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FLAVEDON OD (80mg): COMPOSITION*: Each hard gelatine capsule contains-Trimetazidine hydrochloride I.P. (as extended release pellets) 80 mg & Excipients q.s. INDICATIONS*: For the treatment of Ischaemic heart disease (angina pectoris, sequelae of infarction). DOSAGE AND ADMINISTRATION*: Posology: The dose is one capsule of 80mg of trimetazidine once daily during breakfast. The benefit of the treatment should be assessed after three months and trimetazidine should be discontinued if there is no treatment response. Special populations: Patients with renal impairment. In patients with moderate renal impairment (creatinine clearance [30-60] ml/min) the recommended dose is reduced. Elderly patients may have increased trimetazidine exposure due to age-related decrease in renal function. In patients with moderate renal impairment (creatinine clearance [30-60] ml/min), the recommended dose is reduced. Dose titration in elderly patients should be exercised with caution. Paediatric population: The safety and efficacy of trimetazidine in children aged below 18 years have not been established. No data are available. Method of administration: Capsule must be taken orally without opening it, once daily i.e. one in the morning during breakfast. CONTRAINDICATIONS*: Hypersensitivity to the active substance or to any of the excipients. Parkinson disease, parkinsonian symptoms, tremors, restless leg syndrome, and other related movement disorders, Severe renal impairment (creatinine clearance < 30ml/min). WARNINGS*: This medicine is not a curative treatment for angina attacks, nor is it indicated as an initial treatment for unstable angina or myocardial infarction, nor in the pre-hospital phase or during the first days of hospitalization. In the event of an angina attack, the coronaropathy should be re-evaluated and an adaptation of the treatment considered. Trimetazidine can cause or worsen parkinsonian symptoms (tremor, akinesia, hypertonia), which should be regularly investigated, especially in elderly patients. Falls, may occur, related to gait instability or hypotension, in particular in patients taking antihypertensive treatment. Athletes: This medicine contains an active substance which may give positive reaction in doping tests. INTERACTIONS* FERTILITY* PREGNANCY*: Avoid prescription. BREASTFEEDING*: Should not be used. DRIVE & USE MACHINES*: Caution because cases of dizziness and drowsiness have been observed. UNDESIRABLE EFFECTS*: Common: dizziness, headache, abdominal pain, diarrhoea, dyspepsia, nausea, vomiting, rash, pruritus, urticaria, anemia. Rare: palpitations, extrasystoles, tachycardia, arterial hypertension, orthostatic hypotension that may be associated with malaise, dizziness or fall, in particular in patients taking antihypertensive treatment, flushing. Not known: parkinsonian symptoms (tremor, akinesia, hypertonia), gait instability, restless leg syndrome, other related movement disorders, usually reversible after treatment discontinuation, sleep disorders (insomnia, drowsiness), vertigo, constipation, ACEI (acida generalised exanthematous pustulosis), angioedema, agranulocytosis, thrombocytopenia, thrombocytopenic purpura, hepatitis. OVERDOSE* “PROPERTIES”: Trimetazidine acts as a metabolic agent, preserving the myocardial high-energy phosphate intracellular levels. Anti-ischemic effects are achieved without concomitant haemodynamic effects.

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\textit{Preference with Evidence}
Addressing Risk of Allergy following COVID-19 Vaccination in India – Reassure, Rethink and Revise

Milind Y Nadkar

The term diathesis is one of Greek origin that indicates tendency or predisposition. In the context of allergy, allergic diathesis is a vast canvas that refers to conditions ranging from very mild self-limiting illnesses to extremely severe disease that can also lead to death. The World Allergy Organization [WAO] has outlined definitions for allergy, sensitization, atopy and atopic diseases and these include life-threatening anaphylaxis, food hypersensitivity, certain forms of asthma, rhinitis, conjunctivitis, angioedema, urticaria, dermatitis, eosinophilic disorders, drug hypersensitivity, hymenoptera and insect allergies. Many of these conditions can also occur together in the same individual. The mechanisms underlying the pathogenesis of chronic allergy and allergic inflammation are multi-factorial and result from a combination of genetics and environmental influences. Apart from morbidity and mortality that are well known with them, allergies significantly impact patients’ quality of life and that of their care givers and have consequences for nations as well. Affluence and urbanization of societies is known to be associated with a rise in allergies. Experts within the country have documented the rising prevalence of allergic rhinitis and asthma in India.

Allergies have come to the fore more recently worldwide in the context of vaccination during the COVID-19 pandemic. The earliest reports of anaphylaxis post vaccination came after the use of the mRNA vaccines. All patients recovered without going into shock or the need for endotracheal intubation and no deaths were reported. Subsequently, policy makers of both the United States and the United Kingdom after weighing the benefits and risks have encouraged those with allergies to receive COVID 19 vaccination with some caveats. Our country’s current vaccination policy currently precludes those with “an anaphylactic reaction to a previous dose of a COVID-19 vaccine and immediate or delayed –onset anaphylaxis [or allergic reactions] to vaccines, injectable therapies, pharmaceutical products and food items” from receiving these vaccines.

The present issue of the journal carries an interesting and a particularly relevant paper to this country on the outcomes after any COVID-19 vaccine in patients with documented allergic diathesis by Shukla and colleagues. The authors evaluated a database with these patients 81 of whom had received one dose and 33 the second dose of a COVID-19 vaccine. The vast majority had received COVISHIELD™ while the remainder had received COVAXIN™ and negligible numbers received other vaccines. In all a total of 114 doses were given. None of the patients from the database with contraindications as specified by the Government of India developed any allergic reaction. The three adverse events [AEs] seen were in people without the contraindications but with other allergic diathesis. Two AEs were minor and self limiting while one needed treatment with an anti-histamine and could probably be attributed to polysorbate 80 allergy - a component of COVISHIELD™.

The findings of Shukla and colleagues must be viewed in the context of both strengths and limitations they present. If we were to begin with the latter, a small sample size and very few second doses taken and very few total doses [as a denominator for the AEs seen] immediately come to mind making it difficult that see how government policy can be truly influenced by this study. Secondly, the data from COVAXIN™ and the mRNA vaccines is even smaller compounding the sample size problem. Thirdly, despite having over 200 patients in the database, the small number of second doses taken [33/200] lends itself to selection bias. It is not clear if outcomes were not available for the remainder in the database or if the patients were truly vaccine hesitant. The documentation of hesitancy would have added significant value to the findings. Lastly, patients in the study classified as having a history of anaphylaxis may not necessarily have had anaphylaxis in the past as this is possibly based on their memory [recall bias] or their own understanding of the event rather than a formal classification by a specialist.

The paper though does have its inherent strengths. It is probably the first documented series in the country to have outcomes in patients with allergies and shows that none who fitted the exclusion criteria that exist for COVID-19 vaccine use actually developed an allergic reaction. This paper is hopefully one of many that will come from India in formally defining outcomes following COVID-19 vaccination in this vulnerable group of patients. Second, as the uptake of COVISHIELD™ in India is much higher than COVAXIN™ at this point in time [as also confirmed by this paper] and COVISHIELD™ is the vaccine with Polysorbate -80 and a patient in the Shukla series did have a significant reaction to the second dose, this needs to form the backbone of future allergy research and testing in such patients. This one AE has shown that allergy to a specific vaccine excipient is the likely cause of the allergy rather than vaccine itself. History taking for specific details such as allergy to radio contrast media or bowel preparations by vaccine centre staff [as done by the authors in this study] is crucial. Else, these patients would be clubbed under the broad umbrella of allergy and leaving them bereft of vaccination. Testing for allergy to Polyethylene Glycol [PEG], a key component of mRNA vaccines [whose uptake in India will likely rise...
over time] and Polysorbate 80 present in COVISHIELD™ holds the key to ensuring that patients classified as “allergic” are not denied the benefit of vaccination. This testing called as the Skin Prick Test™ using serial dilutions either of the vaccine or its components is easily possible with trained allergists as also spreading awareness among these patients.

This brings us to the next challenge which is that of trained allergists and the process of allergy testing itself. Allergists in the country are few and far between and this field lacks experts and quality training needed for it to grow as a speciality so that their services can easily be used widely in vaccination centres as seen elsewhere. In India, it largely remains confined primarily to the realms of respiratory medicine but needs to grow and flourish and not just because of the burden of allergic diathesis. The imminent threat of a third wave looming large in the country is generated in this group of individuals about the relative safety of the first vaccine dose or allergy to any vaccine component. They must also immediately seek medical attention if any AE occurs post their departure from the vaccination centre. This will involve engagement with this group of individuals by the scientific community at large 2) the government should rethink the policy regarding contraindications and include and encourage these patients to receive COVID-19 vaccines. This can definitely be done at least at centres that are equipped to handle medical emergencies including anaphylaxis. 3) As more evidence from within the country is generated in this group of individuals about the relative safety of these vaccines in them, the government can revise the existing policy to formally include these patients in the national vaccination program. As the authors have succinctly put it, it is only then that the vaccination program of the country will be truly inclusive.

Finally, what does this study tell us? Despite its small sample size, it does reaffirm that patients with documented allergies in an allergist’s database can take COVID-19 vaccines with reasonable safety and this in line with evidence generated worldwide. As a country we could look at three “Rs” for patients who report allergies -1) reassure them that the risk of true anaphylaxis is exceedingly low and the perceived risk in and of itself should not lead to vaccine hesitancy. They must also encourage them to report past history to the vaccine centre staff especially history of anaphylaxis after the first vaccine dose or allergy to any vaccine component. They must also immediately seek medical attention if any AE occurs post their departure from the vaccination centre.

References

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T2DM: Type 2 diabetes mellitus
BP: Blood pressure
Evaluation of Allergic Reactions following COVID-19 Vaccination in Patients with Documented Allergies

Sunita Chhapola Shukla¹,², Sukant Pandit³, Dhruve Soni³, Nithya J Gogtay⁴

Abstract
Background and Rationale: The government guidance regarding COVID-19 vaccination lists food allergy, drug allergy and history of anaphylaxis as contraindications for receiving vaccination. This study was planned to evaluate such patients listed in the database of an allergy center and who took any COVID-19 vaccine.

Methods: Data on n=255 patients was mined. Inclusions were those over 18 years, any allergic diathesis and receipt of at least one dose of any COVID-19 vaccine. Age, gender, nature of allergy and type of COVID vaccine taken along with outcome of interest [occurrence or otherwise of all allergic reaction post vaccination] was collated.

Results: Data of 227 patients were finally analysed. Eighty one took the first dose and 33 took both doses. None with food and/or drug allergy and/or a history of anaphylaxis developed any adverse event (AE) post vaccination. Three AEs were seen in those with other allergic diathesis. Two AEs [One to COVAXIN™ and one to COVISHIELD™] were only generalized itching that were self-limiting. A female patient had itching with palmar erythema [post COVISHIELD™] which subsided after a week’s treatment with an antihistamine. She had a history of allergy to radiocontrast media containing polyethylene glycol/PEG indicating possible allergy to polysorbate 80 [PEG related compound contained in COVISHIELD™].

Conclusion: No patient fitting contraindications for COVID-19 vaccination laid down by the Indian government developed any allergic reaction post vaccination. The guidelines for vaccination may be revisited to make them more inclusive with appropriate training of the vaccination centre staff.

Background and Rationale
Vaccines today form the mainstay for mitigation of the COVID-19 pandemic. Vaccination prevents severe disease, hospitalization and a fatal event. Several of these vaccines have Emergency Use Authorization [EUA] worldwide. In the United States, two mRNA vaccines [Pfizer and Moderna] were among the early ones to receive EUA. In India, currently COVISHIELD™ [ Serum Institute of India, adenovirus vector vaccine] and COVAXIN™ [inactivated vaccine with a matrix adjuvant] are approved under EUA and more recently Sputnik V™ [adenovirus vector vaccine] has been added to this list¹,²

One of the key challenges with mass administration of vaccines is the guidelines pertaining to individuals with allergy. The initial guidance of the Ministry of Health and Family Welfare released in the form of a letter on 14th January 2021.³ listed several contraindications to their use. These included - anaphylaxis to a previous dose of COVID vaccine, food allergy, drug allergy and allergies to vaccines, pharmaceutical products and injectables. This led to several people with above mentioned medical conditions being refrained to take the vaccine and hence putting them at risk of developing COVID-19 disease. Anecdotal evidence and information in the lay press suggests that many individuals with allergies who chose to get vaccinated, did not develop any severe allergic reactions after either dose. Yet others adhered strictly to these guidelines and either opted to remain unvaccinated or were turned away from vaccination centres due to the perceived risk of serious adverse events [AEs] including anaphylaxis.

The position statement of the World Allergy Organization [WAO] states that the risk of developing anaphylaxis with available COVID-19 vaccines worldwide is <1 per million.⁴ Study suggests that the risk of development of hypersensitivity reaction post mRNA vaccination is 0.63 % and 1.5 % for Pfizer-BioNtech and Moderna vaccine respectively.⁵ The vaccination policies of the United Kingdom and United States do not preclude patients with food and/or drug allergies to these vaccines⁶,⁷ though persons with a history of anaphylaxis need to be assessed by an allergist and then decide further management for the patient.⁸

The lead author [SCS] of this paper runs an allergy centre where patients with documented allergic diathesis get diagnosed and treated for various allergies. Individuals with history of atopy get sensitized to allergens early in life due to atopic march and grow into adults with multiple allergy spectrum e.g.- allergic rhinitis, bronchial asthma, skin allergy, food and drug allergies etc.⁹ Many of these patients consult regarding COVID-19 vaccination in view of their allergy history. An evaluation of this database would lend insights into the outcomes of these individuals post COVID-19 vaccination.
Material and Methods

Ethics – The study protocol was approved by the Institutional Ethics Committee.

Selection criteria - All adult patients [over the age of 18 years] in the allergy centre’s database were assessed. Inclusions were those with any allergic diatheses, including those with food and/or drug allergy and/or history of anaphylaxis who had undergone thorough clinical evaluation and allergy testing. Data was collected from their forms regarding their vaccine dosage and any allergic Adverse Event Following Immunization (AEFI). Exclusions were patient less than 18 years of age, incomplete demographics and incomplete allergy testing data. Privacy and confidentiality were maintained using unique identifiers.

Data extraction and outcome of interest – The extracted data included age, gender, nature of allergy [food, drug or other], whether COVID vaccination taken [or not] and if taken whether there was any allergic reaction post vaccination [the outcome of interest]. In the event of a documented allergic reaction following vaccination [to any COVID-19 vaccine], the following were noted – whether the reaction occurred after first, second or both doses and the severity of the reaction was recorded using the modified Hartwig -Siegel scale.10

Results

Demographics and final sample – The total number of patients registered in the database are n=255 of which n=227 fulfilled the selection criteria. The median [range] age is of these patients is 36 [26-56] years. There were a total of 123 [54.1%] women and 104 [45.8%] men. The details are summarized in Table 1. Details of various allergies is given in Table 2. Most of the patients had multiple clinical presentation of allergy spectrum e.g. allergic rhinitis, allergic asthma, skin allergy, food allergy, drug allergy or anaphylaxis etc.

Table 1: Demographic and vaccination profile of the patients

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Number</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient forms screened</td>
<td>257</td>
<td></td>
</tr>
<tr>
<td>Sample eligible for the study</td>
<td>227</td>
<td></td>
</tr>
<tr>
<td>Median [range] age in years</td>
<td>36 [26-56]</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>123</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>104</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Details of Allergies

<table>
<thead>
<tr>
<th>Criteria</th>
<th>nN [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food allergy [with or without drug allergy and history of anaphylaxis]</td>
<td>90 [39.6]</td>
</tr>
<tr>
<td>Drug allergy [with or without food allergy and history of anaphylaxis]</td>
<td>22 [9.7]</td>
</tr>
<tr>
<td>History of anaphylaxis [with or without food or drug allergy]</td>
<td>22 [9.7]</td>
</tr>
<tr>
<td>Any allergy diathesis e.g. allergic rhinitis, asthma, skin allergy [without food allergy, drug allergy or history of anaphylaxis]</td>
<td>121 [53.3]</td>
</tr>
<tr>
<td>Food allergy alone</td>
<td>71 [31.3]</td>
</tr>
<tr>
<td>Drug allergy alone</td>
<td>9 [4.0]</td>
</tr>
<tr>
<td>History of anaphylaxis</td>
<td>5 [2.2]</td>
</tr>
<tr>
<td>Food and drug allergy</td>
<td>4 [1.8]</td>
</tr>
<tr>
<td>Food allergy with a history of anaphylaxis</td>
<td>8 [3.5]</td>
</tr>
<tr>
<td>Drug allergy with a history of anaphylaxis</td>
<td>2 [0.9]</td>
</tr>
<tr>
<td>Food allergy, drug allergy and a history of anaphylaxis</td>
<td>7 [3.1]</td>
</tr>
</tbody>
</table>

Table 3: Details of vaccination

<table>
<thead>
<tr>
<th>Criteria</th>
<th>First Dose (N = 81) n (%)</th>
<th>Second Dose (N = 33) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients from the database who received any COVID-19 vaccine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COVISHIELD™</td>
<td>69 (85.2)</td>
<td>25 (75.7)</td>
</tr>
<tr>
<td>COVAXIN™</td>
<td>10 (12.3)</td>
<td>7 (21.2)</td>
</tr>
<tr>
<td>Moderna™</td>
<td>1 (1.2)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Sputnik V™</td>
<td>1 (1.2)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Discussion

The present study analyzed mined data of 227 patients with multiple allergies. Of these 81 patients took at least one dose of the vaccine and 33 received both doses. These patients had multiple allergic diathesis in which almost half of them (39) had either food and/or drug allergy and/or a past history of anaphylaxis. No patient with either of these allergies developed any AEs. Three mild AEs which included two AE of itching and one of rash post vaccination were seen in the general allergic diathesis category indicating reasonable safety of the COVID-19 vaccination in this group of patients.

The risk of an allergic reaction following vaccination remains an important concern for patients and policy makers alike. During the early phase of vaccine development, patients with allergies are excluded from the human clinical trials and these reactions come to light only when a large number of people are vaccinated.11 The EUA of the mRNA vaccines Pfizer and Moderna brought to fore cases of anaphylaxis associated with these vaccines with the current prevalence figures at 4.7 per million and 2.5 per million respectively.12 Usually it is the excipients, preservatives and adjuvants rather than the vaccine itself that are the likely culprits for causing reactions.13 The challenge with regards to the mRNA vaccines lies in the use of high molecular weight Polyethylene Glycol [PEG2000] which envelopes the naked mRNA and prevents its degradation. PEG is widely used in food additives, tablet binders, bone cements and bowel preparations. IgE-mediated reactions to polyethylene glycol (PEG) and its derivatives are the most suspected reasons for allergic reactions to the mRNA vaccines which
is a novel technology in itself. In India, Moderna the mRNA vaccine was accorded approval in June 2021 but at present, it uptake is less compared to COVISHIELD™ and COVAXIN™. COVISHIELD™ contains Polysorbate 80 (P-80) which has a lower molecular weight and has cross-reactivity with PEG.

The vaccine and consequently the compound of interest in terms of vaccine allergy in India is P-80 that has a similar structure to PEG but a lower molecular weight. Therefore patients with a history of reactions to PEG should be advised about taking COVISHIELD™. The female patient with the rash following COVISHIELD™ which is good enough to identify and treat any serious AEFI. Often times, a vasovagal attack after vaccination is interpreted as anaphylaxis. Hence, the healthcare worker should be aware of the difference between anaphylaxis, syncope and vasovagal attack (Table 6) and similarly the grading of the anaphylaxis (Table 7) as the management depends on it.

In our study, the low number of second doses taken is likely due to the waiting period of 64 days between both doses. We can only surmise that the remainder of the patients in the database who are yet unvaccinated are largely vaccine hesitant and unwilling to bypass the guidelines. Their belief is reinforced at vaccine centers where many are turned away after history taking as center staff are also hesitant. Such patients should be referred to and evaluated by an allergist for further management. The answer to this hitherto neglected group of patients lies in revising the guidelines, offering allergy testing and more specifically allergy testing for PEG and polysorbate 80 wherever expertise exists or refer patients to an allergist for confirmation. Patients with allergies should be encouraged to visit vaccination centers and get vaccinated with any available COVID-19 vaccine. Education of vaccine center staff and facilitating specialist medical care at these centers to manage the very rare immediate reactions should be promoted. Only then will the Indian COVID-19 vaccination program be truly inclusive.

**Table 4: Adverse Events [AEs] post vaccination**

<table>
<thead>
<tr>
<th>Allergic Diathesis</th>
<th>COVID vaccine first dose</th>
<th>COVID vaccine second dose</th>
<th>Serious AEs after either dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food allergy (with or without drug allergy or history of anaphylaxis) (n=90)</td>
<td>32/90 COVISHIELD™ 28</td>
<td>13/32 COVISHIELD™ 11</td>
<td>None</td>
</tr>
<tr>
<td>Drug allergy (with or without food allergy or history of anaphylaxis) (n=22)</td>
<td>9/22 COVAXIN™ 8</td>
<td>2/9 COVAXIN™ 1</td>
<td>None</td>
</tr>
<tr>
<td>History of anaphylaxis (with or without food or drug allergy) (n=22)</td>
<td>12/22 COVAXIN™ 11</td>
<td>3/12 COVAXIN™ 5</td>
<td>None</td>
</tr>
<tr>
<td>Drug allergy (n=9)</td>
<td>3/9 COVAXIN™ 3</td>
<td>1/3 COVAXIN™ 1</td>
<td>None</td>
</tr>
<tr>
<td>Food allergy (n=71)</td>
<td>22/71 COVAXIN™ 19</td>
<td>9/22 COVAXIN™ 7</td>
<td>None</td>
</tr>
<tr>
<td>Drug allergy and history of anaphylaxis (n=7)</td>
<td>3/7 COVAXIN™ 2</td>
<td>1/3 COVAXIN™ 1</td>
<td>None</td>
</tr>
<tr>
<td>Allergic diathesis without food or drug allergy or history of anaphylaxis (n=121)</td>
<td>42/121 Sputnik 34</td>
<td>17/42 Sputnik 11</td>
<td>None</td>
</tr>
</tbody>
</table>

Three mild AEs. One patient each developed itching (Level 1 severity a per Hartwig scale) after first dose of COVISHIELD™ and COVAXIN™. One patient developed palmar rash and warm extremities (Level 3 severity as per Hartwig scale) after second dose of COVISHIELD™ and required anti-histaminic for a week to resolve.

**Table 6: Summary of the main difference in clinical signs and symptoms between vasovagal and anaphylaxis**

<table>
<thead>
<tr>
<th>Observations</th>
<th>Vasovagal attack</th>
<th>Anaphylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse</td>
<td>Bradycardia</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Normal</td>
<td>Hypotensive</td>
</tr>
<tr>
<td>Hoarseness of voice</td>
<td>Absent</td>
<td>Present (progressive)</td>
</tr>
<tr>
<td>Cough, Wheeze and Stridor</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Skin color</td>
<td>Pale</td>
<td>Reddish pink</td>
</tr>
<tr>
<td>Angioedema, Urticaria</td>
<td>Absent</td>
<td>Present</td>
</tr>
</tbody>
</table>

Onset of time | Almost immediate | Within minutes to hours |

**Conclusion**

No patient fitting contraindications for COVID-19 vaccination laid down by the Indian government developed any allergic reaction post vaccination. The guidelines for vaccination may be revisited to make them more inclusive with appropriate training of the vaccination centre staff.

**References**

COVID Associated Mucormycosis: A Study on the Spectrum of Clinical, Biochemical and Radiological Findings in A Series of Ten Patients

Pranabananda Pal\textsuperscript{1*}, Nandini Chatterjee\textsuperscript{2}, Soumitra Ghosh\textsuperscript{3}, Biman Kanti Ray\textsuperscript{4}, Pradip Mukhopadhyay\textsuperscript{5}, Kaustav Bhuinia\textsuperscript{6}, Smiti Rani Srivastava\textsuperscript{7}, Souvik Adhikari\textsuperscript{8}, Debasish Barman\textsuperscript{9}, Binata Banerjee\textsuperscript{10}, Madhumita Mukhopadhyay\textsuperscript{11}, Jyotirmoy Pal\textsuperscript{12}

Abstract

**Background:** There is more than twofold rise in prevalence of mucormycosis cases in India during the COVID-19 pandemic which needs to be evaluated.

**Aims:** The study aimed to document the spectrum of cases of mucormycosis seen at our Institute during COVID-19 times.

**Methods:** The study is a retrospective observational study carried out at our Institute from May 2021 to mid-June 2021. All patients with biopsy-proven mucormycosis were enrolled in the study. The patients were subjected to complete history taking, ophthalmological examination, and imaging studies. The patients were treated with a multidisciplinary approach with antifungal therapy as well as surgical intervention when needed.

Table 7: Grading of Anaphylaxis\textsuperscript{18}

<table>
<thead>
<tr>
<th>Grade</th>
<th>Skin</th>
<th>Gastrointestinal</th>
<th>Respiratory</th>
<th>Cardiovascular</th>
<th>Neurological</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Localized rash and pruritus</td>
<td>Oral discomfort</td>
<td>Pharyngeal itchiness and discomfort</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Urticaria</td>
<td>Lip swelling</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Angioedema</td>
<td>Nausea, Vomiting, Diarrhea,</td>
<td>Mild nasal congestion/ rhinorrhea</td>
<td>Loss of activity</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Generalized pruritus and rash, urticaria, angioedema</td>
<td>Repeated vomiting/diarrhea, persistent colic</td>
<td>Severe nasal congestion/rhinorrhea, continuous coughing, laryngeal itchiness</td>
<td>Tachycardia</td>
<td>Anxiety</td>
</tr>
<tr>
<td>3</td>
<td>As Above</td>
<td>Choking sensation, husky voice, barking cough, wheeze, dyspnea, cyanosis</td>
<td>Arrhythmia, Hypotension</td>
<td>Irritability, Impending doom</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>As above</td>
<td>Respiratory arrest</td>
<td>Severe bradycardia, severe hypotension, cardiac arrest</td>
<td>-</td>
<td>Loss of consciousness</td>
</tr>
<tr>
<td>5</td>
<td>As above</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

\textsuperscript{18} Ito K. Diagnosis of food allergies: the impact of oral food challenge testing. Asia Pac Allergy 2014; 4:48-53.


\section*{COVID-19 Vaccines for People with Allergies | CDC}

\section*{What to Do if You Had an Allergic Reaction After Getting a COVID-19 Vaccine | CDC}

\section*{COVID-19 Vaccine | CDC}

\section*{Putting Risk Into Perspective. J Allergy Clin Immunol 2021; 148(2), 367-382.}

\section*{COVID-19 Vaccine | CDC}

Results: Ten patients (n=10) were seen, with a mean age of 50.3 years. The major risk factors included recent use of steroids, uncontrolled diabetes, and CKD. The most common presentation was swelling of unilateral eye and ptosis, followed by loss of vision. Inflammatory marker (CRP) and d-dimer were raised at presentation in all cases. Imaging showed the spread of infection from paranasal sinus to orbit and brain via cavernous sinus, which was a poor prognostic factor. Intraocular Amphotericin-B was given to all patients for at least 4 weeks. Two patients were discharged after completion of treatment and mortality was seen in three patients.

Conclusion: We present an array of COVID-associated-mucormycosis (CAM) cases from Eastern India. CAM is presenting with rhino-orbito-cerebral involvement. There is poor outcome with cerebral involvement and high incidence of adverse effects with deoxycholate formulation of amphotericin-B. The causal association of COVID-19 with mucormycosis needs to be unearthed but possible preventive role of anticoagulation should be evaluated.

