among patients

<table>
<thead>
<tr>
<th>Complication</th>
<th>Number of Patients</th>
<th>Recovered</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARDS</td>
<td>9</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Renal failure</td>
<td>5</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>MODS (Multi organ dysfunction syndrome)</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Meningoencephalitis</td>
<td>6</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>None</td>
<td>81</td>
<td>81</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>105</td>
<td>100</td>
<td>5</td>
</tr>
</tbody>
</table>

Immunochromatographic assay.

After admission all fever patients were evaluated by recording history, performing thorough clinical examination and sending appropriate laboratory investigations. A diagnosis of scrub typhus is confirmed when a patient with an Acute febrile illness (AFI) had a positive Immunofluorescence or ELISA, further strengthened by either the presence of eschar or exclusion of other causes of fever.

All the blood parameters to evaluate a case of fever sent these include hemoglobin, total count, differential count, platelet count, ESR, CRP, Liver function test, sodium potassium urea creatinine. Other investigations like Ultrasonography abdomen, Chest x ray, cerebrospinal fluid study, echocardiography done in specific cases

The patients were followed up to look for an outcome on the basis of the duration of hospital stay and survival.

Fig. 1: Eschar in Undergarment areas in Scrub Patients

Fig. 2: Pie chart representing the complication among patients. Out of total 24 ICU patients, 13 patients required vasopressor support. Out of total 5 deaths, 3 patients died from ARDS and two patients from MODS

Fig. 2: Pie chart representing the complication among patients. Out of total 24 ICU patients, 13 patients required vasopressor support. Out of total 5 deaths, 3 patients died from ARDS and two patients from MODS
Table 3: CSF picture of 6 patients who developed meningoencephalitis

<table>
<thead>
<tr>
<th>Patient Indication</th>
<th>Cell</th>
<th>Protein</th>
<th>Sugar</th>
<th>Gene Xpert</th>
<th>C/S</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Convulsion</td>
<td>2-5</td>
<td>191</td>
<td>57</td>
<td>-ve</td>
<td>-ve</td>
</tr>
<tr>
<td>2 Headache with neck rigidity</td>
<td>30(5(N)</td>
<td>79</td>
<td>63</td>
<td>-ve</td>
<td>-ve</td>
</tr>
<tr>
<td>3 Altered sensorium</td>
<td>25(L)</td>
<td>81</td>
<td>88</td>
<td>-ve</td>
<td>-ve</td>
</tr>
<tr>
<td>4 Altered sensorium with convulsion</td>
<td>25(L)</td>
<td>40</td>
<td>50</td>
<td>-ve</td>
<td>-ve</td>
</tr>
<tr>
<td>5 Fever with neck rigidity</td>
<td>90(L)</td>
<td>102</td>
<td>50</td>
<td>-ve</td>
<td>-ve</td>
</tr>
<tr>
<td>6 Altered sensorium</td>
<td>8</td>
<td>78</td>
<td>52</td>
<td>-ve</td>
<td>-ve</td>
</tr>
</tbody>
</table>

N: Neutrophil L: Lymphocyte; CSF findings show that cell type and counts are variable. Protein content in CSF is mildly increased whereas sugar is normal in all the six cases.

In case of most patients, the duration of hospital stay was between 6-10 days with 10% patients crossing 10 days.

Fever was present in all patients and eschar in 35% of the patients. In our study, 95% of the patients were discharged after treatment while only 5% succumbed to death.

Specific systemic sign symptoms were absent in most patients. Among those symptomatic, respiratory involvement was maximum followed by neurological and gastrointestinal involvement. Ultrasound evidence of organomegaly (hepatomegaly or splenomegaly) was found in 24% of the patients.

Discussion

This study was conducted in the Medicine department of VIMS, Ramakrishna Mission Seva Pratishthan located in Kolkata. It’s a tertiary care center, a large population from Southern part of West Bengal use to attend our hospital. This area is mixture of rural and urban area, largely this area being urbanized.

Among our 105 adult patients 65 were male and 40 were female. All the cases were detected by Immunochromatography assay. In a comparative study among ICT (Immunochromatographic test), IFT and ELISA for Scrub typhus Kiran Pote et al. mentioned ICT have 100% specificity.1 So its effective tool to “rule in” the Scrub diagnosis. In our study the affected male population was slightly higher than female. The same thing is noted in standard literature. In our study most of the population affected are between 40 to 60 years age group. In a study in Meghalaya by Sivarajan S et al in 2012, the median age of presentation was 36.29 years2.

Depending on the severity patients were categorized & 23% patients were admitted in ICU and 77% patients admitted in ward. In our study all patients had fever that was 100%. It is comparable to study by Sharma et al. In their study 85% patients had high grade fever.3 Overall case fatality is 8 to 13 percent according to standard literature.3 In our study, case fatality is 5 percent. It is slightly lower than other study. It may be due to prompt diagnosis and early treatment. Patient presented with respiratory problem like dyspnea, cough in 17 percent cases in our study. It is comparatively less than standard literature. There it is 42 to 64 percent.4,5 ARDS is only about 25 percent in a study by Sharma et al.3 In our study 9 patients developed ARDS which is 9% of the total patients (Figure 2).

In our study gastrointestinal involvement like pain abdomen, vomiting and diarrhea was found in 25% percent patients. Organomegaly like hepatomegaly splenomegaly (ultrasound finding) was seen in 24% cases. In a study by Sivarajan et al, there was pain abdomen in 26 percent, nausea vomiting in 23 % cases, hepatomegaly in 26.7% & splenomegaly 24.4%.2 In our study 18 % of patients had neurological symptoms like headache, convulsion & altered sensorium. It is comparable to standard literature like by Varghese GM et al in 2013 in south India in a study, there was altered sensorium in 24.6% cases & convulsions in 6.5% cases.6 Lymphadenopathy was found in 4% of our patients. In a study done by Takhar RP et al in 2017, out of 66 patients diagnosed to have scrub typhus, lymphadenopathy was found in 12 patients. Skin rash was found in 2% patients in our study. In a study by Balasubramanian P et al, done in 2016 rash was found in 4% of the patients which is almost consistent with our finding. In our study anemia is defined by Hemoglobin less than 11 g/dl. 32 percent patient had anemia on admission. It is comparable to other study like study by Sharma et al showed anemia in 54% cases of Scrub Typhus.3

Leukocytosis which is defined as WBC count more than 11000 was found in 35% of our patient population. In a study done by Palak Gupta et al in 2016, leukocytosis was found in 28% of the patients.6

In our study thrombocytopenia (platelet count less than 1.5 Lakh) was found in 23% of the patients. Similar thrombocytopenia was seen in a study by Gupta et al in 2016 and it was 40%.6

In our study Hyponatremia (sodium less than 135 meq/l) was found in 45% of the patients. Potassium abnormalities (less than 3.5meq/L.) was found in 25% of our patients. In our study kidney function was deranged in quite a good number of patients. Urea more than 20mg/dl was found in 84% of the patients on admission. Creatinine more than 1.2mg/dl was found in 43% of the patients. In a study done by Subbalaksmi MV et al in 2012, Renal failure was seen in 27.8% of the cases.7 Liver abnormalities are quite common in our study and is consistent with other studies also. Serum bilirubin(more than 1.2 mg/dl) was found in 45% of the patients. In a study done by Sharma N et al done in 2016, jaundice was found in 32% of the patients. SGOT more than 70IU was found in 73.33% of our patients. SGPT more than 70IU was found in 62.86% of our patients. In a study in Goa in 2012, it was found that 80 percent patient had hepatitis.8 In a study done by Sharma N et al in 2016, it was shown that deranged hepatic function was found in 61% of patients. Alkaline phosphatase was raised above 150 in 59% of our patients. In a study done by Subbalakshmi MV et al in 2012, it was shown that Alkaline phosphatase was elevated in 62.5% of patients.

Albumin level was low (less than 3.5) in 87% of our patients. In a study in Goa in 2012, it was found that 60 percent patient had low albumin. In our study CRP is elevated (>6mg/dl) in 99% of the patients.

Average level of CRP in severe patients is 120.9mg/dl where it is 89mg/ dl in mild to moderate patients, p value 0.05 here which is mildly significant. There was no significant variation of serum sodium level between mild to moderate and severe group. Average sodium level was about 133meq/l. SGOT level elevation was more in severe patients, p value 0.073 in our study which is not significant. In spite of that higher SGOT was observed in
severe cases and might be associated with higher mortality. SGPT variation was seen here, severe group has higher SGPT with p value 0.049(significant). Albumin was much lower in severe group. In severe group average albumin 2.90mg/dl whereas in mild to moderate group it was 3.11mg/dl. p value 0.00 which is significant.

Creatinine level is elevated more in severe group compared to mild to moderate group. This association has a p value of 0.2 which is statistically insignificant. In multiple case series acute renal failure has been described as potentially fatal complications and many patients required hemodialysis. CSF study done in six patients who had neurological symptoms Table 2. There were no consistent neurological symptoms among them two of them had meningeal signs whether three of them had encephalitis like presentation, only one of them had convulsion. Cell count and protein content of the CSF also varied without any specific correlation with the symptoms.

Out of three pregnant patients enrolled in our study, they were successfully treated with azithromycin with favorable pregnancy outcome.

**Conclusion**
In our study the clinical profile of Scrub typhus patients presenting in a tertiary care hospital has been studied. It shows that it affects males slightly higher than females in age group of 40-60 years mostly. Most cases can be managed in ward. Fever is found in all cases. Neurological, respiratory and gastrointestinal symptoms are often present, but symptoms were inconsistent, varied presentation without any specific distribution of symptoms. A transient erythematous rash over trunk and upper arm noted in few patients. Neurological, gastrointestinal and respiratory symptoms had dissociated presentation most of the time, though in very severe cases all the systems were affected, and presentation was like MODS (multi organ dysfunction syndrome). Anemia, leukocytosis, hyponatremia, low albumin, transaminitis, elevated ESR and CRP, deranged kidney function are the common laboratory derangements found. Hypoalbuminemia, leukocytosis, raised CRP, elevated SGPT and SGOT levels had positive correlation with severe diseases. Though mortality was high in cases with MODS, most of the cases can be managed at word with only oral medicines. So early diagnosis is the key factor, but difficulty is there is no specific symptoms that can give clue, and here comes the importance of doing Scrub IgM test, even a point of care low cost Immunochromatographic (ICT) test will suffice Considering Scrub typhus, a reemerging disease we have to be more vigilant and have to do test in all fever patients where definite diagnosis could not be made with routine tests for fever.

**References**

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**Analytical Study of the Risk Factors Affecting the Fracture Risk in Rheumatoid arthritis Patients using FRAX Algorithm**

**Mukesh Sharma¹, Paramjeet Singh²*, Arun Joshi³**

**Abstract**

**Objectives:** The present study aimed to calculate the risk of osteoporotic fracture in patients of Rheumatoid arthritis (RA) by Fracture Risk Assessment Tool (FRAX) and its relationship with osteoporotic-specific risk factors.

**Methods:** This was a observational cross-sectional analytical study conducted from January 2019 to September 2020 where 185 patients, aged 40-90 years, who presented to the Rheumatology Clinic meeting the ACR/EULAR (2010) Classification Criteria for Rheumatoid Arthritis were included in the study and matched with 185 healthy individuals. We assessed the severity of the disease by using the DAS28 score. In addition, we evaluated the FRAX algorithm for all patients and controls to determine the...
10-year fracture risk of major osteoporotic fracture and hip fracture.

Results: RA patients had a significantly higher mean 10-year risk of major osteoporotic fracture (4.77 ± 5.04 vs 2.05 ± 1.84, P<0.05) and significantly higher mean 10-year risk of hip fracture (1.71 ± 2.81 vs 0.5 ± 0.95) (p<0.05). There was a significant positive correlation of duration of disease, previous fracture, parent fractured hip with major osteoporotic fracture (r=0.257, 0.435, 0.169 respectively) and with hip fracture (r=0.26, 0.369, 0.212 respectively). We saw no correlation of fracture risk with ESR (mm/hr), DAS28, CRP (mg/dL), glucocorticoid use, smoking, and alcohol use.

Conclusion: The risk of hip fracture and major osteoporotic fracture significantly increased in both male and female patients with RA as assessed by the FRAX algorithm. Duration of the disease, previous fracture, and parent fracture hip showed a significant correlation with major osteoporotic fracture and hip fracture. Therefore, the early recognition and treatment of RA hold importance in reducing the fracture risk.

Rheumatoid arthritis (RA), a chronic debilitating disease, carries a substantial economic and health impact.1,2

RA patients have a low bone mineral density (BMD).3-5 Among RA patients, the incidence of osteoporosis (OP) is 15-20% at the hip and spine.12 It increases the fracture risk and thus adds to the overall morbidity of the disease.10,11

The underlying pathogenesis of osteoporosis in RA lies in the inverse association of inflammatory cytokines and bone mass. The elevated cytokines (IL-1, IL-6 and TNF-α) during the active phase of the disease reduces the muscle mass and consecutively the bone mass.13 Furthermore, disease duration, seropositivity for anti-cyclic citrullinated peptide antibody (anti-CCP) and rheumatoid factor (RF) have also shown an association with bone loss in RA.8,9

The predominant risk factors affecting osteoporosis and osteoporotic fractures in RA are increasing age, female gender, physical inactivity, low body mass index (BMI), previous history of fractures, long duration of the disease and use of steroids.10 In the study by Lee et al,11 older age (≥70 years), low BMI (<25), longer disease duration (≥10 years), higher Health Assessment Questionnaire (HAQ) score, and higher cumulative glucocorticoid dose were significantly associated with osteoporosis.12

A web-based algorithm– Fracture Risk Assessment Tool [FRAX, (http://www.sheffield.ac.uk/FRAX)] can calculate 10-year probability of major osteoporosis-related fractures: vertebral, hip, forearm or humerus, and hip fracture in males and females-based on the various clinical risk factors such as duration of the disease, use of steroids and BMD.13 The use of the FRAX tool in determining the risk of fracture in cases with RA has been pursued in previous studies because RA has shown a significant association with bone loss and osteoporosis.14-17 Various intervention guidelines have been laid down, one of the most convincing being the National Osteoporosis Foundation (NOF)18,11 recommendation- where the 10-year probability of major osteoporotic fracture > 20% and hip fracture > 3% is significant for intervention, and FRAX helps initiate it.

FRAX score has been previously applied as a risk predictor for fracture in patients with RA, showing a strong correlation with BMD.19,11 This taught us to measure the fracture risk through FRAX and assess the factors affecting the fracture risk.

The present study was aimed to calculate the risk of osteoporotic fracture in patients of RA by FRAX (without BMD) and its relationship with osteoporotic-specific risk factors. Such a study has not been done in the past on RA patients in the Kumaon region of Uttarakhand. It thus will provide regional data on osteoporosis in RA and the associated risk factors.

Methods

This observational cross-sectional analytical study was conducted in the Rheumatology Clinic of Dr. Susheela Tiwari Government Hospital, Haldwani, Nainital, Uttarakhand, after obtaining clearance from the hospital Ethics Committee. The study was conducted from January 2019 to September 2020, in which we included 185 patients with rheumatoid arthritis aged between 40-90 years. Any RA patient with Type-1 diabetes, Type 2 diabetes, hypothyroidism, osteogenesis imperfecta, hypogonadism, premature menopause(<45 years of age), chronic malnutrition, chronic proton pump inhibitors use, malabsorption, chronic liver and kidney disease were excluded from the study. A gender and age-matched control group (n=185) was selected, consisting of healthy individuals from the hospital clinic staff and patient attendants. We took a written informed consent from the
The sample size calculation was based on the study of Looker AC et al., who observed that the probability of increased hip fracture in the age group of 50 years and above is 19%. Taking these values as a reference and assuming the risk of osteoporotic fracture is twice in rheumatoid arthritis patients than a healthy population, the minimum required sample size with 95% power of the study and 5% significance level is 141 patients in each study group. The total sample size taken is 370 (185 patients per group) to reduce the margin of error.

The diagnosis of rheumatoid arthritis was under the American College of Rheumatology (ACR)/European League against Rheumatism (EULAR) (2010) Classification. We took the complete demographic, personal and clinical history of the patients. A history of hypertension, diabetes, smoking, alcohol consumption, previous fracture, parental history of hip fracture, duration of rheumatoid arthritis and quantification of steroid use was also obtained. The fasting blood samples of the patients were collected for Complete Blood Count (Haemoglobin, Total Leucocyte Count, Differential Cell Count, Platelet Count), Acute Phase Reactants (C-Reactive Protein, Erythrocyte Sedimentation Rate), Liver Function Test (Alkaline Phosphatase, Alanine Transaminase, Aspartate Transaminase, S. Bilirubin: Total and Direct), S. Creatinine, and Rheumatoid Factor. ESR was done using Westergren’s method, and CRP was done by Latex agglutination. We did x-ray posteroanterior film of both wrists and hands.

The severity of the disease was assessed by using the DAS28ESR score. A DAS 28 cut off of 2.6 was taken to evaluate the active RA. India-specific FRAX score (http://www.sheffield.ac.uk/FRAX) was assessed for all patients and controls to determine 10-year fracture risk of major osteoporotic fracture and hip fracture. We planned the pharmacological intervention as per NOF. The outcome measures were a 10-year risk of major osteoporotic fracture(%) and hip fracture(%).

Statistical analysis

The data was entered in Microsoft EXCEL and analysed using SPSS version 21.0. The data presentation was done as mean with standard deviation (SD) for normally distributed and median (interquartile range 25-75%) for not normally distributed data and number (%).

An Independent t-test, age, major osteoporotic fracture and hip fracture was compared using Mann Whitney test. In addition, gender, smoking, alcohol use, the previous fracture were compared using the Chi-Square test and glucocorticoid use. Secondary osteoporosis and parental fractured hip were compared using Fisher’s Exact test. Spearman rank correlation coefficient/ Point biserial correlation coefficient was used to assess the correlation of various parameters with fracture risk. A $p$-value of $<0.05$ was considered statistically significant.

Results

A total of 192 cases of RA were screened, among which seven were excluded, and 185 were finally enrolled. Concurrently, 185 age and gender-matched controls were enrolled, among which 112 were patient relatives, and 73 were hospital staff members (Figure 1).

A total of 370 participants were cross-sectionally assessed, among

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**Table 1: Distribution of baseline demographic and clinical characteristics of study population**

<table>
<thead>
<tr>
<th>Variables</th>
<th>RA patients (n=185)</th>
<th>Controls (n=185)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51 (46-60)</td>
<td>50 (45-55)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>156 (84.32%)</td>
<td>133 (71.89%)</td>
</tr>
<tr>
<td>Male</td>
<td>29 (15.68%)</td>
<td>52 (28.11%)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.09 ± 4.86</td>
<td>25.52 ± 5.02</td>
</tr>
<tr>
<td>Duration of disease (years)</td>
<td>8(4-14)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2: Correlation of major osteoporotic fracture and hip fracture with risk factors in RA patients**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Duration of disease (years)</th>
<th>ESR (mm/hr)</th>
<th>DAS28</th>
<th>CRP (mg/dL)</th>
<th>Glucocorticoid use</th>
<th>Smoking</th>
<th>Alcohol use</th>
<th>Previous fracture</th>
<th>Parent fractured hip</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major osteoporotic fracture</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td>0.113</td>
<td>-0.047</td>
<td>0.028</td>
<td>-0.09</td>
<td>0.124</td>
<td>-0.043</td>
<td>-0.004</td>
<td>0.435</td>
<td>0.169</td>
</tr>
<tr>
<td>P value</td>
<td>0.12*</td>
<td>0.52*</td>
<td>0.71*</td>
<td>0.23*</td>
<td>0.09#</td>
<td>0.56f</td>
<td>0.95#</td>
<td>&lt;0.01#</td>
<td>0.02#</td>
</tr>
<tr>
<td>Hip fracture</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td>0.119</td>
<td>-0.04</td>
<td>0.027</td>
<td>-0.085</td>
<td>0.073</td>
<td>0.034</td>
<td>0.060</td>
<td>0.369</td>
<td>0.212</td>
</tr>
<tr>
<td>P value</td>
<td>0.11*</td>
<td>0.59*</td>
<td>0.72*</td>
<td>0.26*</td>
<td>0.32#</td>
<td>0.64f</td>
<td>0.41f</td>
<td>&lt;0.01#</td>
<td>&lt;0.01#</td>
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</tbody>
</table>

*Spearman rank correlation coefficient, #Point biserial correlation coefficient
which 185 were cases of RA and 185 were age and gender-matched controls. The median age of the patients and controls was comparable (51 vs 50), with most cases lying in the age group of 40-50 years.