Introduction

Mucormycosis is an opportunistic fungal infection caused by fungi of order Mucorales which includes multiple genera including Rhizopus, Rhizomucor, Mucor, Actinomucor, and Lichtheimia (formerly Absidia, etc). This is highly invasive and relentlessly progressive, resulting in higher rates of morbidity and mortality. These fungi are a common commensal in healthy individuals and cause infection primarily in immunocompromised patients with uncontrolled diabetes, defects in phagocytic function (neutropenia or glucocorticoid treatment), and/or elevated free iron level (supports fungal growth). The estimated prevalence of mucormycosis is around 70 times higher in India than that in global data. However, during the second wave of COVID-19 pandemic in India, there is surge of rhino-orbito-cerebral mucormycosis (ROCM) cases which has made India the highest burden of mucormycosis cases. Multiple risk factors including overuse of steroids, poor control of hyperglycemia, ketoacidosis, increased serum-free iron (due to hyperferritinemia and acidosis), and lymphopenia (reflected in high neutrophil-lymphocyte ratio, NLR) are classical risk factors. Along with these, careless use of multiple antibiotics, overuse of zinc supplements, and poor mask hygiene are being suspected as possible risk factors but the exact cause is yet to come forward. The unique nature of COVID-associated mucormycosis (CAM) cases is a predilection to rhino-orbital involvement. Whether COVID-19 infection is an independent risk factor of ROCM is a valid research question to be answered in the future.

The progressive nature of ROCM needs to be managed promptly with great concern as delay in appropriate management leads to worse outcome. Hence early diagnosis and treatment with a multidisciplinary team are necessary consisting of experts in the diagnostic field (microbiology, pathology, radiology), medical (internal medicine, neuro-medicine, critical care), and surgical (otorhinolaryngology, ophthalmology, neurosurgery) care.

Methods

Case records, biochemical and radiological investigations of patients admitted to our institute in May and June 2021 were retrospectively analyzed and data of ten patients (n=10) of histopathologically diagnosed mucormycosis cases were obtained. A detailed history was taken and examination was done as per prefixed proforma. Figure 1 shows the institutional protocol of management of cases.

Though liposomal amphotericin-B is the standard choice of therapy, due to financial constraints deoxycholate formulation of the drug was given to the patients as per government guidelines and it was associated with high incidence of adverse effects. We took the help of descriptive statistical tools by using descriptive and inferential statistics via Microsoft Excel 2016 and SPSS version 20.0 to assess the clinical spectrum of the disease.

Results

We present clinical, biochemical, and imaging findings of ten patients with CAM after a retrospective review and detailed clinical examination. A summary of background and risk factor profile is summarized in Table 1 and clinico-radiological and biochemical findings of all the cases are summarized in Table 2.

Case 1: A 58-year-old female, known diabetic for six years, on regular oral hypoglycemic agents (OHA), presented with right orbital swelling (Figure 1A) and diplopia for 5 days in post-COVID period (Day 30). During COVID she was prescribed multiple antibiotics, and there was history of steroid therapy and oxygen requirement. Biochemical investigation revealed increased CRP, raised neutrophil-lymphocyte ratio (NLR) and D-dimer. KOH mount microscopy was positive for broad aseptate hyphae suggestive of Mucorales. Diagnostic nasal endoscopy (DNE) showed necrotic mucosa on the right middle meatus and ophthalmological examination was normal. MRI showed involvement of nasal cavity, maxillary and ethmoid sinus along with signal changes in extraocular muscles and optic nerve on the right side [Figure 1B]. She was treated with Endoscopic debridement of the affected areas and Amphotericin-B is being continued for 4wks. Endoscopic biopsy was sent for HPE which showed non-septate hyphae with right-angle branching in H&E stain. She’s now hemodynamically stable and has a preserved vision with favorable course indicating halted progression of the disease.

Case 2: A 65 years old male, known DM for 1 year and recent use of steroid during COVID, presented with left eye ptosis and complete ophthalmoplegia for 1 week and loss of vision (LOV) in left eye for 1day. DNE showed pale mucosa on the left middle turbinate and mycological evidence of mucor was positive in KOH mount preparation. MRI showed involvement of nose, PNS, and left orbital apex. Endoscopic debridement with orbital clearance was done.

Case 3: A 64 years old female, known diabetic for 12 years who received multiple antibiotics, steroids, and oxygen therapy during COVID developed blackish discharge from
right nose and black discoloration of the hard palate (Fig 2A). There was bilateral complete LOV with non-reactive, dilated pupils. MRI revealed the extensive destruction of bilateral maxillary, ethmoid and frontal sinus (Figures 2E,2F). There was evidence of acute infarction at right basi-frontal lobe of forebrain (Figures 2C,2D). Biochemical parameters showed raised CRP and D-dimer. She underwent open debridement with craniotomy but succumbed to death in the postoperative period due to septic shock.

Case 4: A 38 years old male non-diabetic but history of steroid use recently developed toothache following recovery of COVID and dental extraction was done by dentist. However, following extraction, there was development of oro-antral fistula and persistent discharge from the site of extraction [Figure 3]. KOH mount microscopy from the pus was suggestive of mucor and he was started on Amphotericin-B. MRI brain showed there is evidence of disease spread to the medial wall of orbit along with maxillary and ethmoid sinus. he underwent endoscopic debridement of the diseased area and currently on antifungal therapy with favorable prognosis.

Case 5: A 36 years old non-diabetic male with recent history of steroid use recently developed toothache following recovery of COVID and dental extraction was done by dentist. However, following extraction, there was development of oro-antral fistula and persistent discharge from the site of extraction [Figure 3]. KOH mount microscopy from the pus was suggestive of mucor and he was started on Amphotericin-B. MRI brain showed there is evidence of disease spread to the medial wall of orbit along with maxillary and ethmoid sinus. he underwent endoscopic debridement of the diseased area and currently on antifungal therapy with favorable prognosis.
therapy during COVID developed right eye ptosis and loss of vision. MRI brain showed early involvement of cavernous sinus along with right maxillary and ethmoid sinus and orbit. He had undergone open debridement of the disease with craniotomy and is now being treated in critical care unit.

**Case 6:** A 66 years female, known DM and CKD with severe COVID while on treatment with antibiotic, steroid, and O2 therapy developed black discoloration of palate and loss of vision in the bilateral eye. On imaging, she had involvement of bilateral orbit. She was started on Amphotericin-B but succumbed to death before any surgical intervention can be done.

**CASE 7:** A 62y non-diabetic male with a recent history of steroids presented with unilateral headache and diplopia. On examination, there was left eye ptosis with complete ophthalmoplegia and LOV. Imaging study showed disease spread from ethmoid sinus to orbital apex and destruction of lamina papyracea and he underwent endoscopic debridement with orbital clearance.

**Case 8:** A 57 years old male with recent DM and history of multiple antibiotics use presented with right eye swelling and sudden onset LOV. He had no perception of light on the right eye and on fundus examination, there was pale retina with “cherry red spot” - suggestive of CRAO (Fig. 4c). Imaging study showed destruction of right middle turbinate and ethmoid sinus and contrast enhancement in right orbital apex. The patient underwent infrastructure maxillectomy with orbital decompression and now on IV Amphotericin-B therapy.

**Case 9:** A 28 years old female health worker, non-diabetic presented with left maxillary pain and toothache in post-COVID period. DNE showed pale discoloration of mucosa on middle turbinate with no bleeding during endoscopic punch biopsy. Mycological evidence of invasive disease was positive and she was given Amphotericin-B for 2 weeks and then shifted to oral Posaconazole therapy due to agranulocytosis following AmB therapy.

**Case 10:** A 32 years old male with DM developed gum pain following recovery from COVID and underwent CT scan which revealed left maxillary sinusitis. He underwent Left FESS in outside hospital and the debrided sample showed evidence of invasive mucormycosis. He was referred to our institute and started on antifungal therapy. On review surgery endoscopy guided clearance of disease was done from the left ethmoid sinus. The patient was shifted to Posaconazole therapy after severe anaphylaxis following Amphotericin-B.

**Analysis and Discussion**

The most common site of systemic mucormycosis is rhino-orbito-cerebral type in 40% cases but the COVID-associated cases are mostly rhino-orbital and rhino-orbito-cerebral type. The estimated incidence of those are 42% and 24% respectively in the systematic review by Pal R. et al. All of the patients included in our study had either rhino-orbital (60%) or rhino-orbito-cerebral involvement (40%).

All of them had a recent history of COVID-19 infection. The mean duration between diagnosis of COVID-19 and development of symptoms of mucor was days 22.9 days (5-40 days). Age distribution of the patients revealed a mean age of patients was 50.6 years. In this case study, recent steroid use was the most common risk factor (80%), followed by history of DM (70%), CKD (10%), and alcoholism (10%). Among the diabetic patients, 4 patients (57%) were long-term diabetic and 3 patients had recently diagnosed diabetic (43%). Overuse of steroids in dose and duration was evident as 5 patients had no history of hypoxia out of 8 patients (62.5%) who received steroids. There were use of two or more antibiotics in 7 out of 10 (70%) patients indicating there is indiscriminate use of antibiotics for viral illness.

The presenting features of ROCM are widely varied. The most commonly encountered symptom was swelling of the unilateral eye (60%). Headache and loosening of teeth with gum pain were early warning symptoms whether the involvement of extra-ocular muscles (ptosis and complete ophthalmoplegia) or palate (ulcer, black discoloration) was signs of advanced spread of infection. There was loss of vision (LOV) in 4 patients (40%) among them three were due to direct involvement of optic nerve and one had developed central retinal artery occlusion (CRAO). Early reporting to medical facility leading to prompt
Table 2: Clinico-biochemical findings and summary of management of cases

<table>
<thead>
<tr>
<th>Case No</th>
<th>Presenting features</th>
<th>Biochemical findings</th>
<th>Surgical procedure</th>
<th>Medical therapy</th>
<th>Serious adverse effects</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Right eye swelling, Diplopia</td>
<td>CRP 121, D-DIMER 5.2, NLR 5.9</td>
<td>Endoscopic debridement + orbital clearance</td>
<td>AmB</td>
<td>Hypokalemia</td>
<td>On therapy</td>
</tr>
<tr>
<td>2</td>
<td>Left eye swelling and ptosis, Total ophthalmoplegia, LOV</td>
<td>CRP 62, D-DIMER 1.6, NLR 6.5</td>
<td>Endoscopic debridement + orbital clearance</td>
<td>AmB</td>
<td>Hypokalemia</td>
<td>On therapy</td>
</tr>
<tr>
<td>3</td>
<td>Right nose discharge, B/L orbital swelling</td>
<td>CRP 147, D-DIMER 3.3, NLR 8.5</td>
<td>Open debridement + Orbit exenteration</td>
<td>AmB</td>
<td>Hypokalemia</td>
<td>Died</td>
</tr>
<tr>
<td>4</td>
<td>Right eye swelling and ptosis, LOV</td>
<td>CRP 80, D-DIMER 0.63, NLR 5.6</td>
<td>Open debridement + Orbit exenteration</td>
<td>AmB</td>
<td>Hypomagnesemia</td>
<td>Died</td>
</tr>
<tr>
<td>5</td>
<td>Black discoloration following dental extraction</td>
<td>CRP 80, D-DIMER 6.2, NLR 8.8</td>
<td>Endoscopic debridement</td>
<td>AmB</td>
<td>Hypokalemia</td>
<td>On therapy</td>
</tr>
<tr>
<td>6</td>
<td>Black discoloration of palate and LOV</td>
<td>CRP 250, D-DIMER 8.2, NLR 12</td>
<td>Death before surgery</td>
<td>AmB</td>
<td>AKI</td>
<td>Died</td>
</tr>
<tr>
<td>7</td>
<td>Left eye swelling and ptosis, Total ophthalmoplegia, LOV</td>
<td>CRP 11, D-DIMER 6.9, NLR 7.7</td>
<td>Open total maxillectomy + orbital clearance</td>
<td>AmB</td>
<td>Hypokalemia</td>
<td>On therapy</td>
</tr>
<tr>
<td>8</td>
<td>Right eye swelling and ptosis, LOV</td>
<td>CRP 55, D-DIMER 2, NLR 5.5</td>
<td>Endoscopic medial maxillectomy</td>
<td>AmB</td>
<td>Hypokalemia</td>
<td>On therapy</td>
</tr>
<tr>
<td>9</td>
<td>Headache, Maxillary pain</td>
<td>CRP 30, D-DIMER 0.3, NLR 3.2</td>
<td>Left-sided FESS + debridement</td>
<td>AmB and oral PSZ</td>
<td>Hypokalemia</td>
<td>Discharged</td>
</tr>
<tr>
<td>10</td>
<td>Headache, Loosening of teeth, Gam pain</td>
<td>CRP 32, D-DIMER 4.1, NLR 8</td>
<td>Right-sided FESS+ debridement</td>
<td>AmB and oral PSZ</td>
<td>Hypokalemia</td>
<td>Discharged</td>
</tr>
</tbody>
</table>

Abbreviations: AKI Acute Kidney Injury, AmB Amphotericin-B, DM diabetes mellitus, CKD chronic kidney disease, PSZ Posaconazole, NLR neutrophil-lymphocyte ratio, LOV loss of vision, FESS functional endoscopic sinus surgery. D-dimer: normal value <0.5mcg/ml, CRP C- reactive protein: normal value <5mg/dl.

Fig. 2: (Case 3): (A,B) clinical picture showing bilateral orbital swelling and discoloration of palate. (C,D) T2 FLAIR and DWI sequence showing acute infarct at right forebrain. (E,F) Extensive necrosis of bilateral PNS and orbit (right>left)
invasive mucormycosis with infarction of the tissue around paranasal sinus is unclear and raises the question: infarction or invasion, which one is the first (‘The egg or the chick’ dilemma). Along with the focus to prevent the classical risk factors of ROCM, the role of post-COVID hyperinflammatory state causing possible venous thrombosis that can act as a nidus for growth and angio-invasion of the fungal pathogen which is a usual commensal in paranasal sinus area needs to be explored. Usage of anticoagulants in COVID-19 remains an area of research with no definite guidelines published to date to address the timing, dosage, and duration of anticoagulation. Most internationally published guidelines, based on consensus statements and expert opinions, rarely address the requirement of post-discharge thromboprophylaxis. In this context, the need for standard guidelines on anticoagulant policy to address the risk of post-discharge thrombotic events, evident from persistently high D-dimer should be evaluated in future research.

The medical management of the patients was done with deoxycholate formulation of Amphotericin-B in the dose of 1 mg/kg/day in all patients and continued for a minimum of four weeks depending on the tolerability. All recovered patients were started on additional 4 weeks to 8 weeks of oral Posaconazole therapy depending on the underlying condition of patients.

The infection is associated with

managed with the latter. However, in resource-poor countries like India, the deoxycholate formulation may be used with strict vigilance on the serious adverse effects.

A total of 9 patients were managed by surgical intervention, of which 7 patients were managed by endoscopic debridement (77%) and in 3 patients open debridement with orbital exenteration/clearance (23%) was done. Radical debridement was associated with high mortality (66%) due to an increased chance of postoperative complications. Hence endoscopic approach should be the choice of intervention of choice where possible as it is associated with a favorable prognosis. Overall mortality was seen in 3 out 9 patients (33.3%) managed in our setup.

Very few studies were available online for comparison of mortality rate as the entity CAM is novel and yet to be explored by the clinicians. The updated systematic review of literature by Pal R et al. reported 34% overall mortality where there was the use of liposomal formulation of Amphotericin-B as the primary drug of choice. Here we have observed similar mortality using cheaper deoxycholate formulation of the drug which is an indicator of the similar efficacy of two formulations despite poor adverse effect profile of the latter. However, management of the adverse effects were cumbersome considering the rising prevalence of the disease in Indian hospitals due to the prolonged duration of therapy.

Conclusion

COVID-associated mucormycosis cases have a variety of presentation which needs high levels of suspicion from clinicians. We propose that patients recovering from COVID should be screened for symptoms of ROCM during routine follow-up. Apart from control of uncontrolled DM and judicious use of steroids and antibiotics, proper anticoagulation protocol to be followed during and after COVID-19 infection.

Management of patients with deoxycholate amphotericin-B is associated with serious adverse effects which should be closely monitored. Endoscopic surgery should be done, when possible, for clearance of necrotic tissues.

The infection is associated with
high mortality, especially if cerebral involvement is there.

**Take Home Message**

1. COVID-associated-mucormycosis predominantly presents as ROCM.
2. Cerebral involvement predisposes to poor outcome.
3. Amphotericin-B deoxycholate is an effective option but adverse effects need to be monitored and managed carefully.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

**References**

3. AK AK, Gupta V. Rhino-orbital Cerebral Mucormycosis. [Updated 2021 May 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan.-.
Assessment of Risk Factors for COVID-19 in Health Care Workers: A Nested Case-Control Study

Smita Santosh Chavhan¹, Balkrishna Adsul², Prasad Tukaram Dhikale³, Kirti Kinge³, Chinmay Gokhale³, Aniket Ingale³, Nilam Jadhav⁴

Abstract

Objectives: To study the risk factors for SARS-CoV-2 infection in health care workers (HCWs) exposed to COVID-19 patients.

Material and Methods: This was a nested case-control study of health care workers (HCWs) in a Dedicated COVID Hospital (DCH). The data collection was done from Dec 2020 to Feb 2021. The study was part of an international multi-center study by the World Health Organisation (WHO). The detailed protocol of this study is published by WHO.²

Definitions

The Doctors, nurses, housekeeping, and other staff working in this DCH were considered as HCWs. HCWs working in this DCH with confirmed COVID-19 were recruited as cases and other HCWs working in this DCH in the same Ward/ICU/office without infection were recruited as controls (incidence density sampling). Three controls were taken per case. The questions were in the Likert scale.

Results: There were 25 cases and their 75 controls. There was no significant difference between cases and controls with respect to age, sex, occupation, education, and comorbidities and all controls were negative for antibodies at the time of the interview. Most (70%) of the HCWs were doctors by profession followed by nurses (19%). All HCWs were trained in IPC (infection prevention and control). Most (96%) HCWs reported that PPE (personal protective equipment) is available in sufficient quantity. There was no significant difference between cases and controls with respect to those having direct contact with the patient's materials, surroundings, and following hand hygiene.

Conclusion: Adequate availability of PPE, IPC training of HCWs are important for preventing COVID-19 but do not completely reduce risk among HCWs.

Introduction

Healthcare workers (HCWs) are frequently exposed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and are at increased risk of suffering from coronavirus disease 2019 (COVID-19). In a large prospective cohort study in the USA and UK front-line healthcare workers had a twofold increase in the risk of a positive test after multivariable adjustment.³

SARS-CoV-2 infection can transmit by respiratory droplets, contact with bodily fluids and with contaminated surfaces.² Understanding the risk factors for infection with SARS-CoV-2 is important for preventing infections in HCWs and updating infection prevention and control (IPC) measures at health care facilities.²,⁴

The objective was to study the risk factors for SARS-CoV-2 infection in health care workers exposed to COVID-19 patients.

Material and Methods

Study Setting: The study was done in a DCH with 1850 beds including 300 ICU beds in a metropolitan city.

Study design and population: This was a nested case-control study of healthcare workers (HCWs). The data collection was done from Dec 2020 to Feb 2021. The study was part of an international multi-center study by the World Health Organisation (WHO).²

Exposure to COVID-19 patients was defined as:

- close contact (within 1 metre and for more than 15 minutes) with a suspected/probable/confirmed COVID-19 patient(s); or
- indirect contact with fomites (for example, clothes, linen, utensils, furniture, and so on) or with materials, devices or equipment linked to a suspected/probable/confirmed COVID-19 patient(s).

A CASE was defined as a health worker:

- exposed in a health care setting to a COVID-19 patient in the 14 days prior to the health worker's confirmation test; and
- who is a confirmed COVID-19 case.

Exclusion criterion

- having a confirmed COVID-19 case among their close contacts, including in their household, within the previous 14 days (with the exception of the COVID-19 patient(s) to which they were exposed).
Table 1: Sociodemographic characteristics and adherence to IPC in cases and controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Categories/Options</th>
<th>Cases (%)</th>
<th>Controls (%)</th>
<th>Total</th>
<th>chi square value, df, p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>(Mean ± SD)</td>
<td>30.28 ± 8.14</td>
<td>27.44 ± 6.22</td>
<td>*p = 0.071</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td>Male 12 (48)</td>
<td>23 (30.7)</td>
<td>35</td>
<td>2.476, 1, 0.116</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female 13(52)</td>
<td>52(69.3)</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td>Doctor 15(60)</td>
<td>55(73.3)</td>
<td>70</td>
<td>1.587, 1, 0.208</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other HCWs 10 (40)</td>
<td>20 (26.7)</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>Primary and secondary 4 (16)</td>
<td>5 (6.7)</td>
<td>9</td>
<td>1.994, 1, 0.182</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tertiary and Professional 21 (84)</td>
<td>70 (93.3)</td>
<td>91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Yes 3 (12)</td>
<td>8 (10.7)</td>
<td>11</td>
<td></td>
<td># 1</td>
</tr>
<tr>
<td></td>
<td>No 22 (88)</td>
<td>67 (89.3)</td>
<td>89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days worked for COVID19 patients in past 14 days</td>
<td>11.84(± 1.11)</td>
<td>11.93(± 1.85)</td>
<td>*p = 0.081</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPC training</td>
<td>Only Practical/ theoretical 4(16)</td>
<td>24(32)</td>
<td>28</td>
<td>2.381, 1, 0.123</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Both 21(84)</td>
<td>51(68)</td>
<td>72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow hand hygiene</td>
<td>Always, as recommended 21 (84)</td>
<td>54 (72)</td>
<td>75</td>
<td>0.144, 1, 0.230</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Others 4 (16)</td>
<td>21 (28)</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use Alcohol-based hand rub or soap water before touching a patient</td>
<td>Always, as recommended 21 (84)</td>
<td>58 (77.3)</td>
<td>79</td>
<td>0.502, 1, 0.478</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Others 4 (16)</td>
<td>17 (22.7)</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use Alcohol-based hand rub or soap water before aseptic procedures</td>
<td>Always, as recommended 21 (84)</td>
<td>59 (77.3)</td>
<td>80</td>
<td>0.333, 1, 0.564</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Others 4 (16)</td>
<td>16 (21.3)</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use Alcohol-based hand rub or soap water after (risk of) body fluid exposure</td>
<td>Always, as recommended 19 (76)</td>
<td>63 (84)</td>
<td>82</td>
<td>0.535</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Others 6 (24)</td>
<td>12 (16)</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use Alcohol based handrub or soap water after touching patient’s surroundings</td>
<td>Always, as recommended 18 (72)</td>
<td>55 (73.3)</td>
<td>73</td>
<td>0.017, 1, 0.897</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Others 7 (28)</td>
<td>20 (26.7)</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is Alcohol-based hand rub available at point of care</td>
<td>Yes 24 (96)</td>
<td>69 (92)</td>
<td>93</td>
<td>0.877</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Others 1 (4)</td>
<td>6 (8)</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>^ Do you follow IPC standard precautions when in contact with any patient?</td>
<td>Always, as recommended 19 (76)</td>
<td>40 (54.8)</td>
<td>59</td>
<td>3.495, 1, 0.062</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Others 6 (24)</td>
<td>33 (45.2)</td>
<td>39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>^ Do you wear recommended PPE when indicated?</td>
<td>Always, as recommended 22 (88)</td>
<td>63 (85.1)</td>
<td>85</td>
<td>0.999</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Others 3 (12)</td>
<td>11 (14.9)</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is PPE available in sufficient quantity in the health care facility?</td>
<td>Yes 24 (96)</td>
<td>72 (96)</td>
<td>96</td>
<td>0.999</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No 1 (4)</td>
<td>3 (4)</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If No, which PPE is missing?</td>
<td>Head cover 1 (4)</td>
<td>1 (1.3)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>mask 0</td>
<td>1 (1.3)</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>shoe covers 0</td>
<td>1 (1.3)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not applicable 24 (96)</td>
<td>72 (96)</td>
<td>96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>^ How many COVID-19 patients have you been exposed to during your occupational duties</td>
<td>less than or equal to 20 6(24)</td>
<td>5 (6.7)</td>
<td>11</td>
<td>6.257, 1, 0.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>21-200 8 (32)</td>
<td>24 (32)</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>201-500=3 6 (24)</td>
<td>19 (25.3)</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;500 =4 5 (20)</td>
<td>26 (36.6)</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you had direct contact with the patient’s materials since their admission?</td>
<td>Yes 0</td>
<td>6 (8)</td>
<td>6</td>
<td>$ 0.265</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No 25 (100)</td>
<td>59 (78.6)</td>
<td>94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you had direct contact with the surfaces around the patient?</td>
<td>Yes 1 (4.5)</td>
<td>7 (10.4)</td>
<td>8 (9)</td>
<td>0.674</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No 21 (85.5)</td>
<td>60 (89.6)</td>
<td>81 (91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you had close contact(within1 meter) with the patients since their admission</td>
<td>Yes 17(68)</td>
<td>61 (81.3)</td>
<td>78</td>
<td>1.943, 1, 0.163</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No 8 (32)</td>
<td>14(18.7)</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>79</td>
<td>100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

^t-test, *p value (2 sided) Fischer’s Exact test, ^ missing values (≤2%)^ A CONTROL was defined as a health worker
• exposed in a health care setting to a COVID-19 patient in the 14 days prior to recruitment; AND • who is not being classified as a suspected OR probable OR confirmed COVID-19 case.

Exclusion criterion
• having a positive serology test to SARS-CoV-2.

Three controls were taken per case.

Data collection and analysis
The data collector and analyzer were blinded about the cases and controls and data was collected about the demographic and epidemiological information, along with information on risk factors related to infection prevention and control (IPC) from both cases and controls. In this incidence density case-control study matching by time and workplace was done.

The questions were in Likert scale.

For example
Is Alcohol-based hand rub available at the point of care?

a) Yes b) No c) Occasionally d) Not sure

Do you use alcohol-based hand rub or soap and water after (risk of) body fluid exposure?

a) Always, as recommended b) Most of the time c) Occasionally d) Rarely e) Never
Table 2: Exposures history of HCWs who had close contact (within 1 meter) to the COVID-19 infected patient(s)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Categories/Options</th>
<th>Cases(%)</th>
<th>Controls(%)</th>
<th>Total</th>
<th>chi square value, df, p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>If yes, how many times (total)</td>
<td>&lt;10</td>
<td>0</td>
<td>7 (11.5)</td>
<td>7 (9)</td>
<td>2.984, 2, 0.081</td>
</tr>
<tr>
<td></td>
<td>10 to 50</td>
<td>7 (41.2)</td>
<td>16 (26.2)</td>
<td>23 (29.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;50 times</td>
<td>10 (58.8)</td>
<td>38 (62.3)</td>
<td>48 (61.5)</td>
<td></td>
</tr>
<tr>
<td>If yes, did you have prolonged face-to-face exposure (&gt;15 minutes)?</td>
<td>Yes</td>
<td>5 (29.4)</td>
<td>19 (31.1)</td>
<td>24 (30.8)</td>
<td>0.018, 1, 0.89</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>12 (70.6)</td>
<td>42 (69)</td>
<td>54 (69.2)</td>
<td></td>
</tr>
<tr>
<td>If yes, did you wear recommended PPE?</td>
<td>Yes</td>
<td>5 (29.4)</td>
<td>19 (31)</td>
<td>24 (30.8)</td>
<td>0.018, 1, 0.89</td>
</tr>
<tr>
<td></td>
<td>Not applicable</td>
<td>12 (70.6)</td>
<td>42 (69)</td>
<td>54 (69.2)</td>
<td></td>
</tr>
<tr>
<td>If yes, what type?</td>
<td>Face shield, gloves, Coverall, Respirator (N95), Shoe cover</td>
<td>5 (29.4)</td>
<td>19 (31)</td>
<td>24 (30.8)</td>
<td>0.018, 1, 0.89</td>
</tr>
<tr>
<td></td>
<td>Not applicable</td>
<td>12 (70.6)</td>
<td>42 (69)</td>
<td>54 (69.2)</td>
<td></td>
</tr>
<tr>
<td>If yes, Did you remove gloves after patient contact</td>
<td>Yes</td>
<td>16 (94.1)</td>
<td>57 (93.4)</td>
<td>73 (93.6)</td>
<td>0.999</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1 (5.9)</td>
<td>4 (6.5)</td>
<td>5 (6.4)</td>
<td></td>
</tr>
<tr>
<td>If yes, did you perform hand hygiene before contact with the patient?</td>
<td>Always, as recommended</td>
<td>14 (82.4)</td>
<td>50 (82)</td>
<td>64 (82)</td>
<td>0.999</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>3 (17.7)</td>
<td>11 (18)</td>
<td>14 (18)</td>
<td></td>
</tr>
<tr>
<td>If yes, what did you use to perform hand hygiene before contact with the patient?</td>
<td>Alcohol-based hand rub</td>
<td>13 (76.5)</td>
<td>56 (91.8)</td>
<td>69 (88.5)</td>
<td>0.196</td>
</tr>
<tr>
<td></td>
<td>Soap and water</td>
<td>4 (23.5)</td>
<td>5 (8.2)</td>
<td>9 (11.5)</td>
<td></td>
</tr>
<tr>
<td>If yes, did you perform hand hygiene after contact with the patient?</td>
<td>Always, as recommended</td>
<td>14 (82.4)</td>
<td>54 (88.5)</td>
<td>68 (87.1)</td>
<td>0.872</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>3 (17.6)</td>
<td>7 (11.5)</td>
<td>10 (12.9)</td>
<td></td>
</tr>
<tr>
<td>If yes, what did you use to perform hand hygiene after contact with the patient?</td>
<td>Alcohol-based hand rub</td>
<td>13 (76.5)</td>
<td>56 (91.8)</td>
<td>69 (88.5)</td>
<td>0.196</td>
</tr>
<tr>
<td></td>
<td>Soap and water</td>
<td>4 (23.5)</td>
<td>5 (8.2)</td>
<td>9 (11.5)</td>
<td></td>
</tr>
<tr>
<td>If yes were you present for any aerosolizing procedures performed on patient</td>
<td>Yes</td>
<td>9 (52.9)</td>
<td>31 (50.8)</td>
<td>40 (51.5)</td>
<td>0.482, 2, 0.786</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>4 (23.5)</td>
<td>19 (31.1)</td>
<td>23 (29.5)</td>
<td></td>
</tr>
<tr>
<td>If Yes, did you wear PPE?</td>
<td>Yes</td>
<td>9 (52.9)</td>
<td>31 (50.8)</td>
<td>40 (51.5)</td>
<td>0.023, 1, 0.877</td>
</tr>
<tr>
<td></td>
<td>Not applicable</td>
<td>8 (47.1)</td>
<td>30 (49.2)</td>
<td>38 (49.5)</td>
<td></td>
</tr>
<tr>
<td>If Yes, what type?</td>
<td>Face shield, gloves, Coverall, Respirator(N95), Shoe cover</td>
<td>9 (52.9)</td>
<td>31 (50.8)</td>
<td>40 (51.5)</td>
<td>0.023, 1, 0.877</td>
</tr>
<tr>
<td></td>
<td>Not applicable</td>
<td>8 (47.1)</td>
<td>30 (49.2)</td>
<td>38 (49.5)</td>
<td></td>
</tr>
<tr>
<td>If Yes, did you come into contact with the patient’s body fluids?</td>
<td>Yes</td>
<td>11 (64.7)</td>
<td>32 (52.5)</td>
<td>43 (55.1)</td>
<td>0.80, 1, 0.369</td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>6(35.3)</td>
<td>29 (47.5)</td>
<td>35(44.8)</td>
<td></td>
</tr>
<tr>
<td>Nasal fluids</td>
<td>Yes</td>
<td>1 (5.9)</td>
<td>9 (14.8)</td>
<td>10 (12.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>4 (23.5)</td>
<td>13 (21.3)</td>
<td>17 (21.6)</td>
<td></td>
</tr>
<tr>
<td>Oral fluids</td>
<td>Yes</td>
<td>3 (17.6)</td>
<td>5 (8.2)</td>
<td>8 (10.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>7(42.4)</td>
<td>19 (31.1)</td>
<td>26 (32.9)</td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>Yes</td>
<td>5 (29.4)</td>
<td>21 (34.4)</td>
<td>26 (33.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>7 (42.4)</td>
<td>21 (34.4)</td>
<td>28 (35.8)</td>
<td></td>
</tr>
<tr>
<td>Urine</td>
<td>Yes</td>
<td>2 (11.8)</td>
<td>3 (4.9)</td>
<td>5 (6.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>10 (58.8)</td>
<td>42 (69)</td>
<td>52 (64.9)</td>
<td></td>
</tr>
<tr>
<td>Wearing PPE</td>
<td>Yes</td>
<td>11 (64.7)</td>
<td>32 (52.5)</td>
<td>43 (55.1)</td>
<td>0.80, 1, 0.369</td>
</tr>
<tr>
<td></td>
<td>Not applicable</td>
<td>6(35.3)</td>
<td>29 (47.5)</td>
<td>35(44.8)</td>
<td></td>
</tr>
<tr>
<td>Which PPE</td>
<td>Face shield, gloves, Coverall, Respirator(N95), Shoe cover</td>
<td>11 (64.7)</td>
<td>32 (52.5)</td>
<td>43 (55.1)</td>
<td>0.80, 1, 0.369</td>
</tr>
<tr>
<td></td>
<td>Not applicable</td>
<td>6 (35.3)</td>
<td>29 (47.5)</td>
<td>35(44.8)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>61</td>
<td>78</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

WANTAI SARS-CoV-2 Ab ELISA provided by WHO was used for qualitative testing antibody (IgM+IgG). Blood samples from cases and controls for serology testing were collected at the time of interview.

**Statistical Analysis:** Data entry was done by using Microsoft Excel version 2010 and statistical analysis was done using IBM SPSS Statistics for windows, version 16. In addition to the descriptive analysis, Chi square test, t test and Fischer’s exact test were used. The level of significance was fixed at 0.05.

**Results**

The descriptive and analytical statistics on the sociodemographic, training and adherence to infection prevention and control (IPC), exposures to COVID-19 infected patients of cases and controls were presented. Most (82%) of the HCWs were from the age group 21-30 years. The age (Mean ± SD) of cases was 30.28 ± 8.14 years and for controls 27.44 ± 6.22 years. As shown in Table 1 there was no significant difference between cases and controls with respect to age, sex, occupation, education, and comorbidities. Most (70%) of the HCWs were doctor by profession, followed by Nurses (19%). The comorbidities present were obesity, hypothyroidism, hyperthyroidism, heart disease, asthma, tuberculosis, gout, Migraine, Polycystic ovarian disease. In past 14 days prior to interview the HCWs were working for 11.91± 1.69 days for COVID-19 patients. All controls and 18 cases had negative antibody titer at the time of interview. None of the HCWs were immunised against COVID 19.

All HCWs were working for COVID patients and all had received IPC (infection prevention and control) training. Most (75%) HCWs reported that they always followed hand hygiene and it was not significantly different in cases and controls. Most (96%) HCWs reported that PPE (personal protective equipment) is available in sufficient quantity in this health care facility. There was no significant difference between cases and controls with respect to those having direct contact with the patient’s materials and surroundings. Majority (78%) HCWs reported that they had close contact (within 1 meter) with the patients since their admission and it was not significantly different in cases and controls.

The detailed exposure history
of these 78 HCWs who had close contact (within 1 meter) with the patients since their admission is given in Table 2.

All the HCWs who had prolonged face-to-face exposure with COVID-19 patients were using face shield, gloves, coverall, shoe cover, respirator (N95) after test fitting. Most of the patients performed hand hygiene before and after contact with the patient and it was not significantly different in cases and controls. Many 43 (55.1%) HCWs came into contact with the patient’s body fluids and it was not significantly different in cases and controls.

Discussion

The cases and controls were similar with respect to age, sex, occupation, education, and comorbidities and all controls were negative for antibodies at the time of interview. There was no significant difference between cases and controls with respect to those having direct contact with the patient’s materials, surroundings, and following hand hygiene. The majority of HCWs reported that they had close contact (within 1 meter) with the patients since their admission and it was not significantly different in cases and controls.

In our study most (96%) HCWs reported that PPE is available in sufficient quantity in the health care facility. All the HCWs were trained in IPC. All the HCWs who had prolonged face-to-face exposure with COVID-19 patients were using appropriate PPE. A prospective, cohort study in UK and USA of the general community including HCWs showed that HCWs with inadequate PPE had increased risk. However, adequate availability of PPE did not completely reduce risk among HCWs, also Black, Asians were affected more. A study among ICU health workers showed that lack of PPE, unavailability of fit-tested size N95 respirators, and performing aerosol-generating procedures were risk factors for COVID19. A study of HCWs with COVID 19 showed an association between lack of PPE, lack of IPC training and infection with SARS –CoV-2.

In a retrospective case-control study in a tertiary care Hospital in Delhi type of HCW, inappropriate PPE use, performing a procedure during exposure, and taking fewer doses of Hydroxychloroquine were associated with COVID 19. We did not find any such association to be significant in our study.

The strengths of the study was the incidence density case-control study design allowing for matching by time and health facility, double-blinding, use of a validated questionnaire and all the controls were negative for antibodies also. The limitation of the study was the small sample size and may be social desirability bias.

Conclusion

Adequate availability of PPE, IPC training of HCWs are important for preventing COVID19 but do not completely reduce risk among HCWs.

Funding: The study was funded by WHO

Acknowledgment: This study was part of an international multi-centre study by WHO. We thank the WHO for funding, and designing of the study.

References

Evaluation of COVID-19 Studies Registered with the Clinical Trials Registry of India [CTRI] – A database Analysis

Chaudhari VL1, Godbole CJ2, Bendkhale SR2, Desai NN3, Gogtay NJ4, Thatte UM5

Abstract

Objective: To evaluate nature of COVID-19 studies registered with Clinical Trials Registry of India [CTRI].

Methods: An audit of all studies registered between March 2020 and January 2021 was done. We mined www.ctri.nic.in with keywords- ‘COVID-19, SARS CoV2 and corona virus’. The variables considered for analysis were total number of studies, nature of study (interventional/observational), type (Allopathy/AYUSH/Miscellaneous), source of funding (Pharmaceutical Industry/Government/Institute/Self-funded), site (national/multinational and states in India), health category (patient/healthy human volunteer) and duration of the study. The comparison between the medicinal systems was done using the ANOVA. All analysis were done at 5% significance.

Results: A total of N=1071 COVID-19 studies were registered. More than half were from the Miscellaneous category [for example behavioral, questionnaire-based studies]. A fourth of registered studies were from AYUSH followed by Allopathy which accounted for a fifth. Observational and interventional studies accounted for approximately 50% each of the total studies with the bulk belonging to the miscellaneous category. Amongst interventional studies, half were from AYUSH. Approximately 41% of these were funded by Ministry of AYUSH. A statistically significant difference was seen between the three medicinal systems [p <0.01]. Maximum studies were registered from Maharashtra (16%).

Conclusion: Majority studies were registered from May to August 2020 and from Maharashtra. The AYUSH studies were maximally registered and their findings need to be urgently disseminated to guide policy for the country.

Methodology

Ethics

The Institutional Ethics Committee accorded a waiver from review for the study as data was available in the public domain.

Study procedure and search strategy

The website (www.ctri.nic.in) was searched using the keyword “COVID-19, SARS-CoV2 AND corona virus” to identify all studies registered for COVID-19 infections from 1st March 2020 to 28th February 2021, a twelve-month period. The registered clinical trials (CTs) were categorized into three broad medicinal systems; Allopathy (Drug, Vaccine, Biologicals), AYUSH (Ayurveda, Yoga & Naturopathy, Unani, Siddha, Homeopathy) and Miscellaneous (Behavioural, Diagnostic, Medical Devices, Nutraceuticals, Others). For each study, we analysed study design related characteristics such as nature (Interventional/Observational), randomization (Randomized/Non-randomized), source of funding (Pharmaceutical Industry/Government of India/Institute Funded), geographical mapping of the clinical trials (National/Multinational and state wise distribution in India), number of study arms (one, two or multi arm), blinding (Open-label/Blinded), phase of the trial (Phase I-IV/Seamless/post marketing study), sample size (≤30, 31-100, 101-1000 and >1000), and study duration (≤3 months, 3 to 6 months, 6 to 12 months, >12months); regulatory approval status from- ethics committee (Approved/Under review) and Drugs Controller of India (DCI) (Approved/Not required); and participant related characteristics such as health type (Patient/Healthy Human participant), age (Paediatric/Adults).

Introduction

The World Health Organization [WHO] declared the corona virus infection as a pandemic on 12th March 2020. As of April 2021, most countries across the globe are seeing a second or third wave or even a fourth wave of this pandemic with increasing number of cases and strained healthcare systems despite the roll out of vaccines under Emergency Use Authorization [EUA]. To date, there is no definitive treatment [anti- viral] for disease management and most drugs used are repurposed.

Analyses of clinical trial registries yields useful information on direction of research during a pandemic. Thorlund K et al in their analysis showed that 500 clinical trials have been registered internationally at eight clinical trial registries as of 21st April 2020. India as a country differs from other countries as along with allopathy, complementary and alternative systems of medicine [CAM] abound and are widely used. An analysis of the Clinical Trials Registry of India [CTRI] would yield useful information not only on clinical trials during the pandemic but also enable comparison of nature of studies registered in India relative to elsewhere in the world and hence, this present study was envisaged.

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Received: ; Accepted:
Interventional
Nature of Study
Randomized
Non-Randomized
Source of funding
Self-funded
Government funded
Research institute
Pharmaceutical industry
Non-funded
Source of funding
Countries
National (Indian)
Multinational
Other than India
Number of study arms
One
Two
Multi-arm
Not mentioned
Blinding
Open Label
Blinded
Not applicable
Phase
I
II
III
IV
Seamless
PMX
Not mentioned
Table 1: General characteristics of COVID-19 related registered clinical trials between March 2020 and February 2021 (n=1071)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
<th>Allopathy (%)</th>
<th>AYUSH (%)</th>
<th>Miscellaneous (%)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Nature of Study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interventional</td>
<td>528 (49.3)</td>
<td>169 (32)</td>
<td>260 (49.2)</td>
<td>99 (18.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Observational</td>
<td>543 (50.7)</td>
<td>40 (7.4)</td>
<td>16 (2.9)</td>
<td>487 (90.7)</td>
<td>a,b</td>
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<tr>
<td>Type of Randomization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomized</td>
<td>379 (35.4)</td>
<td>142 (37.5)</td>
<td>164 (43.3)</td>
<td>73 (19.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-Randomized</td>
<td>62 (5.8)</td>
<td>8 (12.9)</td>
<td>33 (53.2)</td>
<td>21 (33.9)</td>
<td></td>
</tr>
<tr>
<td>Not applicable</td>
<td>630 (58.8)</td>
<td>59 (9.4)</td>
<td>79 (12.5)</td>
<td>492 (78.1)</td>
<td>a,b</td>
</tr>
<tr>
<td>Study Design Related Characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Source of funding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-funded</td>
<td>224 (20.9)</td>
<td>35 (15.6)</td>
<td>16 (7.1)</td>
<td>173 (77.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Government funded</td>
<td>272 (25.4)</td>
<td>59 (21.7)</td>
<td>114 (41.9)</td>
<td>99 (36.4)</td>
<td></td>
</tr>
<tr>
<td>Research institute</td>
<td>371 (34.6)</td>
<td>53 (14.3)</td>
<td>78 (21.0)</td>
<td>240 (64.7)</td>
<td>a</td>
</tr>
<tr>
<td>Pharmaceutical industry</td>
<td>141 (13.2)</td>
<td>58 (41.1)</td>
<td>49 (34.8)</td>
<td>34 (24.1)</td>
<td></td>
</tr>
<tr>
<td>Non-funded</td>
<td>63 (5.9)</td>
<td>4 (6.3)</td>
<td>19 (30.2)</td>
<td>40 (63.5)</td>
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</tr>
<tr>
<td>Status of Ethics committee approval</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Approved</td>
<td>1008 (94.1)</td>
<td>173 (17.2)</td>
<td>262 (26.0)</td>
<td>573 (56.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Under review</td>
<td>63 (5.9)</td>
<td>36 (57.1)</td>
<td>14 (22.2)</td>
<td>13 (20.6)</td>
<td></td>
</tr>
<tr>
<td>Status of DCI approval</td>
<td>66 (6.2)</td>
<td>59 (89.4)</td>
<td>2 (3.0)</td>
<td>5 (7.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Not required</td>
<td>1005 (95.8)</td>
<td>150 (14.9)</td>
<td>274 (27.3)</td>
<td>581 (57.8)</td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>131 (10.4)</td>
<td>23 (20.7)</td>
<td>30 (27.0)</td>
<td>58 (52.3)</td>
<td>0.243</td>
</tr>
<tr>
<td>51-100</td>
<td>396 (37.0)</td>
<td>90 (22.7)</td>
<td>113 (28.5)</td>
<td>193 (48.7)</td>
<td></td>
</tr>
<tr>
<td>&gt;100</td>
<td>455 (42.4)</td>
<td>74 (16.3)</td>
<td>97 (21.3)</td>
<td>284 (62.4)</td>
<td></td>
</tr>
<tr>
<td>Study Duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤3months</td>
<td>460 (43.0)</td>
<td>58 (12.6)</td>
<td>127 (27.6)</td>
<td>275 (59.8)</td>
<td>a,b</td>
</tr>
<tr>
<td>&gt; 3 to 6 months</td>
<td>342 (32.0)</td>
<td>72 (21.1)</td>
<td>116 (33.9)</td>
<td>154 (45.0)</td>
<td></td>
</tr>
<tr>
<td>&gt; 6 to 12 months</td>
<td>182 (17.0)</td>
<td>58 (31.9)</td>
<td>27 (14.8)</td>
<td>97 (53.3)</td>
<td></td>
</tr>
<tr>
<td>Approvals</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only Patient</td>
<td>730 (68.2)</td>
<td>174 (23.8)</td>
<td>181 (24.8)</td>
<td>375 (51.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Only Healthy</td>
<td>316 (29.5)</td>
<td>34 (10.8)</td>
<td>92 (29.1)</td>
<td>190 (60.1)</td>
<td>a,b</td>
</tr>
<tr>
<td>Human Volunteer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>25 (2.3)</td>
<td>1 (4.0)</td>
<td>3 (12.0)</td>
<td>21 (84.0)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only Paediatric</td>
<td>21 (2.0)</td>
<td>2 (9.5)</td>
<td>1 (4.8)</td>
<td>18 (85.7)</td>
<td>0.11</td>
</tr>
<tr>
<td>Only Adult</td>
<td>240 (22.4)</td>
<td>27 (11.3)</td>
<td>80 (33.3)</td>
<td>133 (55.4)</td>
<td></td>
</tr>
<tr>
<td>Only Elderly</td>
<td>5 (0.4)</td>
<td>1 (20.0)</td>
<td>2 (40.0)</td>
<td>2 (40.0)</td>
<td></td>
</tr>
<tr>
<td>Paediatric + Adult</td>
<td>21 (2.0)</td>
<td>3 (14.3)</td>
<td>3 (14.3)</td>
<td>15 (71.4)</td>
<td></td>
</tr>
<tr>
<td>Adult + Elderly</td>
<td>636 (59.4)</td>
<td>164 (25.8)</td>
<td>155 (24.4)</td>
<td>317 (49.8)</td>
<td></td>
</tr>
<tr>
<td>Paediatric + adult + elderly</td>
<td>148 (13.8)</td>
<td>12 (8.1)</td>
<td>35 (23.6)</td>
<td>101 (68.2)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only men</td>
<td>5 (0.4)</td>
<td>2 (40.0)</td>
<td>2 (40.0)</td>
<td>1 (20.0)</td>
<td>0.07</td>
</tr>
<tr>
<td>Only women</td>
<td>27 (2.6)</td>
<td>0 (0.0)</td>
<td>1 (3.7)</td>
<td>26 (96.3)</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>1039 (97.0)</td>
<td>207 (19.9)</td>
<td>273 (26.3)</td>
<td>559 (53.8)</td>
<td></td>
</tr>
</tbody>
</table>

One-way analysis of variance [ANOVA] was applied followed by post-hoc Tukey Kramer test for the covariates which were found statistically significant on ANOVA. a statistically significant (p<0.05) difference found when compared with Allopathy, b statistically significant (p<0.05) difference found when compared with AYUSH.

Results

Demographic data

Our search yielded a total of N=1071 [from 1349 sites] COVID-19 CTs for the 12-month period. Of these, 586/1071 [55%] were from the Miscellaneous category [behavioral, questionnaire-based studies, Diagnostic, Medical Devices, Nutraceuticals, Others] followed by AYUSH studies (276/1071, 26%) and then studies in the field of Allopathy (209/1071, 19%) (Table 1). A total 992 (92.6%) CTs were single center while 79 (7.4%) were multicentric. The majority of studies were from Maharashtra (212/1349, 15.7%) followed by Delhi (206/1349, 14.7%) and Karnataka (196/1349, 14.0%). The states with the lowest number of CTs were Goa and Himachal Pradesh (3/1396, 0.2%). Eighty-nine studies were registered per month on an average with the vast majority of studies (523/1071, 48.8%) being registered between May and August 2020 (Figure 1).

General characteristics of the registered CTs (Table 1)

• Nature of the study and type of medicinal system [N=1071]: A total of 543/1071 studies (50.7%) were observational in nature and the remaining 528/1071 (49.7%) interventional. Majority of the interventional studies were from AYUSH (260/528; 49.2%) followed by Allopathy (169/528; 32.0%). Observational studies were maximally

Statistical analysis

Both descriptive and inferential statistics were applied. Categorical data (nature of the trial, source of funding, DCI and IEC approval, blinding type, type of randomization, health type and study duration) are presented as proportions. The comparison between Allopathy vs AYUSH vs. Miscellaneous was done using one-way analysis of variance (ANOVA) followed by post-hoc Tukey Kramer test for multiple comparisons. All statistical analysis was done using Statistical Package for the Social Sciences (SPSS) version 20, IBM Corporation, Armonk, New York and statistical significance was set at <0.05.
from the miscellaneous category (487/543; 89.7%).

- **Source of funding:** Out of 1071 CTs, 371 (34.6%) were funded by independent research institutes while 272 (25.4%) were government funded and 141 (13.2%) were pharmaceutical industry sponsored. Among the government funded studies Ministry of AYUSH funded majority of research (114/272; 41.9%). the research from miscellaneous category was largely self-funded (173/224; 77.2%).

- **Country of recruitment:** Majority [1031/1071 96.3%] studies were recruiting participants from India while the remaining 32/1071, 3.0% were multinational CTs. Eight (0.7%) clinical trials from Bangladesh were also registered in CTRI.

- **Number of study arms:** A total of 541/1071 studies did not mention the number of study arms, while 353 (33%) CTs had a comparator arm (two arms), 120 (11.2%) CTs were single arm and only 57 (5.3%) were multi-arm studies with a range of 3 to 7 arms.

- **Study duration:** Out of 1071 CTs, majority 460 (43%) CTs had a duration ≤3months, followed by 342 (32%) with a duration of >3 to 6 months and 87 (8%) CTs with a duration more than a year.

- **Approvals:** Of 1071 registered CTs, 1008 (94.1%) CTs were approved from Ethics Committee while only 63 (5.9%) CTs were in still ‘under review’ at the time of our analysis. The DCl approval was not required for 1005 (93.8%) CTs and only 66 (6.2%) CTs were approved from the DCl.

- **Participant related demographics:** A total 730/ 1071 (68.2%) CTs were recruiting only patients while 316 (29.5%) CTs were recruiting only the healthy human participants. CTs involving Adults and/or elderly were found to be 636/1071 (59.4%) while 240 (22.4%) CTs were recruiting only adult participants. A total of 1039/1071 (97%) CTs recruiting both the genders and only 27 (2.6%) CTs were recruiting only women in the study.

### Between system comparison

- **Comparison of AYUSH versus Allopathy** - This comparison showed that interventionalal studies were more in AYUSH [49% versus 32%], their studies were of a shorter duration [7% versus 24%], had fewer ethics committee approvals [22% versus 57%] and had more healthy participant studies relative to studies in patients [29% versus 11%]. All these differences were significant at p < 0.01.

- **Comparison of Allopathy versus Studies classified as Miscellaneous** – This comparison showed that Allopathy had fewer observational studies [7% versus 89%], more studies that were randomized [89% versus 7%], more studies that were blinded [72% versus 11%], and greater ethics committee approvals [57% versus 17%]. All these differences were significant at p < 0.01.

- **Comparison of AYUSH studies versus Studies classified as Miscellaneous** - This comparison showed that observational studies were more in the miscellaneous group [3% versus 89%], there were more self-funded studies in the miscellaneous group [7% versus 77%], and miscellaneous studies were also of a longer duration [7% vs 69%]. All these differences between miscellaneous and AYUSH studies were significant at p < 0.01.

### Discussion

We evaluated in this study, the nature of the COVID-19 studies registered in the CTRI and found that more than half were from the Miscellaneous category [behavioural, questionnaire-based studies, Diagnostic, Medical Devices, Nutraceuticals and others]. A fourth of registered studies were from AYUSH followed by Allopathy which accounted for a fifth. Observational and interventional studies accounted for approximately 50% each of the total studies registered with the bulk belonging to the miscellaneous category. In almost half of the registered CTs, the number of study arms was not mentioned making them likely to be cross sectional or questionnaire based. The fact that CAM studies were maximally registered indicates that India essentially chose to work with its own systems of medicine during the pandemic.

The corollary is that the country’s contribution to bringing out a repurposed drug for the mitigation or control of the pandemic was limited.

Approximately 40% studies were registered from Maharashtra and Delhi and nearly 50% studies were registered between May and August 2020 correlating with the disease burden from the first wave. These findings are consistent with studies by Charan et al.8 and Bhapkar et al.9 with their analysis of ClinicalTrials. Gov wherein 47% studies were Allopathy-based. This again...
drives home the point that repurposing of existing allopathic drugs in India was limited during the pandemic with some notable exceptions such as Itolizumab and 2-Deoxy-D glucose.10,11

Most of the AYUSH research was funded by the government agencies like Ministry of AYUSH or its councils viz. Central Council for Research in Ayurvedic Sciences (CCRAS), Central Council for Research in Siddha (CCRS), Central Council for Research in Unani Medicine (CRUM), Central Council for Research in Homeopathy (CCHR) and their allied institutes. This is in alignment with findings of Bhapkar et al7 and Londhe D et al.12 A much larger number of AYUSH CTs [20.2 vs 33%, p=0.243] had a sample size of greater than 1000 participants and with a shorter [less than 6 months] study duration [61.5 vs 33.7%, p<0.001] indicating a faster rate of recruitment and quick completion. The real meaningful impact of the funds spent will be seen only if these studies are published or results available in the public domain for treating physicians to make informed choices about treatment options and this is an ethical imperative. Only three percent of AYUSH studies required DCI approval in comparison to allopathy (89.4%). The former studies are registered with the AYUSH research portal. However, details such as type, nature, study design, sample size, participant selection criteria, endpoints are not available on this portal unlike the CTRI which is all encompassing and this is an area that the Ministry of AYUSH can address. Healthy human participants were recruited in 29.1% of the AYUSH CTs which is significantly more as compared to allopathy [10.8%, p<0.001] indicating that AYUSH studies were likely to have been preventive in nature. These results when published or available in the public domain can help using these treatments for contacts in the community setting to minimize the burden on the hospitals.