There was a female predominance in both cases and controls, but the gender distribution was comparable (84.32% females in RA and 71.89% in controls, p>0.05). The Mean ± SD body mass index (kg/m²) in RA patients was 24.09 ± 4.86 and in controls was 25.52 ± 5.02, p<0.01.

In the present study, in 36.76% of patients, the duration of disease(years) was >10 years, followed by ≤5 years (35.68%). The median duration of the disease was eight years.

Among the risk factors, smoking (9.19% vs 18.38%, p<0.05) and alcohol consumption (3.24% vs 10.81%, p=0.01) was significantly less among cases as compared to controls. The history of previous fractures was comparable among cases and controls (15.68% vs 10.27%, p>0.05) (Table 1).

The mean DAS score in the study was 4.02 ± 1.09. Based on DAS activity, in the majority (52.43%) of patients, disease activity was moderate, followed by high (21.62%) and low (18.92%). Patients were in remission in only 13 out of 185 cases (7.03%).

The median (IQR) 10-year risk of major osteoporotic fracture in RA patients was 2.7(1.40-5.90), which was significantly higher as compared to controls 1.30(0.90-2.20), p<0.01. In addition, the median (IQR) 10-year risk of major osteoporotic fracture was more in females [2(1.20-3.90)] as compared to the males [1.40(1-3.90)], p=0.01; both of which were significantly higher than controls.

The median (IQR) 10-year risk of hip fracture in RA patients [1.30(0.90-2.20)] was significantly more than controls [0.20(0.10-0.40), p<0.0001]. The 10-year risk of hip fracture was comparable in females [0.3(0.1-1)] and males [0.2(0.1-1.2); both of which were higher than controls.

As per the FRAX and NOF guidelines, the candidates requiring pharmacological intervention has been shown in Figure 2.

Previous fractures showed a significant correlation with major osteoporotic fracture (r =0.435 and p <.01) and hip fracture (r =0.369 and p <.01). Also, there was a significant correlation of parental history of hip fracture with major osteoporotic fracture (r =0.169 and p =0.02) and hip fracture (r =0.212 and p <0.01) (Table 2).

Discussion

Ours is one of the few studies of the use of FRAX in the Indian population to assess the risk of hip and major osteoporotic fracture and the factors affecting them. The study holds strength as we compared the fracture risk through FRAX among RA patients and compared them with the controls.

In our study, the FRAX score showed a higher risk of fractures, which was observed in both males and females.

Similar results were reported by Subasinghe et al,13 who found a significantly higher fracture risk among cases of RA as compared to controls. In a study by Klop C et al,15 UK FRAX overestimated fracture risk in RA but performed well for hip fracture in the general population after linkage to hospitalisations. This may be due to the underlying differences in rheumatoid inflammation, immobility, nutritional problems, and weight loss among different nationalities.25

In this study, we also assessed the risk of various confounding variables such as duration, inflammation (ESR, CRP), disease activity, use of glucocorticoids, smoking, alcohol and history of fractures. This was done as they play a role in decreasing BMD and should be considered in evaluating fracture risk assessment in RA patients.23

In our study, duration of disease showed a significant correlation with major osteoporotic (MOP) fracture (r =0.257 and p =0.0004) and hip fracture (r =0.260 and p =0.0004) such that the patients with higher disease duration had more fracture risk.

Among other studies, the study by Meng et al,21 identified disease duration as a significant risk factor for osteoporotic fractures in Chinese RA patients. Even Phuan-Udom R et al,17 reported that disease duration was significantly associated with the 10-year probabilities of major osteoporotic and hip fractures (p 0.017, 0.009). In a study by Choi et al,29 disease duration (OR 1.01, 95% CI 1–1.01) was independent risk factors for fracture in patients with rheumatoid arthritis, as was seen in the present study.

Previous fractures also showed a significant correlation with major osteoporotic fracture (r =0.435 and p <0.0001) and hip fracture (r =0.369 and p <0.0001). Also, there was a significant correlation of parental history of hip fracture with major osteoporotic fracture (r =0.169 and p =0.0211) and hip fracture (r =0.212 and p =0.0038), which suggests that the previous fracture makes a person prone to future risk of fracture. These findings have been supported by Phuan-Udom R et al,17 who also found that previous fracture and parental history of hip fracture (P=0.003) correlated with risk fracture.

We found no significant correlation of risk fracture with ESR and CRP. Along similar lines, Meng et al,25 found no correlation between ESR and CRP with major osteoporotic and hip fractures. In contrast, a study by Wafa et al,25 Tourinho et al.26, and Hauser et al27 found that high ESR was an independent risk factor of bone loss and may show a correlation with risk of fracture in an indirect manner. However, since ESR and CRP are non-specific markers of inflammation, they may not predict fracture risk. The actual association (if any exists) of CRP and ESR will have to be analysed in future case-control studies on a bigger sample size after removing the confounding factors.

The present study found no significant correlation of risk fracture with DAS 28 severity of RA. As for disease activity measured by DAS28, the correlation with osteoporotic fractures is still inconclusive.20,29,25,30

Even the use of steroids showed no significant correlation of risk fracture. This might be because we used a low dose of Glucocorticoids in our patients, and by reducing the disease severity, it can have a positive effect on BMD of RA patients.31,32 Even the use of GC and its association with fracture risk remains inconclusive in RA.17,25,32,27 Particularly, an increase in fracture risk was found to be associated with three months of oral glucocorticoids and glucocorticoid ≥7.5 mg/day usage.25 It was mentioned in the study25 that long-term use of glucocorticoids could inhibit the intestinal absorption of calcium and encourage excretion of calcium, resulting in low levels of
serum calcium and reduced bone resorption.

Smoking status constitutes part of the FRAX algorithm for assessing osteoporotic fracture risk. Literature shows that smokers carrying the HLA DR4 shared epitope have a higher risk of RA development. Smoking releases > 4,000 compounds that affect the cardiovascular and respiratory systems and bone and joint health. We found no significant association of risk fracture with smoking and alcohol use as reported previously. This may be because specifically for smoking the duration of smoking and pack-years may hold importance in affecting the fracture risk.

The study was limited by the fact that the patients were not followed for the next ten years to know in actuality if those patients suffered from fractures or not. Secondly, BMD was not measured. Future long-term studies are recommended to validate the findings of FRAX in Indian settings because FRAX is a dynamic tool, and we have to repeat it over time for better prediction. It may be relatively ineffective if information about the probability of fracture is provided to patient only one point in time because the risk of fracture is different in the first five years and the next five years of the 10-year overhaul.

Conclusion

It can be concluded that the risk of hip fracture and major osteoporotic fracture was significantly more in both male and female patients with rheumatoid arthritis as assessed by FRAX algorithm. Duration of the disease, previous fracture, and parent fracture hip showed a significant correlation with major osteoporotic fracture and hip fracture. The early recognition and treatment of RA holds importance in reducing the fracture risk.

References

### Key Parameters of Combination

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<tr>
<th></th>
<th>Allegra-M (Fexofenadine + Montelukast)</th>
<th>Levocetirizine + Montelukast</th>
<th>Bilastine + Montelukast</th>
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<tr>
<td>Bioequivalence published data(^1,4)</td>
<td>Yes</td>
<td>No</td>
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<td>Synergistic effect(^1,3,4)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<td>HTH efficacy data in Indian patients(^4)</td>
<td>Yes</td>
<td>Yes</td>
<td>No HTH data</td>
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<td>HTH efficacy (TNSS)(^4)</td>
<td>92.5%</td>
<td>85.6%</td>
<td>No HTH data</td>
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<tr>
<td>HTH safety data (Sedation)(^6)</td>
<td>9.6%</td>
<td>23.2%</td>
<td>No HTH data</td>
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</tbody>
</table>

### References:
2. This dissolution study compares Allegra M, Allegra, Singulair and one Fexofenadine + Montelukast fixed dose combination available as a monolayered tablet in India. Data on File, 2012 (b)

Achieving UNAIDS Viral Suppression Goal: Experience from a Tertiary Care Public Hospital, Western India

Ranjana Thate¹, Nayana Ingole², Vaishali Solanke – Surase³, Kavita Joshi⁴, Smrati Bajpai⁴, Shrikala Acharya⁵, Gita Nataraj⁶*

Abstract

Introduction: Targeted HIV 1 viral load testing has been recommended in 2010 only for suspected cases of antiretroviral therapy failure. India is committed to achieve UNAIDS ‘90-90-90’ target by 2020. The third 90 target was to ensure all people receiving antiretroviral therapy (ART) are virologically suppressed. Implementation of routine viral load testing in national programme helps us in assessing early treatment failure and the need to switch to second line therapy; thus eventually reducing drug resistance and improving patient outcomes.

Aims: Study was aimed to determine the proportions of patients responding to antiretroviral therapy, correlates of viral suppression & the discordance between virological and immunological failure.

Design: Retrospective analysis.

Material & Methods: As per the NACO policy, all patients diagnosed as HIV positive are started on antiretroviral therapy and are monitored regularly. The patient’s adherence details are noted down during regular follow up visit and patient is referred for routine HIV 1 VL and/or CD4 testing as per National guidelines. Analysis of data was carried out retrospectively for all patients referred for HIV 1 viral load and/or CD4 testing during the study period from July 2019 to June 2020. Confidentiality of the patient was maintained at all times as per routine protocol.

Results: A total of 7601 PLHIV on antiretroviral therapy, 3813 samples were tested for both HIV 1 VL and CD4 counts and these results were further analyzed. 3616 (94.8%) showed virological suppression and 197 (5.2%) showed virological failure. Among virologically failed group, 46.2% (91/197) underwent retesting after adherence counseling and among these 48.4% (44/91) showed viral suppression. Virological failure was significantly high in younger PLHIV receiving second or third line ART for less than 5 years duration who were non adherent. Immunological discordance was seen in 28.3% of PLHIV.

Conclusion: In the present study, 95.99% patients showed virological suppression indicating that the third “90” target is being exceeded.

Introduction

HIV continues to be a major public health issue worldwide. In 2019, globally, an estimated 38.0 million people were living with HIV.¹ India has the highest burden of HIV in the world. Currently, the overall HIV adult prevalence in India is 0.26% with an estimated ~2.1 million PLHIV (People living with HIV). Out of these, 1.26 million are registered in the National AIDS Control Programme (NACP) and 1.32 million are on antiretroviral therapy (ART).²

The goal of antiretroviral therapy (ART) is to achieve and maintain continuous virological suppression of less than 1000 copies/ml to allow immune reconstitution, minimize the emergence of resistance, prevent HIV-related morbidity and mortality, and to block further transmission.³ PLHIV who maintain an undetectable viral load have no risk of sexual transmission to an HIV-negative partner, which has become the message of the U = U (Undetectable = Untransmittable) campaign.⁴ Due to lack of routine VL monitoring for ART, a patient was designated as having treatment failure only after 6 – 12 months of failure of CD4 reconstitution. In the meantime patient was continued with the same ARVs with further delay in switching over to second-line therapy.⁵ In a previous study from this institute, it was observed that immunological criteria do not accurately predict virological failure resulting in significant misclassification of therapeutic responses.⁶ In addition to clinical and immunological monitoring of PLHIV on ART, World Health Organization in 2013 endorsed the use of viral load testing for monitoring the response to ART and diagnosing treatment failure.⁷ NACO has scaled up the routine HIV-1 Viral Load testing in a phased manner and expanded viral load testing laboratory services.⁸

One year experience with routine HIV 1 viral load testing in a tertiary care public hospital in western India was studied to find out the proportion of patients responding to antiretroviral therapy, to determine correlates of viral suppression and to determine the discordance between virological and immunological failure.

Material and Methods

All PLHIV are routinely referred to the department of microbiology
of a tertiary care hospital in Western India for CD4 count estimation and/or HIV 1 viral load testing as per NACO guidelines. PLHIV are referred for routine viral load testing after 6 month of ART initiation and yearly thereafter. Those who are failing immunologically or clinically are referred for targeted viral load testing. Those who are failing virologically due to inadequate adherence to ART are referred for adherence testing after 3 months of adherence counseling.

A retrospective analysis of data was carried out for all PLHIV referred for viral load testing from July 2019 to June 2020 after institutional ethics committee approval. All PLHIV who were receiving ART for more than or equal to six months were included in the study. Patient’s demographic details, adherence history, duration of ART and ART regimen being received were noted down. Confidentiality of the patient was maintained at all times as per routine protocol and all data was analyzed. HIV 1 viral load was analyzed using Abbott m2000 system (Abbott laboratories, Abbott Park, Illinois, USA). CD4 counts were estimated using BD FACS Calibur flowcytometry (FACS Calibur, Beckton Dickinson Bio- sciences, Franklin Lakes, NJ) from July 2019 to Sept 2019 and by using Partec Cyflow flowcytometry (Sysmex Partec Gmbh, Kobe, Japan) from October 2019 to June 2020. Manufacturers’ instructions were followed for carrying out all the tests.

Virological failure was defined as viral load ≥1000 copies/ml. Immunological failure was defined as fall of CD4 count to pre-therapy baseline (or below) or 50% fall from the on treatment peak value or persistent CD4 levels below 100 cells/mm3.

In accordance with National AIDS Control Organization (NACO) guidelines, patients consuming 95% or more of prescribed pills were considered as “adherent”, while those consuming less than 95% of prescribed pills were labeled as “non-adherent” to ART. All PLHIV who were failing virologically were counseled for adherence as per national guidelines and HIV 1 viral load assay was repeated after three months of adherence counseling.

Student “t” test was used to compare the means of viral load in log 10 copies/ml and CD4 counts in the virologically failed and virologically suppressed groups. Chi square test was used for univariate analysis and forward conditional logistic regression was done for multivariate analysis.

Results and Findings

A total of 7601 PLHIV on antiretroviral therapy were tested for HIV1 viral load and/or CD4 counts during the study period. Among these, 3788 PLHIV were tested only for CD4 testing. 3813 samples were tested for both HIV 1 viral load and CD4 counts and these results were further analyzed.

3616 (94.8%) showed virological suppression and 197 (5.2%) showed virological failure. Mean (SD) viral load for virologically suppressed group, (0.26(0.73) log 10 copies/ml) was significantly lower than virologically failed group, (4.16(0.79) log 10 copies/ml) (p < 0.0001). Mean (SD) CD4 for virologically suppressed group, (596.9 (277.8) cells/mm³) was significantly higher than virologically failed group, (354.5(240.4) cells/mm³) (p < 0.0001). Among virologically failed group, 46.2% (91/197) underwent retesting after adherence counseling and among these 48.4% (44/91) showed viral suppression and 51.6%(47/91) showed persistent viraemia (Table 1). The final virological failure in the current study was 4.01%. There was no significant association between initial viral load log copies/ml and viral suppression at 3 month of repeat testing. (p=0.08) (Table 1).

To determine correlates of virological suppression, univariate analysis was carried out; Age, test type, adherence, type of ART, duration of ART and immunological response were found to be significantly associated with virological failure (Table 2). Of the 2190

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Table 1: Three month testing of virologically failed group after adherence counseling

<table>
<thead>
<tr>
<th>VL in log 10 copies/ml</th>
<th>Number failing</th>
<th>Number Number Followed up</th>
<th>Follow Up Result</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥3 log</td>
<td>90 (45.7%)</td>
<td>51 (56.7%)</td>
<td>29 (56.9%)</td>
<td>0.000</td>
</tr>
<tr>
<td>3-4 log</td>
<td>114 (80.9%)</td>
<td>27 (19.1%)</td>
<td>20 (39.2%)</td>
<td>6.131</td>
</tr>
<tr>
<td>4-5 log</td>
<td>37 (18.8%)</td>
<td>13 (35.1%)</td>
<td>2 (3.9%)</td>
<td>2.497</td>
</tr>
<tr>
<td>5-6 log</td>
<td>10 (5.0%)</td>
<td>0</td>
<td>0</td>
<td>15.055</td>
</tr>
<tr>
<td>&gt;6 log</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>197</td>
<td>91 (46.2%)</td>
<td>44 (48.4%)</td>
<td>6.5(6.5%)</td>
</tr>
</tbody>
</table>

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Table 2: Factors affecting virological failure

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Virologically suppressed group</th>
<th>Virologically failed group</th>
<th>Total</th>
<th>(P value)</th>
<th>Odds ratio</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2075 (94.75%)</td>
<td>115 (5.25%)</td>
<td>2190</td>
<td>0.79</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Female</td>
<td>1538 (94.94%)</td>
<td>82 (5.06%)</td>
<td>1620</td>
<td>0.005</td>
<td>6.131</td>
<td>2.497</td>
</tr>
<tr>
<td>Age Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-19 years</td>
<td>114 (80.9%)</td>
<td>27 (19.1%)</td>
<td>141</td>
<td>0.000</td>
<td>6.131</td>
<td>2.497</td>
</tr>
<tr>
<td>20-39 years</td>
<td>831 (92.1%)</td>
<td>71 (7.9%)</td>
<td>902</td>
<td>0.023</td>
<td>6.131</td>
<td>2.497</td>
</tr>
<tr>
<td>40-59 years</td>
<td>831 (91.6%)</td>
<td>91 (3.7%)</td>
<td>922</td>
<td>0.023</td>
<td>6.131</td>
<td>2.497</td>
</tr>
<tr>
<td>≥60 years</td>
<td>280 (97.2%)</td>
<td>8 (2.8%)</td>
<td>288</td>
<td>0.000</td>
<td>6.131</td>
<td>2.497</td>
</tr>
<tr>
<td>Immunological Response</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failed</td>
<td>984 (90.7%)</td>
<td>101 (9.3%)</td>
<td>1085</td>
<td>0.000</td>
<td>6.131</td>
<td>2.497</td>
</tr>
<tr>
<td>Competent</td>
<td>2632 (96.5%)</td>
<td>96 (3.5%)</td>
<td>2728</td>
<td>0.000</td>
<td>6.131</td>
<td>2.497</td>
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<td>Test Type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Routine</td>
<td>3590 (95.9%)</td>
<td>150 (4.1%)</td>
<td>3740</td>
<td>0.000</td>
<td>6.131</td>
<td>2.497</td>
</tr>
<tr>
<td>Targeted</td>
<td>74 (88.1%)</td>
<td>10 (11.9%)</td>
<td>84</td>
<td>0.033</td>
<td>6.131</td>
<td>2.497</td>
</tr>
<tr>
<td>Adherence testing</td>
<td>38 (50.0%)</td>
<td>37 (49.3%)</td>
<td>75</td>
<td>0.033</td>
<td>6.131</td>
<td>2.497</td>
</tr>
<tr>
<td>ART Adherence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adherent (&gt;95%)</td>
<td>3445 (95.2%)</td>
<td>173 (4.8%)</td>
<td>3618</td>
<td>0.000</td>
<td>6.131</td>
<td>2.497</td>
</tr>
<tr>
<td>Non adherent (&gt;95%)</td>
<td>1711 (87.6%)</td>
<td>24 (12.3%)</td>
<td>195</td>
<td>0.000</td>
<td>6.131</td>
<td>2.497</td>
</tr>
<tr>
<td>Type of ART</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st line ART</td>
<td>3091 (96.4%)</td>
<td>117 (3.6%)</td>
<td>3208</td>
<td>0.000</td>
<td>6.131</td>
<td>2.497</td>
</tr>
<tr>
<td>2nd line ART</td>
<td>523 (86.9%)</td>
<td>79 (13.1%)</td>
<td>602</td>
<td>0.000</td>
<td>6.131</td>
<td>2.497</td>
</tr>
<tr>
<td>3rd line ART</td>
<td>266 (66.6%)</td>
<td>133 (33.3%)</td>
<td>399</td>
<td>0.000</td>
<td>6.131</td>
<td>2.497</td>
</tr>
<tr>
<td>Duration of ART</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>2086 (87.4%)</td>
<td>30 (12.6%)</td>
<td>238</td>
<td>0.000</td>
<td>6.131</td>
<td>2.497</td>
</tr>
<tr>
<td>1-5 years</td>
<td>1160 (93.6%)</td>
<td>76 (6.3%)</td>
<td>1236</td>
<td>0.000</td>
<td>6.131</td>
<td>2.497</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>2248 (96.2%)</td>
<td>88 (3.8%)</td>
<td>2336</td>
<td>0.000</td>
<td>6.131</td>
<td>2.497</td>
</tr>
</tbody>
</table>
men and 1620 women tested for HIV 1 viral load, 94.75% (2075) and 94.94% (1538) showed virological suppression respectively and this difference was not significant statistically (p= 0.79) (Table 2).