We found only 3% of registered studies were conducted as global trials whereas majority of the CTs came from within the country. Similar findings were reported by Charan et al.6 Despite having 20% of the global DALSYS, India is still not a favoured country for the conduct of global clinical trials despite the hyped potential.13 The reasons as outlined by other authors such as few states doing high quality research, deficiencies in functioning of Ethics Committees, limited understanding of clinical research by the lay public and low literacy continue to plague the country.14 However, the regulatory functioning during the pandemic has been exemplary with the turnaround time for projects submitted to the Central Licensing Authority being just 24 hrs [with a median of 1 day and range as 1-111days, data sent for publication]. If this trend continues beyond the pandemic, it augurs well for the country for the conduct of global studies global clinical trials. Eight studies from Bangladesh were registered in CTRI as India has permitted without their own registries to use CTRI.

In summary, maximum studies were registered from May 2020 to August 2020 conducting the maximum research during the pandemic. Governmental funding for CAM has been substantial. The AYUSH clinical trials contributed maximum in the COVID-19 related clinical research and their findings need to be urgently disseminated to guide policy and mitigate any future waves that may arise with COVID-19.

References

India’s Novel Immunomodulator

For Gram –ve Sepsis,

Sepsivac®
(Heat killed Mw)

Save More Lives

A randomized trial of Mycobacterium w is severe presumed gram negative sepsis (MIST)

- Mycobacterium w in combination with standard care reduced the 28-day mortality compared to standard care alone
- The time to hospital mortality was significantly longer in those receiving Mw versus the placebo group (median 13 vs. 8.5 days)
- Significant reduction in mortality by 11%

Use of immunomodulator Mw in addition to the standard care improved the survival rates

Intradermal Administration Dosage

0.3 ml per day for 3 consecutive days
(0.1 ml intradermal at 3 different sites)

Each kit contains:
- 1 vial
- 3 syringes
- 3 needles of 24 G (to draw medicine)
- 3 needles of 26 G (to inject medicine)
Study of Pulmonary Arterial Hypertension in Patients of Chronic Kidney Disease Stage IV and V

Atul Mann1*, Geeta Kampani2, Sandeep Bansal3, Sunil Ranga4

Abstract

Introduction: Pulmonary arterial hypertension (PAH) is an overlooked complication in CKD. PAH may be induced or aggravated by various risk factors found in CKD but the pathogenesis is not fully elucidated.

Aim: To study the occurrence of PAH in CKD stage 4 and 5 and to study the risk factors for development of PAH in these patients.

Method: An observational cross-sectional study was conducted on 100 patients of CKD stage 4 and 5 at VMMC and Safdarjung Hospital and all necessary investigations were done.

Results: Out of 100 CKD patients, PAH was found in 61 patients, of which 23 had mild, 34 had moderate and 4 had severe PAH. Significant association was seen of systolic and diastolic blood pressure with high systolic blood pressure also associated with increased PAH severity. Significant association was seen of haemodialysis, arteriovenous fistula (AVF), CKD severity & haemodialysis duration. Increased haemodialysis duration & AVF were significantly associated with PAH severity also. Anaemia, low calcium, high phosphate, increased calcium-phosphate product and increased intact-parathormone were significantly associated with PAH while except calcium, these were also significantly associated with increased PAH severity. Lower LVEF% was also significantly associated with PAH and its severity. None of them was an independent significant risk factor for PAH.

Conclusion: PAH is an important complication in CKD and its severity increases with deterioration of renal function in CKD. Various risk factors are present and treatment of these can decrease the progress and severity of PAH, thereby decreasing the morbidity and mortality in CKD.

Introduction

Cardiovascular disease is the most common cause of morbidity and mortality in patients with chronic kidney disease (CKD).1 The focus is usually on left ventricular failure causing increased morbidity and mortality in the patients of CKD whereas pulmonary arterial hypertension (PAH) is an overlooked cardiovascular complication of CKD, especially in end-stage renal disease (ESRD).

Elevated pulmonary arterial pressure (PAP) can be observed secondary to heart, lung, or systemic disorders. PAH is defined as “a mean pulmonary artery pressure more than or equal to 25 mmHg at rest or 30 mmHg at exercise.”2

The pathogenesis of PAH is not fully elucidated in patients of CKD.3 It is considered to be because of the interaction of multiple aspects of altered cardiovascular physiology, elevated left ventricular filling pressure and pulmonary venous hypertension due to myocardial dysfunction are some of the important causes of PAH in CKD.4 The other important factors implicated are increased cardiac output (CO),5 volume overload, anemia, increased pulmonary blood flow due to shunting across arteriovenous fistula (AVF),6 endothelial dysfunction leading to pulmonary vasoconstriction,7 decreased compliance of pulmonary vasculature, exposure to dialysis membranes, pulmonary artery calcification and stiffening secondary to hyperparathyroidism, increased thromboxane B2, and increased pro-brain natriuretic peptide.

In a recent review by H. Suresh et al,8 the prevalence of PH in patients with CKD especially ESRD, is found to be around 43.5%. The mortality rate in the study population was also two times higher among the patients with PH compared to those without PH and the mean dialysis duration was found to be higher among the patients with PH than those without PH. Majority of the cases in stage 3 and 4 CKD had mild PH but in stage 5, it was predominantly moderate PH which indicates that PH increases in severity with progression of CKD.

Qian Zhang et al,9 in their study noted the overall prevalence of PH to be 47.38%, of which mild, moderate and severe PH accounted for 22.13, 15.04 and 10.21%, respectively. They found that prevalence of PH was much higher in patients who were on dialysis when compared to non-dialysis patients. Independent risk factors of PH in CKD patients were found to be body mass index (BMI), proteinuria, triglyceride (TG), hemoglobin, parathyroid hormone (PTH) and estimated glomerular filtration rate (eGFR) and pro-brain natriuretic peptide.

Mehta KS et al10 in their cross sectional and prospective study also found that out of total 200 patients included in their study, 121 patients (60.5%) had PH. Majority, 56 (46.28%) of CKD patients showed moderate PH. Significant association was seen between PH and presence of diabetes.

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Received: 08.12.2020; Accepted: 12.01.2021
Table 1: Characteristics of patients with and without PH

<table>
<thead>
<tr>
<th>Parameters</th>
<th>With PH (n=61)</th>
<th>Without PH (n=39)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>31.21 ± 8.69</td>
<td>33.28 ± 8.85</td>
<td>0.263</td>
</tr>
<tr>
<td>BMI</td>
<td>22.64 ± 1.66</td>
<td>22.3 ± 1.62</td>
<td>0.316</td>
</tr>
<tr>
<td>SBP</td>
<td>148.3 ± 11.91</td>
<td>136.44 ± 12.12</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DBP</td>
<td>87.54 ± 7.47</td>
<td>82.97 ± 6.42</td>
<td>0.0007</td>
</tr>
<tr>
<td>CKD stage 4</td>
<td>19</td>
<td>31</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CKD stage 5</td>
<td>42</td>
<td>8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Presence of hemodialysis</td>
<td>49</td>
<td>18</td>
<td>0.0004</td>
</tr>
<tr>
<td>Hemodialysis duration (weeks)</td>
<td>11.12 ± 4.99</td>
<td>5.78 ± 3.56</td>
<td>0.0001</td>
</tr>
<tr>
<td>Presence of AVF</td>
<td>11</td>
<td>0</td>
<td>0.006</td>
</tr>
<tr>
<td>Presence of diabetes</td>
<td>11</td>
<td>10</td>
<td>0.362</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>7.35 ± 0.56</td>
<td>8.29 ± 0.41</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>S. Uric Acid</td>
<td>7.14 ± 0.95</td>
<td>7.08 ± 1.05</td>
<td>0.655</td>
</tr>
<tr>
<td>S. Calcium</td>
<td>7.59 ± 0.48</td>
<td>8.16 ± 0.39</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>S. Phosphate</td>
<td>6.79 ± 0.7</td>
<td>4.37 ± 0.43</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Calcium Phosphate product</td>
<td>51.3 ± 3.86</td>
<td>35.58 ± 3.43</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>iPTH</td>
<td>396.21 ± 62.69</td>
<td>138.79 ± 36.28</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVEF%</td>
<td>35.77 ± 6.14</td>
<td>52.69 ± 5.6</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

hypertension, presence of AVF, CKD stage, CKD duration, presence of hemodialysis, HD duration, calcium phosphate product and S. creatinine levels. They also found that severity of PH increased with increased duration of CKD and increased duration of hemodialysis.

However the relationship between PH and CKD has been inconsistent so far. Another study conducted by Ezgi Coskun Yenigun et al.11 showed that the prevalence of PH in patients with early stage CKD was similar to those with stage 5 CKD and no significant difference was noted in PH in cases undergoing hemodialysis and those without hemodialysis. Another prospective study done by Unal et al.12 showed that AVF flow rate does not affect remarkably the systolic PAP.

PH is an independent predictor of increased mortality in patients with CKD and its presence has been recently suggested to be associated with a poor outcome13 in these patients. Hence further studies are needed to assess the association of PH in CKD patients. This study was conducted to study the occurrence of PH in CKD focusing on stage IV and V patients and to study the risk factors for development of PH in CKD stage IV and V.

Materials and Methods

This was an observational cross section study conducted on 100 patients of CKD stage 4 and 5 (based on KDIGO 2012 criteria) attending medicine OPD or admitted to the medicine wards in VMMC and Safdarjung Hospital, New Delhi from 2018-2020. Each patient was subjected to detailed history and clinical examination and relevant investigations were done including CBC, KFT, random blood sugar, S. Electrolytes, S. Calcium, S. Phosphate, S. iPTH, S. uric acid, urine routine and microscopy, USG abdomen, Chest X-Ray, ECG and echocardiography.

PH was diagnosed on the basis of echocardiography with mean pulmonary arterial pressure (MPAP) of ≥25mmHg at rest was taken as diagnostic of pulmonary arterial hypertension. Pulmonary hypertension was classified as:

- Mild (25-40 mmHg)
- Moderate (40-60 mmHg)
- Severe (>60 mmHg)

Inclusion Criteria
1. Patients of CKD in stage IV and V.
2. Age ≥18 years.

Exclusion Criteria
- Valvular heart disease
- Congenital heart diseases
- Chronic obstructive pulmonary disease
- Chronic parenchymal lung disease
- HIV-infected patients
- Chronic liver disease
- Connective tissue diseases
- Hyperthyroidism and hypothyroidism.
- Pregnancy
- Chronic thromboembolic disorders.

Statistical Analysis
Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non parametric test was used.

Statistical tests were applied as follows:
1. Quantitative variables were compared using Unpaired t-test/Mann-Whitney Test (when the data sets were not normally distributed) between CKD Stage 4 and 5.
2. Qualitative variables were compared using Chi-Square test / Fisher’s exact test.

A p value of <0.05 was considered statistically significant.

The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Results and Observations

Out of 100 patients of CKD stage 4 and 5, 50 patients (50.00%) were of CKD stage 4 and 50 patients (50.00%) were of CKD stage 5.

Pulmonary hypertension was found in 61 patients (61.00%) of the study population, of which 43 were males and 18 were females with no significant association seen of gender with presence of PH (p value of 0.091).

Different characteristics of patients with and without PH is shown in Table 1.
patients (6.56%) had severe PH.

Different characteristics of patients with mild, moderate and severe PH is shown in Table 2.

High systolic blood pressure was found to be significantly associated with increased severity of PH. Also as the CKD stage increased, severity of PH also increased significantly. Patients with increased duration of dialysis and patients with AVF had increased severity of PH. Low hemoglobin, increased serum phosphate, increased calcium phosphate product and increased intact parathormone were also found to be significantly associated with increased severity of PH. Also patients with low LVEF% had higher severity of PH.

Univariate logistic regression was done to find out significant risk factor of pulmonary hypertension as shown in Table 3.

On performing univariate logistic regression analysis, increased systolic blood pressure, increased diastolic blood pressure, low GFR, more dialysis duration, low hemoglobin, low serum calcium, increased serum phosphate, increased calcium phosphate product, increased intact parathormone, low LVEF, higher CKD stage and hemodialysis were found to be significant risk factors of pulmonary hypertension.

Multivariate logistic regression was performed to find out the independent significant risk factor of pulmonary hypertension as shown in Table 4.

On performing multivariate logistic regression after adjusting for confounding factors, none of the factors was found to be an independent significant risk factor for pulmonary hypertension.

### Discussion

In our study on 100 CKD patients of stage 4 and 5, the mean age of the patients was 32.02 ± 8.8 years and male:female ratio was 1.8:1. Number of patients in CKD stage 4 and 5 were 50 each, of which 61% patients were found to have pulmonary hypertension.

In a study by H. Suresh et al, 108 CKD patients of stage 3-5 were evaluated and followed up at 0, 3 and 6 months, PH was found in 43.5% of the patients which increased progressively to 49.14% and 50% at 3 and 6 months respectively. In another study by Zhang et al the overall prevalence of PH was 47.38% in CKD stage 1–5. F. Fabbian et al reported 39.28% PH cases and S.A. Faqih et al reported just 16.21% of PH cases in CKD patients. All the studies concluded that there was high prevalence of PH among CKD patients. Higher prevalence of PH in our study comparing to other studies can be because of the higher severity of CKD stages, i.e., CKD stage 4 and 5. No patient in our study were of CKD stage 1-3.

### Association of PH with parameters

There was no effect of age and sex of the patients on prevalence of PH in our study, this result was similar to the study by Mehta et al. F. Fabbian et al and S.A. Faqih et al reported 39.28% PH cases and S.A. Faqih et al reported just 16.21% of PH cases in CKD patients. All the studies concluded that there was high prevalence of PH among CKD patients. Higher prevalence of PH in our study comparing to other studies can be because of the higher severity of CKD stages, i.e., CKD stage 4 and 5. No patient in our study were of CKD stage 1-3.

### Table 2: Characteristics of patients with mild, moderate and severe PH

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mild PH (n=23)</th>
<th>Moderate PH (n=34)</th>
<th>Severe PH (n=4)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>33.61 ± 10</td>
<td>28 ± 5.78</td>
<td>44.75 ± 2.06</td>
<td>0.002</td>
</tr>
<tr>
<td>BMI</td>
<td>22.52 ± 1.71</td>
<td>22.56 ± 1.41</td>
<td>23.95 ± 3.07</td>
<td>0.010</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>143.04 ± 12.68</td>
<td>151.82 ± 8.94</td>
<td>148.5 ± 20.68</td>
<td>0.006</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>85.83 ± 7.08</td>
<td>88.41 ± 7.5</td>
<td>90 ± 9.52</td>
<td>0.245</td>
</tr>
<tr>
<td>CKD stage 4</td>
<td>16</td>
<td>3</td>
<td>0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CKD stage 5</td>
<td>7</td>
<td>31</td>
<td>4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Presence of Hemodialysis</td>
<td>15</td>
<td>30</td>
<td>4</td>
<td>0.068</td>
</tr>
<tr>
<td>Hemodialysis duration (weeks)</td>
<td>6.47 ± 1.92</td>
<td>12.47 ± 4.31</td>
<td>18.5 ± 1.91</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Presence of AVF</td>
<td>0</td>
<td>8</td>
<td>3</td>
<td>0.001</td>
</tr>
<tr>
<td>Presence of Diabetes</td>
<td>7</td>
<td>1</td>
<td>3</td>
<td>0.0003</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>7.74 ± 0.36</td>
<td>7.14 ± 0.54</td>
<td>6.95 ± 0.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>S. Uric Acid (mg/dL)</td>
<td>7.18 ± 1.06</td>
<td>6.99 ± 0.84</td>
<td>8.15 ± 0.66</td>
<td>0.073</td>
</tr>
<tr>
<td>S. Calcium (mg/dL)</td>
<td>7.8 ± 0.53</td>
<td>7.47 ± 0.38</td>
<td>7.42 ± 0.72</td>
<td>0.078</td>
</tr>
<tr>
<td>S. Phosphate</td>
<td>6.27 ± 0.59</td>
<td>7.08 ± 0.6</td>
<td>7.28 ± 0.15</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Calcium Phosphate Product</td>
<td>48.71 ± 3.65</td>
<td>52.75 ± 2.98</td>
<td>53.94 ± 4.18</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>iPTH</td>
<td>345.65 ± 56.39</td>
<td>422.85 ± 44.76</td>
<td>460.5 ± 9.68</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVEF%</td>
<td>39.35 ± 4.34</td>
<td>33.44 ± 6.07</td>
<td>35 ± 7.07</td>
<td>0.001</td>
</tr>
</tbody>
</table>

### Table 3: Univariate logistic regression to find out significant risk factor of pulmonary hypertension

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta coefficient</th>
<th>Standard error</th>
<th>P value</th>
<th>Odds ratio</th>
<th>Lower bound</th>
<th>Upper bound</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>-0.027</td>
<td>0.024</td>
<td>0.260</td>
<td>0.974</td>
<td>0.930</td>
<td>1.020</td>
<td>0.100</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.078</td>
<td>0.020</td>
<td>0.0001</td>
<td>1.082</td>
<td>1.040</td>
<td>1.125</td>
<td>0.035</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.086</td>
<td>0.030</td>
<td>0.005</td>
<td>1.090</td>
<td>1.027</td>
<td>1.156</td>
<td>0.194</td>
</tr>
<tr>
<td>Dialysis duration</td>
<td>0.291</td>
<td>0.090</td>
<td>0.001</td>
<td>1.338</td>
<td>1.121</td>
<td>1.598</td>
<td>0.402</td>
</tr>
<tr>
<td>Hemoglobin (gm/dl)</td>
<td>-3.604</td>
<td>0.706</td>
<td>&lt;0.0001</td>
<td>0.027</td>
<td>0.007</td>
<td>0.109</td>
<td>0.642</td>
</tr>
<tr>
<td>S. Uric Acid (mg/dL)</td>
<td>0.051</td>
<td>0.210</td>
<td>0.807</td>
<td>1.053</td>
<td>0.698</td>
<td>1.588</td>
<td>0.084</td>
</tr>
<tr>
<td>S. Calcium (mg/dL)</td>
<td>-2.745</td>
<td>0.629</td>
<td>&lt;0.0001</td>
<td>0.064</td>
<td>0.019</td>
<td>0.220</td>
<td>0.420</td>
</tr>
<tr>
<td>S. Phosphate (mg/dl)</td>
<td>7.293</td>
<td>2.774</td>
<td>0.009</td>
<td>1469.558</td>
<td>6.391</td>
<td>337904.967</td>
<td>0.965</td>
</tr>
<tr>
<td>Calcium Phosphate product</td>
<td>1.552</td>
<td>0.681</td>
<td>0.023</td>
<td>4.719</td>
<td>1.243</td>
<td>17.913</td>
<td>0.963</td>
</tr>
<tr>
<td>Intact parathormone</td>
<td>0.076</td>
<td>0.034</td>
<td>0.024</td>
<td>1.079</td>
<td>1.010</td>
<td>1.152</td>
<td>0.975</td>
</tr>
<tr>
<td>LVEF%</td>
<td>-0.533</td>
<td>0.139</td>
<td>0.0001</td>
<td>0.587</td>
<td>0.447</td>
<td>0.771</td>
<td>0.870</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>0.160</td>
<td>0.878</td>
<td>0.855</td>
<td>1.174</td>
<td>0.210</td>
<td>6.558</td>
<td>0.084</td>
</tr>
<tr>
<td>18.5-24.9 (Normal)</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>25-29.9 (Overweight)</td>
<td>0.160</td>
<td>0.878</td>
<td>0.855</td>
<td>1.174</td>
<td>0.210</td>
<td>6.558</td>
<td>0.343</td>
</tr>
<tr>
<td>CKD stage 4</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>CKD stage 5</td>
<td>2.089</td>
<td>0.478</td>
<td>&lt;0.0001</td>
<td>8.077</td>
<td>3.164</td>
<td>20.621</td>
<td>0.213</td>
</tr>
<tr>
<td>On hemodialysis</td>
<td>1.527</td>
<td>0.454</td>
<td>0.001</td>
<td>4.602</td>
<td>1.892</td>
<td>11.195</td>
<td>0.231</td>
</tr>
<tr>
<td>Presence of AVF</td>
<td>2.890</td>
<td>1.524</td>
<td>0.058</td>
<td>17.990</td>
<td>9.098</td>
<td>356.615</td>
<td>0.193</td>
</tr>
<tr>
<td>Diabetes status</td>
<td>-0.447</td>
<td>0.495</td>
<td>0.367</td>
<td>0.640</td>
<td>0.242</td>
<td>1.689</td>
<td>0.094</td>
</tr>
</tbody>
</table>
association between raised SBP and DBP with PH in our study whereas no significant association was seen between diabetes and prevalence of PH. Navaneethan et al. and Mehta et al. found a significant association of SBP, DBP and diabetes with PH but in contrast studies conducted by H. Suresh et al. and Y. Havluku et al. did not find the association of SBP, DBP and diabetes with PH to be significant. The difference may be explained by the fact that most of the patients of CKD are already on some medications to control hypertension and diabetes. Hypertension and diabetes mellitus trigger left ventricular diastolic dysfunction, an alteration bound to increase pulmonary venous and arterial pressure. This suggests that there may exist an association of HTN and DM with PH which can have an indirect impact on the pulmonary vasculature causing PH.

In our study, 50% patients were of CKD stage 4 and 50% patients were of CKD stage 5. PH was noted in 38% patients in CKD stage 4 and 84% patients in CKD stage 5 inferring that more advanced the CKD stage is, the higher is the incidence of PH. Similar results were noted in the study by Mehta et al. and Navaneethan et al. In the study by Mehta et al., none of the patients in CKD stage 2 had PH, while 9.91%, 21.48%, and 68.59% patients of CKD stage 3, 4, and 5, respectively had PH suggesting statistically significant association between CKD stages and PH.

Our cohort showed statistically significant presence of PH in patients on Hemodialysis (HD) and a positive correlation was found of duration of HD with PH. Similar association was seen in studies conducted by H. Suresh et al., F. Fabbian et al. and Mehta et al. In contrast in study by Yigla M et al., there was an inverse relationship of PH with duration of HD. This was explained by shorter survival and referral of patients with PH for kidney transplantation.

In our study, all 11 patients with AVF had PH, whereas out of 89 patients without AVF, 50 patients (56.18%) had PH while 39 patients (43.82%) did not have PH. We found this association of presence of AVF with presence of PH to be significant. Study by Mehta et al. Y. Havlucu et al. also showed a significant association of AVF with PH. Yigla M et al. in their study also noticed that almost 40% of patients undergoing long term hemodialysis via an arteriovenous access had PH. The increased prevalence of PH in patients of AVF is due to increased cardiac output causing increased load on pulmonary vasculature contributing to PH.

In our study, there is an association of decreased hemoglobin with PH which is also associated in similar manner in various previous studies conducted by H. Suresh et al., Zhang et al., Navaneethan et al. and Yigla M et al. It is seen that decrease in hemoglobin leads to LV failure due to anemia mediated hypoxemic stress and increased cardiac output contributing to PH.

Among the various biochemical parameters, a rise in calcium phosphate product was significantly associated with PH in our study which corroborated to other studies conducted by H.Suresh et al. and Y. Havluku et al. As compared to the patients without PH, patients with PH had significantly lower Calcium levels (7.59 vs 8.16) but significantly higher Phosphate levels (6.79 vs 4.37) and thus the mean Calcium phosphate product was significantly more in patients with PH (51.3 vs 35.85). However, among the renal function tests, Serum uric acid was comparable among the patients with and without PH.

The association of raised iPTH with PH was significant in our study. This was consistent with the studies done by Zhang et al. and Magdy M. Emara et al. which also showed raised iPTH to be significantly associated with PH in CKD patients. Hence increased iPTH could contribute to PH in CKD patients by causing pulmonary artery calcification and stiffening.

In our study, we noticed that a decrease in LVEF was significantly associated with PH patients. This is one of the most important mechanism contributing to PH in CKD patients and has been extensively evaluated in many studies. In study conducted by H. Suresh et al., HFrEF was present in 20.4% of CKD patients and its prevalence among the patients with and without PH was 38.3% and 6.6%, respectively suggesting that the mean EF among the patients with PH was significantly lower, compared to those without PH. Also, HFpEF was present in 85.2% of cases and the prevalence of HFpEF was significantly higher among the patients with PH, compared to those without PH. Zhang et al. and Magdy M. Emara et al. also found that decreased LVEF was significantly associated with PH. LV failure in CKD can be due to multiple factors mainly chronic volume overload, uremia mediated cardiac myocyte dysregulation, DM, HTN, anemia mediated hypoxemic stress and myocardial stiffness secondary to myocardial infarction, another frequent complication of CKD.

Studies done by H. Suresh et al., K. Ramasubbu et al. and Magdy M. Emara et al. showed that the mortality rate among those with PH was significantly higher, compared to those without PH. Study by H. Suresh et al. showed that the mortality rate was twice among those with PH, compared to those without PH. K. Ramasubbu et al. showed increased mortality of 26% in cases of PH against 6% in cases without PH and observed increase in mortality with increasing severity of PH. Navaneethan et al. showed...
PH as an independent predictor of mortality and cardiovascular events in CKD. There was no mortality in our study. However, since our study was an observational cross sectional study, we could not follow up the patients in subsequent months.

**Association of severity of PH with parameters**

In our study on 100 CKD patients of stage 4 and 5, 61 patients had PH out of which majority of the patients had moderate PH (55.74%), while 37.70% of patients had mild PH. Only 6.56% patients had severe PH.

In our study a significant increase in BMI (kg/m²) with severity of pulmonary hypertension was seen. Similar results were observed by Zhang et al9 where patients with higher BMI had severe PH. However, in a study by K. Ramasubbu et al20 although there was no direct relation however, which had no direct relation to the severity of PH. They found that moderate to severe PH might occur in any stages of CKD, indicating that PH was a multi-factorial disorder in ESRD. They also explained that this result might be due to the prostacyclin therapy used for the treatment of CKD stage 3-5, which has a cytoprotective and antiproliferative effect and hence, the distribution of mild-moderate-severe PH in CKD stage 3-5 might be varied due to prostacyclin.

In our study, no significant association was seen in patients receiving hemodialysis with stage of PH. However, significant association was seen in dialysis duration with stage of PH. Similar results were found by Mehta et al10 where a statistically significant association between duration on HD and severity of PH was seen. Similarly, Zhang et al9 also showed that patients with severe PH had longer HD duration of 20.29 ± 17.64 months which was statistically significant.

In our study, significant association was seen in systolic blood pressure with severity of PH while no significant association was seen in diastolic blood pressure with stage of PH. In studies by Zhang et al9 and K. Ramasubbu et al20 no significant association was seen in either systolic blood pressure or diastolic blood pressure with severity of PH. Hence, although hypertension is associated with the presence of PH in CKD patients in most of the previous studies, no definitive association was seen with the severity of PH.

In our study we also found a significant association between stage of CKD and severity of PH. Similar results were observed by H. Suresh et al11 where they found that among patients with CKD stage 3 and 4, majority had mild PH, but in stage 5, it was predominantly moderate PH indicating that PH increased in severity with progression of CKD, although this was not statistically significant as there were few patients in CKD stage 3 and 4. In contrast, in study by Zhang et al9 they found that the prevalence of PH increased with increased CKD stage, however, which had no direct relation to the severity of PH. They found that moderate to severe PH might occur in any stages of CKD, indicating that PH was a multi-factorial disorder in ESRD. They also explained that this result might be due to the prostacyclin therapy used for the treatment of CKD stage 3-5, which has a cytoprotective and antiproliferative effect and hence, the distribution of mild-moderate-severe PH in CKD stage 3-5 might be varied due to prostacyclin.

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In our study, significant association was seen in the distribution of presence of AVF with stage of pulmonary hypertension. However in the study by K. Ramasubbu et al20 no such association was seen, they explained that although heart failure will aggravate due to the higher output imposed by the AVF, but a 25%-30% increase in basal cardiac output over a relatively short period of time is not enough to predispose to high flow induced changes in the pulmonary vascular bed leading to PH.

In our study, hemoglobin in mild pulmonary hypertension was significantly higher as compared to moderate and severe pulmonary hypertension and a significant association was seen in decrease of hemoglobin with stage of pulmonary hypertension. However, in the study by Zhang et al9 no association was seen with decrease in Hb and severity of PH and patients of mild and severe PH had similar Hb values.

Our study also showed a significant association of increased phosphate, increased calcium phosphate product and increased iPTH with the severity of PH. In contrast, in their study showed no such association between calcium, phosphate and calcium phosphate values with severity of PH, however they noticed that iPTH values in severe PH was much higher compared to mild and moderate PH.

In our study, low LVEF showed significant association with the increased severity of PH. Similar association was noted by Zhang et al9 where LVEF% decreased with increased severity of PH, however patients with even severe PH had mean LVEF% of 54.26 ± 9.66%. Similarly in the study by Ramasubbu et al20 although there was a significant decrease in LV function with increasing severity of PH, the mean LVEF in patients with PH was still preserved (mean LVEF 53.2% ± 14.7%) suggesting that diastolic heart failure with preserved LV systolic function may be the mechanism for elevated filling pressures in a significant proportion of patients which in turn may contribute the development of PH.

In our study none of the factors was found to be an independent significant risk factor for pulmonary hypertension. However in the study by Zhang et al9 patient’s BMI, Hb, triglycerides, iPTH and eGFR were found to be independent risk factors for the development of PH. Similarly in the study by Navaneethan et al10 older age, anemia (hemoglobin <10 g/dl), lower LVEF%, and presence of LVH were independently associated with higher risk of PH and in the study by F. Fabbian et al11 dialysis duration and diastolic blood pressure were independently associated with PH.

**Limitations of our Study**

1. Our study was an observational cross sectional study including only stages 4 and 5 cases of CKD, therefore we could not see the presence of PAH in CKD stages 1-3. A follow up of these cases would give a better assessment of severity of PAH and mortality with duration of the disease.

2. PAH was diagnosed by echocardiography which is observer dependent. Right heart catheterization is the gold standard for diagnosing PAH but was not done in our patients.

Thus we concluded that pulmonary arterial hypertension is significantly associated in patients of CKD and increase in severity of PAH occurs with deterioration of renal function in CKD cases. Anemia, duration of dialysis, hypertension, hyperparathyroidism, AV fistula, increased calcium phosphate product and left ventricular failure are risk factors for development of PAH. Treatment of these risk factors can decrease the progress and severity of PAH, thereby decreasing the morbidity and mortality in CKD.
Parenteral Iron Therapy in Patients with Heart Failure in a Resource Constrained Setting In India - Our Experience

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Abstract

Objectives: To assess the prevalence of Iron Deficiency and impact of Parenteral Iron therapy in patients with Symptomatic Heart failure, the role of exercise capacity and serial Echocardiography in assessing treatment response.

Methods: Study was performed in a Government Hospital for 24 months, December 2017 to December 2019. 120 participants were recruited. Patients with symptomatic heart failure and Serum Ferritin <100 mg/dl were recruited and those with diagnosed Ischemic Cardiomyopathy or unwilling to give consent were excluded. They underwent a functional assessment and 2D Echo at baseline, after 30 and 90 days of IV Carboxymaltose. The data was analysed represented in appropriate figures. A P value <0.05 was considered significant.

Results: Of 120 patients recruited, 28 were male and 92 were female. The mean age of presentation was 44 +/- 5.4 years. The Mean baseline Haemoglobin was 11.7 +/- 0.38 gm/dl. The baseline Ferritin levels were 16.69 +/- 2.9 ug/L. HfPEF was predominant with 65% cases. The NYHA status and 6min HWT tests showed a statistically significant improvement and Echocardiography findings showed a statistically insignificant improvement after Parenteral Iron.

Conclusion: Iron Deficiency is a major risk factor in Heart Failure including HfPEF and prevails in the younger population. Parenteral Iron Carboxymaltose followed by oral iron supplementation is effective in Heart Failure patients, especially in HfPEF. Functional capacity and NYHA status appear to be the time tested markers for Iron repletion.

References

HF trials, leading to a guideline recommendation for Parenteral Ferric Carboxymaltose (FCM) therapy in symptomatic Heart Failure reduced Ejection Fraction (HFrEF) patients in the European Society Of Cardiology Heart Failure Guidelines, 2018 (Class IIa Level of Evidence- A). These studies showed that FCM improved symptoms, quality of life, and functional capacity, irrespective of the presence of anaemia and that the drug was well tolerated and safe. At 1-year follow-up, FCM was also associated with a reduction in the risk of first hospitalization for worsening HF.

Exercise intolerance is one of the hallmarks of chronic HF, and it is further reduced in the presence of iron deficiency. Although a number of observational studies in the past showed that intravenous iron (FCM) therapy was shown to increase 6-minute walking test distance in patients with HF, it was only in the EFFECT HF study that this observation was conclusively proven beyond doubt using Cardiopulmonary Exercise testing (CPET). Hence, Functional capacity and exercise tolerance have become the historical benchmarks to assess response to iron therapy in patients with or without heart failure. It has been a well-documented fact that improvement in functional capacity is one of the earliest marker of response to iron therapy.

Over the last decade, a lot of work pertaining to role of iron deficiency in patients with HFrEF has shown a definitive role of Iron replacement therapy in HFrEF, the same is not true for patients with Heart Failure preserved Ejection Fraction (HFpEF). Though a number clinical trials and systematic reviews of observational studies have proved that Iron deficiency is prevalent in HFpEF patients, the benefits of iron replacement in these patients remains an enigma. The results of the FAIR- HFpEF study still awaited, this enigma remains to be unravelled.

Although majority of studies in the past have shown a significant improvement in the exercise capacity, Functional Status and 6 minute Hall Walk Test, improvement in objective parameters like Left Ventricular Ejection Fraction (LVEF) and Left Ventricular Dimensions has not been found. In fact one of the studies which used Global Longitudinal Strain Rate (GLS) imaging in patients with Iron Deficiency Anemia reported a negative result in improvement of GLS parameters after Iron therapy. Hence, Objective Echocardiographic Imaging to monitor response to parenteral FCM therapy continues to remain a mystery.

With the aim to allay some of the above mentioned problems in patients with Iron Deficiency and heart Failure undergoing parenteral FCM, the authors aim to study the prevalence of Iron Deficiency in patients with HFpEF, the response to parenteral FCM therapy in all patients with Heart Failure and the applicability of GLS imaging to assess response to parenteral FCM therapy.

**Aims and Objectives**

1. To assess the prevalence of Iron Deficiency impact of Parenteral Iron Therapy in patients with Symptomatic Heart failure including HFpEF.

**Materials and Methods**

This study was carried out in a Government Run University Hospital with Advanced Cardiac Care facilities in Mumbai. The study period was for 24 months, between December 2017 to December 2019. At total of 120 participants of both gender were recruited using table of random numbers. All patients with symptomatic heart failure symptoms and Serum Ferritin <100 mg/dl were recruited regardless of the Left Ventricular Function. Pregnant ladies were also included. All patients with diagnosed Ischemic Cardiomyopathy and those unwilling to give consent were excluded. All patients underwent a functional assessment, 2D Echo and 2D LV Global Strain at baseline, after 30 days and at 90 days of IV Carboxymaltose therapy. The patients were screened and recruited by one investigator and underwent an Echocardiographic assessment by another investigator to eliminate bias. All patients were enrolled and assessed by the same investigators to eliminate inter-observer bias. The echocardiographic assessment was performed on an Inhouse 2D Echocardiography machine, GE Vivid T8. Blood investigations were outsourced to a private pathology laboratory in the vicinity of the hospital. Iron deficit was calculated using the Ganzoni Equation. The data was summarized and represented in appropriate tables and figures. The data was analysed using the SPSS statistical analysis software and represented in appropriate figures. Students t-test was used to compare parameters. A P value <0.05 was considered significant.

**Results**

A total of 120 individuals were recruited in this study. Of these 120, 28 were male and 92 were female. 09 females of the study group were Antepartum with HFrEF. The Baseline Demographic data of the study population has been depicted in Table 1. The mean age of presentation was 44 +/- 5.4 years (2 SD). The study population was female predominant (76.67%). The Mean baseline Haemoglobin was 11.7 +/- 0.38 gm/dl (2SD). The baseline Ferritin levels were 16.69 +/- 2.9 ug/L (2SD). The most common Heart failure profile was Heart Failure Preserved Ejection Fraction (HFpEF) with 65% cases. The changes in the functional status, 6 minute Hall Walk Test, LV Dimensions, Table 1: Baseline Demographic Data

<table>
<thead>
<tr>
<th>Column 1</th>
<th>Column 2</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>44 ± 5.4</td>
</tr>
<tr>
<td>Gender (Male/Female) (%)</td>
<td>28/92 (23.3/76.67)</td>
</tr>
<tr>
<td>Etiology: (%)</td>
<td>26 (21.67)</td>
</tr>
<tr>
<td>Tachycardiomypathy</td>
<td>07 (5.8)</td>
</tr>
<tr>
<td>HFrEF</td>
<td>78 (65)</td>
</tr>
<tr>
<td>ANC with HFrEF</td>
<td>09 (7.5)</td>
</tr>
<tr>
<td>Mean Baseline Hb (gm/dl)</td>
<td>11.7 ± 0.38</td>
</tr>
<tr>
<td>Mean Baseline Serum Ferritin (ug/L)</td>
<td>16.69 ±2.9</td>
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Table 2: Changes in functional status, 2D echocardiographic parameters after parenteral iron therapy

<table>
<thead>
<tr>
<th>Column 1</th>
<th>Baseline</th>
<th>30 Days</th>
<th>90 Days</th>
<th>P1</th>
<th>P2</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA (1-4)</td>
<td>2.9 ±0.10</td>
<td>2.6±0.17</td>
<td>2.06±0.09</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>6 Minute Hall Walk Test (m)</td>
<td>139.93±10.8</td>
<td>145.4±11.3</td>
<td>159.2±13.8</td>
<td>&lt;0.0602</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>47.2±3.6</td>
<td>47.4±4.1</td>
<td>48.2±3.6</td>
<td>0.8416</td>
<td>0.2865</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>37.4±3.6</td>
<td>38±3.9</td>
<td>37.9±3.6</td>
<td>0.6234</td>
<td>0.5963</td>
</tr>
</tbody>
</table>
Left Ventricular Ejection Fraction (LVEF) and Global Longitudinal Strain (GLS) after IV Iron Carboxymaltose therapy have been depicted in Table 2. The NYHA Functional status and 6 minute Hall Walk test results showed a statistically significant improvement while the LVEF, LV Dimensions and strain Echo findings did not reveal a statistically significant improvement after Parenteral Iron therapy. The Functional status and 6 minute hall walk tests showed a significant improvement at 30 days (p<0.0001 and p= 0.0602 respectively) and 90 days (p= <0.0001 and p= <0.0001 respectively) of parenteral iron therapy.

Discussion

Numerous mechanisms unrelated to hemodynamic dysfunction may underlie impaired exercise tolerance in patients with chronic heart failure. Among them, inadequate oxygen supply and impaired oxygen use by skeletal muscle during exercise contribute to poor clinical status. In addition, anaemia may aggravate symptoms in patients with heart failure. Targeting these abnormalities may confer functional benefits to such patients. Iron plays a key role in oxygen uptake, transport, and storage, as well as oxidative metabolism in the skeletal muscle; it also is involved in erythropoiesis. Traditionally, iron deficiency has been considered to have clinical consequences only in the presence of anaemia. Alternatively, a reduced haemoglobin level can be viewed as the end result of a process beginning with the gradual depletion of iron stores. Iron deficiency in patients with or without anaemia attenuates aerobic performance and is accompanied by reports of fatigue and exercise intolerance. The repletion of iron in patients who have iron deficiency without heart failure improves cognitive, symptomatic, and exercise performance. Recently, it has been recognized that patients with heart failure may be prone to the development of iron deficiency because of a depletion of iron stores or defective iron absorption and the reduced availability of iron recycled in the reticuloendothelial system.

With the growing interest in the role of Iron in the pathophysiology of Heart Failure over the last decade, a number of multicentre Randomised Control trials have effectively proven the role of parenteral Iron therapy in patients with Heart Failure and Iron Deficiency. However, the last decade has seen a significant change in the way Heart Failure is defined and classified. The consensus statement of recent Societal guidelines have defined Heart Failure as Heart Failure Preserved Ejection (HFpEF, LVEF ≥50%), Heart Failure Mid-Range Ejection Fraction (HFrEF, LVEF 40-49%) and Heart Failure reduced Ejection Fraction (HFrEF, LVEF <40 %). Most of the studies performed in the past to ascertain the benefits of various pharmacological agents in Heart Failure incorporated patients with HFrEF. There is very little body of evidence regarding therapy in HFrEF and HfPEF. Most of the trials pertaining to HfPEF are either ongoing or have drawn a negative result. With this in the background, the findings of our study seem to be of some definite clinical benefit in our pursuit for adequate pharmacotherapy in Heart Failure patients. The highlights of the results of our study have been listed below and are discussed in detail subsequently.

A significant number of the patients in the study had HfPEF (56%), were women (76.67%) and were relatively young (mean age - 44 +/- 5yrs). The mean Haemoglobin of the study population was within normal range suggesting an Iron deficient non anaemic population. The mean ferritin of the study population (16.69 +/- 2.9 ug/l) was in the range of Iron deficiency necessitating Iron replenishment therapy. The NYHA Functional class and 6 Minute Hall Walk Test were the only objective parameters to show a statistically significant improvement after parenteral FCM therapy. Echocardiographic parameters including Strain rate imaging (GLS) did not show a statistically significant improvement after parenteral FCM therapy in the study period.

Before we discuss further about the implications of our study, it is prudent that we decode the body of evidence that we already have unearthed the past. Amongst the multi centre trials carried out so far on the effect of FCM in Heart Failure patients, 3 trials have had a profound impact on the therapeutic outcomes, namely the FAIR-HF, CONFIRM-HF and EFFECT-HF. The FAIR HF trial, the largest amongst the trials till date, was the first trial to show a significant improvement in the patient reported Global Assessment, NYHA Class and 6 minute Hall Walk Test at 6 months (50 % versus 28 %, p<0.001). This was a randomised trial of 459 patients with HF (LVEF<45 %) and Iron Deficiency (ID) with haemoglobin in the 95–135 g/l range randomised to ferric carboxymaltose or placebo. The CONFIRM-HF trial, a study of 304 patients with HF and ID in which participants were randomised to IV ferric carboxymaltose or placebo. The authors reported significant improvements in 6-minute walk test, NYHA class and Quality of Life, as well as time to first hospitalisation. The most recent trial, EFFECT-HF trial evaluated 172 patients with HF and ID and suggested an improvement in peak VO2 with IV iron replacement. Quite a few metaanalysis of randomised trials of IV iron in HF patients with ID have suggested a substantial reduction in all-cause mortality, cardiovascular hospitalisation and HF hospitalisation with IV iron, as well as significant improvements NYHA class, 6-minute walk test and symptom questionnaire scores. Nevertheless, evidence is still awaited from large outcome trials to determine the long-term prognostic benefit of IV iron replacement in HF. The results of the trials involving parenteral Iron therapy in HfPEF are of importance for guiding therapy in these patients.

A significant proportion of the patients in our study were HfPEF and were younger than the average age of the study population of other studies. Most of the studies included elderly population (>60 years) in their studies. Our findings suggest that ID is a significant problem in young HF patients a well, especially women.

Our patients showed very low serum ferritin levels with near normal haemoglobin levels suggesting that Serum Ferritin is a robust early marker for detecting ID than Haemoglobin. This has been documented in various studies and ratified by ours.

NYHA functional status and 6 minute hall walk test were the only parameters to show significant improvement in our study population. The age old observation of improvement in clinical symptoms as the first sign of iron repletion still holds true. Multiple studies in the past have proven time...
and again that functional class and exercise capacity are the only robust methods of assessing iron repletion. This has been further substantiated by out study. The exercise performance of our study subjects improved as early as 15 days after IV FCM therapy, earlier than previous studies. The exercise performance of HF patients undergoing parenteral FCM is scarce, whatever has been published has delivered negative results. The GLS parameters were not helpful to act as therapy guiding tools in our patients. Hence, it appears that GLS is inappropriate to monitor therapy in HF patients receiving iron therapy.

It was also observed that pregnant ladies with symptoms of heart failure may have a so-called normal LV systolic function and haemoglobin and still be Iron Deficient. Vigilant investigations will certainly help to treat this iron deficiency and prevent unnecessary investigations.

Despite quite a few interesting aspects revealed by this study, this study has many limitations. This was a single centre unblinded study, hence is liable to investigator as well as patient bias. Also, the study period was only 24 months as compared to other larger studies which had a longer follow-up. Hence, it is likely that the improvement in Echocardiographic parameters may take longer than the follow up period and are likely to be missed. The sample size of 120 is rather small to extrapolate these findings the general population and hence larger multi centre studies are needed to confirm these findings.

Conclusion

Iron Deficiency continues to be a major risk factor in Indian population with Heart Failure, including Heart Failure preserved Ejection Fraction (HFpEF) and appears to prevail in the younger population. Serum Ferritin is the earliest marker for iron deficiency. Parenteral Iron Carboxymaltose Therapy followed by oral iron supplementation appears to be an effective treatment strategy for Heart Failure patients, including those with HFpEF. Functional capacity and NYHA status appear to be the time-tested markers for sensing successful Iron repletion. Global Longitudinal Strain and Echocardiography do not appear to be adequate tools to monitor therapy in Heart Failure patients with Iron Deficiency.

What is Already Known

1. Iron Deficiency is widely prevalent in Heart Failure Patients
2. Serum Ferritin is the earliest marker for iron deficiency
3. Parenteral Iron therapy is known to reduce hospitalisation rates in patients with HFrEF

What this Study Adds

1. Iron deficiency seems to be a prevailing risk factor for HFpEF
2. Younger patients with heart failure are more likely to be iron deficient.
3. Functional capacity and not echocardiography appears to be an adequate tool to monitor therapy response.

Conflict of Interest

The authors report no relationships that could be construed as a conflict of interest.

References

Fever of Unknown Origin in Older Adults: A Prospective Observational Study from North India

Bipin Kumar Yadav\(^1\), Ashok Kumar Pannu\(^{2*}\), Rajender Kumar\(^2\), Manish Rohilla\(^2\), Savita Kumari\(^3\)

Abstract

**Objectives:** Fever of unknown origin (FUO) has different etiology in different age groups. We aimed to determine the spectrum of FUO in older patients and to establish the underlying etiology.

**Methods:** This was a hospital-based prospective observational study conducted between January 2018 to June 2019 at Postgraduate Institute of Medical Education and Research, Chandigarh, India. Fifty-one consecutive patients aged 60 years and above met the qualitative criteria of FUO.

**Results:** The etiological distribution was infections in 21 patients (41.2%), malignancies in 16 (31.4%) and non-infectious inflammatory disorders in 8 (15.7%). Six patients (11.8%) remained undiagnosed. Among infections, 15 patients (29.4%) had tuberculosis, and 10 had an extrapulmonary disease. Twelve out of 16 cases with malignancies had a hematological cause, and eight had lymphoma. Regarding decisive methods of diagnosis, 18F-fluorodeoxyglucose positron emission tomography was diagnostic in 17 out of 27 patients (63%) and computed tomography in 21 out of 42 cases (50%). Imaging or endoscopy-guided procedures provided a diagnostic clue in 12 out of 14 patients (85.7%), and bone marrow examination results were useful in 9 out of 19 (47.4%).

**Conclusions:** Infections and malignancies contributed to about three-fourths of cases, with tuberculosis and lymphoma being the commonest etiologies.

Introduction

Fever of unknown origin (FUO) remains one of the most puzzling medical illnesses to solve for clinicians. The differential diagnosis is a vast undertaking. Common etiologies include infections, non-infectious inflammatory disorders (NIIDs) (including connective tissue disorders, autoimmune diseases, vasculitides) and malignancies; however, approximately one in four cases remains undiagnosed despite thorough, intensive investigations along with the use of modern technology.\(^1\)-\(^10\) The causes of FUO are influenced by multiple factors, including epidemiology, demographic characteristics, host’s immune status, available laboratory or imaging facilities, outpatient or inpatient investigations, etc.

Prolonged fever is a worrisome symptom in the elderly population and is heterogeneous in terms of clinical features and co-morbidities than young adults, and may have different etiologies with a separate diagnostic algorithm, management, or outcome. Despite the worldwide increase in the aged population, studies addressing FUO in this group are lacking, with only one (almost three-decade-old) prospective series so far to the best of our knowledge.\(^11\) In the present study, we aimed to prospectively investigate the spectrum, etiology, and diagnostic approach of FUO in elderly patients.

Methods

**Study population**

This hospital-based prospective observational study was conducted in a tertiary care center in north India, from January 2018 to June 2019.

**Case definition**

Older patients aged 60 years and above presenting to the medical outpatient department or medicine ward of the Internal Medicine unit with a diagnosis of FUO were included. Age 60 years or above is defined as elderly according to India’s National policy on older persons.\(^2\) The diagnosis of FUO is defined as fever with a temperature of 101°F (38.3°C) or above for at least three weeks and uncertain diagnosis after a thorough medical history, physical examination and the routine obligatory laboratory investigations (qualitative criterion for FUO).\(^3\) The basic investigations include erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), hemoglobin, platelets, total leucocyte count and differential, serum sodium, potassium, calcium, creatinine, total protein, protein electrophoresis, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine kinase, antinuclear antibodies (ANA), rheumatoid factor (RF), ferritin, urinalysis, cultures of blood and urine, Mantoux or tuberculin skin test (TST), chest radiograph, and abdominal ultrasound. We excluded patients with known immunocompromised states such as acquired immunodeficiency syndrome, neutropenia and hypogammaglobulinemia, and patients who developed fever after hospital admission.

**Standard protocol approvals and patient consent**

The Institutional Ethics Committee approved the study (No.: INT/IEC/2018/000618). We obtained written, informed consent from all study participants.

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Mycobacterium tuberculosis was done in amplification test (Xpert MTB/Rif) for the clinical possibilities. Nucleic acid investigations of blood and body fluids were performed according to the qualitative criteria of FUO. Other initial laboratory tests according to leading to a likely diagnosis. Laboratory abnormality, potentially through a thorough history taking and by potentially diagnostic clues (PDC) the diagnostic workup was guided. All conditions were managed as fluid analysis from a serous cavity, permitted it, invasive procedures such collected. If the clinical condition and samples of blood and urine were reviewed of systems was completed, data and physical examination with medical history, socio-demographic sample size. On enrolment, a clinical data and for its diagnostic value and to guide antimicrobial treatment along with blood culture. We also used serum procalcitonin, a novel biomarker for bacterial infection (especially gram-negative sepsis), for its diagnostic value and to guide antimicrobial treatment along with blood culture.

For body imaging, 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) with computed tomography (CT) imaging was preferred to the contrast-enhanced (CE) CT chest and abdomen. However, in cases when FDG-PET/CT was not readily available because of technical difficulties or non-availability of an early date, a CECT was done when required. FNAC, tissue biopsy, BM examination, and imaging or endoscopy-guided invasive procedure were performed to establish a diagnosis and when judged to be appropriate.

### Statistical analysis
The patients were divided according to the etiology of FUO into infectious disorders, malignant disorders, NIIDs, and undiagnosed. For data analysis, we used Statistical Package for the Social Sciences (SPSS), version 16 for Windows. The descriptive statistics were summarized as categorical data in percentages and proportions, whereas all the continuous variables were summarized using mean ± standard deviation (SD) or median with interquartile range (IQR). The association of the classified or categorical data on various causes of FUO with the etiologies was analyzed using the Chi-square test. The measurable data was tested for its normality using the Kolmogorov Smirnov test. The continuous variables were compared for various etiologies using ANOVA or other appropriate tests (e.g., Kruskal, Mann-Whitney) depending upon their normality or skewness. A p-value of <0.05 was set for statistical significance.

### Results

#### Study sample and demographic profile
We enrolled 51 patients aged 60 years and above with FUO (defined with qualitative criteria) and were evaluated in the medical outpatient or inpatient service. The median age was 64 years, ranging from 60 to 92 years. The male to female ratio was 1.6:1.

#### Clinical spectrum of the FUO
The median duration of fever was two months, ranging from three weeks to three years. Involuntary weight loss was the most frequent accompanying complaint, seen in 82.4% of patients, followed by cough (31.4%), pain abdomen (27.5%), shortness of breath (13.7%), joint pains (7.8%), and skin rash (2%). On physical examination, hepatomegaly was the most common finding, noted in 19 (37.3%) patients; peripheral lymphadenopathy (33.3%) and splenomegaly (29.4%) were the next common.

#### Etiological classification
Among the 51 patients, the etiological distribution of FUO was infections in 21 patients (41.2%), malignancies in 16 patients (31.4%) and NIIDs in 8 patients (15.7%). No etiology was found in 6 patients (11.8%). Clinical and laboratory parameters in different groups of FUO are given in Table 1. Only platelet counts showed a significant difference among the groups (p=0.023), with the lowest count in neoplastic disorders. Mann-Whitney U test for pairwise comparisons showed that a significant difference existed only between malignant diseases and infections (p=0.005).

### Table 1: Baseline characteristics of FUO patients with comparison in different groups

<table>
<thead>
<tr>
<th>Parameter(s)</th>
<th>All (N=51)</th>
<th>Infections (N=21)</th>
<th>Malignancies (N=16)</th>
<th>NIIDs (N=8)</th>
<th>Undiagnosed (N=6)</th>
<th>p - value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64 (6)</td>
<td>65 (7)</td>
<td>63.5 (3)</td>
<td>63 (10)</td>
<td>65.5 (10)</td>
<td>0.82</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>21.2 (±2.65)</td>
<td>21.15 (±2.8)</td>
<td>20.5 (±2.5)</td>
<td>21.9 (±1.55)</td>
<td>21.9 (±3.8)</td>
<td>0.582*</td>
</tr>
<tr>
<td>Fever (days)</td>
<td>60 (100)</td>
<td>60 (58)</td>
<td>90 (135)</td>
<td>50.5 (41)</td>
<td>112 (384)</td>
<td>0.552</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>8.6 (3.5)</td>
<td>10.1 (3.7)</td>
<td>8.1 (3.4)</td>
<td>8.1 (4.1)</td>
<td>8.3 (2.7)</td>
<td>0.09</td>
</tr>
<tr>
<td>TLC (per mm³)</td>
<td>8500 (6000)</td>
<td>11600 (6650)</td>
<td>6455 (8350)</td>
<td>8550 (11800)</td>
<td>10650 (6050)</td>
<td>0.102</td>
</tr>
<tr>
<td>Differential count</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil (%)</td>
<td>70 (18)</td>
<td>72 (17)</td>
<td>70.5 (23)</td>
<td>73 (23)</td>
<td>68.0 (18)</td>
<td>0.34</td>
</tr>
<tr>
<td>Lymphocyte (%)</td>
<td>19 (12)</td>
<td>15 (14)</td>
<td>17 (15)</td>
<td>18 (14)</td>
<td>19.5 (9)</td>
<td>0.574</td>
</tr>
<tr>
<td>Monocyte (%)</td>
<td>7 (7)</td>
<td>7 (5)</td>
<td>9.5 (9)</td>
<td>5.5 (6)</td>
<td>9.0 (8)</td>
<td>0.815</td>
</tr>
<tr>
<td>Platelets (x10³/mm³)</td>
<td>215 (274)</td>
<td>328 (230)</td>
<td>104 (141)</td>
<td>312 (303)</td>
<td>218 (204)</td>
<td>0.023</td>
</tr>
<tr>
<td>ALT (U/l)</td>
<td>24 (30)</td>
<td>28 (25)</td>
<td>25.5 (32)</td>
<td>16.3 (11)</td>
<td>32.5 (46)</td>
<td>0.289</td>
</tr>
<tr>
<td>ALP (U/l)</td>
<td>139 (125)</td>
<td>139 (216)</td>
<td>181.5 (160)</td>
<td>102 (56)</td>
<td>146.5 (148)</td>
<td>0.218</td>
</tr>
<tr>
<td>LDH (U/l)</td>
<td>331 (275)</td>
<td>300 (281)</td>
<td>463.5 (514)</td>
<td>295 (166)</td>
<td>531 (621)</td>
<td>0.055</td>
</tr>
<tr>
<td>Total protein (g/dl)</td>
<td>6.1 (±1.4)</td>
<td>6.32 (±1.3)</td>
<td>5.5 (±1.3)</td>
<td>6.2 (±1.6)</td>
<td>6.7 (±1.7)</td>
<td>0.294*</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>2.8 (1.1)</td>
<td>3.04 (1.02)</td>
<td>2.4 (1.0)</td>
<td>2.8 (1.6)</td>
<td>2.9 (2.1)</td>
<td>0.513</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>3.25 (2.11)</td>
<td>4.02 (3.3)</td>
<td>3.2 (2.2)</td>
<td>3.05 (1.2)</td>
<td>3.6 (3.3)</td>
<td>0.695</td>
</tr>
<tr>
<td>ESR (mm per hour)</td>
<td>46.4 (±21.0)</td>
<td>42.7 (±14.1)</td>
<td>65.6 (±32.0)</td>
<td>45.8 (±18.6)</td>
<td>0.493*</td>
<td></td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>24.8 (68.5)</td>
<td>25 (78)</td>
<td>24.5 (514)</td>
<td>26.35 (63)</td>
<td>0.886</td>
<td></td>
</tr>
<tr>
<td>Procalcitonin (ng/ml)</td>
<td>0.47 (0.81)</td>
<td>0.31 (0.8)</td>
<td>0.49 (0.54)</td>
<td>0.93 (0.54)</td>
<td>0.31 (0.86)</td>
<td>0.306</td>
</tr>
<tr>
<td>Ferritin (ng/ml)</td>
<td>498 (468)</td>
<td>432 (1395)</td>
<td>4897 (1569)</td>
<td>478 (489)</td>
<td>612 (396)</td>
<td>0.175</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>15 (8.25)</td>
<td>13 (7)</td>
<td>16 (9)</td>
<td>16 (5)</td>
<td>16 (21)</td>
<td>0.322</td>
</tr>
</tbody>
</table>

Note: Values are given as n (%), mean ± SD, or median (IQR). Applied statistical tests- #Kruskal for median (IQR) values, ANOVA for mean (±SD) values. Abbreviation: NIIDs- Non-infectious inflammatory disorders; TLC-Total leucocyte count; ALT- Alanine transaminase; ALP- Alkaline phosphatase; LDH-Lactate dehydrogenase; ESR- Erythrocyte sedimentation rate; CRP- C-reactive protein.