To rule out confounding factors, the significant risk factors were further analyzed by multivariate analysis. The significant risk of failure was 6.1 (2.497 - 15.055) and 2.5 (1.140 - 5.640) times more in age groups 0-19 years and 20-39 years respectively compared to PLHIV≥60years. For the age group 40-59 years, though the risk of failure was 1.37 (0.629 to 3.008) times more compared to ≥60 years, the difference was not statistically significant (Table 2).

Those on ART who were failing immunologically were 3.1(2.255 -4.314) times at higher risk of virological failure when compared to immunologically competent group (p= 0.000) (Table 2). Immunological discordance was seen in 28.3% of PLHIV.

Patients undergoing routine or targeted testing had a significantly lower odds ratio of 0.073 and 0.267 respectively for viral load failure compared to those undergoing adherence testing (Table 2). The risk of developing virological failure was also significantly lower in PLHIV undergoing routine testing as compared to targeted testing (p<0.00048). Adherent PLHIV had significantly lower risk (0.320) of virological failure when compared to non-adherent PLHIV (p = 0.000) (Table 2).

Those receiving 1st line ART were at significantly lower risk of failure, while those receiving ART for <1 year and 1 to 5 years duration were 5.9 (3.571-9.853) and 1.6 (odds 1.185-2.382) times at higher risk of failure (Table 2).

Discussion

Globally, viral load (VL) testing has been used in patients on ART to determine the prognosis and the risk of disease progression, and identify treatment failures. The incidence of virological failure has been described from 3.9% to 36% in public health ART programme in India and elsewhere. However, the Joint United Nations Programme on HIV/AIDS (UNAIDS) with the aim of “Ending the AIDS” epidemic by 2030, launched the 90-90-90 project. To know the last ‘90’ i.e. number of PLHIV receiving ART who are virally suppressed, it was imperative that all PLHIV receiving ART be monitored by HIV 1 viral load testing. Hence, NACO started routine viral load testing. In the present study, 95.99% patients showed virological suppression indicating that the third goal is being attained within the planned duration in the present cohort of patients.

Virological monitoring assists in multiple ways - detecting early virological failure, guiding in the need for targeted adherence interventions and avoiding unnecessary switches in therapy. In the present study, initial virological failure was 5.2% and the mean(SD) viral load in virologically failed group was 4.16 (0.79) log 10 copies/ml. Neogi U et al from India also showed similar range of viral load in virologically failed group. High viral load is an indirect indicator of drug resistance and may also be seen in non-adherent patients. Among virologically failed group, 48.4% showed virological suppression on retesting after adherence counseling (Table 1). Hoffman CJ et al (South Africa) and Jobanputra K et al (Swaziland) showed suppression in 41% and 61% of patients respectively after adherence counseling. This finding highlights the necessity of counseling and the significance of adherence.

Adherence to antiretroviral drugs (ARVs) is a major facilitator for improving the outcome of care for PLWHIV. In the present study, adherent PLHIV had significantly lower risk (odds ratio- 0.320) of virological failure when compared to non-adherent PLHIV (P= 0.000) (Table-2). This might be because non-adherence to therapy allows periods of viral replication, is associated with intermittent viraemia leading to the development of drug resistance resulting in limited treatment effectiveness.

In the current study, odds of developing virological failure was highest in the younger age group (0-19 years) (Table 2). In a public health setup, ART centers are functional on working days only and during routine office hours. This makes it difficult for the school/college going children or young working adults to visit the ART centre regularly. Treatment adherence in long-term pediatric conditions is also a complex issue as reported by Santer et al. Similar significant association between virological failure and age group has been reported by various authors. This suggests that the needs of young HIV-infected patients should be looked into. Health care providers may counsel the patients and caregivers regarding psychological, behavioural and socioeconomic factors that lead to non-adherence to ART & thus minimize impact on daily life.

CD4 T-cell counts have till recently been the most commonly used parameter to monitor the efficiency of antiretroviral treatment. There are groups of patients where viral replication is suppressed appropriately but without immunologic recovery. Also, patients who are recovering immunologically, may still have high viral load. These two scenarios are known as discordant responses. In the current study, those who were failing immunologically were 3.1(2.255 -4.314) times significantly at higher risk of virological failure when compared to immunologically competent group (P= 0.000) (Table 2) and immunological discordance was found in 28.3% cases. This finding was consistent with a previous study on immunological discordance in our institute. Multiple studies done worldwide have shown the prevalence of discordance ranging from 8% to more than 20%. WHO immunological criteria has low sensitivity and positive predictive value in detecting treatment failure. This may misclassify treatment failure and result in unessential or delayed switch to second-line ART.

It has been well established that virological failure precedes immunological failure which precedes clinical failure. In the present study, 4.1% of asymptomatic patients tested routinely were found to be failing virologically which could have otherwise gone undetected. (Table 2)

Staying on a failing regimen is not only associated with an increased mortality, but it also promotes the transmission of resistant viruses in the community and limits the development of potent and tolerable regimens in the future. In the current study, those receiving 1st line ART were significantly at lower risk of failure compared to second and third line of ART (Table 2). Similar findings have been reported by Francis Kiweewa et al. Only those
patients who fail first line therapy are put on second line regimen. PLHIV who are poorly adherent to first line therapy usually continue the same trend when shifted to second line therapy. 22

Evidence has illustrated that a short duration of ART increases the risk of virological failure. In this study, PLHIV on ART for < 1 year were at highest risk of treatment failure when compared to those receiving ART for > 5 yrs duration (Table 2). This may be justified as the likelihood of interrupting ARV drugs and developing resistance associated with drug side effects and non-compliance early in the initiation of ART is very high.23 Cambiano V et al have reported that PLHIV who are adherent for more than 10 years usually remain adherent which is advantageous for patients as viral suppression may be sustained for many years.24

To conclude, current study authenticates that the 3rd 90 target of NACO/UNAIDS is being exceeded in the cohort of patients receiving ART at a public hospital in Western India. However, targeted interventions are required in young PLHIV receiving second or third line ART for less than 5 years duration who are non-adherent and have concomitant immunological failure for better treatment outcome.

Ethical committee approval letter

This study was approved by the Institutional Ethical Committee (Project no EC/OA-151/2019).

Authors’ Role

RT conceptualized the research data, was the primary investigator of data, tabulation of data and literature search for the study. Author GN and NI contributed to the study design, drafting the protocol, statistical analysis and reviewing and approving the article. Author VS and SA contributed to review & revision of the manuscript and final approval of the work to be published.

References

Salmeterol-Fluticasone: The Role Revisited

Agam Vora1, Raja Dhar2, Lancelot Pinto3, Parvaiz Koul4, Pratyusha Gaonkar5

Abstract
Apart from the individual diseases, some patients also show overlapping manifestations of asthma and COPD. Nevertheless, the diagnosis of COPD is often delayed due to inaccessibility to spirometry; the prevalence of the asthma COPD overlap phenotype is rather high given the exposure to biomass smoke. Furthermore, the rates of exacerbations are twice as high compared to the patients with either of the diseases. A treatment strategy that would reduce the risk of exacerbations would contribute immensely to the management of such patients. Evidence of eosinophilia (marker of inflammation) in patients with asthma, asthma COPD overlap phenotype or COPD alone should prompt treatment with a combination of inhaled corticosteroids (ICS)/long-acting β-agonists (LABA); several studies have shown improvement in the airflow limitation and reduction in the rate of exacerbations with salmeterol-fluticasone combination (SFC). Considering the association of COPD and cardiovascular diseases (CVD), it is critical to determine the cardiovascular safety of the LABA in such patients. Salmeterol is a highly selective partial β-2 agonist; the TORCH study and the studies comparing formoterol and salmeterol infer that there is no increased risk of new cardiovascular adverse events either with Salmeterol or SFC. Furthermore, the combination may provide certain degree of cardio-protection. Since COPD per se increases the risk of CVD, the cardio-safety of salmeterol outweighs its onset of action. SFC has well substantiated benefits in patients with asthma, COPD and high-risk patients such as those with an overlap of COPD and asthma symptoms, patients with elevated eosinophils and pre-existing CVD. An advisory board was hence conducted, which discussed the role of combination of salmeterol and fluticasone (SFC) not only in asthma and COPD but also in asthma COPD overlap phenotype. Based on the panel's clinical experience and the expertise derived thereof, the propositions regarding the place of SFC therapy in patients with stable and uncontrolled asthma, asthma COPD overlap phenotype and COPD has been put forth.

Introduction
Salmeterol, a LABA and fluticasone propionate, an ICS, have demonstrated individual and synergistic pharmacodynamic advantages in the management of obstructive airway diseases such as asthma and COPD. Therefore, the combination of these two drugs could be particularly effective in patients with characteristics of both these diseases, based on levels of a biomarker, which can be easily determined. An advisory board was hence conducted, which discussed the role of combination of salmeterol and fluticasone (SFC) not only in asthma and COPD but also in asthma COPD overlap phenotype. Based on our clinical experience and the expertise derived thereof, we have also put forth our propositions regarding place of SFC therapy in patients with stable and uncontrolled asthma, asthma COPD overlap phenotype and COPD. Patients with asthma and COPD inherently are at an increased risk of cardiovascular diseases and vice-versa; we sought to review evidence regarding its safety in these high-risk patients given the very high β2-selectivity of its LABA component, salmeterol.

Since the use of ICS along with LABA encompasses 70% of the COPD cases, particularly at high doses, the interest in its associated events of pneumonia has been reignited. We sought to evaluate the available evidence to infer whether pneumonia is a true risk and ICS use should be considered, since the benefit risk ratio of SFC in COPD is high, given its effect on the reduction in exacerbations and improvement in the respiratory and HR-QoL. SFC was associated with no increased risk of mortality. On the contrary, there was a deceleration in the decline of the lung function, which could improve survival. This was well-substantiated by a 3-year survival study conducted by Soriano et al. which showed significantly greater survival in the SFC group when compared with non-ICS/non-LABA pharmacotherapy. Asthma patients with COPD phenotype and COPD: Eosinophilia
Asthma is often under-diagnosed, which creates a substantial burden on individuals and disrupts their quality of life. In a survey which aimed to study the prevalence of asthma in the elderly, Parameswaran et al. found that 24% of the 390 patients were diagnosed with asthma. Of the 95 patients diagnosed with asthma, most of them were lifelong never-smokers and only 7% reported a previous diagnosis of asthma. In spite of concrete indication of reversible and significant airflow limitation, only 21 were receiving inhaled glucocorticoid therapy. Even if one assumed that all the ex-smokers had COPD rather than asthma, this suggests that more than 70 percent of the asthma patients were undiagnosed. Underdiagnosis may be due to an absence of a standardised method of diagnosis for asthma. In India, wherein
the prevalence of COPD is likely to be high due to exposure to biomass smoke (BMS), COPD is underdiagnosed partly because diagnosis is mostly based on symptoms and also due to the fact that symptomatic people are often late in seeking care because of insufficient disease awareness.\(^8\) Underutilization of spirometry is regarded as the most robust indicator for inappropriate diagnosis of COPD. Additionally, factors such as knowledge of associated risk factors, patient demographics, language barriers and comorbid diseases like bronchiectasis, heart failure and formerly treated tuberculosis should be taken into consideration.\(^9\) A worrisome lack of tuberculosis should be taken into heart failure and formerly treated comorbid diseases like bronchiectasis.

Additionally, factors such as knowledge for inappropriate diagnosis of COPD. Underutilization of spirometry is hypothesized to be a common basis of asthma inflammatory diseases and those who are managed by primary care physicians.\(^10\)

Earlier known as asthmaticiform bronchitis which is currently referred to as Asthma- chronic obstructive pulmonary disease overlap or asthma patients with COPD phenotype was based on the proposed Dutch inflammatory attributes have not been taken into consideration.\(^11\) COPD patients with asthma phenotype represents a large proportion of COPD patients with absolute eosinophil count (AEC) as an important biomarker to distinguish the former from COPD ( peripheral eosinophilia (36% vs 7.6%, p=0.002) as corroborated by Sharma et al. in a retrospective, observational study.\(^16\) Unlike asthma in which some phenotypes are eosinophilic and others are neutrophilic or both, in COPD 10 to 40% of subjects have sputum eosinophilia. Earlier identification will facilitate appropriate treatment of this discrete clinical phenotype not clearly represented in clinical trials particularly, in the most severe forms.\(^11-17\) Moreover, eosinophilic COPD has been recognized as a distinct phenotype.\(^20\) Globally, eosinophilia in COPD (spum eosinophil counts ≥3%) has also been reported during acute exacerbations in nearly 28% of cases and in ~34-58% of patients with COPD in stable condition.\(^21-26\) A study conducted in Thrissur, India found peripheral blood eosinophilia in 39% of the COPD patients. Further, in a developing country like India, where three-fourth of the domestic energy is in the form of biomass, an estimated ~66% of Indian families use biomass fuel as the main resource for domestic cooking.\(^27\) Biomass fuel can be accounted for 5-6% of the national burden of disease.\(^28\) A cross-sectional study in India found confirmed cases of COPD in 18.4% among 2868 women exposed to BMS for 10-25 years.\(^29\) Further, a meta-analysis found that women exposed to BMS were 2.4 time more likely to develop COPD.\(^30\) Given the higher exposure to BMS, the ratio of male to female COPD patients in India 1.5 : 1.0 seems realistic.\(^31\) In a cross-sectional study in India, significant eosinophilia (eosinophils ≥3%) was found in subjects exposed to BMS (non-smokers) than smokers (71% vs 49.4%, p=0.04). Thus, even after adjusting for severity and clinical symptoms, significant eosinophilic inflammation was observed in stable BMS-COPD compared to smokers.\(^32\)

FP reduces eosinophils, CD8:CD4 ratio in bronchial epithelium, neutrophils in sputum and systemic markers of inflammation.\(^33\) Similar results have also been found for SFC and a reduction of inflammatory markers may also be correlated to a drop in the exacerbation rates.\(^33\) Two studies, INSPIRE and TRISTAN of 2- and 1-year duration respectively analysed moderate and severe exacerbation rates based on same eosinophils cut-offs. For patients with ≥2% eosinophils, SFC was associated with significant reductions in exacerbation rates versus LAMA (rate ratio (RR)=0.75, 95% CI 0.60 to 0.92, p=0.006) and versus placebo (RR=0.63, 95% CI 0.50 to 0.79, p<0.001).\(^34\) In INSPIRE, a 25% reduction in annual moderate/severe exacerbation rate with SFC versus LAMA was observed in the ≥2% eosinophils subgroup (p=0.006).\(^34\) Statistically significant reductions in the rate of exacerbations were observed in the ≥2% eosinophils subgroup in the TRISTAN study with SFC and monotherapies compared to placebo ([SFC 37%; p<0.001] (FP 28%; p=0.005) (SAL 30% p=0.002).\(^35\) No significant difference was seen in the <2% eosinophil subgroup in either of the studies. The 44-week randomized, double-blind parallel-group study- VIVACE (Impact of Salmeterol/Fluticasone Propionate versus Salmeterol on Exacerbations in Severe COPD) showed that ICS added to LABA reduces exacerbation...
risk by 35%. Another randomized clinical trial, ISOLDE conducted in 751 patients treated with FP for 3 years, when analysed on the basis of baseline blood eosinophil count found that unlike patients with eosinophils <2%, in patients with eosinophils ≥2%, the rate of post-bronchodilator FEV1 decline decreased significantly by 33.9 mL/year versus placebo (p=0.003).36

Compared to the non-ICS/ICS withdrawal/placebo group, a recent meta-analysis revealed a statistically significant reduction (17%; P=0.03) in the exacerbations of moderate-severe COPD patients with ≥2% (200/mm³ AEC cut-off) blood eosinophils undergoing ICS therapy.37 Thus, the indication of using ICS in COPD is more substantiated in patients with increased blood eosinophil levels.38 Accordingly, a baseline blood eosinophil count of ≥2% (identified the high sensitivity of this cut-off point for the presence of a raised sputum eosinophil count) identifies a group of COPD patients with slower rates of decline in FEV1 when treated with ICS like FP. There is a greater reduction in the exacerbation rate with ICS/LABA, compared to placebo or LAMA, in individuals with a pre-treatment blood eosinophil level ≥2%.

The addition of fluticasone to salmeterol not only reduces the rate of exacerbation but it also improves the airflow limitation and quality of life compared with the use of a LABA alone in a randomised controlled trial.14,38 Moreover, the 3-year survival was significantly greater in SFC users (78.6%) compared to the non-ICS (63.6%) group (prescribed short-acting β-agonists, xanthines, anticholinergics, and combined bronchodilators, since diagnosis with COPD). Even after adjusting for confounders, the survival benefit observed was maximum in SFC group versus the non-ICS group. Mortality decreased with the increasing use of SFC.4

GOLD has stated that the blood eosinophil count ≥100 cells/μL or 1% should be contemplated not only for ICS treatment in patients with COPD experiencing one exacerbation despite LAMA/LABA but also for gauging the efficacy of ICS for precluding exacerbations. For COPD patients with high eosinophil counts and no history of pneumonia, ICS is recommended as part of therapy, as treatment benefits like improved lung function and decreased symptoms and rate of exacerbations are high while risk of pneumonia relatively low.40 However, when high eosinophil counts are found and history of pneumonia is documented, the benefits and risks must be individualized for optimal benefit. An ICS should be included in such patients who suffer persistent exacerbations, resulting in frequent hospital admissions when being treated with dual bronchodilator therapy.41 The benefits of ICS have been found to outweigh the risks.39 The GOLD 2021 strategy also recommends use of ICS/LABA in COPD patients with eosinophils ≥ 300 cell/mL.42 Since asthma patients with COPD phenotype is associated with a higher exacerbation rate compared to either of the diseases.38

Per the analysis of the data from large COPD registries in the US and Europe, asthma patients with COPD phenotype were prescribed similar treatments as compared to the COPD patients with only 18% of asthma patients with COPD phenotype not receiving an ICS. Reviews of therapy for asthma patients with COPD phenotype recommend an ICS as an imperative early maintenance therapy.43 Also, since the asthma patients with COPD phenotype have more of a Th2 mechanism of disease than the Th1-based COPD patient, ICS therapy largely precedes LAMA therapy in treatment algorithms.44

In the Korean COPD subgroup study cohort, asthma patients with COPD phenotype were assessed and followed up for a year and exacerbation analysis was conducted. ICS treatment significantly decreased exacerbation in asthma patients with COPD phenotype according to the specialists’ diagnoses and the GOLD/GINA criteria. The only factor linked to decreased exacerbation after ICS treatment was a blood eosinophil count of ≥300 cells/mL (IRR=0.52, P=0.03) regardless of the diagnostic criteria of the combined phenotype.44 Another cohort of the KOLD study with mild-to-moderate airflow limitation, showed a significant increase in FEV1 following 3 months of treatment with ICS/LABA including SFC in the combined phenotype group compared with COPD alone.45

A randomized, open-label study showed that a 4-week treatment with SFC improved lung function in asthma patients with COPD phenotype, without inducing change in heart rate or any other cardiovascular symptoms. These findings indicate that SFC has the potential to be used as a regular treatment for asthma patients with COPD phenotype or vice versa.44 Current guidelines recommend ICS/LABA in patients with severe airflow limitation and frequent exacerbations based on the evidence from clinical trials, but in real clinical practice, ICS/LABA are also used in COPD patients with mild-to-moderate airflow limitation.44

There are several salient pragmatic grounds to use FDC inhalers in asthma patients with COPD phenotype and patients with COPD alone including patient acceptance and cost-effectiveness. Inhaler preference when tested in both groups found that one-third of the patients felt extremely satisfied with their device. The ‘ease of use/suitability of inhaler device’ was cited as a premise to prescribe the device by physician with
other device features such as ‘simple instructions and easy to follow’ serving a predominant role in asthma patients with COPD phenotype and patients COPD alone. 43

**Stable and Uncontrolled Asthma**

Based on their clinical experience, the panel of advisors opined that dose flexibility or adjustable dosing is unnecessary in patients with stable asthma. This opinion is substantiated by a long-term efficacy study, which found that a stable-dose regimen of SFC provided significantly greater symptom-free days, reduced exacerbation rates and offered greater HRQoL benefits compared with formoterol/budesonide adjustable maintenance dosing (FOR/BUD AMD). 46 Though the various bodies recommend formoterol over salmeterol owing to its faster onset, there is adequate reason to believe that once wouldn’t hold any additional clinical significance in stable asthmatics. Hence, the panel of advisors believe that there is no reason that stable patients should not be continued on SFC. Moreover, in patients with tremors and tachycardia that are related to formoterol may be administered salmeterol fluticasone combination instead.