#### Data collection
The number of patients enrolled during the study period determined the sample size. On enrolment, a clinical research form, including a detailed medical history, socio-demographic data and physical examination with review of systems was completed, and samples of blood and urine were collected. If the clinical condition permitted it, invasive procedures such as fluid analysis from a serous cavity, fine needle aspiration cytology (FNAC) and bone marrow (BM) or tissue biopsy were obtained under local anesthesia. All conditions were managed according to standard protocols, and the diagnostic workup was guided by potentially diagnostic clues (PDC) through a thorough history taking and clinical examination. A PDC is defined as any localizing clinical feature or laboratory abnormality, potentially leading to a likely diagnosis. Laboratory investigations All patients underwent routine initial laboratory tests according to the qualitative criteria of FUO. Other investigations of blood and body fluids were performed according to the clinical possibilities. Nucleic acid amplification test (Xpert MTB/Rif) for Mycobacterium tuberculosis was done in addition to other conventional tests in patients with suspected tuberculosis (TB). We also used serum procalcitonin, a novel biomarker for bacterial infection (especially gram-negative sepsis), for its diagnostic value and to guide antimicrobial treatment along with blood culture.

#### Data analysis
For body imaging, 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) with computed tomography (CT) imaging was preferred to the contrast-enhanced (CE) CT chest and abdomen. However, in cases when FDG-PET/CT was not readily available because of technical difficulties or non-availability of an early date, a CECT was done when required. FNAC, tissue biopsy, BM examination, and imaging or endoscopy-guided invasive procedure were performed to establish a diagnosis and when judged to be appropriate.
Infections

Among the 21 cases of infectious diseases, TB was observed in 15 patients (29.4%). Principle sites of the infection were lung in 5 cases, and extrapulmonary in 10 cases (gastrointestinal in 4, lymph nodal in 2, the central nervous system in 2, pleural in 1 and pericardial in 1); however, both pulmonary and extrapulmonary involvement was present in three cases. A definitive (microbiological or pathological) diagnosis was established in six cases, and a characteristic imaging finding consistent with TB on radiology or PET diagnosed three cases. Rest six patients received the diagnosis of TB based on the constellation of clinical and radiological features (e.g., history of recent contact with active TB, evening fever, matted cervical lymphadenopathy, positive TST, ileocecal involvement on imaging or colonoscopy, etc.) along with the response to empirical anti-tuberculosis therapy (ATT) within six to eight-week duration.

Overall, 10 out of 51 patients received empirical ATT along with ongoing investigation for a definitive etiology; in whom six patients showed an optimal response, one died on follow-up, and three cases had a different diagnosis (pulmonary amyloidosis, lymphomatous infiltration of lung and non-resolving bacterial pneumonia caused by *Pseudomonas aeruginosa*). TST was done in all 51 patients and was positive in five patients, including two TB patients. TST positivity was not statistically different between TB and other etiologies of FUO (p=0.058).

A liver abscess was initially not picked up on ultrasound, but CT detected it. A patient had cardiac murmur on repeated physical examination but with sterile blood cultures and normal transthoracic echocardiography; however, subsequently, transesophageal echocardiography showed aortic valve vegetation. A patient with unrecognized peripanillary mass complicated with cholangitis, which responded to broad-spectrum antibiotics and biliary drainage. A partially (inadequately) treated enteric fever went on two months until repeated blood cultures grew *Salmonella typhi*.

Serum procalcitonin was done in all patients and was increased (>0.5 ng/ml) in 21 patients with a high median value in NIIDs patients. On the other hand, the patient with *P. aeruginosa* infection had a normal value (0.4 ng/ml).

A patient with diffuse enlargement of both adrenals and hepatosplenomegaly on CT was diagnosed as disseminated histoplasmosis after FNAC from a cervical lymph node.

Two patients died in the infectious disease group, i.e., culture-negative endocarditis with severe aortic regurgitation and pulmonary TB.

Malignant disorders

In our study, malignancies were present in 16 patients (31.4%). Hematological neoplasms account for 12 cases (23.5%), including six non-Hodgkin’s lymphoma (NHL), two Hodgkin’s lymphoma (HL), one myelodysplastic syndrome, one acute myeloid leukemia, one hairy cell leukemia and one primary amyloidosis. Types of NHL were peripheral T cell lymphoma, diffuse large B cell lymphoma, anaplastic large cell lymphoma, and two B cell NHL. The patient with peripheral T cell lymphoma died after one month of hospital stay due to advanced disease and hospital-acquired infection. All lymphoma patients had Ann Arbor stage IV and poor International Prognostic Index (4 or 5 factors).

A patient with left hilar opacity of lung on radio-imaging, initially received empirical ATT was diagnosed the primary amyloidosis after FNAC from a cervical node and lung biopsy from hilar opacity. One HL patient also had lung infiltration on lung biopsy.

Solid tumor malignancies (N=4) causing FUO in the elderly were lung adenocarcinoma, carcinoma prostate with BM metastasis, metastatic squamous cell carcinoma with unknown primary and advanced follicular carcinoma of thyroid (Hurthle cell histology).

NIIDs

This cohort had eight NIIDs cases; five cases of connective tissue disorders, i.e., systemic lupus erythematosus (SLE), Sjogren syndrome, rheumatoid arthritis (RA)-associated secondary amyloidosis, inflammatory polyarthritis, and undifferentiated connective tissue disease, two cases of glomerulonephritis ( crescentic glomerulonephritis and pauci-immune glomerulonephritis) and one case of IgG4-related tubulointerstitial nephritis. The patients with pauci-immune glomerulonephritis and IgG4-related disease had increased abnormal FDG uptake in renal parenchyma on PET scan and were subsequently diagnosed on a kidney biopsy.

All 51 patients were investigated for RF and ANA. RF was positive in two cases but didn’t contribute to a diagnosis. The patient with RA-associated secondary amyloidosis was RF negative but anti-cyclic citrullinated peptide positive. ANA (by indirect immunofluorescence assay) was positive in 15 patients (six NIIDs, four malignancies, three infections, and two undiagnosed); however, we detected only one SLE patient (male). Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis was not observed in this cohort; however, ANCA (by ELISA) was falsely positive in three out of 38 patients (pulmonary TB, SLE, hairy cell leukemia, NHL). Similarly, angiotensin-converted enzyme (ACE) level was performed in 14 patients and was elevated (<1.5 times of upper limit of normal) in three cases (pulmonary TB, disseminated TB, B cell NHL). Sarcoidosis was not observed in this cohort.

Undiagnosed group

Six patients (11.8%) remained undiagnosed. Three of these had disseminated disease with multiple space-occupying lesions in the spleen on imaging, in whom two died, and one continued to have fever. One patient with a four-month fever, generalized lymphadenopathy, anemia, and thrombocytopenia remained undiagnosed despite FDG-PET/CT, thoracoabdominal CECT, BM biopsy, and image-guided invasive procedures. Fever resolved in two male patients during investigation workup, and they remained afebrile on follow-up of approximately six months.

Decisive methods of diagnosis

**Imaging modalities**

Body CT was performed in 42 patients (82.35%), and it provided PDCs in half of them. In contrast, FDG-PET/CT was done in 27 cases (52.94%), out of which 17 contributed to the diagnosis (diagnostic utility 62.96%). In 20 patients, the FDG-PET/CT was done after a body CT, and only in two cases, it detected a different PDC. Total
TABLE 2: Etiological classification of FUO in older adults in various series

<table>
<thead>
<tr>
<th>Study (Author, year)</th>
<th>Place</th>
<th>Size (N)</th>
<th>Infections</th>
<th>Malignancies</th>
<th>Hematological</th>
<th>Solid tumor</th>
<th>NIIDs</th>
<th>Miscellaneous</th>
<th>Undiagnosed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esposito et al., 1979</td>
<td>Boston</td>
<td>111</td>
<td>41 (36.9%)</td>
<td>26 (23.4%)</td>
<td>15</td>
<td>11</td>
<td>28 (25.2%)</td>
<td>10 (9.0%)</td>
<td>6 (5.4%)</td>
</tr>
<tr>
<td>Barrier et al., 1982</td>
<td>France</td>
<td>46</td>
<td>19 (41.3%)</td>
<td>6 (13.0%)</td>
<td>2</td>
<td>4</td>
<td>13 (30.3%)</td>
<td>7 (2.1%)</td>
<td>1 (2.1%)</td>
</tr>
<tr>
<td>Knookaert et al., 1993</td>
<td>Belgium</td>
<td>47</td>
<td>12 (25.0%)</td>
<td>6 (12.0%)</td>
<td>3</td>
<td>8</td>
<td>15 (31.0%)</td>
<td>8 (17.0%)</td>
<td>8 (17.0%)</td>
</tr>
<tr>
<td>Ikunni et al., 1994</td>
<td>Japan</td>
<td>31</td>
<td>8 (25.8%)</td>
<td>9 (29.0%)</td>
<td>6</td>
<td>3</td>
<td>7 (22.6%)</td>
<td>3 (9.8%)</td>
<td>3 (9.8%)</td>
</tr>
<tr>
<td>Zemone et al., 2006</td>
<td>France</td>
<td>61</td>
<td>9 (14.8%)</td>
<td>9 (14.8%)</td>
<td>3</td>
<td>3</td>
<td>22 (36.1%)</td>
<td>3 (4.9%)</td>
<td>3 (4.9%)</td>
</tr>
<tr>
<td>Turkolov et al., 2011</td>
<td>Serbia</td>
<td>50</td>
<td>30 (60.0%)</td>
<td>9 (18.0%)</td>
<td>NA</td>
<td>0</td>
<td>6 (12.0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>This study, 2019</td>
<td>India</td>
<td>51</td>
<td>21 (41.2%)</td>
<td>16 (31.4%)</td>
<td>NA</td>
<td>NA</td>
<td>30 (60.0%)</td>
<td>9 (18.0%)</td>
<td>6 (12.0%)</td>
</tr>
</tbody>
</table>

Abbreviation: NIIDs- Non-infectious inflammatory disorders; NA- Not available

Discussion

FUO series have significant variations because of the differences in study population (demographic and geographic factors), study period, study design (retrospective or prospective), case definitions and place of the study (patient referral pattern, availability of the investigations and experience of the investigators). The index study, a prospective case series of 51 elderly FUO patients with no known immunodeficiency fulfilling the practical qualitative criterion, shows that a combination of clinical features, whole-body imaging, and invasive procedures enables to diagnose most cases.

FUO Etiologies

Table 2 compares the etiological spectrum of elderly FUO in major case series.11,13-16

Our series confirms the previous observation that infection, notably TB, remains the most important cause of the geriatric FUO. The elderly population is at increased susceptibility to infections than younger adults, often with insidious onset, nonspecific or atypical presentation, delay in diagnosis, and worse outcomes. TB (especially extrapulmonary) should always be considered in older patients with FUO in both endemic as well as nonendemic regions, given the high risk of its reactivation due to age-related impaired cell-mediated immunity.11,13-16 Enabled T-cell functions are also responsible for the disease’s atypical clinical or radiological features, hematogenous spread with miliary or disseminated forms and a low probability of TST positivity.13-14 Thus, the geriatric TB is difficult to differentiate from conditions like lymphoma, histoplasmosis, or sarcoidosis, as we experienced in this study.

Abscess and infective endocarditis were among the common infectious causes in many geriatric FUO studies; however, only one case of each was seen in this sample. As sporadic cases of histoplasmosis may intermittently occur in nonendemic areas, we detected one case of progressive disseminated histoplasmosis producing elderly FUO. Viral infections (human immunodeficiency virus, Epstein Barr virus, cytomegalovirus, etc.), endemic parasitosis (visceral leishmaniasis, tropical splenomegaly syndrome, etc.) and Rickettsial infections were not found.

Most published data on FUO in adults and especially in the elderly found malignancy, mainly hematological and metastatic solid tumor as a common etiology, so was in our study. Lymphoma remained the leading malignant disorder and was accompanied by a combination of poor prognostic factors, including advanced age, presence of B symptoms, a disseminated disease, and a delay in diagnosis. Our observation establishes the prior wisdom in oncology practice: malignancies producing prolonged fever are aggressive and advanced.

In several previous studies, NIIDs constitute an important cause for elderly FUO patients. In our sample, the NIIDs group was in third place. Four FUO cases of our NIIDs group had fever localization in their kidneys. All of them had rapidly progressive renal failure and abnormal urinalysis. A kidney biopsy clinched the diagnosis, and subsequently, renal functions improved with immunosuppressive therapy. In two of them, FDG-PET/CT showed a hypermetabolic renal lesion, which was initially mistaken as pyelonephritis. Two patients had an inflammatory joint disease and responded to nonsteroidal anti-inflammatory drugs and low-dose steroids. Systemic lupus erythematosus and Sjogren syndrome are important causes of fever in young females; however, each was diagnosed in one patient in our older group.

Giant cell arteritis (GCA) was a common cause in previous elderly FUO studies. Knockaert DC et al. found it the most frequent cause (17%) in a series of 47 patients.11 Moreover, many
algorithms advise temporal artery biopsy in undiagnosed cases to explore subclinical involvement of the artery.7–9,11 In our series, GCA was not found. One undiagnosed patient underwent a Doppler ultrasound of the temporal artery (a useful investigation for directional biopsy), but no abnormality was detected. The absence of GCA in this sample is the low incidence of this condition in India, and also, fever is not a common symptom in reported case series.19–21,25–28

Systemic amyloidosis has never been reported as a cause of FUO in the elderly. We found it in two cases; one had primary amyloidosis (AL type) involving lung and lymph nodes, and the other had RA-associated secondary amyloidosis (AA type) with renal involvement.

We did not observe drug fever, factitious fever (artificially induced fever; e.g., intravenous administration of contaminated water), fraudulent fever (falsely recorded fever by manipulation of a thermometer), venous thromboembolism, subacute thyroiditis, hemophagocytic lymphohistiocytosis or other miscellaneous causes.9

Two out of six undiagnosed patients died in this series. However, some previous studies found a good prognosis in undiagnosed FUO in the elderly.5,6

Diagnostic testing

In clinical practice, a definitive diagnosis of the disease usually requires a shred of pathological or microbiological evidence in a background of clinical and radiological features. Accordingly, 29 cases (56.86%) had a definitive diagnosis (9 infections, 16 malignancies, and 4 NIIDs). Peripheral lymph nodes and BM were easily accessible sites for pathological examination; however, imaging or endoscopy-guided invasive interventions had the most excellent diagnostic utility (85.7%). Here, we experienced a changing role of radiology and nuclear imaging from making the diagnosis based on imaging findings to localizing the site of maximum disease activity for subsequent guided interventions. Body imaging (FDG-PET/CT or CECT) provided a PDC in about 60% of cases.

Inflammatory markers such as ESR, CRP, ferritin, and fibrinogen increase in response to inflammatory states, including infections, malignancies and NIIDs, and may also be affected by many noninflammatory factors.7–10,21,30 Concurring with previous data on adult FUO, this study also failed to establish their role in differentiating major groups of FUO. Their primary usefulness is that high levels detect a significant underlying disease and declining levels show a response to the treatment (empirical or definitive). Serum procalcitonin also didn’t show any utility and was somewhat misleading to start or continue antibiotics in this elderly FUO cohort, similar to a recent study on adult FUO.10

Routine immunological serological testing with RF and ANA are recommended in basic laboratory investigations for adult FUO to get a PDC for many NIIDs of young adults such as RA, SLE, autoimmune hepatitis, mixed connective tissue disease, adult-onset Still’s disease, etc.7–9 However, our report did not support their necessary testing in an elderly cohort, as testing them in a population with low pre-test probability results in a misleading PDC. Positive results are nonspecific and can be found in healthy adults with high prevalence in older age.11 Similarly, given the low prevalence of ANCA-associated vasculitis and sarcoidosis, testing ANCA and ACE levels in clinical conditions, not suggestive of these disorders may cause false-positive results. This study reinforced the fact that false-positive ANCA might occur in other NIIDs, malignancies or infections, and mild elevation of ACE levels (up to two times) can be seen in many conditions, including TB and lymphoma.32–34

We found BM examination a useful procedure to diagnose older FUO patients. It was performed in more than one-third of our study subjects (N=19) and served as a PDC in about half of them (47.4%). This diagnostic utility (47.4%) of BM examination was much higher than in previous studies on adult FUO (not limited to elderly) from Hot A et al (23.7%, N=130), Larson et al (14%, N=55), de Kleijn et al (20%, N=49), Ahmed et al (16%, N=51), and Bleeker-Rovers et al (0%, N=21).3,4,35–37

Role of empirical treatment

Published data and clinicians dealing with FUO patients recommend against empirical treatment, whenever possible, until the cause is discovered.38 However, empirical treatment may be advised in two circumstances: (1) clinically deteriorating patient, suspected to have a disease with poor prognosis; (2) when a sufficient attempt with available investigations does not reach a diagnosis but has excluded a differential diagnosis which can be masked by the empirical therapy. Both conditions require a shared decision of the patient and the physician, critical observation, and ongoing evaluation for a definitive cause. Based on these principles and concurring with previous studies, we suggest a role of the therapeutic or diagnostic trial of ATT in elderly FUO patients in endemic regions.11,39

Conclusion

In this largest prospective study of elderly FUO, infections and malignancies contributed about three-fourths of the cases, TB and lymphoma being the most frequent causes. A combination of clinical features, body imaging, and invasive procedures enables the diagnosis of most elderly FUO patients. As most of the FUO cases have a multifocal illness, body imaging reveals the site of significant disease bulk for subsequent tissue sampling besides the characteristic radiological features. Imaging or endoscopy-guided interventions and BM examination have a high diagnostic utility in geriatric FUO evaluation.

References

Abstract

Background: Chikungunya is a globally spreading infectious arboviral disease transmitted from a diurnal bite of the Aedes aegypti and Aedes albopictus Mosquitoes. It is a disease with sporadic outbreaks. It is now resurfacing in South East Asia especially in India, where it is found to have high mortality and morbidity and presenting with atypical presentation, especially with the neurotropic presentation.

Objective: To review clinical profile of patients who required admission in the Intensive care unit with atypical presentation of Chikungunya and to study their clinical spectrum and outcome over a course of three years in India.

Method and findings: Using Established guidelines, we conducted a prospective study in a Tertiary care center where we identified patients who required intensive care admissions and were admitted with complicated chikungunya infection and then evaluated their clinical progression of the disease.

Conclusion: CHIKV infection is rapidly emerging in more than 100 countries and more and more atypical serious neurological manifestations are seen in elderly populations. Many of these patients have high morbidity and mortality.

Introduction

Chikungunya is a verb in the Kimakonde dialect spoken by

of India from the 1st September 2016 till 31st August 2019.

**Material and Method**

After an Ethics committee approval, a single-center, Intensive care prospective, and descriptive study was designed.

All patients that were admitted to the intensive care unit of the hospital from 1st Sept 2016 to 31st August 2019 diagnosed to have Chikungunya fever either by Chikungunya RT PCR test or Chikungunya IgM antibodies, (A single standardized testing kit was used throughout the study to ensure consistency of the test), were considered for the study.

**Inclusion Criteria**

>16 years of age at the time of Admission

Chikungunya Rt PCR or Chikungunya IgM antibodies positive

Required Intensive Care Admission

**Exclusion Criteria**

<16 years of age at the time of Admission

Pregnant female

Patient with chronic arthritis or Skin diseases

**Patient identification and follow-up**

All patients requiring intensive care (ICU) were transferred from the ER and/or directly from the outpatient department and having symptoms suspicious of Chikungunya were screened using a Standardized Chikungunya RT PCR test and/or for Chikungunya IgM antibodies. Patients with either of the test positive were identified and considered for enrollment, All Patients who tested positive on either of the test had their biographic information, chief complaints, and history and physical examination documented on the medical record system as per the inclusion criteria.

Total (n=52) Patients required Intensive care admission and were progressively monitored.

Uniform progress case sheets were used, to ensure that the clinical progression, the day-to-day clinical manifestation, and outcome could be documented and analyzed in a standardized method.

Although this was a year-round study, the maximal number of cases were documented after the post-monsoon season during the months of August to December in all the three years.

**Results**

Total of 470 patients were screened based on their clinical history for chikungunya by Rt PCR or IgM Antibodies.

Out of these 52 patients were either positive for standardized chikungunya RT PCR, Antibodies or both and needed ICU admission were included in the study for further analysis.

67% (35 Patients) of the Intensive care patients were males, and 33% (17 Patients) were females, having a male preponderance of 2:1. Out of 52 patients, 13.6% (7 patients) had coinfection with Dengue fever.
The Admission in the Intensive care unit with CHIKV over the course of the three years 2016-2018 is depicted in the Table 1.

The youngest patient admitted in the Intensive care with Chikungunya was 24 years old and the oldest being 89 years.

The most common preexisting comorbidities were (Figure 1).

The most common symptoms present were (Figure 2).

Routine Biochemistry Revealed thrombocytopenia in 13 patients (25%), with the lowest platelet counts being about 15,500/µL, leukopenia was observed in 9 patients (17%) lowest being 1750/µL. Hyponatremia was the commonest electrolyte imbalance seen in almost 28 patients (50.3%), patients lowest being 104 mEq/L. Hypernatremia in 5 patients (9%) of Patients highest being 162 mEq/L while Rhabdomyolysis was seen in 36 patients (77.7%), with the highest document CPK value of 7988U/L.

Of the 52 Patients that were admitted to the Intensive care unit, we had 14 patients with various skin rashes, 7 patients had Erythema, 6 patients had a Maculopapular rash and 1 patient had oral ulcers (Figure 3).

33 patients had Neurological involvement with a varying degree of neurologic presentation. 24 patients had a variable degree of altered sensorium, 5 patients had dysphagia, and 4 patients had seizures during their stay in the Intensive care unit (Table 2).

Depending on clinical presentation 20 patients required CSF analysis out of these 8 patients had chikungunya positive in CSF.

16 patients underwent EEG examination of which 9 had diffuse encephalopathy 2 had epileptic discharges and 5 had normal EEG.

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The mortality rate was 25% (13 Patients) and 75% (39 patients) were discharged. 32% (n=17) had a severe manifestation of the disease. 15% were bedridden during their entire length of stay within the ICU: 3.8% required Tracheostomy, and 1.93% had residual neurological involvement upon discharge.

The average length of stay in ICU was 8 days with the maximum length of stay being 110 days (Table 3).

### Discussion

After an extensive review of literature on PubMed using the keyword “Chikungunya in India”, and limiting our search to review articles between March 2015 to March 2020, we found numerous individual case reports, reporting atypical neurotropic presentation of Chikungunya within the Indian Subcontinent, especially in the Geriatric population. One interesting finding was that the infection was seen in periodic phases.3

CHIKV is an enveloped RNA virus with a genome consisting of five structural proteins; E1, E2, E3, Capsid protein, 6k and four non-structural proteins 1(nsP1), 2(nsP2), 3(nsP3), and 4(nsP4).3,5 Studies have indicated that 70-97% of infected people will...
develop symptoms of the disease, of these individuals who were more than 65 years of age, and had underlying comorbidities with Hypertension, Diabetes Mellitus, and Coronary vascular disease were more likely to have an atypical presentation of the disease.

Until recently, Chikungunya fever was considered a non-fatal disease with sporadic deaths reported. However, the 2004–2008 epidemic saw a global increase in crude death rates. In various studies mortality rate between 4.5 % to 4.9% was reported in Mauritius and India respectively. However, both studies concluded that Chikungunya patients with neurotropic involvement had the highest morbidity and high mortality.7,8

Chikungunya infection has been found to cause both Central and peripheral neurological involvement to a varying degree. Neurological Complications take center stage accounting for up to 25% of atypical and 60% of severe atypical cases, in recent years they are the major cause of morbidity, mortality, and disability in the elderly population.9,11

Chikungunya infection was first described in 1953 in Tanzania, up to 2004, no major serious complication has been reported. In all these years chikungunya infection spread from Africa to South East Asia, Pacific Islands. A large epidemic was seen in 2013 in America and now over 100 countries have reported incidences of chikungunya infection.11,12

Immediately post these epidemics, Chikungunya fever having co-infection with other virus or bacteria were soon being reported in the literature, the most common co-infection included other mosquito-transmitted diseases-like malaria (Transmitted from the bite of the Nocturnal Female Anopheles Mosquito), Dengue, Yellow fever, Zika virus (All of these are transmitted by the same vector as Chikungunya Fever) or the Japanese encephalitis.13-15

The atypical and more severe forms of chikungunya were being described in both acute and convalescent phases with variable presentations like acute disseminated encephalomyelitis (ADEM), Guillain barre Syndrome (GBS).16-19

Our literature reviews of neurological manifestation of chikungunya in India started describing neurotropic involvement of chikungunya in India from 2005 onward after the major urban outbreaks were being reported from India.20,21

Probable reason for rising incidence of CHIKV infection could be:
1. Frequent travel and availability of immunologically naïve population
2. Peri domestic mosquitoes as vectors
4. Chikungunya transmission by Aedes Albopictus was associated with an AA. Substitution in E1 protein mutation (E1:A226V), that reportedly allowed more efficient transmission.22,23

Exact reason for increasing morbidity and neurotropism is not really known.

Numerous studies in animal models have also found that chikungunya can also disseminate to the CNS, where it infects the choroid plexuses and can then reach the CSF and infects the meningeal and ependymal cells that envelopes the CNS. It is not known to infect microvascular endothelium and neurons. However meningeal involvement and the presence of co-existing diseases in the geriatric population may explain the neurotropism seen in these patients.24

Numerous meta-analysis has suggested that the neuro complications account for about 25% of atypical cases of chikungunya fever and were a major cause of death and disability.25 In our study we noticed high mortality about 25 % (no.-13), these was probably due to high incidence of elderly populations with comorbidities and neurological involvement.19

Two independent mechanism have been proposed for neurological symptoms.
1. Direct viral CNS involvement.
2. Autoimmune.

Various studies have shown that in the direct Central nervous system involvement, the chikungunya virus enters into the choroid plexus and directly infects the meninges, ependymal cells, and astrocytes. This disrupts the Blood-Brain Barrier (BBB). This method of infection was commonly seen in infants, the elderly, and patients who had immunosuppression especially those with a weaker innate or adaptive immunity. This theory was later supported by a high ratio of chikungunya RT PCR in CSF and a short latency period before the infection.

An autoimmune mechanism was the second theory that was proposed, and in such patients, there was a prolonged latency period, before the initiation of neurological signs and symptoms and these patients responded best with Immunsuppressive therapy. The proposed Mechanism seemed to be the formation of autoantibodies from a molecular mimicry that occurred between the antigens of the pathogens and the host neural system. Leading to demyelination and delaying of nerve conduction or against gangliosides cells. A study from the epidemic of the chikungunya virus infection on Reunion Island, France, in 2005–2006 showed direct neurotoxicity as the major mechanism of Infection however this was in stark difference to the studies on the Indian population that proposed autoimmunity as the primary mechanism of involvement.26

However, our present study shows a greater number of patients showing direct neurological involvement rather than auto immune involvement.

Treatment of chikungunya is mainly supportive and treatment strategies include anti-pyretics, Non-steroidal anti-inflammatory drugs (NSAIDs) and Steroids. There are various literatures regarding role of antibiotics, antiviral, antimalarial agents such as hydroxylorquine in treatment of chikungunya. There is no valid justification for its use in acute stage of illness.27,28

Conclusions

CHIKV infection is emerging as a serious global viral infection with varying degrees of severity and atypical presentations, the exact cause of this remains partially elusive. However, many theories have been hypothesized for neurotropic involvement. The direct viral form of Neuro-Chikungunya seems to occur more frequently in the elderly population with co-morbidities and has shown to have high morbidity and mortality as also seen in our study. High index of suspicion, multispecialty care and judicious use of immunsuppressive therapies can improve the otherwise poor prognosis. As so far there is no
effective antiviral therapy available, research must be directed towards an effective vaccine development and other immunomodulatory treatment.29

Limitation of our study

This was a single institutional progressive study and so the numbers were limited, we believe a larger multicentral study should be conducted to map a detailed clinical spectrum and evaluate the extent of neurological involvement of chikungunya seen in the Indian continent.

We did not do genomic sequencing of the CHIKV genome to look for any mutations.

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Abbreviations


References

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INDICATIONS:

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

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Dosage of Glycomet GP should be individualized on the basis of effectiveness and tolerability while not exceeding the maximum recommended daily dose of glimepiride 8 mg and metformin 2000 mg. Initial dose: 1 tablet of Glycomet GP should be administered once daily during breakfast or the first main meal. Do not crush or break tablets.

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*A where immunity is reduced (Deesak T. et al.)*

References:

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Prevalence of Risk Factors of Non-communicable Diseases among Adolescents of a Rural Area in Darjeeling District of West Bengal

Shashi Kala¹, Sharmistha Bhattacherjee², Romy Biswas³, Abhijit Mukherjee⁴, Saikat Datta⁵*

Abstract
Introduction: Adolescence is the transitional period between childhood and adulthood when new health behaviors are laid down, which may track in to adulthood and have lifelong impact. Global trends show that these NCD-related behaviors are gradually rising among young people, and that they establish patterns of behavior that persist throughout life and are often hard to alter. Objective: To find out the prevalence and socio demographic predictors of risk factors of non communicable diseases among adolescents of a rural area. Methods: A community based cross sectional study was conducted among 365 adolescents residing in a rural area of Siliguri subdivision. They were interviewed and measurements were taken using standard procedure. Results: The prevalence of behavioural factors for NCDs like tobacco use, alcohol use, unhealthy diet, physically inactivity was 18.4%, 4.7%, 87.1% and 23.0% respectively; metabolic risk factors like overweight, hypertension, and abdominal obesity 28.5%, 17.5%, 1.4% respectively. After adjustment, the odds of behavioural and metabolic risk factors were found highest among the males, participants whose mothers were not working and those who belonged to Hindu families and lower socioeconomic class. Conclusion: The proportion of risk factors of non communicable diseases among the rural adolescents was quite high. Given the associated health problems and costs, non communicable diseases have become an issue of serious concern.

Introduction
Modern lifestyle has radically revolutionized the way we live and has led to the emergence and spread of lifestyle disease, also known as chronic non communicable diseases. Consequently, non-communicable diseases (NCDs) have become a key contributor to the morbidity mortality and disability in both developed countries and developing countries. Presently, NCDs cause more deaths than all other causes of mortality combined. Deaths due to NCDs are likely to escalate from 38 million in 2012 to 52 million by 2030. In the economic perspective, treatment of NCDs is exorbitantly high and lengthy which reduces millions of people into poverty annually, stifling development.¹

The picture is worse in India, where NCDs contribute to 60 % of all deaths which translates to around 5.87 million deaths. Besides this, India shares more than two-third of the total deaths due to NCDs in the South-East Asia Region of WHO.² Underlying these non communicable diseases, there are a few common and preventable risk factors. The risk factors are mainly behavioral (tobacco use, physical inactivity, unhealthy diet, and the harmful use of alcohol) that result in key metabolic/metabolic changes (raised blood pressure, overweight/obesity, raised blood glucose and raised cholesterol).³

Adolescence, midway between childhood and adulthood, is perhaps the last best chance to build positive healthy behaviors and limit unhealthy behaviors, including tobacco and alcohol use, poor eating habits, and not as much of exercise. This is the time when new health behaviors are laid down, which may track in to adulthood and have lifelong impact. Global trends show that these NCD-related behaviors are gradually rising among young people, and that they establish patterns of behavior that continue throughout life and are often hard to amend.¹ Consequently, it becomes important to monitor these risk factors in this age group with the aim to encourage the development of healthy adult life style and thereby reduce the risk of morbidity and mortality from NCDs.

As per Census 2011, overall 20.4% of the West Bengal population belongs to adolescents.⁴ However, there is dearth of published studies depicting NCD risk factor profile among the adolescents. In this perspective the present study was intended to generate information regarding the magnitude of risk factors of NCDs among the adolescents of rural area of Siliguri Subdivision of Darjeeling District, which will finally help authorities to plan community-based programs/interventions targeting the risk factors, which in turn can lead to a fall in the occurrence of NCDs.

Objectives
1. To find out the prevalence of risk...
factors of non communicable diseases among adolescents of a rural area.

2. To determine the socio demographic predictors affecting the prevalence of risk factors of non communicable diseases.

Methodology

A community-based cross-sectional study was done among adolescents of Siliguri subdivision of Darjeeling district from April to August 2016. The study population comprised of all adolescents (aged 10-19 years) residing in the study area for at least 1 year. However, adolescents with documented mental illness and other debilitating illness were excluded.

A sample size of 384 was calculated using single population proportion formula by taking the proportion (p) of adolescents using tobacco in any form as 13.1%. Supposing 95% confidence level, 5% absolute precision, design effect of 2 and non-response rate of 10% the final sample size was calculated as 385, which was rounded off to 390 for an equal sub-sample of 13 each from 30 clusters (tea gardens/villages).

Firstly, 30 clusters were selected from a list of villages/tea gardens using the probability proportional to size method. In each cluster, with a random start from the center, consecutive households were visited to select 13 willing adolescents. If there were more than one adolescent in a single house, only one adolescent was selected from each household randomly.

Outcome variable

Presence of behavioural or metabolic risk factors was considered as the outcome variables.

Explanatory variables

Explanatory variables were age, gender, religion, mother’s occupation and socio-economic status of the family.

Ethical committee approval

Prior to conduction of study, ethical clearance was obtained from the Institutional Ethics Committee of North Bengal Medical College, Siliguri, West Bengal, India. Informed consent and assent were obtained from the guardians and the participating adolescents respectively and they were also reassured that full confidentiality would be maintained within the limits of medical ethics.

Data collection

The data were gathered from the study population at their households by using a predesigned, pretested, semi-structured proforma which included details of socio-demographic characteristics (age, gender, religion, caste, occupational status, educational status, parent’s education and occupation and socioeconomic status) and information of different risk factors of non-communicable diseases (smoking, alcohol, unhealthy diet and physical inactivity). Customization of the questionnaire was done by initial translation, back-translation, and re-translation, followed by pre-testing of the questionnaire among a convenience sample of 30 adolescents attending the General OPD of North Bengal Medical College and Hospital.

Anthropometric characteristics and blood pressure measurements were done by the investigators during daytime at the household setting of the participant. In case of female participant, a female attendant was present during examination.

Measurements of risk factors

Blood pressure (BP): According to the standardized technique, BP was measured after at least 5 min of rest, on the non-dominant arm of participants, at the level of the heart, while participants remained seated with back support. A calibrated mercury sphygmomanometer with suitable cuff size was used. Two measurements were taken and averaged for analysis.

Height measurement: The participants were asked to take out their shoes/slippers and head gear. They were then asked to stand with feet together, heels against the wall and knees straight. They were asked to look straight ahead and not incline their head up with eyes at the same level as the ear. The height was measured using non stretchable measuring tape to the nearest of 0.1cm.

Weight measurement: Weight was measured using standard portable weighing machine. The weighing machine was placed on a firm flat surface. Calibration of the scale was done at the beginning of measurement and before each measurement. Then participants were asked to remove their shoes/ slippers and socks and heavy outer garments and asked to step onto scale. The participants were asked to stand still with face forward and arms placed on the sides. The weight was measured to the nearest of 0.1 kilograms (kg). Body mass index was computed (weight [kg]/height$^2$ [m$^2$]).

Measurement of waist circumference: Participants were asked to get rid of their heavy outer garments and remain in minimal clothing. Then they were asked to breathe normally and stand with their feet together. The measuring tape was held firmly, ensuring its horizontal position and loose enough to allow one finger between the tape and the subject’s body. This measurement was taken at the end of a normal expiration; with the arms relaxed at the sides; and at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest (hip bone) to the nearest of 0.1cm.

Behavioral risk factors for non-communicable diseases were defined as follows:

1. Tobacco use: Participants were grouped into current smokers of cigarettes or bidis (yes/no) or use of smokeless tobacco (yes/no) in the 7 days prior to the interview and frequency of such was noted. Smoking or use of smokeless tobacco more than once in last 7 days was considered as risk factor.

2. Alcohol consumption: Participants were questioned about alcohol use (yes/no) and classified as users or non-users, where users had consumed one or more standard alcoholic drinks in the last 30 days.

3. Inadequate fruit and vegetable consumption: Average daily number portions of fruits/vegetables consumed by the study participants over the last 7 days were calculated. Daily fruit and vegetable consumption of less than 5 portions was considered to be inadequate, per the WHO recommendations of NCD behavioral risk factor indicators.

4. Physical inactivity: The participants were enquired about the time spent in moderate physical activities during a typical week. Adolescents who reported doing less than 30 minutes of work for at least 3 days per week were considered as having the risk factor.

Metabolic risk factors for NCD were defined as follows:

1. Overweight: World Health Organization...
Organization (WHO) guidelines for BMI for adolescents were used to classify the study participants.

2. Abdominal obesity: As per the WHO definition, waist circumference of >102 cm in men and >88 cm in women was defined as having abdominal obesity.

3. Hypertension: Normal BP was defined as an average systolic BP (SBP) and/or diastolic BP (DBP) <90th percentile for age, sex and height. Prehypertension was recognized if the mean SBP and/or DBP was ≥90th and <95th percentile for age, sex and height, or if the average SBP was >120 mmHg or DBP was >80 mmHg for adolescents. Hypertension (stages 1 and 2) was defined as average SBP and/or DBP ≥95th percentile, while average SBP and/or DBP >99th percentile plus 5 mmHg indicated stage 2 disease.

Statistical analysis

The data collected were compiled, entered and analysed by IBM SPSS version 20. The proportion of risk factors was expressed in number and percentages. To find out the predictors, binary logistic regression analysis was used. The dependent variable in the analysis were behavioural risk factors and metabolic risk factors, which were converted to dichotomous variables, where having one or more risk factors was considered as 1 and not having any was considered as 0. The predictor variables used for the analysis were age group, gender, religion, mothers’s occupational status and socio-economic status. Multicollinearity among the independent variables was identified by the Variance Inflation Factor (VIF) test (<2).

Results

Among the 390 adolescents recruited for the study, complete data could be collected from 365 participants. The mean±SD age of the participants was 14.3 ± 2.8 years. Majority of the study population were early adolescents (43.8%), males (61.4%) and belonged to families practising Hinduism (96.2%) and belonging to a lower socio-economic stratum (64.1%).

The proportion of behavioural factors for NCDs like tobacco use, alcohol use, unhealthy diet, physically inactivity was 18.4%, 4.7%, 87.1% and 23.0% respectively; metabolic risk factors like overweight, hypertension, and abdominal obesity 28.5%, 17.5%, 1.4% respectively (Table 1).

Similarly, higher odds of metabolic risk factors were found in males, participants whose mothers were not working and those who belonged to Hindu families and lower socioeconomic class. However, the odds were higher in the early adolescent age group (10-13 years) than their older counterparts.

In the same way, after adjusting for the predictors, the model elucidated between 7.9% (Cox and Snell R-square) and 10.7% (Nagelkerke Rsquare) of variance of metabolic risk factors in the study subjects, and rightly classified 49.7% of cases. The input of the independent variables was not significant. [Hosmer and Lemeshow Test Chi square value was 4.263 and significance was 0.833.]

Discussion

In the present times, risk factors of non communicable diseases have become a major public health challenge worldwide, the effect of which is grave in terms of premature morbidity, mortality, and economic loss. There is a developing body of evidence which suggests that most of these diseases have their roots in the behaviours acquired during adolescence. So it becomes imperative to study the prevalence of risk factors among adolescents.

The present study infers that the risk factors was quite prevalent among the rural adolescents. The figures were quite high compared to a study

| Table 1: Prevalence of risk factors of non-communicable diseases among the study population n=365 |
|---------|---|---|
| Behavioural risk factors | N | % |
| Tobacco use | 67 | 18.4 |
| Alcohol use | 17 | 4.7 |
| Unhealthy diet | 318 | 87.1 |
| Physically inactive | 84 | 23.0 |
| Metabolic risk factors | | |
| Over weight | 104 | 28.5 |
| Abdominal obesity | 5 | 1.4 |
| Hypertension | 64 | 17.5 |
| | | |

| Table 2: Predictors of risk factors of non-communicable diseases among the study population n=365 |
|---|---|---|---|---|---|---|
| Behavioural risk factors | Metabolic risk factors | Total |
| Present | Absent | AOR (95% CI) | Present | Absent | AOR (95% CI) |
| Age group | | | | | | |
| Early adolescent (10-13 years) | 143 (89.4) | 17 (10.6) | 1 (Referent) | 89 (55.6) | 71 (44.4) | 1 (Referent) | 160 (43.8) |
| Mid adolescent (14-16 years) | 95 (88.8) | 12 (11.2) | 0.97 (0.44 - 2.18) | 32 (29.9) | 75 (70.1) | 0.34 (0.20 - 0.57) | 107 (29.3) |
| Late adolescent (17-19 years) | 95 (96.9) | 3 (3.1) | 4.48 (1.24 - 16.11) | 29 (28.6) | 70 (71.4) | 0.31 (0.18 - 0.55) | 98 (26.8) |
| Gender | | | | | | | |
| Female | 126 (89.4) | 15 (10.6) | 1 (Referent) | 57 (40.4) | 84 (59.6) | 1 (Referent) | 141 (38.6) |
| Male | 207 (92.4) | 17 (7.6) | 1.56 (0.72 - 3.35) | 92 (41.1) | 132 (58.9) | 1.24 (0.59 - 2.65) | 224 (61.4) |
| Religion | | | | | | | |
| Muslim | 13 (92.9) | 1 (7.1) | 1 (Referent) | 5 (35.7) | 9 (64.3) | 1 (Referent) | 14 (3.8) |
| Hindu | 320 (91.2) | 31 (8.8) | 1.29 (0.15 - 10.83) | 144 (41.0) | 207 (59.0) | 1.16 (0.36 - 3.66) | 351 (96.2) |
| Mother’s occupation | | | | | | | |
| Stay at home | 228 (91.9) | 20 (8.1) | 1 (Referent) | 108 (43.5) | 140 (56.5) | 1 (Referent) | 248 (67.9) |
| Working | 105 (89.7) | 12 (10.3) | 0.80 (0.37 - 1.74) | 41 (35.0) | 76 (65.0) | 0.67 (0.42 - 1.08) | 117 (32.1) |
| Socio-economic status | | | | | | | |
| Lower SES | 218 (93.2) | 16 (6.8) | 1 (Referent) | 102 (43.6) | 132 (56.4) | 1 (Referent) | 234 (64.1) |
| Higher SES | 115 (87.8) | 16 (12.2) | 0.39 (0.18 - 0.85) | 47 (35.9) | 84 (64.1) | 0.80 (0.50 - 1.29) | 131 (35.9) |
| Total | 333 (91.2) | 32 (8.8) | 1 (Referent) | 216 (59.2) | 149 (40.8) | 1 (Referent) | 365 (100.0) |
among high school going adolescents in Mangalore. This may be due to difference in dietary and social habits in Eastern and Southern India.

Initiation of tobacco most commonly happens during adolescence, who are the key targets of the tobacco industry when recruiting new smokers. According to Global Youth Tobacco Survey (GYTS), 14.6% of students currently use any form of tobacco; 4.4% currently smoke cigarettes; 12.5% currently use some other form of tobacco. This may be attributed to psychosocial reasons like peer pressures, curiosity, yearning for excitement and experimentation or as a stress buster.

Use of alcohol by adolescents has become a major issue nowadays. Recent evidence suggests that brain development continues well into adolescence and that alcohol consumption can affect such development. Similar to the present study, a study by Mohanan et al in Udupi district of Karnataka found that the prevalence of alcohol consumption was 5.7%.

Mushrooming of fast-food eateries and eating-out practices contribute to unhealthy dietary habits among adolescents. Contrary to the popular belief, this trend is not limited to urban areas, but has spread to rural areas, like the present study, as well. Similar observations were seen in studies done in urban Delhi and rural Karnataka.

Traditionally, daily active play and physical activity are an integral part of life for children and adolescents which is also essential for their healthy growth and development. However, computers and social media have decreased the need and desire for children to move and play. The present study and studies done in other parts of the country and world reflect the same fact.

The proportion of overweight children and adolescents has dramatically increased over the recent years and has become a major public health challenge for policy makers. Overweight and abdominal obesity in adolescents can result in myriad health effects, including type 2 diabetes, obstructive sleep apnea, hypertension, dyslipidemia, and the metabolic syndrome. A systematic review by de Moraes et al found the prevalence of abdominal obesity varied from 3.8% to 51.7% in adolescents from developing countries which was higher than the figures in developed countries.

Hypertension among adolescents has important health implication over development of cardiovascular diseases in adulthood. A recent study in urban Delhi revealed that the total prevalence of hypertension was 8%. However, the figures in the present study were much higher.

**Predictors of risk factors**

**Age**

The odds of having behavioural risk factors were found to increase with age. With increasing age, adolescents are less under the supervision of parents and have more peer influence. However, the decreasing odds of metabolic risk factors with age may be due to experimentation with looks among the older adolescents.

**Gender**

Males and females have different levels of exposure and vulnerability to NCD risk factors. Quite obviously, a study among adolescents of urban Delhi also reported higher odds of lifestyle risk factors among males, which was quite similar to the present study.

**Religion**

Religion may have a significant role in the shaping of behaviours among adolescents. In Muslims, use of alcohol beverages is mostly prohibited. On the other hand, the dietary practices among Hindus and Muslims are quite dissimilar which may be reason for the findings of the present study. A study by Gupta et al found that the risk factors for coronary heart disease were more prevalent among the Hindu study participants than their Muslim counterparts.

**Maternal occupation**

The role of a mother is paramount to developing healthy habits in adolescents. Presently, the redefining of the role of women from housewives to working mothers has significant implications for child development. It has often been argued that adolescent having working mothers are under lessened supervision which may tend to increase the risk of negative peer influences leading to involvement in numerous unhealthy behaviours. However, the present study reveals a completely different picture. This may be due to the small proportion of adolescents with working mothers in the current study.

**Socioeconomic status**

Once thought of as diseases of the affluent society, in the present era NCDs have been found to have close links with poverty, and the rapid rise in NCDs is predicted to hinder poverty alleviation programs in low-income countries. Evidence suggests that often the lowest income households have the highest proportions of NCD risk factors. Similar picture was observed in the present study. The reason for this may be detrimental behaviours linked to NCDs such as smoking and alcohol abuse are often a coping strategy for the stresses and challenges poor people face in their daily lives. Moreover, the preventive services which can be accessed by higher income groups may not be afforded by people of lower income groups.

**Conclusion**

The result of the present study gives an idea that the risk factors for NCD are widely prevalent among rural adolescents. The proportion of risk factors of non-communicable diseases among the adolescents, together with the associated health problems and costs, is a cause of vital concern among health care professionals and parents. The study recommends that an all-inclusive school based education scheme and a family based approach to be initiated to prevent such unhealthy practices.

**Limitations of the study**

The behavioural risk factors were self-reported and thus there may be a chance of social desirability bias. Besides, the inherent limitation of cross-sectional study cannot be ruled out as there were no longitudinal inferences.

**Future scope of the study**

A longitudinal study can be done to know the extent and progress of risk factors of non-communicable diseases from childhood to adolescence, so that timely interventions can be taken.

**What this study adds**

With the advent of newer means of entertainment and dietary practices, rural adolescents have begun to embrace these harmful behaviours, like their urban peers, which are taking a massive toll on their health and future.
Comparative Effects of Pegylated Erythropoietin and Darbepoetin Alfa on Erythropoietin Hyporesponsive Anemia of Patients with Chronic Kidney Disease on Maintenance Hemodialysis

Nitya Nand1*, Raghu Nandan2, Deepak Jain3

Abstract

Objectives: This study was carried out to evaluate the effect of pegylated erythropoietin and to compare its effects with the effects of darbepoetin alfa on anemia of chronic kidney patients on maintenance hemodialysis having erythropoietin hyporesponsiveness.

Methods: Forty adult patients of chronic kidney disease (CKD) with erythropoietin hyporesponsiveness undergoing maintenance hemodialysis were included in the study. These patients were randomly divided into two groups, Group A consisting of 20 patients who received Subcutaneous Pegylated erythropoietin at a dose of 0.6 mcg/kg body weight, once in every two weeks along with intravenous iron 100 mg/week for 3 months. Group B patients received subcutaneous darbepoetin alfa at a dose of 0.45 mcg/kg body weight once weekly along with iv iron 100mg/week for 3 months. Hematological, renal and inflammatory parameters such as erythrocyte sedimentation rate, C reactive protein, serum ferritin and transferrin saturation were measured at monthly intervals for three months, compiled and analyzed statistically.

Results: At the end of the study, in group A there was a significant rise in the hemoglobin, haematocrit and transferrin saturation (p < 0.001 for each of them) while there was a significant decrease in serum ferritin levels (p<0.001). In group

Introduction

Chronic kidney disease (CKD) is an important, chronic, non-communicable disease epidemic that affects the world, including India. A normocytic normochromic anemia develops in patients with CKD usually when the GFR falls below 30 ml/ min. Anaemia in CKD patients has been effectively treated with Erythropoietin stimulating agents (ESA). However hyporesponsiveness is one of the major issues in patients undergoing hemodialysis. Improving

References


ESA hyporesponsiveness not only improves patient’s quality of life, but also reduces the burden of the cost of care. Factors causing erythropoietin hyporesponsiveness include iron deficiency, various infections, inadequate dialysis, chronic blood loss, hyperparathyroidism, aluminium toxicity, malnutrition, vitamin deficiency and others.

The shorter half lives of conventional ESAs including erythropoietin alfa and beta, necessitates frequent administration to maintain target Hb levels. In this context, introduction of newer ESAs Darbepoetin alfa, the 2nd generation ESA and Polyethylene glycol EPO (Peg-Epo) also referred to as “continuous erythropoietin receptor activator (C.E.R.A) the 3rd generation ESA as made marked influence on the dosage intervals of the ESAs for correction of anemia in CKD patients due to their longer half lives. Though both the newer ESAs have longer half-lives, studies have shown that Peg–EPO stimulates erythropoiesis more effectively when administered intravenously or subcutaneously at a prolonged dosing interval. This study was planned to evaluate and compare the effects of these newer ESAs on anemia of CKD patients on maintenance hemodialysis.