Furthermore, in patients with uncontrolled and long-standing asthma, there lies a risk of several comorbidities, particularly CVD. 45-49 In such patients it is reasonable to choose salmeterol over formoterol considering its favourable cardio-safety profile.

**Asthma, COPD and Cardiovascular Comorbidities**

Chronic, systemic inflammation underlies the pathogenic mechanism not only of asthma and COPD but also of several cardiovascular diseases. 2 Asthma is not only characterized by chronic airway inflammation but also beyond it. Many studies have shown that inflammatory processes are common to the pathophysiology of asthma, atherosclerosis and endothelial dysfunction. Additionally, the data confirming the association between the pathogenesis of asthma and coagulation, anticoagulant pathways, the fibrinolytic system, and platelets has significantly increased. A retrospective registry showed the overall prevalence of asthma with CVD to be more than 88%. 30 Several studies have found that asthma is related to an increased incidence of CVD compared to the non-asthmatics. 2 However, the correlation of COPD and CVD is more prominent as compared to the association of asthma with CVD. 51 In COPD, the two main etiological causes namely smoking and BMS, may give rise to various inflammatory responses in predisposed individuals. Inflammatory mediators in the systemic circulation chronically may cause progressive development of atherosclerosis, thus consequently leading to coronary heart disease and heart failure. 31 Therefore, systemic inflammatory response in COPD increases the risk for CVD. 32-34 Apart from the systemic inflammation, the processes that are believed to link CVD and COPD include lung hyperinflation, hypoxaemia, pulmonary hypertension and oxidative stress, exacerbations and genetics as well as COPD phenotype 35 Figure 1.

Conversely, CVD risk factors of systemic and vascular inflammation, such as abdominal obesity, diabetes and physical inactivity are also correlated with diminished pulmonary function, away hyper-reactivity and ultimately COPD, corroborating the premise that systemic inflammation related to CVD may affect COPD. 34

PH-pulmonary hypertension, LVH-left ventricular hypertrophy, LVSD-left ventricular systolic dysfunction, LVDD-left ventricular diastolic dysfunction, HF-heart failure, IHĐ-ischemic heart disease, CV-cardiovascular

The high prevalence of cardiovascular co-morbidities in patients with COPD was discussed by the board members and has been estimated by prospective case-control, retrospective and cross-sectional studies. Patients with COPD demonstrate an increased risk of carotid plaque formation, IHD, HF, arrhythmia, right and left ventricular dysfunction, left ventricular systolic dysfunction and pulmonary hypertension. 55-59 Figure 2. Pulmonary artery systolic pressure, systemic hypertension, pulmonary hypertension and LV dysfunction also increased with the severity of COPD. 53,60 A meta-analysis of observational studies inferred that there is twice as much rise in the probability of a diagnosis of any CVD in people with COPD compared to non-COPD patients. 61 Another meta-analysis of ten studies with 40,6426 participants found that asthma patients were associated with an increased risk of CVD and all-cause mortality, albeit greater in women than men. 2

Since IHD, ventricular hypertrophy, and arrhythmias are rather common in patients with chronic symptoms of COPD and asthma, such patients may be at an increased risk of cardiovascular events which may occur from \( \beta \)-adrenergic stimulation with LABA. 2,24
In patients with cardiovascular comorbidities, an otherwise tolerable level of side-effects may not be acceptable and instead may be a factor worth receiving more caution. Due to low receptor density of nontarget tissues, full β2-agonists may cause more severe side effects, such as higher rate of tachycardia and drop in serum potassium, than partial agonists. Salmeterol is a highly selective partial β2 agonist. A multicentre, randomized study comparing salmeterol and placebo in patients with asthma found no clinically significant between-group differences either in pulse rate, ECG QTc interval, ventricular or supraventricular ectopic events or arterial BP or frequency of adverse cardiovascular events. Salmeterol was well tolerated through the year, with a cardiovascular safety profile indistinguishable from that of placebo. A randomized, single-blind, study in COPD patients with pre-existing cardiac arrhythmias and hypoxemia showed a higher heart rate, more frequent supraventricular or ventricular premature beats with formoterol than salmeterol. Tremor was noted in lesser number of patients taking salmeterol than formoterol (2 vs 5) and palpitation occurred in four patients taking formoterol but none with salmeterol. Adverse effects, such as tachycardia, tremor and hypokalaemia, are minimal with salmeterol at standard doses. Less tremors were noted even when highest doses of salmeterol and formoterol were compared. Hence, salmeterol allows a better safety edge than formoterol.

Pooled analysis of seven clinical trials was conducted to evaluate the cardiovascular safety of salmeterol (50 μg bid), in patients with COPD and compared to placebo. This analysis included the use of a sizeable safety database that was distinctly illustrative of the COPD population, with patient profile encompassing various important subgroups namely the entire gamut of disease severity, smokers, geriatric patients and those with comorbid cardiovascular conditions. This analysis did not find any significant difference between salmeterol and placebo for any of the parameters assessed. Analysis of the Holter monitoring data which determines the heart rhythm showed no effect on the mean or maximum 24-h heart rate, signifying that salmeterol does not induce significant sympathetic stimulation of the heart in patients with COPD. No clinically pertinent variations were observed in the incidence of ventricular or supraventricular tachycardia or qualitative ECG measurements, QT intervals, pulse rates, and SBP/DBP between the salmeterol and placebo groups. Thus, the pooled analysis concluded that the cardiovascular safety profile of salmeterol is not dissimilar to placebo, in patients with COPD.

Several other studies have evaluated the cardiovascular safety of salmeterol either alone or with ICS (fluticasone). Cazzola et al. in a randomized double-blind, double-dummy study measured sPAP using transthoracic Doppler echocardiography and found that it significantly (p<0.05) decreased in comparison with baseline at 15, 30, and 60min post inhalation. The study did not find any association between the maximum increase in FEV(1) and maximum decline in sPAP after inhalation of salmeterol (r(2)=0.071). The heart rate did not change in a significant manner (p>0.05). Aortic pulse wave velocity (APWV) which is a marker of arterial stiffness and a good predictor for the cardiovascular events was found to be significantly reduced (~0.49 m·s−1, p=0.045) with SFC compared to placebo in a 12-week, multicentre, randomised, double-blind, placebo-controlled study. A meta-analysis by Rodrigo et al, found that compared to LAMA, use of SFC was associated with a lower incidence in CV mortality and MI incidence. Further, Wedzicha et al., in a 2-year, double-blind, double-dummy parallel study showed a significant decrease in the all-cause mortality rate (6% vs 3%; P=0.032) compared with LAMA. Cardiac disorder associated deaths were also higher in LAMA than SFC (3% vs 1%). In those subjects with pre-existing co-morbid CVD, the mortality rate was higher in the LAMA compared to the SFC group (8% vs 3%).

Post-hoc analysis of the TORCH study, suggested that the probability of patients having a CV AE by 3 years was the lowest for SFC (20.8%) versus placebo (24.2%), salmeterol (22.7%) and fluticasone propionate (24.3%). Compared to placebo, treatment with SFC was related to a significant reduction in the possibility of a CV AE by 3 years in patients on CV therapy at baseline (27.9% versus 33.5%, respectively; p<0.05). The probability of patients having a serious CV AE by 3 years was lowest for SFC compared to the placebo and the monotherapies, respectively (12.5% vs 15.4%, 13.6%, 14.7%). Likewise, regarding the ischaemic CV AE, the probability was lowest for SFC (11.3% vs 14.6%,13.4%, 13.8%). There was no significant difference between placebo and SFC in terms of overall and CV-related mortality. Thus, SFC might have advantageous effects on decreasing CV events in patients being treated with CV medications at baseline or with moderate COPD. However, the SUMMIT study comparing fluticasone furoate/vilanterol (FV) with the respective monotherapies and placebo did not find significant reduction in the risk of mortality compared to the placebo. Thus, FV in the SUMMIT study did not replicate the results of the TORCH post hoc analysis.

Thus, both pooled analysis of a large safety database and the large prospective TORCH study in patients with moderate to severe COPD and studies comparing formoterol and salmeterol infer that there is no increased risk of new cardiovascular AEs either with Salmeterol or SFC. On the contrary, its combination with an ICS like Fluticasone may provide certain degree of cardioprotection. These data suggest a protective effect of ICS and highlight the cardiovascular safety of salmeterol; hence, SFC can be used to manage asthma and COPD without increased risk of CVE. When we consider these diseases, which by themselves are a risk factor for CVD, the difference in side effect profile would take precedence over the onset of action; therefore, salmeterol should be preferred over formoterol in ICS/LABA combination. Lastly, the duration of action of salmeterol is longer than formoterol since the long side-chain of salmeterol binds to the exosite at the receptor site, which allows it to repetitively fasten and unfasten with the active site, resulting in a long duration of action.

Secondary Pneumonia with ICS

In asthma and COPD, ICS has demonstrated decrease in the total
frequency of exacerbations and enhancement in the quality of life.77-80 The correlation between use of ICS and predisposition to pneumonia has been better described in patients with COPD than in asthma.81 Incongruously, studies have reported higher incidence of pneumonia with fluticasone use in asthma and COPD patients.33,72,89,94 Nevertheless, these data should be reviewed on the basis of certain factors which cast a doubt whether these studies reflect the true incidences of pneumonia. The studies which have reported higher incidence of pneumonia with fluticasone were not designed to evaluate the risk of pneumonia and hence did not confirm the same radiographically. The diagnosis in most of the relevant studies was based on clinical judgement of signs and symptoms. However, clinical signs and symptoms of COPD exacerbations and pneumonia often overlap which may result in under or over-diagnosis of pneumonia, especially when chest radiographs are not used for the confirmation of the clinical diagnosis. Hence, true incidence of pneumonia with fluticasone may be different from what has been reported.

A recent open-label randomized study in 194 patients with COPD found that in the formoterol/budesonide treated group, pneumonia (7.8% vs 1.1; P=0.038) was more common than with SFC.83 A meta-analysis of clinical randomized trials of asthmatics using fluticasone propionate and budesonide found that patients did not have an elevated risk of pneumonia, even at higher doses or between the various ICSs.44 Secondary analysis of the Lung Injury Prediction Score (LIPS) cohort, which included patients with COPD (N=589) and patients with asthma (N=440), prehospital ICS use was not individually related to an increased risk for pneumonia needing hospitalization after correcting for various confounders. There were no statistically significant differences between COPD, asthma, and non-COPD/asthma subgroups.85 Though randomized controlled trials of ICS use in COPD have suggested an unadjusted risk of mortality related to pneumonia; none of these found a difference between ICS users and non-users.33,72,89,94 Further even various observational studies reported largely similar or reduced mortality among Fluticasone users, notwithstanding increased risk of pneumonia.86,89 A study of Veterans Affairs (VA) hospitals evaluated the correlation of ICS (including fluticasone) exposure with mortality in hospitalized COPD subjects with pneumonia. The use of ICS demonstrated a protective effect against 30-day mortality. The retrospective analysis of VA healthcare database found no significant association between ICS use including fluticasone and clinical outcomes in patients with COPD who suffered from pneumonia.86 When a nested case-control study was evaluated, it also demonstrated a lesser 30-day mortality risk of after hospitalization for pneumonia (13.3% vs 17.2% (p < 0.001)).87 A single-center cohort study observed that ICS use particularly fluticasone was associated with fewer complications and lower mortality, since it was evidently the most commonly used ICS in Spain during this study period.88 Studies comparing COPD exacerbation rates between patients being treated with either salmeterol or SFC demonstrated that all-cause mortality was comparable for patients hospitalized with pneumonia irrespective of the previous use of ICS.89

In the TORCH study, although there was a significantly higher frequency of pneumonia, it did not lead to an increased risk of mortality.90 With further subgroup analysis, the probability of pneumonia with SFC in COPD patients (GOLD stage II) was lesser than that observed in the total population. The number of deaths in patients on treatment were very less and hence could not be analysed by GOLD stage.90 In a post hoc analysis of TORCH, the reports of serious adverse events with pneumonia namely death, hospitalisation or prolongation of hospitalisation as a percentage of the total pneumonias were not more frequent in the fluticasone or SFC groups compared with placebo (∼60%). This finding suggests that the probability of pneumonia leading to an arduous clinical situation is unlikely. Absence of opportunistic pathogens in any pneumonia episode further corroborates this finding.91

Also, in the patients with COPD randomised to receive either SFC or salmeterol alone in a 44-week randomized, double-blind, parallel-group multicentre study, there was no difference in the mortality associated with pneumonia between SFC and Non-ICS group.92 A single case of pneumonia was documented as a secondary cause of death in each group, however, whether the alleged cases of pneumonia were true cases or simply a different clinical picture of an episode of exacerbation is uncertain; while there was a definite and significant decrease in overall exacerbations with the addition of fluticasone to salmeterol (-35%; P<0.0001).14 The INSPIRE study, which compared SFC with a LAMA (tiotropium) found that though there was a small rise in pneumonia, the mortality was lower in the SFC group (3% vs 6%; P=).14 Also, a nested case-control design that included greater than one lakh seventy-five thousand patients with COPD failed to show increased risk of mortality in spite of higher incidence of pneumonia with ICS use including fluticasone.84 Rather, on performing regression analyses of the results of data of hospitalised COPD patients with pneumonia from US Veterans Affairs hospitals, mortality was found to be significantly lower at 30- and 90-days (9% at 30 days and 16% at 90 days).92

Even with the increased pneumonia incidence, COPD patients on fluticasone therapy have lower mortality due to the blunted systemic inflammatory response. The investigators have shown that inhaled fluticasone propionate helps decrease the invasion of epithelial cells in the airway by microbes such as Streptococcus pneumoniae and Haemophilus influenzae thereby decreasing the bacterial load.91,92 Studies have also demonstrated reduced hazard of parapneumonic effusion due to the reduction of excessive local inflammatory responses and necessity for mechanical ventilation.90 Of note is a trial conducted for a year in patients with COPD with budesonide 640 μg and 320 μg, which found rise in the pneumonia adverse events, these doses were comparable to fluticasone 400 μg and 200 μg.93 Also, given its lower potency than fluticasone, budesonide may have been favourably advised to patients with COPD of a lesser severity who are at a lower risk of pneumonia, compared to those with greater severity.94 Even geriatric patients and those with severe COPD are at an
increased risk of pneumonia. 3 COPD per se increases the susceptibility to pneumonia based on the presence of chronic bronchitis with tenacious mucus production, and the presence of potential pathogenic bacteria in the airways. 31,32 Also, the existence of bacteria in the airway of patients with stable COPD and higher numbers during exacerbations have been linked with greater inflammation. 33 Further, COPD also increases the pneumonia associated hospitalization more so for patients with severe underlying disease. Further, the dose of ICS prescribed for severe cases of COPD to prevent exacerbation is also likely to be high. 34

There was no increase in mortality with SFC even in patients with pneumonia and reduced exacerbation rates were observed compared to LABA and LAMA alone, the impact of this combination on the overall health status and quality of life is noteworthy. The pivotal studies, TORCH and INSPIRE suggested no association with the incidence of pneumonia and overall change in health status assessed by St George’s Respiratory Questionnaire. 35,36 A recent meta-analysis of more than thirteen thousand patients with COPD demonstrated that ICS including fluticasone use of for more than 6 months duration slowed the rate of decline in quality of life as measured by the St George’s Respiratory Questionnaire. 37 Though there are different quality-of-life measures in studies included in the meta-analysis, more than 70% studies reported a statistically significant improvement in St George’s Respiratory Questionnaire scores. 38 A new-user cohort study suggested weakening of the risk of pneumonia subsequent to continual use for a minimum of six months, whereas RCTs require about 6 months of use before treatment differences surface. Meta-analyses of RCTs show attenuation of the risk of pneumonia after >2 years of ICS usage. 39,40 Thus, the apparent increased pneumonia risk associated with fluticasone therapy is balanced with the known favourable effects of ICS use on quality of life and reduction of morbidity. 39

Conclusion

Basic treatment strategies that focus on the use of inhalers utilized in the treatment of both asthma and COPD are foundational approaches for the treatment of asthma patients with COPD phenotype or vice versa. Patients with COPD, such as those with blood eosinophilia or asthma, respond well to SFC even at low doses. 100 ICS/LABA like SFC could be a basic maintenance therapy in asthma patients with COPD phenotype or vice versa. 41 Given the established efficacy and cardiovascular safety of the LABA component of SFC in COPD, it would also be a preferred ICS/LABA combination in COPD and asthma patients with COPD phenotype with pre-existing CVD including arterial stiffness, pulmonary hypertension, arrhythmia. In COPD patients, pneumonia is much less common than exacerbations. Though there appears to be a slightly higher increased risk of pneumonia, treatment with ICS does not cause an increase in all-cause mortality. These data indicate that such adverse effects may occur inconsistently. Rather there was no difference in ICS and non-ICS users with regard to mortality. There was significantly a higher survival rate among SFC users compared to non-ICS users with an absolute difference of 15%. 4,101

Adding fluticasone to salmeterol contributes important benefits, such as preventing exacerbations and slowing pulmonary function decline. SFC also has a significant effect on improvement in HR-QoL with more than four-unit change in the SGRQ score in 35% patients. 33 Thus, SFC has proven and validated benefits in patients with asthma, COPD and high-risk patients such as those with overlapping symptoms, patients with elevated eosinophils, pre-existing CVD. Use of a fixed-dose combination like salmeterol and fluticasone has been found to be extremely satisfactory given its ease of use, which is critical for the end-users suffering from asthma, COPD and asthma patients with COPD phenotype or vice versa.

Abbreviations


Conflict of Interest

This paper forms part of a supplement commissioned and funded by Lupin Limited. The supplement contains papers based on presentations from an Advisory Board of health-care professionals held on 6th December, 2020, which was sponsored by Lupin Limited. All participants received an honorarium from Lupin Limited for their participation in the Advisory meeting. Pratyusha Gaonkar is an employee of Lupin Ltd.

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References


An Evaluation of Efficacy and Safety of Tofacitinib, A JAK Inhibitor in the Management of Hospitalized Patients with Mild to Moderate COVID-19 - An Open-Label Randomized Controlled Study

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Abstract
Several systemic anti-inflammatory and immunomodulatory agents were tried in the management of hyper inflammatory manifestations of COVID 19. JAK inhibitors have been widely deployed in rheumatology due to their benefits in managing uncontrolled inflammation. Tofacitinib is one of the most widely studied immunomodulators in rheumatology. We assessed the safety and efficacy of Tofacitinib in an open-labeled randomized control study, in addition to the standard of care (SOC) in hospitalized adults with mild to moderate COVID-19 pneumonia. Patients (n=100) with COVID 19 pneumonia admitted during October -December 2020 were randomly assigned to either control (N=50) (SOC treatment alone) or to study groups (N=50) receiving Tofacitinib in addition. Patients, reporting positive RT-PCR for SARS-COV2 and radiological evidence of pneumonia were hospitalized for over 7 days. The study group received Tofacitinib for 14 days irrespective of the discharge status and was followed up to 28 days. There was a greater relative reduction in levels of important markers of inflammation in the Tofacitinib group than in the control group (CRP:78% vs 45%; Ferritin:15% vs 10%; D. Dimer: 37% vs 15%) although there were no differences in duration of hospitalizations or oxygen requirement. Tofacitinib, 10 mg was well-tolerated and was devoid of any serious adverse event. We are the first to record the benefits of Tofacitinib in India to our knowledge although a Brazilian study conducted around the same time showed mortality benefit in severe COVID. We conclude that Tofacitinib use is safe and aids in the reduction of the overwhelming inflammatory response during COVID-19 infections.

Introduction

COVID-19 pandemic posed innumerable challenges to the global community and has played havoc to healthcare delivery. Since there was no single antiviral agent or their combinations showing therapeutically meaningful benefit there remained a huge need to look at many other supportive measures. While there is a strong ongoing effort to vaccinate the entire human race, hospitalized vulnerable population continue to have an unmet need for effective, safe and easy to administer therapeutic solutions. SARS-CoV-2 infection is not only a respiratory infection but is shown to trigger a generalized systemic immunological and inflammatory hyper responsiveness.¹ Severe manifestations of SARS-CoV-2 infection resulting in a respiratory failure are associated with an exaggerated immune response driven by proinflammatory cytokine/chemokine including interleukin-6, tumor necrosis factor α, and other cytokines in a pattern called a cytokine storm.¹ These excessive inflammatory and immunological responses necessitated the re-purposing of several systemic anti-inflammatory and immunomodulatory agents.

An interesting mechanistic benefit is offered by a class of immunomodulatory drugs showing a promising dual role in modulating secondary immune response while displaying an antiviral property. Baricitinib, a selective oral JAK1/2 inhibitor with moderate activity against TYK2 (Tyrosine kinase 2)² licensed for the treatment of rheumatoid arthritis (RA) seems to possess an affinity for AP2-associated protein AAK1, imparting anti-viral effects that could interfere with SARS-CoV2 endocytosis.²,³

Tofacitinib is a first-generation selective oral JAK1/3 inhibitor. Different Tyrosine kinase inhibitors exert different effects in patients with the same disease.² This is in part attributed to the differences in uptake mechanisms.³ Accordingly, we intended to test the efficacy and safety of a JAK inhibitor, Tofacitinib, previously approved for rheumatoid arthritis, in treating COVID-19 infections. In this open-labeled randomized control study, we assessed the efficacy of Tofacitinib, a JAK kinase inhibitor along with standard of care compared to standard of care treatment alone in hospitalized adult patients with mild to moderate COVID-19 pneumonia.

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Materials and Methods

Study design

An open-label pilot study was conducted on 100 patients with COVID-19 pneumonia admitted to Chengalpet Government Medical College, Chennai, India. The study period was October 2020-December 2020. In a 1:1 ratio, the 100 patients were randomly assigned to either control (N=50) group receiving standard of care treatment alone or to study (N=50) group receiving standard of care + Tofacitinib treatment. This pilot study was conducted in accordance with the Good clinical practice and ethical principles of the Declaration of Helsinki. All eligible patients provided their informed consent prior to their participation in the study. Institutional ethics committee clearance was obtained.

Inclusion criteria

Hospitalized adult patients in the age group of 18 - 65 years, diagnosed positive for SARS-CoV2 infection by RT-PCR and radiological imaging (Chest X-ray or CT scan) confirmed pneumonia with lower respiratory tract infection features indicating moderate pneumonia. An institutional protocol for defining mild to moderate cases of COVID-19 disease was identified based on the Comprehensive Guidelines for Management of COVID-19 patients, defined by the Directorate General of Health Services, MoHFW, Government of India. In addition to having one or many of the COVID-19 symptoms including fever, cough, body ache, weakness, gastrointestinal problems, loss of taste and smell, and shortness of breath, mild to moderate COVID-19 disease definition includes presence of bilateral pneumonia with or without ground glass opacity and in absence of consolidation, not requiring intubation at enrolment; arterial oxygen saturation (SpO2) > 94% (mild) or 90-93% (moderate) at room-air, and respiratory rate of 16-30/min.

Exclusion criteria

Patients on mechanical ventilation at the time of admission, with known allergy to tofacitinib, participants who are immunocompromised, with known immunodeficiencies, or taking potent immunosuppressive agents or any potent cytochrome P450 inhibitors within the past 30 days, or those receiving any corticosteroid treatment for 14 consecutive days prior to screening were excluded.

Table 1: Demographic profile of the participants

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</tr>
<tr>
<td>BA, N (%)</td>
<td>3</td>
<td>0 (0.0)</td>
<td>3 (6.0)</td>
<td>0.242</td>
</tr>
<tr>
<td>Seizure disorder, N (%)</td>
<td>1</td>
<td>0 (0.0)</td>
<td>1 (2.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Heart disease, N (%)</td>
<td>5</td>
<td>4 (8.0)</td>
<td>1 (2.0)</td>
<td>0.362</td>
</tr>
<tr>
<td>Hypothyroidism, N (%)</td>
<td>4</td>
<td>3 (6.0)</td>
<td>1 (2.0)</td>
<td>0.617</td>
</tr>
<tr>
<td>Parkinson’s disease, N (%)</td>
<td>1</td>
<td>0 (0.0)</td>
<td>1 (2.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>COPD, N (%)</td>
<td>1</td>
<td>1 (2.0)</td>
<td>0 (0.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>RHD-MS, N (%)</td>
<td>1</td>
<td>1 (2.0)</td>
<td>0 (0.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>No comorbidity, N (%)</td>
<td>38</td>
<td>23 (46.0)</td>
<td>15 (30.0)</td>
<td>0.099</td>
</tr>
<tr>
<td>Concomitant therapy given to patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone, N (%)</td>
<td>96</td>
<td>47 (94.0)</td>
<td>49 (98.0)</td>
<td>0.617</td>
</tr>
<tr>
<td>Enoxaparin, N (%)</td>
<td>99</td>
<td>49 (98.0)</td>
<td>50 (100.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Heparin, N (%)</td>
<td>1</td>
<td>1 (2.0)</td>
<td>0 (0.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Remdesivir, N (%)</td>
<td>98</td>
<td>49 (98.0)</td>
<td>49 (98.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Dexamethasone, N (%)</td>
<td>85</td>
<td>46 (92.0)</td>
<td>39 (78.0)</td>
<td>0.050</td>
</tr>
<tr>
<td>Methylprednisolone, N (%)</td>
<td>15</td>
<td>4 (8.0)</td>
<td>11 (22.0)</td>
<td>0.050</td>
</tr>
</tbody>
</table>

Table 2: Baseline CT-score of the patient population

<table>
<thead>
<tr>
<th>Grade</th>
<th>Control population N (%)</th>
<th>Study population N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23 (46)</td>
<td>15 (30)</td>
</tr>
<tr>
<td>2</td>
<td>22 (44)</td>
<td>27 (54)</td>
</tr>
<tr>
<td>3</td>
<td>5 (10)</td>
<td>8 (16)</td>
</tr>
</tbody>
</table>
Other criteria for exclusions were history of major adverse cardiovascular event (MACE) and/or recent (one year) revascularization, history of deep venous thrombosis (DVT) or pulmonary embolism (PE), pre-existent neurodegenerative disease, severe hepatic or renal impairment, severe anemia (hemoglobin <8 g/dl), history of any malignancy or lymphoproliferative disorders that requires active treatment.

All patients were kept under observation in the hospital for 7 days, irrespective of positive outcomes and were followed up over phone for up to 28 days.

### Treatment

Standard of care treatment included Ceftriaxone, Enoxaparin, Heparin, Remdesivir, Dexamethasone, Methylprednisolone at the recommended dosing and supplementary oxygen wherever required. Tofacitinib was administered in a dose of 10 mg PO BID for 14 days, considering the prevention of a probable rebound of cytokine release syndrome due to an abrupt cessation of immunomodulatory therapy.

### Outcome measures

Primary outcomes were the proportion of patients not requiring any form of mechanical ventilation or high flow oxygen or ECMO at day 7 or mortality. Secondary outcome measures were the difference in levels of inflammatory markers such as Interleukin-6 (IL6), serum ferritin and CRP between baseline estimate and day 7, changes in radiological and clinical presentations.

### Statistical analysis

Since it is a pilot study, we adopted a convenient sampling method to arrive at the number as 50 patients in each arm. The different parameters were tested for proportions using a Chi-square test. The difference in median or mean was tested with Mann-Whitney and student’s t-test, respectively. Comparison of change in parameters from baseline was evaluated using paired t-test. The level of statistical significance is considered at 5%.

### Results

#### Baseline characteristics

Patient demographics (Table 1) including age, gender distribution, existence of comorbidities and concomitant therapy to the patients is not significantly different ($P>0.05$) between the control and the study group. The baseline CT- score of the included patient is provided in Table 2. Most of the patients in the control group (46%) had a lower CT score of grade-1, whereas most of the patients in the treatment group (70%) had higher CT-score of grade-2 and 3. The clinical history of the included patients and the prevailing symptoms at the time of admission were not significantly different between the two groups (Table 3).

#### Oxygen saturation status and ICU care of the participants

During the hospital stay and for a follow-up period of up to 14 days, there was no mortality in both the groups. The SpO2 levels of the included participants were $>94\%$ and did not

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**Table 3: Baseline clinical history of the participants**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control Group (N=50)</th>
<th>Study Group (N=50)</th>
<th>p-value</th>
<th>Control Group (N=50)</th>
<th>Study Group (N=50)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>35 (70.0)</td>
<td>41 (82.0)</td>
<td>1.000</td>
<td>6 (3-7)</td>
<td>4 (3-7)</td>
<td>0.278</td>
</tr>
<tr>
<td>Cough</td>
<td>30 (60.0)</td>
<td>30 (60.0)</td>
<td>0.958</td>
<td>5 (3-7)</td>
<td>5 (3-7)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (2.0)</td>
<td>3 (6.0)</td>
<td>0.500</td>
<td>1 (1-1)</td>
<td>3 (1-7)</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>19 (38.0)</td>
<td>26 (52.0)</td>
<td>0.001</td>
<td>3 (3-5)</td>
<td>2 (1-3)</td>
<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td>0 (0.0)</td>
<td>1 (2.0)</td>
<td></td>
<td>1 (1-1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sore throat</td>
<td>2 (4.0)</td>
<td>2 (4.0)</td>
<td></td>
<td>7 (4-9)</td>
<td>6 (5-7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Myalgia</td>
<td>6 (12.0)</td>
<td>1 (2.0)</td>
<td></td>
<td>3 (3-5)</td>
<td>3 (3-3)</td>
<td>1.000</td>
</tr>
<tr>
<td>Loss of smell and taste</td>
<td>2 (4.0)</td>
<td>0 (0.0)</td>
<td>0.495</td>
<td>6 (5-7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Giddiness</td>
<td>1 (2.0)</td>
<td>0 (0.0)</td>
<td>1.000</td>
<td>5 (5-5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>2 (4.0)</td>
<td>0 (0.0)</td>
<td>0.495</td>
<td>3 (2-3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (2.0)</td>
<td>0 (0.0)</td>
<td>1.000</td>
<td>3 (3-3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizure</td>
<td>0 (0.0)</td>
<td>1 (2.0)</td>
<td>1.000</td>
<td>0 (0.0)</td>
<td>1 (2.0)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

**Table 4: Baseline CT- score status of the participants**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control Group (N=50)</th>
<th>Study Group (N=50)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT- score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>46%</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>26%</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>18%</td>
<td>37%</td>
<td></td>
</tr>
</tbody>
</table>

**Table 5: Baseline clinical history of the participants**

<table>
<thead>
<tr>
<th>Variables</th>
<th>N (%)</th>
<th>Days, median (IQR)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>35 (70.0)</td>
<td>6 (3-7)</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>30 (60.0)</td>
<td>5 (3-7)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (2.0)</td>
<td>1 (1-1)</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>19 (38.0)</td>
<td>3 (3-5)</td>
<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td>0 (0.0)</td>
<td>1 (1-1)</td>
<td></td>
</tr>
<tr>
<td>Sore throat</td>
<td>2 (4.0)</td>
<td>7 (4-9)</td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>6 (12.0)</td>
<td>4 (3-5)</td>
<td></td>
</tr>
<tr>
<td>Loss of smell and taste</td>
<td>2 (4.0)</td>
<td>6 (5-7)</td>
<td></td>
</tr>
<tr>
<td>Giddiness</td>
<td>1 (2.0)</td>
<td>5 (5-5)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>2 (4.0)</td>
<td>3 (2-3)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (2.0)</td>
<td>3 (3-3)</td>
<td></td>
</tr>
<tr>
<td>Seizure</td>
<td>0 (0.0)</td>
<td>1 (2.0)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 4: SpO2 levels (Oxygen saturation) of the participants**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control Group (N=50)</th>
<th>Study Group (N=50)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SpO2, median (IQR)</td>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>98 (96-98)</td>
<td>97 (95-98)</td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td>98 (96-98)</td>
<td>97 (95-98)</td>
<td></td>
</tr>
<tr>
<td>Day 5</td>
<td>98 (96-98)</td>
<td>97 (96-98)</td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>98 (97-99)</td>
<td>98 (97-98)</td>
<td></td>
</tr>
<tr>
<td>Discharge</td>
<td>98 (97-99)</td>
<td>98 (98-98)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 5: O2 supplement and ICU care of the participants**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control Group (N=50)</th>
<th>Study Group (N=50)</th>
<th>Test performed</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FiO2, N (%)</td>
<td>13 (26.0)</td>
<td>14 (28.0)</td>
<td>Chi-square test</td>
<td>0.822</td>
</tr>
<tr>
<td>Liters, median (IQR)</td>
<td>6 (4-8)</td>
<td>6 (4-8)</td>
<td>Mann-Whitney U test</td>
<td>0.867</td>
</tr>
<tr>
<td>ICU care, N (%)</td>
<td>0 (0.0)</td>
<td>1 (2.0)</td>
<td>Fisher exact</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Fig. 2: Comparing the declining trend of anti-inflammatory CRP (panel A), Ferritin (panel B) and anticoagulatory D.Dimer (panel C) levels in the SOC (Standard of Care) and TOF (Tofacitinib) + SOC treatment groups.
The inflammatory markers, CRP and Ferritin levels were significantly reduced in comparison to the baseline in both the groups (Figure 2). The percentage reduction in the CRP and the D.Dimer levels was more pronounced in the study group than the control group (Figure 2).

Percentage decrease in the inflammatory and coagulation marker levels were significantly higher in the treatment group compared to the control group (Table 6A and 6B) suggesting a greater anti-inflammatory immunomodulatory benefit attributable to Tofacitinib. Baseline Ferritin levels were higher in the study group (P=0.006) while the percentage drop in Ferritin levels was significantly higher in the treatment group as compared to the control (Table 6A). There were no adverse reactions reported both in the control group as well as in the study group. Specifically, there were no drug-induced adverse reactions observed during the study. Supplementary information pertaining to other blood and electrolyte parameters of the patients in the two groups is presented in Table 7.

**Discussion**

In this pilot open labeled randomized control study conducted in a population of 100 patients with moderate COVID-19 infections, including Tofacitinib, a Jak kinase inhibitor with the SOC seems to be safe and efficacious option with immunomodulatory potential. In the current scenario of emerging infections and to address the treatment challenges of variable cytokine response to COVID-19 infections, there has been a drive to quickly explore the potency of safe drugs and repurpose them for alternate use. Virus infection induced aberrant anti-inflammatory response is not uncommon. This has been observed as rising cytokine levels with COVID-19 disease severity, eventually leading to cytokine storm and death in certain cases. With the rapid spread of COVID-19 infections, this cytokine storm mediated death remains significant in the global population. Therefore, early intervention to curtail and control an impending cytokine storm is a practical approach.

Tofacitinib therapy was well tolerated among the patients. For a follow-up period of up to 28 days, there had been no reported mortality

---

### Table 6A: Inflammatory and coagulation panel of the participants. Intragroup comparison of the change in marker levels by day 7

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline Median (IQR)</th>
<th>Day 7 Median (IQR)</th>
<th>P-value</th>
<th>Percentage difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP, median (IQR)</td>
<td>Control Group (N=50) 9.7 (7.0-26.0)</td>
<td>Study Group (N=50) 10.6 (3.3-24.0)</td>
<td>&lt;0.001*</td>
<td>48.45</td>
</tr>
<tr>
<td>Ferritin, median (IQR)</td>
<td>Control Group (N=50) 196.0 (81.6-369.0)</td>
<td>Study Group (N=50) 304.5 (224.2-432.0)</td>
<td>&lt;0.001*</td>
<td>10.20</td>
</tr>
<tr>
<td>DIMER, median (IQR)</td>
<td>Control Group (N=50) 688.5 (552.6-1738.5)</td>
<td>Study Group (N=50) 599.0 (500.8-888.6)</td>
<td>&lt;0.001*</td>
<td>14.91</td>
</tr>
</tbody>
</table>

*Statistically significant at 5% level of significance between the baseline and day 7 estimates of each group.

### Table 6B: Inflammatory and coagulation panel of the participants. Comparison of marker levels between the study and the control group

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control Group (N=50)</th>
<th>Study Group (N=50)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP, median (IQR)</td>
<td>Baseline 9.7 (7.0-26.0)</td>
<td>Day 7 10.6 (3.3-24.0)</td>
<td>0.514</td>
</tr>
<tr>
<td>Ferritin, median (IQR)</td>
<td>Baseline 196.0 (81.6-369.0)</td>
<td>Day 7 176.0 (102.0-220.2)</td>
<td>0.008*</td>
</tr>
<tr>
<td>DIMER, median (IQR)</td>
<td>Baseline 688.5 (552.6-1738.5)</td>
<td>Day 7 568.8 (343.0-786.0)</td>
<td>0.008*</td>
</tr>
</tbody>
</table>

*Statistically significant at 5% level of significance comparing the control to the study group estimates.

### Table 7: CBC, RFT, LFT and Electrolytes level of the participants (Mann Whitney U test)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Study Group (N=50)</th>
<th>Control Group (N=50)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC, median (IQR)</td>
<td>7.2 (5.8-9.5)</td>
<td>7.6 (6.2-9.9)</td>
<td>0.381</td>
</tr>
<tr>
<td>RBC, median (IQR)</td>
<td>4.7 (4.4-4.9)</td>
<td>4.8 (4.4-5.1)</td>
<td>0.501</td>
</tr>
<tr>
<td>HB, median (IQR)</td>
<td>13.0 (12.0-14.0)</td>
<td>12.9 (11.7-14.4)</td>
<td>0.722</td>
</tr>
<tr>
<td>HCT, median (IQR)</td>
<td>37.4 (35.0-41.0)</td>
<td>37.0 (35.0-43.0)</td>
<td>0.798</td>
</tr>
<tr>
<td>MCV, median (IQR)</td>
<td>82.0 (78.0-85.0)</td>
<td>81.6 (78.0-85.0)</td>
<td>0.874</td>
</tr>
<tr>
<td>MCH, median (IQR)</td>
<td>27.0 (26.0-30.0)</td>
<td>27.0 (26.0-28.0)</td>
<td>0.254</td>
</tr>
<tr>
<td>MCHC, median (IQR)</td>
<td>34.0 (32.0-35.0)</td>
<td>33.5 (32.0-34.8)</td>
<td>0.191</td>
</tr>
<tr>
<td>PLT, median (IQR)</td>
<td>2.1 (1.9-3.1)</td>
<td>2.5 (1.9-3.2)</td>
<td>0.839</td>
</tr>
<tr>
<td>L, median (IQR)</td>
<td>18.5 (11.1-25.0)</td>
<td>20.0 (12.0-27.0)</td>
<td>0.490</td>
</tr>
<tr>
<td>M, median (IQR)</td>
<td>5.0 (3.5-8.0)</td>
<td>6.0 (4.0-8.0)</td>
<td>0.129</td>
</tr>
<tr>
<td>N, median (IQR)</td>
<td>76.5 (67.0-82.7)</td>
<td>74.5 (65.0-82.0)</td>
<td>0.617</td>
</tr>
<tr>
<td>RBS, median (IQR)</td>
<td>174.0</td>
<td>172.5</td>
<td>0.981</td>
</tr>
<tr>
<td>UREA, median (IQR)</td>
<td>24.5 (20.0-36.0)</td>
<td>30.0 (25.0-36.0)</td>
<td>0.058</td>
</tr>
<tr>
<td>CREA, median (IQR)</td>
<td>0.9 (0.7-1.1)</td>
<td>1.0 (0.9-1.2)</td>
<td>0.022*</td>
</tr>
<tr>
<td>Na, median (IQR)</td>
<td>136.0</td>
<td>136.0</td>
<td>0.327</td>
</tr>
<tr>
<td>K, median (IQR)</td>
<td>4.1 (3.8-4.3)</td>
<td>4.0 (3.9-4.3)</td>
<td>0.639</td>
</tr>
<tr>
<td>Cl, median (IQR)</td>
<td>104.5</td>
<td>101.0</td>
<td>0.066</td>
</tr>
<tr>
<td>TB, median (IQR)</td>
<td>0.6 (0.6-7.0)</td>
<td>0.5 (0.6-7.0)</td>
<td>0.020*</td>
</tr>
<tr>
<td>DB, median (IQR)</td>
<td>0.2 (0.2-0.2)</td>
<td>0.2 (0.2-0.2)</td>
<td>0.789</td>
</tr>
<tr>
<td>BI, median (IQR)</td>
<td>0.4 (0.4-0.5)</td>
<td>0.4 (0.3-0.4)</td>
<td>0.004*</td>
</tr>
<tr>
<td>AST, median (IQR)</td>
<td>21.5 (16.0-29.0)</td>
<td>28.0 (19.0-34.0)</td>
<td>0.076</td>
</tr>
<tr>
<td>ALT, median (IQR)</td>
<td>24.0 (20.0-32.0)</td>
<td>25.0 (19.0-35.0)</td>
<td>0.956</td>
</tr>
<tr>
<td>ALP, median (IQR)</td>
<td>64.0 (48.0-107.0)</td>
<td>56.0 (45.0-69.0)</td>
<td>0.011*</td>
</tr>
<tr>
<td>TP, median (IQR)</td>
<td>7.0 (6.7-7.3)</td>
<td>6.9 (6.7-7.2)</td>
<td>0.317</td>
</tr>
<tr>
<td>ALB, median (IQR)</td>
<td>4.0 (3.9-4.3)</td>
<td>4.0 (3.9-4.2)</td>
<td>0.671</td>
</tr>
<tr>
<td>GLO, median (IQR)</td>
<td>3.0 (2.6-3.1)</td>
<td>3.0 (2.7-3.1)</td>
<td>0.310</td>
</tr>
</tbody>
</table>

*Statistically significant at 5% level of significance.
in both groups. During the hospital stay, none of the patients required mechanical ventilation. The proportion of patients requiring oxygen support was comparable between the two groups. Interestingly, the inflammatory and coagulation panel markers in the Tofacitinib+ SOC displayed significant differences in the reduction when compared to the SOC-only group. In general, there is a significant difference of CRP and Ferritin levels between the baseline and the day 7 in both groups. The mean percentage reduction is more pronounced in the Tofacitinib group than in the control group (CRP levels: 78% vs 45%; Ferritin levels: 15% vs 10% and D. Dimer levels: 37% vs 15%).

Exploring the broad anti-inflammatory property of Tofacitinib, a recent cohort study demonstrated that Tofacitinib, in combination with Dexamethasone offered a significant survival benefit in hospitalized COVID-19 patients compared to Dexamethasone. Compared to placebo, Tofacitinib treatment resulted in a lower mortality risk or respiratory failure for a period of 28 days.

Five patients in the Tofacitinib group had significantly higher ferritin levels on day 7 in comparison to baseline while there was no such discernible change noticed in the control group. Similarly, seven patients out of fifty in the Tofacitinib group and three in the control group had higher D-Dimer levels on day 7 in comparison to their baseline values. It appears that not all inflammatory and coagulation markers respond uniformly to treatment in all patients and such differential findings need further explanation. However, these increase in levels had no impact on the outcome of the disease course over a follow-up period of up to 28 days. There were no reported adverse reactions due to the drug.

Overall, administering Tofacitinib at a 10 mg dose for a period of 14 days along with the standard of care treatment seems to have an added benefit of an anti-inflammatory response in patients with mild-to-moderate COVID-19 infections. This in concordance with other recently published studies suggests that early intervention of Tofacitinib could be safe and aid in subsiding an overwhelming inflammatory response caused due to COVID-19 infections. This could be explored further in a larger pool of population.

Conclusions

We conclude that incorporating Tofacitinib with the standard of care at a comfortable dosing is safe and has the added benefit of bringing down the inflammatory markers in most patients with mild to moderate COVID-19.

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References

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*English, Hindi, Bengali, Gujarati, Marathi, Punjabi, Tamil, Assamese, Kannada, Malayalam, Oriya and Telugu.
A Case of Pierre Robinson Sequence in an Adult

Kanishka Kumar¹, Jayesh Katarmal², Deepika Pandey²

Case: A 60 year old patient presented to us with 10 days history of cough with expectoration and fever. We diagnosed her to be a case of lower respiratory tract infection based on her clinical findings and history. The patient was always drowsy with type 2 respiratory failure not in proportion to her present condition. Close examination revealed her facial asymmetry with retrognathia. Pierre Robinson Sequence was suspected which was confirmed when other features such as cleft palate and ear skin tags were also found. Patient gave a positive history of difficulty in swallowing solid foods all through her life but had never been evaluated for it.

Pierre Robin sequence consists of clinical triad of micrognathia, glossoptosis, and airway compromise with variable inclusion of cleft palate.¹ The management of the condition includes respiratory support for the blocked airway in the form of nasopharyngeal tubes and feeding support. Definitive treatment involves surgical procedures such as tongue lip adhesion and distraction osteogenesis of the mandible to fix the defect.²

It is a unique case as we have not been able to find any such report in an adult patient in literature.

References

Anonychia Congenita - Rare Inheritance of a Rare Disorder

Jain Vasudha1, Fatima Jalees2, Priya S2, Varshney Ankit Raj3, Khan Mohammad Tauseef4

Abstract
Non syndromic Anonychia congenita or congenital absence of finger and toe nails is a rare disorder known to occur due to autosomal recessive inheritance of mutation in the R-spondin-4 gene. We present a case of a 32 year old female born of a non-consanguineous marriage presenting with complete absence of finger and toe nails since birth and similar presentation in family members over four generations, suggesting an autosomal dominant inheritance.

Introduction
Absence of finger and toe nails is termed as anonychia.1 Anonychia or hyponychia is a rare disorder attributed to homozygous or compound heterozygous mutation in the R-spondin-4 gene on chromosome 20p13.2,3 Anonychia or hyponychia may be partial or total and is usually associated with other skeletal or limb anomalies and various genetic syndromes like Coffin-Siris syndrome and Nail-patella syndrome. Non syndromic congenital anonychia is a rarer entity with only a few case reports in literature.4,5 The presence of an autosomal dominant form of the disease has not been reported to the best of our knowledge. We present a case of a 32 year old female with complete absence of finger and toe nails over four generations.

Case Report
A 32 year old female, presented with complete absence of fingernails and toenails since birth (Figures 1, 2). She did not have any bony abnormalities, dysmorphic facies or abnormal hair or teeth. Her developmental milestones and intelligence were normal. Her family history was significant for complete anonychia over 4 generations (Figure 3). There was no history of consanguineous marriage among family members.

Discussion
Although syndromes associated with anonychia are usually autosomal dominant (like Coffin-Siris syndrome and nail-patella syndrome), isolated non-syndromic congenital anonychia has an autosomal recessive inheritance pattern. A partial autosomal dominant form of the disease affecting only the thumb is also known.4

Most of the case reports of non-syndromic anonychia are seen in consanguineous marriages and are not known to affect more than one generation.

In this case, presence of anonychia was observed over 4 generations. This along with the absence of a consanguineous marriage precludes the presence of autosomal recessive inheritance. Whether, this can be attributed to autosomal dominant mutation of the same or different gene will be a question for future research. A detailed genetic evaluation could not be done in our case due to financial and technical limitations.

References

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Received: 14.11.2018; Accepted: 20.01.2020
Walter Reed & Yellow Fever

Jayant Pai-Dhungat

Walter Reed (1851-1902) was born in Beloit, Virginia. Reed graduated with a medical degree from the University of Virginia in 1869. He earned a second M.D. a year later at the Bellevue Hospital Medical College in New York City (1870), and gained a position as assistant sanitary officer for the Brooklyn Health in 1873. Reed entered the Medical Corps commission of the U.S. Army in 1875 and was assigned to several remote outposts. Years later, he made bacteriology his specialty. He was promoted to major and professor of clinical and sanitary microscopy at Army Medical School, Washington in 1893.

During the Spanish American war Major Reed headed the commission to study cause and spread of epidemics. He had effectively tackled typhoid epidemic. However, more soldiers were felled by dreaded yellow fever than in the war, Reed travelled to Cuba to tackle yellow fever which was raging in 1897. He disproved the common belief that yellow fever could be transmitted by body fluids, or fomites. He took up idea advanced earlier by Juan Finlay, that organism was transmitted by a mosquito (1900). There was no way of testing the theory on animals and high drama followed; doctors, volunteers of the commission allowed themselves to be bitten by mosquitoes to see if they developed the disease; some did and. Reed’s assistant and friend William Lazear and, volunteer nurse Clara Mass died of yellow fever while on this assignment. This was risky, but fruitful research. Reed and U.S. Army, Board of Yellow Fever Commission in Cuba confirmed the transmission by mosquitoes. In 1901, Reed proved that responsible agent was a filterable virus; the first human disease attributed to virus. Reed’s leadership with Gorga’s cooperation made the building of Panama Canal possible.

Juan Finlay (1833-1915) the Cuban physician was a strong advocate of the transmission theory as the cause of yellow fever and discovered *Aedes Egyptty* mosquito that transmits yellow fever. His unsophisticated experiments were discounted by many but, were the basis of Reed’s research. In fact Finlay handed over few larvae to Reed for experiments.

Reed himself often cited Finlay’s papers in his own articles and gave him credit during his lecture about the discovery. Walter Reed died in 1902. His name adorns the Army Medical Center (1909).
COVID-Inflicted Coagulopathy: Expert Consensus on Management with Novel Oral Anticoagulants in India

HK Chopra¹, Tiny Nair², CK Ponde³, Subhash Kaul⁴, Yatin Mehta⁵, Agam Vora⁶*, Pinaki Mukhopadhyay⁷, PB Jayagopal⁸, Mrutyunjay Behera⁹, Rahul Patil¹⁰, Mahesh Deshpande¹¹, R Anantharaman¹²

Abstract
Coronavirus disease 2019 (COVID-19) is a highly hypercoagulable viral infection complicated as COVID-inflicted coagulopathy (CIC), that is associated with increased risk of morbidity and mortality. International guidelines recommend low molecular weight heparin (LMWH) to treat CIC in both in-hospital and in-home settings. However, in India, using subcutaneous LMWH may not be a feasible option for a vast majority of patients under home management. Additionally, while some evidence advocates the use of novel oral anticoagulants (NOACs), in hospitalized settings, most guidelines find no role of NOACs in hospital settings. On the other hand, the resource crunch faced in recent COVID-19 pandemic in India forced physicians to treat many patients in home settings. These patients had been usually prescribed NOACs for ease of administration and adherence. Therefore, there is a need to form a consensus on the use of NOACs to manage CIC in India.

Pathophysiology and clinical presentations of CIC

Hypercoagulability and inflammation in CIC is multifactorial with cytokine storm, neutrophil extracellular traps (NET) and endotheliitis caused through angiotensin-converting enzyme-2 (ACE-2) receptors forming the unifying theme between COVID-19 infection and thrombosis phenotypes both local and systemic. Prolonged immobilization in COVID results in the Virchow’s triad of endothelial injury, hypercoagulability and blood flow stasis. Coagulopathy appears to be related to thrombo-inflammation and not intrinsic viral activity. Thrombosis and not atherosclerosis is the guiding pathophysiology behind CIC and is

Introduction
Coronavirus disease 2019 (COVID-19), a highly infectious disease caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), usually has mild to moderate course (~80% of cases) but can become severe or critical in approximately 15% and 5% of cases, respectively. COVID-19 has primarily affected the adult population, with very few cases reported in children (<14 years). CIC is a common complication associated with high morbidity and mortality.

A virtual survey (N=810 physicians) conducted by the Indian Academy of Advance Medical Education (AAME) core expert panel showed that 86% of the respondents considered COVID-19 as an important risk factor for deep vein thrombosis (DVT) in hospitalized patients. Venous thromboembolism (VTE) complicates the disease manifestation and presents mainly as pulmonary embolism (PE) and stroke; arterial thrombosis is less common.

Currently, there is no agreement regarding CIC management in the various guidelines. Till date there is no clear cut consensus on the use of oral anticoagulants, especially novel oral anticoagulants (NOACs), in pre COVID (onset of symptoms to confirmed diagnosis), during COVID (hospitalized or under home isolation) and post-COVID situation.

Methodology
This consensus was developed following a series of five symposia held virtually across India in the month of May 2021. The series of symposia were attended by twelve eminent experts from the field of cardiology, pulmonology, critical care, nephrology, neurology and endocrinology. The expert panel in each symposium considered national and international guidelines on management of CIC, available literature and their own clinical experience while formulating this consensus. Available literature in English language was retrieved from Medline and Google Scholar using Boolean operators ‘and/or’ for key words like COVID-19, coagulopathy, anticoagulants, novel oral anticoagulants, NOAC, direct oral anticoagulants or DOAC. Themes on the use of NOACs in CIC that most experts concurred with were accepted as consensus.

HK Chopra¹, Tiny Nair², CK Ponde³, Subhash Kaul⁴, Yatin Mehta⁵, Agam Vora⁶*, Pinaki Mukhopadhyay⁷, PB Jayagopal⁸, Mrutyunjay Behera⁹, Rahul Patil¹⁰, Mahesh Deshpande¹¹, R Anantharaman¹²

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The clinical presentation of CIC resembles a highly hypercoagulable state and associated with severe morbidity and mortality. Major complications in Asian COVID-19 patients include venous complications like DVT (ultrasound confirmed lower limb DVT has been reported in 25-53% cases), and VTE (25% to >85% of the cases). Of the VTE, PE is the most common (computed tomography [CT] confirmed PE has been reported in 40% of cases), significantly more prevalent in younger than older patients (20.5% vs. 14.3%; P < 0.05) and a common cause of death in COVID-19. Acute ischemic stroke (AIS), a serious neurological complication after SARSCoV-2 infection, has been reported in 1.6% of patients (N=1,916) visiting emergency department or hospitalized for COVID-19. Arterial thrombosis is less common in COVID-19 and seen in approximately 3.7% of cases. NOACs cannot be prescribed to patients with mechanical heart valves, severe renal (eGFR <15 mL/min) and in patients with end stage renal disease (ESRD) and/or hepatic impairment.

Role of NOACs in CIC

Four NOACs have been approved so far by the U.S. Food and Drug Administration (FDA), dabigatran, rivaroxaban, apixaban, and edoxaban. Of these, dabigatran is a direct thrombin inhibitor while the other three are direct inhibitors of coagulation factor X. Antifactor Xa agents also have antiviral properties because Factor Xa cleaves SARS-CoV-19 spike proteins and facilitates the entry into the cell. So, using anti-factor Xa agents can play dual role of anticoagulation and probably act as antiviral agents. Of these, fondaparinux needs careful monitoring due to high bleeding risk (HBR). LMWH is usually prescribed in hospitalized patients.

There is abundant literature and real world evidence to prove the efficacy and safety of NOACs in reducing thrombotic risk, VTE, stroke, and PE without increasing bleeding risk. The ARISTOTLE, RE-LY, ENGAGE-AF and ROCKET-AF studies proved the efficacy and safety of NOACs in preventing major thrombotic complications but without increasing bleeding risk. These benefits of NOACs have been concluded through various systematic reviews and meta-analysis of randomized trials as well. Also, NOACs have been found to be effective and safe in Asian population.

NOACs are preferred anticoagulants for extended thromboprophylaxis because of patient adherence and compliance. A review reported that doctors are increasingly using NOACs for extended post stroke thromboprophylaxis based on recommendations of guidelines and also because of improved adherence with these drugs. Systematic review of cost-effective analysis show that NOACs are cost effective drugs for extended thromboprophylaxis.

NOACs can be safely co-administered with most anti-viral drugs (remdesivir, favipiravir and hydroxychloroquine) prescribed to patients with COVID-19; and with caution along with tocilizumab (Table 1).

Patients taking NOACs before the diagnosis of COVID-19 can continue their medication post diagnosis as well. No evidence was found to be available for the use of any form of anticoagulation in the pre-COVID diagnosis phase (onset of symptoms to positive RT-PCR report). NOACs are generally not indicated in hospitalized patients. NOACs cannot be prescribed to patients with mechanical heart valves, severe renal (eGFR <15 mL/min) and in patients with end stage renal disease (ESRD) and/or hepatic impairment.

Comparative clinical advantages of rivaroxaban in CIC

Of the four NOACs, rivaroxaban is the most studied, effective, and

### Table 1: Comparison; rivaroxaban, apixaban and dabigatran

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absorption</strong></td>
<td>Rapid</td>
<td>3-4 hours</td>
<td>Rapid</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>66% without food Up to 100% with food</td>
<td>50%</td>
<td>6%</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>5-9 hours(young) 11-13 hours (elderly)</td>
<td>12 hours</td>
<td>12-17 hours</td>
</tr>
<tr>
<td><strong>Protein binding</strong></td>
<td>92-95%</td>
<td>87%</td>
<td>35%</td>
</tr>
<tr>
<td><strong>Liver metabolism</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Renal excretion</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Effect of diet</strong></td>
<td>Peak levels attain at 3 h on fasting and 4 h with food. Factor Xa inhibition higher with food</td>
<td>No effect on exposure</td>
<td>Delays absorption; time to reach peak level extends to 4 h</td>
</tr>
<tr>
<td><strong>Effect of body weight</strong></td>
<td>Weight &lt; 50 kg have 24% increased exposure &amp; weight &gt; 120 kg have 24% reduced exposure</td>
<td>Weight &lt; 50 kg have 20-30% increased exposure &amp; weight &gt; 120 kg have 20-30% reduced exposure</td>
<td>None</td>
</tr>
<tr>
<td><strong>Effect of renal impairment</strong></td>
<td>Similar increase in exposure with moderate or severe renal impairment</td>
<td>No effect on peak concentration. Increase in exposure of 16, 29, and 44% for creatinine clearance of 51–80, 30–50, and 15–29 ml/min, respectively.</td>
<td>Severely impaired; 6 times higher exposure with half-life 28 h</td>
</tr>
<tr>
<td><strong>Effect of hepatic impairment</strong></td>
<td>Significantly increased on exposure with Child-Pugh classification B</td>
<td>No change in exposure with Child-Pugh classification A or B</td>
<td>None with Child-Pugh classification B</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Once daily</td>
<td>Twice daily</td>
<td>Twice daily</td>
</tr>
<tr>
<td><strong>Adverse drug reactions</strong></td>
<td>&gt;10% haematologic and oncologic haemorrhage; 1–10% pruritus, abdominal pain; &lt; 1% angioedema, cholestasis</td>
<td>&gt;10% haematologic and oncologic haemorrhage; 1–10% haematuria, episcleritis; &lt; 1% hypersensitivity reaction, haemotoma</td>
<td>&gt;10% gastrointestinal symptoms (like dyspepsia); 1–10% gastritis, esophagitis; &lt; 1% allergic oedema, thrombocytopenia</td>
</tr>
<tr>
<td><strong>Cost effectiveness compared to VKA</strong></td>
<td>90%</td>
<td>81%</td>
<td>None</td>
</tr>
<tr>
<td><strong>Drug interactions with commonly used medications to treat viral load</strong></td>
<td>No drug interactions with remdesivir, favipiravir and hydroxychloroquine; and can be given with tocilizumab along with careful clinical monitoring</td>
<td>No drug interactions with remdesivir, favipiravir and hydroxychloroquine; and can be given with tocilizumab along with careful clinical monitoring</td>
<td>No drug interactions with remdesivir, favipiravir and tocilizumab; dose adjustments required with hydroxychloroquine</td>
</tr>
</tbody>
</table>

**Note:** edoxaban is not compared as it is not available in India at the time of writing this consensus

**Key highlights of the table:** Rivaroxaban has specific clinical advantages: No pill load (single pill, once daily dose); No bill load (cost effective); No memory load (easy adherence to once daily); No risk load (at optimized dose); No morbidity/mortality load
emergent NOAC that can be used without fear of drug interactions and bleeding (Table 1). 38,55-59

Rivaroxaban been prospectively studied at reduced dose in renal impaired patients. 46 In patients with ESRD and compromised renal function, rivaroxaban 15 mg once daily dose is found to be superior to apixaban 2.5 mg twice daily dose. 50-52 Also, it is much easier to transition from rivaroxaban to LMWH and vice versa than with apixaban. 52

**General Considerations**

**Diagnosis and laboratory monitoring of CIC**

**Characteristic laboratory findings in CIC**

The understanding of CIC is slowly developing and therefore there is no clear-cut definition for this hypercoagulable state in COVID-19. 27 However, significantly high thrombosis markers, notably, elevated D-dimer levels and fibrin/fibrinogen-degradation products, raised inflammatory markers like C-reactive protein (CRP) and raised immunological markers such as interleukin (IL)-6 are the hallmark of laboratory findings in CIC. 47,63

However, other markers of disseminated intravascular coagulation (DIC) are not raised. 27 Prothrombin time (PT) and activated partial thromboplastin time (aPTT) are only mildly prolonged and platelet counts are either normal or mildly low. 47,63

Coagulopathy appears to be biphasic in some cases; in phase 1 the thrombotic events are associated with longer PT and higher D-dimer levels whereas phase 2 is characterized by higher bleeding with decreasing fibrinogen and D-dimer and longer duration of hospital stay. 64 However, bleeding in most COVID-19 patients is due to inconstant anticoagulation use, thereby stressing the need to monitor anticoagulation in these patients who are actually more thrombosis prone and not bleeding prone. 64

The French multicenter CLOTVID retrospective study showed that high white blood cells (WBCs) (≥12.0 G/L), D-dimers (≥3,000 ng/mL), prothrombin time ratio >1.05 and ferritin levels (≥480 μg/L) at admission in noncritically ill COVID-19 patients are highly predictive of PE and PE should be suspected in these patients and investigated. 55

Key points on diagnosis and monitoring of CIC

1. D-dimer, PT, aPTT, IL-6, fibrinogen and CRP should be done for diagnosing and monitoring of coagulopathy.
2. Clinicians should remain alert regarding follow-up because many patients, especially young patients with no previous risk factors, often develop a cytokine storm around second week (Day 7-9) and therefore thrombosis and inflammatory markers (at least D-dimer and CRP) should be repeated every 48-72 hours in mild to moderate cases and daily in severe cases.

**Timing and intensity (prophylactic or therapeutic) of anticoagulation post COVID-19 diagnosis**

Emerging data suggest there is a survival advantage for those patients with COVID-19 who receive prophylactic anticoagulant therapy within 24 hours of admission. 56 Early prophylactic anticoagulation was associated with a significantly decreased risk of 30-day mortality (by 27%) and in patient mortality (by 31%) in moderate disease patients with no increase in bleeding risk. The benefit was also seen in severe disease. 66

Anticoagulation should be started as soon as possible in all COVID-19 patients requiring anticoagulation, irrespective of the management setting.

**Key points on timing and intensity of anticoagulation for CIC**

Anticoagulant treatments should be started within 24 hours of COVID-19 diagnosis as this is found to reduce mortality in severely affected COVID-19 patients.

**Overview of CIC scenarios considered for consensus**

The experts considered four main scenarios of CIC while formulating the consensus:

- **Two hospital care settings**
  - A. Use of NOAC during prolonged hospital stay (in wards/non-critical care)
  - B. Use of NOAC in ICU (critical care) setting (including special considerations for PE, stroke)

- **Two home care settings**
  - C. Use of NOAC in outpatient/home isolation care
  - D. Use of NOAC in post-hospital discharge care

The experts formulated the consensus on the use of NOACs in CIC in the above four scenarios based around five main themes: indications, duration of therapy, co-administration, individualization and contraindications.

**Managing CIC in hospitalized care setting**

Anticoagulation in CIC is guided by disease severity, thromboembolic risk and bleeding risk (Figure 1). 11 There is not much awareness about risk stratification in COVID positive patients. The usual risk scores for VTE, bleeding and DIC can be used while planning anticoagulation therapy. 11 A position statement from India recommended PADUA model for VTE risk (≥4 as high VTE risk), HAS-BLED score (≥3 as HBR) and ISTH-SIC score for DIC risk (≥5 as high DIC). 11

The algorithm in Figure 2 is intended to provide guidance for prophylactic and therapeutic anticoagulation for adult COVID-19 patients admitted to hospital. 10 The same algorithm has
been suggested in all national59,9–12 and international13–21 guidelines. All COVID-19 positive patients admitted to hospital should receive anticoagulation, unless contraindicated (e.g. severe thrombocytopenia, HBR or active hemorrhage).

A. Use of NOAC during critical care (in ICU setting)

General considerations
All patients presenting to critical care in COVID-19 era should undergo RT-PCR testimmediately, followed by high resolution computed tomography (HRCT) Chest, pulmonary CT angiography, CT Brain, or high pressure ultrasound of leg veins as required.10,53 The usual risk scores can be applied to assess thrombosis, VTE and bleeding risk.11 The management of patient in critical care remains same irrespective of the COVID-19 status.10,67 However, if patient is COVID positive, then the patient needs to be treated in isolation in COVID-ICU and the treatment is superimposed by COVID infection related and CIC related considerations.10,14 Close monitoring of D-dimer, CRP, and fibrinogen is required.10,14,67

The proposed algorithm (Figure 2) that is accepted by most guidelines, recommends that therapeutic anticoagulation should be provided with LMWH in critically ill patients with high risk of thrombosis, or continued hypoxia or rising D-dimer levels or D-dimer persisting ≥5000 ng/mL.53

Enoxaparin is the most commonly used LMWH and its dose should be given as per weight and glomerular filtration rate (GFR) in patients with VTE.

- o ≥50 mL/min=1 mg/kg subcutaneously daily
- o 40-49 mL/min=0.6 mg/kg subcutaneously daily
- o 30-39 mL/min=0.5 mg/kg subcutaneously daily
- o 20-29 mL/min=0.4 mg/kg subcutaneously daily

According to the usually accepted CIC algorithm (Figure 2), NOACs are not indicated in critically ill patients while they are being treated in ICU. NOACs should only be started in patients anticipating discharge.52 On the other hand, according to a position statement from India, therapeutic dose of LMWH, UHF or NOACs should be given to critically ill patients with LBR but high DIC risk. This position statement also recommended intermediate dose prophylaxis (higher than prophylactic but lower than therapeutic) with LMWH or UHF in critically ill COVID-19 patients with low thrombosis risk and high VTE risk,11 and prophylactic dose of LMWH, UHF or NOACs may be given in critically ill patients with HBR or LBR with low VTE and DIC risk.11 The experts concurred that the generally accepted algorithm for anticoagulation should be followed and opined that NOACs have no role in anticoagulation management in critical care.

CIC in PE: General considerations
COVID positive patient population specifically at high risk of developing PE include: males, African Americans, obese, having symptoms such as chest pain and dyspnea; on mechanical ventilation or receiving convalescent plasma (contains procoagulant factors); requiring high fraction of inspired oxygen; high or rising D-dimer and CRP levels; or severe lesions in lung as seen on HRCT.67 Traditional PE risk factors such as diabetes, hypertension, coronary artery disease, chronic heart failure do not seem to increase PE risk in COVID positive patients.67

The French multicenter CLOTVID retrospective study showed that high white blood cells (WBCs) (≥ 12.0 G/L), D-dimers (≥ 3,000 ng/mL), prothrombin time ratio >1.05 and ferritin levels (≥ 480 µg/L) at admission in noncritically ill COVID-19 patients are highly predictive of PE and PE should be suspected in these patients and investigated.65

The experts opined that all of the imaging tests available, HRCT or a pulmonary CT angiogram is effective in diagnosing PE and CIC. However, these tests should be done only if there is a high clinical suspicion, cytokine storm and high inflammatory markers or persistent hypoxia.

Anticoagulation in PE
While the treatment of PE remains the same irrespective of COVID status, anticoagulation for PE prevention and management needs a more aggressive approach in COVID positive patients because of high CIC related fatality and mortality.11,15,16,67

Preventive strategy: prophylactic anticoagulation in ICU
In an ICU setting, empiric use of intermediate (only according to the Indian posiition statement)11 or therapeutic dose anticoagulation with LMWH should be instituted as discussed under critical care.19,53

Management strategy: therapeutic anticoagulation in ICU
Anticoagulation management in PE should be individualized based on patient’s condition, level of PE risk, and whether there are any contraindications for anticoagulation.13,67 Patients who cannot undergo anticoagulation can be treated as usual with Inferior Vena Cava (IVC) filters;13 systemic thrombophrophylaxis or with open or percutaneous thrombectomy (for patients with sustained hypotension on LMWH),13,67 catheter-directed thrombolysis (in right ventricular strain or myocardial necrosis). NOACs have no role in therapeutic anticoagulation.
in patients with PE being managed in ICU setting.\textsuperscript{13,66} The therapeutic doses of LMWH during hospitalization is as discussed under critical care section.

CIC in stroke: General considerations

Most of the strokes in COVID-19 positive patients are of undetermined etiology (48.3%) but strokes due to large artery atherosclerosis (36.6%), small vessel occlusion (10%) and cardioembolic strokes (5%) have also been reported.\textsuperscript{69} In patients with asymptomatic or mild COVID-19, stroke is usually not related to CIC but to underlying pre-existing stroke risk factors such as atrial fibrillation, intracranial atherosclerotic disease, DVT, diabetes, etc.\textsuperscript{26} In patients with moderate to severe COVID-19, CIC is the underlying cause of stroke. Pathophysiology of CIC in stroke is same as that enumerated for PE and CIC in general.\textsuperscript{79}

Though mucormycosis related fatal strokes had been reported before the COVID-19 era,\textsuperscript{71} but with the advent of COVID-19, mucormycosis is being increasingly seen in susceptible patients (those with diabetes, injudicious steroid use, and immunocompromised).\textsuperscript{72}

The basic treatment of stroke remains the same, irrespective of the COVID status\textsuperscript{10} except that COVID protocol are followed in COVID positive patients. The panelists opined that in patients with brain edema and bleedingcryoprecipitates (usual treatment of brain edema/bleeding) may enhance coagulopathy. So fibrinogen levels are tested to guide treatment decisions.

Anticoagulation for ischemic stroke in COVID era

Preventive strategy: prophylactic anticoagulation in ICU

Primary stroke prevention is based on anticoagulation prophylaxis as detailed in the critical care section. All attempt should be made to prevent stroke recurrence by optimizing and individualizing treatment with antihypertensives, lipid-lowering agents, antiplatelets, and anticoagulants based on patient profile.\textsuperscript{14}

Management strategy: therapeutic anticoagulation in ICU

Patients with moderate to severe disease being managed in ICU should be given intermediate or therapeutic LMWH with very close monitoring in ICU.\textsuperscript{9}

Consensus on use of NOAC for managing CIC in ICU

NOACs have no role in anticoagulation management in hospitalized critically ill patients in ICU.

B. Use of NOAC during prolonged hospital stay (in wards/non-critical care)

Patients who are hospitalized but not critically ill are managed with prophylactic doses of LMWH while hospitalized and the dosing is guided by body mass index (BMI) and creatinine clearance.\textsuperscript{53} High dose prophylaxis is required only if D-dimer ≥ 2,000-3,000 ng/mL.\textsuperscript{19} Bikdeli et al (2020) also note that all non-critical hospitalized patients with PE risk factors should be treated with prophylactic LMWH.\textsuperscript{19}

A position statement from India noted that clinicians may use NOAC in hospitalized patients (in wards) based on patient’s bleeding and VTE risk.\textsuperscript{11}

The experts noted that stroke or PE patients who were stabilized in ICU and then sent to wards should be continued on prophylactic anticoagulation with LMWH or UFH.\textsuperscript{9}

However, the experts concurred that during the second wave of COVID-19 pandemic in India, many patients required prolonged hospital stay to manage their symptoms or comorbidities. Based on the position statement by Gnanaraj et al (2020) and their own clinical experience, the experts opined that NOACs, particularly rivaroxaban may be started in these non-critical hospitalized patients if they do not have comorbidities that put them at high risk of thrombosis, bleeding or embolism. However, the experts opined that since CIC is a dynamic entity, clinicians should carefully and daily monitor these patients on NOACs as they may require to switch the patients back to LMWH anytime during the hospital stay. The usual risk scores can be applied to assess thrombosis, VTE and bleeding risk.\textsuperscript{33} Other tests such as echocardiography, and chest X-ray may be done as required.

Consensus on the use of NOAC in non-critical hospitalized patients

NOAC use in non-critical hospitalized setting is individualized based on patient profile:
1. NOACs may be used in non-critical COVID-19 positive patients who are undergoing prolonged hospitalization to manage their symptoms or comorbidities

NOACs can be continued as long as patients have LBR, low VTE and DIC risk
• Patients should be monitored carefully on a daily basis and switched back to LMWH if required.
2. NOACs are not indicated in patients who were initially critically ill (including PE and stroke patients), stabilized in ICU and then shifted to ward. These patients will continue on LMWH or UFH, as started in ICU, during their stay in ward.
3. Of the NOACs, rivaroxaban is preferred due to its clinical benefits (easier transition to LMWH and vice versa; less fear of drug interactions and bleeding, and better efficacy in compromised renal function), and convenient once daily dosing.

Home care settings

C. Use of NOAC in outpatient/home isolation care

COVID-19 positive patients under home isolation should be carefully monitored with thrombotic and inflammatory markers. If their markers are not high, they do not need anticoagulation.\textsuperscript{8,11} However, if these patients were being managed with NOAC for their comorbidities prior to COVID-19 diagnosis, they can continue to take NOAC post COVID-19 diagnosis as well.\textsuperscript{52} Careful monitoring should continue as CIC is dynamic and they may need to be shifted to hospital or on LMWH at home.

Patients with mild COVID-19 disease in home isolation have a high risk of VTE (including PE/stroke) if they have comorbidities like ischemic heart diseases, atrial fibrillation, diabesity, DVT or prior VTE episode, recent surgery, prolonged immobilization, or recent history of acute coronary syndrome (ACS).\textsuperscript{26} These COVID-19 positive patients not admitted to hospitals but at risk of VTE, can be given a prophylactic dose of NOAC, preferably, rivaroxaban 10 mg daily for 31 days or 39 days.\textsuperscript{73} The panelists opined that NOACs can be prescribed in home isolated patients with VTE risk factors, especially if they cannot take subcutaneous LMWH. Careful monitoring with thrombotic and inflammatory markers should continue as CIC is dynamic and they may need to be shifted to hospital or on LMWH at home.

Alternatively, in view of the panelists, patients in home isolation who had minor stroke, but no atheroscleromatic plaque, can be given NOACs instead of aspirin for secondary prevention.\textsuperscript{74}
Coagulopathy

Indications
1. NOACs are ideal therapeutic option for outpatient settings (during home isolation or extended post hospital discharge prophylaxis).
2. During the second COVID-19 wave in India, many patients who should have been hospitalized were getting oxygen therapy at home. So, such patients should be considered as hospitalized. NOACs can be given to these patients instead of LMWH if they have high thrombotic risk (based on D-dimer [most important], CRP, IL-6, fibrinogen etc.)
3. COVID-19 positive patients can be prescribed NOACs during prolonged hospital (wards) stay if they have low thrombosis and low bleeding risk.
4. NOAC may be useful in situations where it is difficult to differentiate between COVID19 induced and heparin induced thrombocytopenia.
5. Of the NOACs, rivaroxaban can be an ideal choice because of abundant literature on its efficacy and safety, convenient once daily dosing, negligible or no drug interactions with other drugs commonly prescribed to decrease viral load and cost effectiveness. Rivaroxaban should be taken with a full stomach to ensure bioavailability and improve adherence.

Co-administration with antivirals
1. NOACs can be safely co-administered along with medications commonly prescribed to decrease viral load (remdesivir, favipiravir and hydroxychloroquine) and with, caution along with tocilizumab.15,26

Individualization of therapy
1. Anticoagulation with NOACs should be individualized. Individualization should be based on:
   - Comorbidity status, application of any kind of risk stratification (bleeding, VTE, DIC), VTE prediction, and use a complimentary D-dimer level
   - Patient phenotype: simultaneous virulence and cytokine storm (present early with high thrombotic and inflammatory markers) or successive virulence followed by cytokine storm (thrombotic and inflammatory markers rise later, often in second week)

Contraindications
1. NOACs are not indicated in the pre-COVID phase.
2. NOACs are not indicated in patients requiring therapeutic anticoagulation for VTE like PE, or stroke or for patients being treated in ICU settings
3. NOACs cannot be prescribed to patients with mechanical heart valves, severe renal (eGFR <15 mL/min and in patients with ESRD) and/or hepatic impairment.26,36,38

Consensus on the use of NOAC in outpatient/home isolation care
NOAC use in home isolated setting is individualized based on patient profile:
1. NOACs do not have a role in home isolated COVID-19 positive patients with low inflammatory and thrombotic markers and no VTE risk.
2. Patients who were on NOACs before COVID-19 diagnosis for their comorbidities can be continued on NOACs post diagnosis but with strict monitoring of inflammatory and thrombotic markers. The duration of NOAC therapy should be guided by the treatment guidelines of their comorbid condition.
3. Though LMWH is preferred in home isolated COVID-19 positive patients with VTE risk factors, NOACs may be used safely if patients are unable to take subcutaneous dosing, but with strict monitoring of inflammatory and thrombotic markers. These patients should have LBR, low VTE and DIC risk
   - Dose and duration: Prophylactic dose of NOAC, preferably, rivaroxaban 10 mg daily should be given for 31 days or 39 days.

D. Use of NOAC in post-hospital discharge care
A retrospective study showed that in COVID-19 positive patients discharged without anticoagulation, the cumulative day 30 post discharge incidence of thrombosis and VTE was 2.5% and 0.6%, respectively and that of major and minor hemorrhage was 0.7% and 2.9%, respectively.31 Therefore, critically ill patients who recovered from COVID-19 and had a documented VTE are usually given a minimum of 3 months of anticoagulation (LMWH or NOAC if LMWH cannot be given in home setting) post discharge.32 Patients with large infarcts are first stabilized in ICU and prophylactic anticoagulation is started. Then after two or more weeks, once the patient is stable, secondary prevention is given based on etiology. NOACs can be given for secondary prevention after patient is discharged.28

Patients who develop post-COVID thrombocytopenia after discharge can also be treated with NOACs.34

Consensus on extended anticoagulation for COVID-19 patients post-hospital discharge
NOAC use in post hospital discharge setting is individualized based on patient profile:
1. Decisions regarding post-discharge prophylactic anticoagulation with NOAC is based on patient’s thrombotic and bleeding risk.
   - Individualization should be based on comorbidity status, application of any kind of risk stratification, VTE prediction, and use a complimentary D-dimer level
2. Patients who develop post-COVID thrombocytopenia after discharge can also be treated with NOACs.

3. Duration of therapy: Prophylactic dose of NOAC, preferably, rivaroxaban 10 mg daily should be given for 31 days to 39 days or 3 months as required.
   - Patients with documented VTE are usually given a minimum of 3 months of anticoagulation (LMWH or NOAC if LMWH cannot be given in home setting) post discharge.

Overall consensus on the use of NOAC in CIC
The overall consensus on the use of NOACs is summarized in Table 2 under four headings: indications, co-administration, individualization and contraindications.

Future prospects
There is conflicting information on the use of NOACs in ICU and hospitalized settings. Therefore, there is felt need to conduct head to head trials to compare NOACs with LMWH in hospitalized patients. Also, more head to head trials comparing the various NOACs in the different clinical settings of CIC will help to understand their individual benefits and risks.

Conclusion
We hope that the consensus arrived on the use of NOACs in CIC will set the path forward for better management of these patients. Except for serious COVID-positive patients in ICU settings, NOACs have an important place in CIC management in both hospitalized and home settings. Contrary to popular belief, we raise an important point that NOACs can be used in hospitalized non-serious ward patients with CIC. In home settings, NOACs have an accepted place as extended anticoagulation to reduce CIC risk post hospital discharge. However, we also recommend that NOACs can be given to COVID-positive patients being home managed if they have high thrombotic risk but LBR. Of the NOACs, rivaroxaban can be an ideal choice because of proven efficacy and safety, convenient once daily dosing, negligible or no drug interactions with other drugs commonly prescribed to decrease viral load and cost effectiveness. It is therefore finally concluded as a consensus statement, that NOAC has come to stay in management of the CIC at home and in hospitalized patients. Usefulness of rivaroxaban has enormous data based logistics as superior selective Xa antagonist with promising potentials of morbidity and mortality benefits in COVID-inflicted
coagulopathy management strategy.

References


Xerostomia: A Neglected Symptom of COVID-19

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Sir,

Covid-19 is known to be associated with a myriad of symptoms. While the cardinal symptoms of fever, dyspnoea or cough are well known to all, there are a host of rare symptoms too, which are being revealed with time. These symptoms may be the source of considerable discomfort to the patient. We here describe one such rare manifestation of Covid-19 infection.

A 70 year old male patient (one dose of Covid vaccine received seven days ago) developed fever and cough. The pulse oximeter reading was 97% to start with. From the second day of illness, the patient started complaining of severe dry mouth, for which he had to take multiple glasses of water of severe dry mouth, for which he had no thyroid disorder. His RT-PCR did not use tobacco in any form and anti-allergic or diuretic medication. He was not on any tricyclic antidepressant, had to take multiple glasses of water of severe dry mouth, for which he had no thyroid disorder. His RT-PCR did not use tobacco in any form and anti-allergic or diuretic medication. He was not on any tricyclic antidepressant, had to take multiple glasses of water daily. 1 Only 20% of their patients had persistent xerostomia more than three weeks after the onset of illness. Till now, xerostomia has not been strongly linked with outcome or severity of the illness.

The exact reason for xerostomia in Covid-19 is still not known. But primary research has revealed that the ACE2 receptor, which is used by the SARS-CoV2 for cellular entry, is abundantly present in the epithelium of salivary glands. Thus, salivary glands may be one of the first sites of viral entry in the human body. The Covid-19 virus is found in the saliva in large quantities. The mucotropic effects of the virus may be responsible for alteration in salivary production and/or flow. Also, virus induced inflammation of the salivary glands may be another potential mechanism of hyposalivation.

Recently, another proposed mechanism of xerostomia is SARS-CoV2 induced autonomic dysfunction.

Xerostomia is responsible for gustatory dysfunction, as found in our patient. In an online questionnaire-based study from Israel, it was seen that more than 50% of the Covid patients complained of some degree of xerostomia. They also frequently complained of "burning mouth" as an association. However, this latter symptom was not reported by our patient. But such high prevalence of xerostomia had not been reported among Covid patients elsewhere.

We present this case to sensitize clinicians about this rare symptom of Covid. On one hand, this can be an early indicator of the infection, even before other symptoms appear. On the other hand, this is one symptom which causes considerable distress to the patient and the treating clinician must enquire about it and try to alleviate it with artificial saliva or mucosal moisturizer.

References


Rare Multisystem Inflammatory Syndrome in Young Adult after COVID-19 Immunization and Subsequent SARS-CoV-2 Infection

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Sir,

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, first identified in China and the resultant pandemic is an ongoing health crisis in the country. One of the most intriguing features of this pandemic is a relatively benign course in children, either due to lack of detection or a relatively mild disease in this age group.

In the second half of 2020, an unfamiliar syndrome termed “Multisystem Inflammatory Syndrome in Children” (MIS-C) was first reported in the United Kingdom (UK) and subsequently worldwide in children and adolescents with likely correlation with SARS-CoV-2 infection. The clinical picture to this entity seen to overlap with known syndromes like toxic shock syndrome (TSS), Kawasaki Disease (KD), and secondary hemophagocytic lymphohistiocytosis (SHLH)/macrophage activation...
syndrome (MAS) included fever, involvement of two or more organ systems, with serological evidence of inflammation and evidence of COVID-19 infection.4

We touch upon another unique entity known as Vaccine-associated enhanced diseases (VAED) which occurs in individuals who have received prior immunization and who are subsequently infected with the pathogen that the vaccine is meant to protect against.5

Herein we report our recent experience in managing a previously COVID vaccinated 19-year-old female with active SARS-CoV-2 infection presenting with a hyperinflammatory syndrome consistent with MIS-C and VAED

A 19-year-old female medical student presented to an emergency room with complaints of chest heaviness and vomiting. She reported past 3 days of low grade fever with core throat. She received both doses of COVID vaccines around 7 weeks before this presentation. On presentation to the emergency room (ER), she was afebrile and pulse was feeble. Her rapid card test for COVID-19 was found to be positive. She collapsed in ER room, had hypotension with acute hypoxia. She was aggressively resuscitated, was intubated and initiated on mechanical ventilation.

Laboratory investigations revealed leukocytosis with acute kidney injury with raised cardiac enzymes and very high inflammatory markers (Table 1). Her COVID-19 PCR from nasopharyngeal swab and COVID-19 IgG quantitative antibody (>400AU/mL) from serum were both positive. The patient was shifted to the intensive care unit (ICU) for further management. She was managed as MIS-C in view of inflammatory multi-system organ involvement. An Echocardiography of inflammatory multi-system organ involvement. She continued to deteriorate, had persistent hypotension with anuria, required high ventilator requirement. She developed bradycardia followed by asystole. Patient could not be revived back and was declared dead.

Vaccine-associated enhanced diseases (VAED) are altered presentations of clinical infections involving patients exposed to a wild-type pathogen after having prior immunized for the same pathogen.6

VAED may present as severe illness or as modified characteristics different from the pattern of illness in unvaccinated patients and may involve multiple organ systems. Classic examples include atypical measles and enhanced respiratory syncytial virus (RSV) occurring from infection in patients after administration of inactivated vaccine for these pathogens.7

On the other hand, MIS-C is considered a post-infectious, possibly immune-mediated systemic disease of unclear mechanism and pathogenesis. Current evidence points towards an acute hyperinflammatory reaction suggesting activation of the innate immune response with massive pro-inflammatory production. SARS-CoV-2 may behave like a superantigen similar to the staphylococcal enterotoxin B receptor and costimulatory molecule CD28, thus mediating Toxic Shock Syndrome like condition.8

Given the broad spectrum of illness associated with SARS-CoV-2 and a widespread occurrence of MIS-C in children and adolescents, there is a theoretical concern of disease enhancement after vaccination against SARS-CoV-2. The Brighton Collaboration Case Definition for MIS-C or Adults was recently published for evaluation of patients after SARS-CoV-2 immunization and the researchers were concerned about prior vaccination with SARS-CoV-2 triggering MIS-C. MIS-C may also be considered AEFIs of special interest in relation to COVID-19 vaccines.9

Most features of our patient’s presentation were consistent with MIS-C, including hypotension, high inflammatory markers and cardiac dysfunction. Our patient was also recently vaccinated with high COVID IgG antibody load and subsequently developed MIS-C with positive nasopharyngeal swab with SARS-CoV. We believe the temporal association after immunization with COVID-19 is important given the theoretical possibility of MIS-S after vaccination.

In this country, vaccination for above 18 years of age has recently been started, our patient received the vaccine on account of being a medical student entering medical school. What we describe here may turn out to be a new condition of an inactivated vaccine-induced multisystem inflammatory syndrome possibly due to over-reaction of immune system primed with the vaccine reacting strongly to a fresh viral infection. The evaluation of this potential enhanced event following immunization has an impact on SARS-CoV-2, given the urgent universal need for safe and effective vaccines particularly in children.

References


COVID-19 Precipitating Vaso-Occlusive Crisis in a Patient of Sickle Cell Anemia with Avascular Necrosis of Femur

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Sir,

The recent ongoing pandemic of Corona virus disease -2019 (COVID-19) which is caused by Sars Cov-2 virus has emerged as the greatest global health problem of the century affecting almost all countries irrespective of geographical, social, demographical, and financial condition.1 The clinical picture is commonly characterized by triad of fever, cough, and shortness of breath (Covid triad) and majority (80-85%) of patients had a benign course whereas about 10% develop complications and 5% had developed critical illness. The outcome of the disease is awful among patients with co-morbidities like diabetes mellitus, hypertension but little is known with genetic diseases.

Sickle Cell Disease (SCD) is the most common genetic disease of the globe including India.2 It is characterized by anemia, jaundice, and vaso-occlusive crisis (VOC). Here we describe a case of homozygous SCD with bilateral avascular necrosis of femur presented with VOC and pneumonia caused by Covid-19 due to of its significance in the present pandemic situation in India.

AS, a 34-year-old man, was admitted to Medicine on 8/7/2021 with chief complaint of fever with generalized malaise 4 days duration, pain in long bones and joints 2 days duration and shortness of breath 1 day duration. He is a diagnosed case of Sickle cell anemia (SCA) with hydroxyurea therapy for last 2 years. He has also pain in both hip joints while walking with limping and while riding bicycle. On examination, he was febrile (100°F, pulse rate of 110/minute, Blood Pressure-110/80 mm of Hg., respiration rate-40/minute, oxygen saturation-82% at room air.

Owing to recent Covid-19 pandemic investigations for Covid-19 along with other investigations were done. Investigations showed Hb-5.0 gm%, total leucocyte count-12,270/cmm, Differential leucocyte count-N:82%, L:16%, E:2%, M-0%, B:0%, platelet count-240 thousand /μL, ESR (Westergren)-35 mm 1st hour. Biochemical investigations showed FBG-90.5 mg/dl, urea-34.0 mg/dl, creatinine-0.9 mg/dl, sodium-141.0 mEq/L, potassium-3.9 mEq/L, bilirubin-4.2 mg/dl, AST-103.0 IU/l, ALT-30.0 IU/L, Alkaline phosphatase-245.0 IU/L. Spo2 was 85.0%.

X-ray chest PA view showed ground glass appearance of lower zones and HRCT thorax showed multifocal patchy ground glass opacities diffusely on bilateral lung parenchyma (CORADS-5) with CT severity index of 18/25. X-ray of both hip joints showed avascular necrosis both head of femur (Figure 1). Rapid Antigen test and RT-PCR for Covid-19 were negative. Biomarkers showed CRP- 118.7 mg/l (normal <3 mg/l), serum ferritin-1001.9 ng/ml (normal 68.0-434.0 ng/ml in males), D-Dimer 20.0mg/ml (normal 0-0.5mg/ml), serum LDH-769.8 IU/l, SARS-COV-2 IgM and IgG index was 0.83 and 14.9. In view of clinical features, HRCT of chest, and raised inflammatory markers, Covid-19 has been diagnosed which was further evidenced by raised antibody.

Hence, final diagnosis of SCA, with avascular necrosis with VOC and Covid pneumonia has been made. He was treated in ICU with oxygen, antibiotic, blood transfusion, and analgesics. He improved symptomatically and was discharged after 14 days.

VOC is an acute complication of SCA which has been precipitated by various viral, bacterial, and parasitic infections. During the present pandemic, Sars-Cov-2 has emerged as a new cause of VOC among the patients with SCA.3,4 The present case describes a case of homozygous SCD with AVN presented with Covid-19 induced VOC and pneumonia with recovery.

Mild clinical course with very low mortality and favorable outcome has been observed among patients of SCD with Covid which is contrary to the assumption of higher risk of adverse outcome with other co-morbidities like Diabetes.3,4 Studies from USA, UK, and France showed that the overall mortality among patients with SCD was very low i.e., 2.17%. However, no study is available from India.

Adult cases with VOC and acute chest syndrome (ACS) due to Covid-19 had been reported. In SCD, Covid-19 can potentially cause severe complication particularly pneumonia either by direct viral infection or by precipitating VOC and ACS.5 In another case series, along with Covid triad, SCD patients with Covid also presented with VOC that has been attributed to rise in interleukin-6 (II-6). It is notable that II-6 can induce VOC in SCD patients without Covid-19. Hence, II-6 blocker tocilizumab may be tried in SCD with Covid induced VOC.6 In a prospective study it has been observed that patients of SCD with Covid-19 has higher VOC than non-covid patients suggesting the causal association of Covid with VOC. Further it has been found that osteonecrosis, splenic sequestration, hepatic crisis was also more in Covid group.7

Another important consideration is osteonecrosis of head of femur which is not only a long-term complication of SCA but also a complication of Covid-19 patients with or without steroid therapy.8 Therefore, osteonecrosis requires special attention among patients of SCD with Covid-19 because it may aggravate osteonecrosis.

The mechanism of good outcome is not clearly understood. Cytokine storm has been attributed as the major cause of critical Covid. In SCA hyposplenism due to autosplenectomy is the cause of lack of hyperimmune syndrome due to Covid.9 Hydroxyurea is another probable cause of low immune response due to Covid in SCA. Studies from USA and UK showed that majority (about 50.0%) of patients of SCA with Covid were on hydroxyurea therapy which...
Round Pneumonia in Adult: A Presenting feature of COVID-19

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Sir

Round pneumonia refers to rounded or oval shaped consolidation seen on radiological investigation in pneumonia. This entity is classically described in children secondary to the infectious pneumonia caused by Streptococcus pneumoniae and H. influenzae.1 This is very rarely seen in adults. This communication highlights round pneumonia in an adult as presenting feature of Covid-19.

A 29-years-old singer male presented with high grade fever with chills and dry cough for last three days. He was completely alright before and denied any significant illness in past. He was non-smoker and denied any history of travel in recent past. Other family members were asymptomatic. On examination, he was febrile with temperature of 38.7 centigrade. There was no abnormality found on physical and respiratory examination. His blood investigations revealed normal blood counts, ESR, blood sugar, renal and liver function tests but raised c-reactive protein of 28.5 mg/L. His D-dimer, IL-6 and serum ferritin levels were all normal. He was kept in isolation at home and received oral azithromycin, doxycycline, hydroxyl chloroquine, paracetamol, vitamin C, zinc and supportive treatment for cough. He improved clinically with above therapy with improved oxygen saturation. A repeat chest x-ray after 10 days revealed complete disappearance of radiographic abnormality seen earlier (Figure 2).

Round pneumonias are infrequent presentation in adults that usually remains underdiagnosed. Contrary to the children, the infection is usually secondary to Q fever, Legionella micdadei or Rickettsia typhi and this needs to be differentiated from neoplastic lesion and other non-infectious causes i.e. round atelectasis, bronchopulmonary sequestration, bronchiolitis obliterans organizing pneumonia, Wegener granulomatosis, septic pulmonary emboli, rheumatoid nodules etc.2

Round pneumonia appears as single or multiple nodular density and predominantly occurs at lower zone as seen in present case. Cavitation is not a usual feature, however focal calcification or speculated margins may be seen. The round appearance on chest x-ray is thought to be due to an infectious process that spread from small peripheral alveoli centrifugally through intra-alveolar channels via pores of Kohn and channels of Lambert and thus explain the non-segmental distribution and round shape of the lesion.3

The gold standard for the diagnosis of Covid-19 is RTPCR as the radiographic abnormalities seen in Covid-19 are broad spectrum and there are no pathognomonic imaging findings to suggest Covid-19 pneumonia, however the chest radiology remains important tool to assess the severity and extension of lower respiratory tract infection. The usual features of Covid-19 pneumonia are peripheral bilateral ground glass opacities (GGO) with or without consolidation or crazy-paving pattern, reverse halo sign or other findings related to organizing pneumonia. Diffuse GGO with no clear distribution, isolated lobar or segmental consolidation was completely alright before and denied any significant illness in past. He was non-smoker and denied any history of travel in recent past. Other family members were asymptomatic. On examination, he was febrile with temperature of 38.7 centigrade. There was no abnormality found on physical and respiratory examination. His blood investigations revealed normal blood counts, ESR, blood sugar, renal and liver function tests but raised c-reactive protein of 28.5 mg/L. His D-dimer, IL-6 and serum ferritin levels were all normal. He was kept in isolation at home and received oral azithromycin, doxycycline, hydroxyl chloroquine, paracetamol, vitamin C, zinc and supportive treatment for cough. He improved clinically with above therapy with improved oxygen saturation. A repeat chest x-ray after 10 days revealed complete disappearance of radiographic abnormality seen earlier (Figure 2).

Round pneumonias are infrequent presentation in adults that usually remains underdiagnosed. Contrary to the children, the infection is usually secondary to Q fever, Legionella micdadei or Rickettsia typhi and this needs to be differentiated from neoplastic lesion and other non-infectious causes i.e. round atelectasis, bronchopulmonary sequestration, bronchiolitis obliterans organizing pneumonia,wegener granulomatosis, septic pulmonary emboli, rheumatoid nodules etc.2 Round pneumonia appears as single or multiple nodular density and predominantly occurs at lower zone as seen in present case. Cavitation is not a usual feature, however focal calcification or speculated margins may be seen. The round appearance on chest x-ray is thought to be due to an infectious process that spread from small peripheral alveoli centrifugally through intra-alveolar channels via pores of Kohn and channels of Lambert and thus explain the non-segmental distribution and round shape of the lesion.3

The gold standard for the diagnosis of Covid-19 is RTPCR as the radiographic abnormalities seen in Covid-19 are broad spectrum and there are no pathognomonic imaging findings to suggest Covid-19 pneumonia, however the chest radiology remains important tool to assess the severity and extension of lower respiratory tract infection. The usual features of Covid-19 pneumonia are peripheral bilateral ground glass opacities (GGO) with or without consolidation or crazy-paving pattern, reverse halo sign or other findings related to organizing pneumonia. Diffuse GGO with no clear distribution, isolated lobar or segmental consolidation...
with no GGO, discrete small nodules (centrilobular, “tree in-bud”), lung cavitation, smooth interlobular septal thickening, pleural effusion etc. are uncommon radiographic findings seen in Covid-19. Multifocal GGO of rounded morphology with or without consolidation are other radiographic presentation, however, solitary ‘typical round pneumonia’ like presentation is very unusual and not described as seen in present case.

In adults, it is important to rule out non-infectious causes especially neoplastic process mimicking round pneumonia. Malignant lesions can be differentiated by asymptomatic presentation, upper lobe location and persistence/progression on serial chest X-ray. The febrile illness presentation and response to antimicrobial agent’s points towards infectious cause, however few cases may require further workup including computed tomography or biopsy.2

References

COVID-19 Deaths: Reasons and Rationale
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Sir,

COVID-19 has affected mankind on this mother earth and caused relentless devastation and suffering everywhere. The healthcare systems and the administration have been trying their best to save every individual from the wrath of COVID-19. However, despite the best possible efforts, the mortality associated with COVID-19 is terrifying. Going by the numbers, death due to COVID-19 is more than 44 lakhs worldwide and in India it is reported to be 4.3 lakhs till date.1 It is not surprising that while nearly 21 crore people have been infected with this deadly virus so far, almost every individual on earth has felt the impact, directly or indirectly.

The second wave of COVID-19 in India in April to June 2021 came with some serious adverse events which included death in large numbers. Here are some rationales behind disproportionate deaths that unfortunately our country had to deal with:

**Paucity of Diagnostic Services and Delayed Disease Assessment**

There was constant struggle in availing health care from getting blood tests to CT scan or X-ray done. Laboratories across the country were overburdened and it took up to three days for RT-PCR test results to become available. These delays were putting many patients at risk. Very few labs were able to perform the tests necessary for COVID 19 prognostication making it harder for the treating doctors to assess the progression of the disease and assess the condition of the patient. There were several sick patients who could manage a bed in hospital but couldn’t get admitted as they didn’t have a COVID-19 report from a certified laboratory.

**Lack of availability of beds and care to the patient**

Bed shortages were huge during COVID 19. BBC news Delhi reported choking of hospitals and administration with increase in cases. Several patients had no choice but to remain at home despite severe symptoms. Lack of facility contributed to death.3 The shortages, mainly in intensive care units persisted. There was discrepancy in rapid resource allocation, lack of coordinated policies on patient triaging, administrative solecisms and in action which led to avoidable treatment delays and hence mortality.2

**Lack of ventilators**

Several states in India grappled with the shortage of ventilators as COVID-19 cases surged. It was reported to be mainly due to a slump in local manufacturing and short supply of ventilators after the initial push from the central government last year. The intensive care units in every tertiary care hospital in the current scenario do not have sufficient ventilator. The COVID-19 patients requiring ventilator during the second wave was beyond the capacity of any private or public sector healthcare system.4

**Lack of availability of oxygen within time frame**

Once they got admitted after lot of struggle to any hospital, the next snag was to arrange medicines and oxygen cylinders / associated devices which help in increasing oxygen supply to the lungs. Delayed oxygen availability was potentially another reason contributing to death. There was also black marketing of drugs and oxygen which was beyond reach of common man.2,3

**(Steroid as the culprit)**

Steroid should be used judiciously in patients whose oxygen saturation falls. Steroid has been associated with high sugar levels which lead to fungal infection and immune-suppression. In India, leaving aside metropolitan and hi-tech cities, steroidin rural areas acted like a ram-baan. However, as the number of hospitalized cases and subsequent deaths increased, unscrupulous use of steroids across the country was evident. People even started self-medicating with steroids and other drugs. Use of steroids in early stages resulted in flaring of COVID-19 which went beyond control.5

**Psychological impact on humans and death**

Social distancing was advocated by public health officials to mitigate the spread. As a result of which a chunk of society felt detached. This led to psychological influence on these people.

There were cases of sudden cardiac arrest, brain haemorrhage, myocardial infarction among young individuals which could be attributed to sudden increase in blood pressure due to anxiety.6

References
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Abridged Prescribing Information:
Composition: Each Olmesar 10/20/40 tablet contains Olmesartan 10/20/40mg. Indication: Hypertension. Dosage: Adult: 20 mg once daily when used individually, increase to 40 mg after 2 weeks of therapy if required. Children (age 6 to 16 years): 10 mg once daily for patients who weigh < 35 kg or 20 mg once daily for patients who weigh ≥ 35 kg. Increase to a maximum of 20 mg for patients who weigh < 55 kg or 40 mg once daily for patients who weigh ≥ 55 kg after 2 weeks of therapy if required. Contraindications: Hypersensitivity to Olmesar, co-administration with aliskiren in diabetic patients, 2nd and 3rd trimester of pregnancy, biliary obstruction. Special Precautions: Assess renal function, BP & volume status during initiation of therapy & dose escalation periodically thereafter. Use with caution in elderly. Children < 1 year of age must not receive Olmesar for hypertension. In patients whose renal function may depend on activity of the renin-angiotensin-aldosterone system (eg, patients with severe CHF), treatment may be associated with oliguria &/or progressive azotemia, rarely resulting in acute renal failure &/or death. Symptomatic hypotension may be anticipated after initiation of treatment in patients with an activated renin-angiotensin system, such as volume &/or salt-depleted patients. In patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or BUN may occur. Adverse Drug Reaction: Most commonly observed adverse reaction is Hypotension, Dizziness, Headache; other ADRs may be Rhinitis, Pharyngitis, Cough, Pain, Angioedema, Pruritus, Rash, Urticaria, Hyperkalemia, Hypotension & Musc spasm. Full prescribing information is available on request.
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