Table 1: Baseline Biochemical Parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group A (Mean±SD)</th>
<th>Group B (Mean±SD)</th>
<th>P (unpaired)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin g/dl</td>
<td>7.06±0.75</td>
<td>7.26±0.88</td>
<td>0.459</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>20.35±2.25</td>
<td>21.13±2.08</td>
<td>0.696</td>
</tr>
<tr>
<td>Blood Urea (mg%)</td>
<td>112.25±16.38</td>
<td>112.4±13.08</td>
<td>0.966</td>
</tr>
<tr>
<td>Serum Creatinine (mg%)</td>
<td>5.87±1.29</td>
<td>6.72±0.85</td>
<td>0.246</td>
</tr>
<tr>
<td>Random Blood Sugar (mg%)</td>
<td>108.25±21.24</td>
<td>113.15±15.80</td>
<td>0.421</td>
</tr>
<tr>
<td>Serum Electrolytes Sodium (meq/l)</td>
<td>141.90±6.70</td>
<td>142.20±5.28</td>
<td>0.876</td>
</tr>
<tr>
<td>Potassium (meq/l)</td>
<td>4.73±0.85</td>
<td>4.95±0.93</td>
<td>0.622</td>
</tr>
<tr>
<td>Serum Uric acid (mg%)</td>
<td>6.99±0.88</td>
<td>7.41±1.77</td>
<td>0.338</td>
</tr>
<tr>
<td>Serum Calcium (mg%)</td>
<td>8.04±0.45</td>
<td>8.01±0.38</td>
<td>0.818</td>
</tr>
<tr>
<td>Serum Phosphate (mg%)</td>
<td>6.31±1.01</td>
<td>6.11±1.78</td>
<td>0.657</td>
</tr>
<tr>
<td>Serum Protein (g/dl)</td>
<td>3.80±0.80</td>
<td>3.90±0.44</td>
<td>0.324</td>
</tr>
<tr>
<td>S. Albumin (g/dl)</td>
<td>1.20±0.54</td>
<td>1.30±0.63</td>
<td>0.586</td>
</tr>
<tr>
<td>G.F.R (ml/min/1.73m²)</td>
<td>7.28±3.04</td>
<td>7.72±3.26</td>
<td>0.658</td>
</tr>
<tr>
<td>Serum Ferritin (ng/ml)</td>
<td>603.40±226.13</td>
<td>576.85±354.24</td>
<td>0.779</td>
</tr>
<tr>
<td>Transferrin saturation (%)</td>
<td>18.55±1.41</td>
<td>18.69±1.40</td>
<td>0.742</td>
</tr>
<tr>
<td>iPTH (pg/ml)</td>
<td>249.05±41.54</td>
<td>252.6±31.44</td>
<td>0.772</td>
</tr>
</tbody>
</table>

Table 2: Comparison of baseline hematological parameters with the parameters at subsequent months in both the groups

<table>
<thead>
<tr>
<th>Group A</th>
<th>0 Month</th>
<th>1 Month</th>
<th>0 vs 1 Month P (paired)</th>
<th>2 Months</th>
<th>0 vs 2 Months P (paired)</th>
<th>3 Months</th>
<th>0 vs 3 Months P (paired)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>7.06±0.75</td>
<td>7.66±0.75</td>
<td>&lt; 0.001</td>
<td>9.46±0.59</td>
<td>&lt; 0.001</td>
<td>10.11±0.69</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>20.35±2.25</td>
<td>21.32±2.31</td>
<td>&lt; 0.001</td>
<td>28.29±1.90</td>
<td>&lt; 0.001</td>
<td>30.04±1.62</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Serum ferritin</td>
<td>603.40±226.13</td>
<td>549.65±180.76</td>
<td>&lt; 0.001</td>
<td>497.30±142.57</td>
<td>&lt; 0.001</td>
<td>457.35±120.45</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Transferrin saturation (%)</td>
<td>18.55±1.41</td>
<td>23.1±1.99</td>
<td>&lt; 0.001</td>
<td>29.19±2.62</td>
<td>&lt; 0.001</td>
<td>34.21±3.25</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group B</th>
<th>0 Month</th>
<th>1 Month</th>
<th>0 vs 1 Month P (paired)</th>
<th>2 Months</th>
<th>0 vs 2 Months P (paired)</th>
<th>3 Months</th>
<th>0 vs 3 Months P (paired)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>7.26±0.88</td>
<td>7.66±0.75</td>
<td>&lt; 0.001</td>
<td>7.42±0.82</td>
<td>P&lt;0.05</td>
<td>7.41±0.68</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>21.13±2.06</td>
<td>20.1±2.31</td>
<td>P&lt;0.01</td>
<td>22.27±2.40</td>
<td>P&lt;0.01</td>
<td>22.23±2.07</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Serum ferritin</td>
<td>576.85±235.2</td>
<td>601.25±267.1</td>
<td>P&lt;0.001</td>
<td>635.75±302.7</td>
<td>P&lt;0.001</td>
<td>664.7±292.7</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Transferrin saturation (%)</td>
<td>18.69±1.40</td>
<td>18.7±1.0</td>
<td>P&lt;0.254</td>
<td>19.0±1.22</td>
<td>P&lt;0.0001</td>
<td>19.1±1.61</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

Material and Methods

Forty adult chronic kidney disease patients receiving subcutaneous erythropoietin 6000 IU twice weekly with i.v iron 100 mg/ week with erythropoietin hyporesponsiveness undergoing maintenance hemodialysis were included in the study. These patients were randomly divided into two groups (20 in each group). Patients in group A received pegylated erythropoietin (0.6 mcg/kg body weight, s/c) once in two weeks and i.v iron 100 mg /week, after the hemodialysis session for 3 months. Patients in group B received darbepoetin alfa (0.45 mcg/ kg body weight, s/c) once weekly and i.v iron 100 mg/week after the hemodialysis session for 3 months. Patients included were adult patients of chronic kidney disease on maintenance hemodialysis who are anemic (Hb < 9 gm/dl) and despite receiving erythropoietin in a dose of 6000 IU twice weekly and injectable iron 100 mg/week for 2 months, showing no improvement in haemoglobin levels or requiring increase in erythropoietin dose to maintain Hb level > 9 gm/dl.

Serum ferritin was measured using a two site sandwich immunoassay based on direct chemiluminometric technology, which uses two antiferritin antibodies at constant amount. Intact parathyroid hormone (iPTH) was measured on the Elecsys 1010 using a sandwich principle. Hs-CRP assay was done using latex-enhanced immunonephelometric assay. Statistical analysis was performed using SPSS software version- 17.0. For comparison of means of same parameter in two groups, unpaired student t test was used and for comparison of means of same parameter in a single group at two different points of time during follow up, paired student t test was used. Repeated measures analysis
of variance (ANOVA) test was used for comparison of means of different parameters at 0, 1, 2 and 3 months and p-values obtained to determine the statistical significance.

**Results**

103 CKD patients who were undergoing regular maintenance hemodialysis were screened. After 1 month of erythropoietin therapy, 61 patients were found to have inadequate rise in Hb (< 1 g/dl rise in Hb in one month). The dose of erythropoietin was increased to 6000 IU S/C twice weekly and response was seen after one month. 8 patients showed good response and were excluded from the study. One patient could not complete the study due to upper GI bleed. Finally 52 patients were labeled as erythropoietin resistant and were randomly divided into two groups, A and B. Group A included 26 patients who received pegylated erythropoietin and Group B included 26 patients who received darbepoetin alfa for 3 months. Out of these 52 patients, 12 patients couldn’t complete the study. 5 patients (2 in group A and 3 in group B) left the study in between due to some unknown causes and 7 patients (4 in group A and 3 in group B) expired during the study. So finally 40 patients (20 in each group) completed the study.

Mean age of study participants were 46.4±14.65 and 46.3 ±14.98 years in group A and group B respectively. Most common cause of CKD was hypertension in both the groups (7 patients in each group) followed by diabetic nephropathy (6 in group A and 5 in group B). The various hematological and renal parameters in both the groups were comparable at baseline (Table 1). At the end of the study, in group A, there was a significant increase in Hb from 7.06±0.75 to 10.11±0.59 g/dl (p<0.001) and hematocrit increased from 20.35±2.25 to 30.04±1.62 % (p<0.001) while mean serum ferritin decreased significantly from 603.40±226.13 to 457.35±120.45 (p<0.001) and transferring saturation increased significantly from 18.24±1.11 to 34.21±3.25 (p<0.001). In group B, the rise in Hemoglobin and hematocrit was statistically significant at the end of first month but it was not significant at second and third months. Also the rise in serum ferritin was found to be statistically significant from 576.85±354.24 to 664.70±292.71 (p<0.001) and the rise in transferring saturation was not statistically significant (p>0.05). The mean rise in the haemoglobin and the hematocrit between the subsequent months was higher in group A as compared to group B (Tables 2, 3) (Figure 1). It was observed that there was gradual reduction in blood urea, serum creatinine, serum uric acid and serum phosphate from baseline to values at 3 months in both the groups, which was statistically significant (p<0.05), which reflected the adequacy of hemodialysis and the changes in serum sodium, serum potassium, serum calcium, serum proteins, iPTH, proteinuria and GFR, blood pressure in both the groups were not found to be statistically significant (p>0.05).

**Discussion**

Anemia is a major co-morbidity of CKD patients. It develops early in the course of CKD and is nearly universal. It is directly correlated with the degree of impairment of renal function and considered one of the hallmarks of the disease. The anaemia of CKD is characterized by hypoproliferative and normocytic normochromic and is due to decreased production of erythropoietin by the diseased kidneys. It contributes to poor quality of life (QOL) and adverse pathophysiogetic consequences both due to effects of decreased oxygen delivery to tissues and to the heart’s compensatory mechanism. Introduction of erythropoiesis stimulating agents has resulted in substantial health benefits, including improved quality of life, reduced blood transfusion requirement, enhance exercise capacity and cognitive functions. However, 5-10 % of patients show hyporesponsiveness and contributes significantly to morbidity, mortality and health care economic burden in CKD. ESA hyporesponsiveness may be due to a number of factors and increasing the dose of EPO and maintaining adequate iron stores, by administering parenteral iron, is the most important measures for reducing the requirements and enhancing the efficacy of ESA. It has also been improved by a number of interventions, including the use of biocompatible membranes, ultrapure dialysate, transplant, nephrectomy, ascorbic acid therapy, vitamin E supplementation, statins and pentoxifylline administration.

Inflammation has also been considered as one of the most important cause of erythropoietin hyporesponsiveness and in turn anemia. Evidence suggests that inflammation is associated with hemoglobin variability and predicts for less stable anemia control in CKD patients. Inflammatory response leads to reduced erythropoiesis by inhibiting erythropoietin secretion, accelerated destruction of erythrocytes and blunting of the reactive increase in erythropoietin in response to reduced hemoglobin levels. Inflammation also causes increased ferritin production and impaired transferrin saturation and this prevents iron delivery to erythrocytes precursors by shunting iron to reticulo endothelial storage pool leading to a state of functional iron deficiency.

Few studies have found that pegylated erythropoietin facilitates iron mobilization from the tissue stores, improve iron utilization by the erythrocyte precursors, thereby causing a significant increase in hematocrit and transferrin saturation and decrease in percentage of hypochromic red cells & serum ferritin and thus can effectively overcome the EPO resistance due to functional iron deficiency. A study done by M Kakimoto-shino et al indicated that long half life erythropoiesis stimulating agents such as pegylated erythropoietin caused significant reductions in hepcidin, reticuloocyte hemoglobin equivalent, ferritin and transferring saturation levels within 1 week of its administration and that a significant increase in hemoglobin was noted within 2 weeks of treatment. Another study done by Marikami et al confirmed that a biweekly dose regimen of pegylated erythropoietin led to continuous erythropoiesis and had a favorable effect on iron metabolism in chronic kidney disease patients on hemodialysis.

In this study, we used pegylated erythropoietin (0.6 mcg/kg body weight, s/c) once in two weeks and i.v iron 100 mg/week for three months to one group and the other group was given darbepoetin alfa (0.45 mcg/kg body weight, s/c) once weekly and i.v iron 100 mg/week for three months and found that the use of pegylated erythropoietin improved anemia, transferrin saturation significantly and...
also reduced the high level of ferritin in these patients.

We also found in this study that in group B patients with normal ferritin level and EPO hyporesponsiveness, where darbepoetin alfa and intravenous iron was given, the rise in hemoglobin, transferrin saturation was not significant and there was also a significant rise in serum ferritin levels at the end of three months, suggestive of persistent EPO hyporesponsiveness. This suggests that the increased response to pegylated erythropoietin in group A patients was probably as a result of better utilization of the available iron by reducing the levels of hepcidin which is a key regulator of iron metabolism. We tried to exclude all other factors responsible for erythropoietin resistance. We used aluminium free rain canal water for the study. Infections were treated aggressively as early as possible. Therefore, probable factor which was operative for the decreased hemoglobin in group B was most probably due to chronic inflammatory state, which is essentially a basic feature of CKD.

It can therefore be concluded that pegylated erythropoietin is better than darbepoetin alfa in overcoming erythropoietin hyporesponsiveness and maintaining stable hemoglobin levels in CKD patients on maintenance hemodialysis. However, further studies are needed to determine whether prolonged dosing intervals will confer the same beneficial effects in these patients and particularly for patients not on dialysis.

References

Scleroderma Renal Crisis is Associated with High Mortality: A Real-World Study from India

Preksha Dwivedi1, Adarsh MB2, Nupoor Acharya3, Raja Ramachandran4, Ritambhra Nada5, Shankar Naidu6, Shefali K Sharma7, Aman Sharma8, Sanjay Jain8, Varun Dhir7*

Abstract

Introduction: Scleroderma renal crisis (SRC) is a life-threatening complication of systemic sclerosis. Since the use of ACE inhibitors in this condition, there has been a significant reduction of mortality rates. However, there is limited data on characteristics and outcomes of SRC from developing countries.

Method: This was a single centre, case-control study from India. The records of all patients admitted in the last 5 years were scrutinized, and patients with SRC (as per the updated consensus classification, 2014) were compared with patients of systemic sclerosis who were admitted for other reasons (controls). Disease characteristics, between cases and controls, were compared using chi-squared test, and odds ratios (OR) were calculated. Survival was compared using Kaplan-Meier statistics.

Results: Ninety-four patients of systemic sclerosis admitted over five-years; among them 15 had SRC. As compared to controls, those with SRC had a significantly higher rates of pericardial effusion (OR 11.7, p=0.02), dilated cardiomyopathy (OR 2.5, p=0.04), myopathy (OR 19.3, p=0.001), taking medium-high dose glucocorticoids (OR 7.9, p=0.009) and recent disease onset (OR 39.3, p=0.01). Despite aggressive control of hypertension with ACE inhibitors, 10/12 patients with SRC died. Mean (SD) survival in patients with SRC (11.5, 95% CI 5.7 to 17.6 months) was significantly lower than controls (66.2, 95% CI 58.4 to 73.9 months, p<0.001).

Conclusion: In this single-centre study from a developing country, scleroderma renal crisis was associated with a dismal prognosis, despite the use of ACEI. The recent use of medium-high dose glucocorticoids was associated with SRC.

Introduction

Scleroderma renal crisis (SRC) is a severe and life-threatening manifestation of systemic sclerosis. The prevalence of SRC varies from 2-15% in patients with systemic sclerosis, being more common in patients with early, diffuse and progressive disease. It was a common cause of death in systemic sclerosis thirty-years ago, accounting for 42% of deaths; however just 6% of deaths are currently ascribed to it.2 The long-term prognosis of SRC still remains poor, with a 5-year mortality of 65%.3

The characteristic clinical features of SRC are malignant hypertension and progressive renal failure; however in 10% of cases, the blood pressure may be normal. The primary insult in this condition is thought to be endothelial injury, which leads to intimal proliferation followed by platelet aggregation and adhesion.4 SRC is associated with features like rapid skin thickening, cardiac complications, large joint contractures, and presence of anti-RNA polymerase III antibody.5 In addition, treatment with corticosteroids and cyclosporine has been found to be associated with its development.

A majority of the literature on SRC is from the Western world, with little data from the developing world. Thus, this study was planned to look at the clinical characteristics, predisposing factors and outcome of patients with SRC from a single Indian centre.

Patients and Methodology

This was retrospective study of patients of systemic sclerosis with scleroderma renal crisis, from a Rheumatology unit of a University hospital in North-India. The study was approved by the institutional ethics committee (IEC/2020/SPL-494 dated 22.04.2020). A waiver for patient consent was obtained from the ethics committee.

We scrutinised records of patients admitted with a diagnosis of systemic sclerosis (fulfilling 2013 classification criteria) between January 2014 to August 2018, and selected those with a diagnosis of SRC as per criteria given below. In addition, patients of systemic sclerosis who were admitted for other reasons, were selected as diseased controls, in a ratio of 1 case: 2 controls. A computer generated random number table was used for the selection of controls. Files of cases and controls were retrieved, and data on clinical and laboratory parameters were extracted with the help of a pre-designed proforma.

Scleroderma renal crisis (SRC) was defined as per the 2014 updated consensus classification.6 This defined blood pressure parameters for SRC, and required the presence of at least one associated feature: >50 % increase in serum creatinine over baseline or

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Table 1: Baseline characteristics of patients with scleroderma renal crisis (SRC) and those without SRC (non-SRC controls) included in this study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SRC (N=15)</th>
<th>Non-SRC Controls (N=30)</th>
<th>P-value</th>
<th>Odds ratio (95% Confidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean(±SD)</td>
<td>47.3±9.6</td>
<td>40.0±11</td>
<td>0.05</td>
<td>39.3 (2.774)</td>
</tr>
<tr>
<td>Female: Male</td>
<td>12.3</td>
<td>28.2</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Diffuse cutaneous, n (%)</td>
<td>12 (80)</td>
<td>19 (63)</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>Disease duration, months, median (IQR)</td>
<td>24 (6-36)</td>
<td>42 (24-111)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Blood pressure, Systolic (mmHg), mean(±SD)</td>
<td>160.9±26.9</td>
<td>115.4±18.9</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Blood pressure, Diastolic (mmHg), mean(±SD)</td>
<td>92.4±12.4</td>
<td>71.8±9.7</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>9.4±1.8</td>
<td>10.8±1.4</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>Serum Creatinine (mg/dl)</td>
<td>6.1±3.3</td>
<td>0.9±1.0</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Platelet count (x10^9/L)</td>
<td>1.7±0.8</td>
<td>2.8±1.2</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td>2.8±0.6</td>
<td>3.7±0.6</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>24-hour urine protein, mg, median (IQR)</td>
<td>578 (316-2500)</td>
<td>140 (87-202)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Lactate dehydrogenase (IU/L)</td>
<td>900.2±314</td>
<td>628.3±129.7</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>ANA, n (%)</td>
<td>10/11(91)</td>
<td>16/17(94)</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Sc70 positive, n (%)</td>
<td>3/10 (30)</td>
<td>4/16 (25)</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Risk factors or associations with scleroderma renal crisis (SRC) – comparison with systemic sclerosis controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SRC (N=15)</th>
<th>Non-SRC Controls (N=30)</th>
<th>P-value</th>
<th>Odds ratio (95% Confidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration &lt; 1y, n (%)</td>
<td>6 (40)</td>
<td>0 (0)</td>
<td>0.01</td>
<td>39.3 (2.774)</td>
</tr>
<tr>
<td>Ongoing steroid use, n (%)</td>
<td>10 (67)</td>
<td>13 (43)</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>Steroid dose, mg/d, median (IQR)</td>
<td>35 (12.5-50)</td>
<td>7.5 (6.2-27.5)</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Steroids dose &gt;15mg/day, n (%)</td>
<td>7 (47)</td>
<td>3 (10)</td>
<td>0.009</td>
<td>7.9 (1.6-37.7)</td>
</tr>
<tr>
<td>Ongoing ACE Inhibitors, n (%)</td>
<td>1 (7)</td>
<td>2 (7)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Current arthritis, n (%)</td>
<td>4 (28)</td>
<td>7 (23)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Current fever, n (%)</td>
<td>8 (56)</td>
<td>6 (20)</td>
<td>0.02</td>
<td>4.6 (1.2-17.7)</td>
</tr>
<tr>
<td>Current myopathy, n (%)</td>
<td>6 (40)</td>
<td>1 (3)</td>
<td>0.001</td>
<td>19.3 (2-182)</td>
</tr>
<tr>
<td>Tendon friction rub, n (%)</td>
<td>1 (7)</td>
<td>0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Hypertensive retinopathy, n (%)</td>
<td>5 (33.3)</td>
<td>0</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Dilated Cardiomyopathy, n (%)</td>
<td>2/15 (13)</td>
<td>1/14 (7)</td>
<td>0.04</td>
<td>2.5 (0.2-31.9)</td>
</tr>
<tr>
<td>Pericardial effusion, n (%)</td>
<td>5/15 (33)</td>
<td>1/21 (5)</td>
<td>0.02</td>
<td>11.7 (1.2-114)</td>
</tr>
<tr>
<td>Microangiopathic Hemolytic anemia, n (%)</td>
<td>5 (33)</td>
<td>0</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Thrombotic Microangiopathy, n (%)</td>
<td>4 (26.6)</td>
<td>0</td>
<td>0.009</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Model to predict development of SRC (dependent variable) using demographic and laboratory variables using binary logistic regression. R-square = 0.719, correct classification as SRC or no SRC in 93%

<table>
<thead>
<tr>
<th>Variables in the Equation</th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>Df</th>
<th>Sig.</th>
<th>Exp(B)</th>
<th>95% C.I for EXP (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age yrs</td>
<td>-.123</td>
<td>.052</td>
<td>5.573</td>
<td>1</td>
<td>.018</td>
<td>.884</td>
<td>.798 .979</td>
</tr>
<tr>
<td>Duration</td>
<td>.030</td>
<td>.021</td>
<td>2.001</td>
<td>1</td>
<td>.157</td>
<td>1.030</td>
<td>.989 .994</td>
</tr>
<tr>
<td>LDH</td>
<td>.000</td>
<td>.000</td>
<td>2.936</td>
<td>1</td>
<td>.087</td>
<td>1.000</td>
<td>1.000 .001</td>
</tr>
<tr>
<td>Hb</td>
<td>.504</td>
<td>.346</td>
<td>2.124</td>
<td>1</td>
<td>.145</td>
<td>1.656</td>
<td>.840 3.262</td>
</tr>
<tr>
<td>Constant</td>
<td>-1.249</td>
<td>3.899</td>
<td>.103</td>
<td></td>
<td>.749</td>
<td>.287</td>
<td></td>
</tr>
</tbody>
</table>

Statistical Analysis

Categorical variables were compared using Pearson’s Chi-squared test (or Fisher’s exact test) and continuous variables using Mann-Whitney U test. Survival analysis was done using the Kaplan-Meier analysis and compared using Log-rank test. A model to predict development of SRC (dependent variable), using demographic and laboratory variables, was made using binary logistic regression. For all statistical analyses, a p-value <0.05 was used to define statistical significance.

Results

Clinical Features

Ninety-four patients of systemic sclerosis were admitted during the five year period; among them 15 had scleroderma renal crisis (SRC). These 15 cases were compared with 30 diseased controls.

SRC patients were significantly older in age, but had a significantly shorter (median) disease duration compared to controls (24, 42 months, p=0.01). As expected, they had higher mean systolic (160.9, 92.4 mm Hg, p<0.001) and diastolic blood pressure readings as compared to controls. Five SRC patients had hypertensive retinopathy and 9 had oliguria, compared to none of the controls. The mean haemoglobin was significantly lower and serum creatinine was significantly higher in SRC patients. A majority of both the cases and controls had a positive anti-nuclear antibody (Table 1).

Factors associated scleroderma renal crisis

Six of the SRC patients had disease duration of less than one year, compared to none in the control group (Odds Ratio, OR 39.3, 95% CI 2 to 774, p=0.001). Significantly more SRC patients (7 of 15) were on ≥ 15mg per day of prednisolone, compared to 3 of 30 controls (Odds ratio 7.9, 95% CI 1.7 to 37.7, p=0.009). Proximal myopathy, dilated cardiomyopathy, pericardial effusion and fever were significantly more common in the SRC group. However, there was no difference in arthritis or tendon friction between SRC and controls (Table 2). On binary logistic regression, a model

with systemic lupus erythematosus or those with an obvious cause of renal failure.

Follow-up data was collected till September 2018 by looking at clinic records, or if these were missing by contacting patients over the telephone. Data that was collected, included ongoing need for dialysis and outcome in terms of survival.
containing the independent variables of age, disease duration, LDH and haemoglobin a had a good predictive ability to correctly classify a patient for SRC (Table 3).

**Treatment received and outcome of SRC patients**

Renal biopsy was performed in only 2 patients with SRC. In the first patient, glomeruli showed evidence of mesangiolysis, arteries showed moderate intimal thickening and medial hypertrophy, and arterioles showed myxoid changes with occasional luminal occlusion. In the second patient’s biopsy, there was necrosis of the cortical region along with fibrin thrombi in the vessels and nuclear debris suggestive of acute cortical necrosis.

All SRC patients received ACE inhibitors (ACEI) at the time of diagnosis of SRC, commonly, enalapril or ramipril. During the hospital stay, 11 patients underwent haemodialysis. Outcomes could be determined in 12 SRC patients; 10 died over a period of 24-months, 7 within three months of admission. The two surviving patients were requiring maintenance haemodialysis. In the control group, there were only two deaths. Mean (SD) survival in patients with SRC (11.5, 95% CI 5.7 to 17.6 months) was significantly lower than controls (66.2, 95% CI 58.4 to 73.9 months, p<0.001) (Figure1).

**Discussion**

In this study from a rheumatology unit of a North-Indian University centre, we report a high mortality in patients of scleroderma renal crisis despite the use of ACE inhibitors. At 3-months, 45% of the patients had died, which was much higher than reported by Steen et al (N=149, 19% of patients had early deaths). By 2-years, the mortality was 85% (10 of 12), again, being much higher than reported in other series (26-34%) from western centers.

The poor survival in the current series is reminiscent of the pre-ACEI era reports from the developed world, where the survival at 1-year was only 10%. This data is unlike the recent reports from western centres (post-ACEI), where good outcomes in the short-term (no dialysis or only temporary dialysis) have increased to 60%. The reason for the poor survival may be related to advanced disease, as apparent by high levels of serum creatinine, at presentation. Steen et al found creatinine> 3.0mg/dl and uncontrolled hypertension at start of therapy predicted poor outcome; present in a majority of our patients. In addition, three-fourth of patients required haemodialysis in our centre, which is much higher than in western centers. These suggest a delay in recognition of the SRC in our patients, which may be related none of these patients were under follow-up with us or at another specialist centre before development of SRC.

The lack of access to renal replacement therapy to patients with kidney disease (acute or chronic) may be another factor contributing to poor outcomes. In India, renal replacement therapy is not a part of the national or state health programme (in most states). Also, a majority of Indian patients do not have medical insurance; thus, there remains huge gap of access to this life saving therapy due to financial reasons.

We found SRC to be associated with recent use of medium-high dose corticosteroids, similar to previous studies that found recent corticosteroid use, prednisolone > 15 mg per day within 6 months, was associated with SRC (odds ratio 4.3). However, some studies, like those by Steen et al and Hesselstrand et al did not find this association in their analysis.

The mean age of patients at onset of SRC was lower in our study than reported earlier. This may be related to an earlier onset of systemic sclerosis per se in India; something also reported in other rheumatic diseases. Consistent with other series, we also found renal involvement in systemic sclerosis to occurs early in the disease course; additionally, SRC was the first presentation in one-fifth of patients similar to some previous reports. In agreement with previous studies, we also found recent onset of muscle weakness, anaemia, presence of pericardial effusion and systolic dysfunction to be associated with SRC.

There is paucity of Indian data on SRC. Gupta et al in a study on renal involvement in scleroderma, did not find a single case of SRC. Another study also reported not a single case of SRC among 100 patients. In a study from Western India, found 12 of 110 patients with systemic sclerosis to have renal involvement, however, did not further specify the type of abnormality. It is not possible for us to give an exact prevalence of SRC in patients with systemic sclerosis at our centre; this not being a prospective study of systemic sclerosis. Almost all patients in this study were new, and not under our follow-up; they were often referred due to renal failure to our hospital - the largest tertiary care government hospital in the region.

The major limitation of this study
was its small sample size, retrospective design and inclusion of only admitted patients. This preclude generalizing the results to all Indian patients, and a larger multicentric study that includes many more patients is needed to confirm these preliminary findings. However, we believe this study does highlight differences in outcomes between the developed and developing world. Another limitation was the limited number of patients who underwent renal biopsy; although patients met the criteria for SRC, however, we cannot exclude other causes of acute kidney injury like ANCA (Myeloperoxidase) overlap, described in a minority of cases. Finally, we did not have data on prevalence of anti-RNA polymerase III, a common association with SRC. Immunoblot strips coated with this antigen was not available commercially and facility for advanced testing like immunoprecipitation was not available; although an ELISA has also been described.20

Conclusion
In conclusion, scleroderma renal crisis is associated with a dismal prognosis, despite use of ACEI, in this single centre study. The severity of the disease, poor access to care and a delay in diagnosis might have resulted in poor outcomes.

Declaration of conflicting interest
None of the authors have any conflicts of interest with regard to this manuscript.

Author Contribution
PD, SKS, AS, SN, VD conceived and designed the study; PD, AMB, NA, RR, RN, SN acquired the data; PD, AMB, VD analysed and interpreted the data; PD, AMB, VD drafted the article and NA, RR, RN, SN, SKS, AS and SN revised it critically for important intellectual content.

All authors approved the final version and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

Clinical Spectrum of Rheumatic Manifestations in HIV Infected Males at a Tertiary Care Hospital

Harshit Khurana1, Vijoy Kumar Jha2, Abha Khurana3, Kumar Abhisheka4

Abstract
Background: In the current era of effective Anti retroviral therapy (ART), and Human Immunodeficiency Virus (HIV) infection becoming a chronic illness, there has been a gradual rise in the prevalence of rheumatic manifestations associated with this disease. These are characterized by a modified clinical course and widened spectrum of a few emerging rheumatic manifestations seen with HIV infection.

Aims and Objectives: To assess the type, frequency, prevalence and clinical spectrum of rheumatic manifestations among

1Physician and Hematologist, 2Physician and Nephrologist, 3Obstetrician and Gynaecologist, 4Physician and Endocrinologist, Command Hospital Air Force Bangalore, Karnataka; *Corresponding Author Received: 15.07.2020; Revised: 23.06.2021; Accepted: 16.07.2021
male patients followed at an HIV clinic of a tertiary care defence hospital.

Materials and Methods: All male patients with confirmed HIV infection at the study centre were studied after obtaining informed consent. A detailed history was taken including the date of seropositivity, symptoms of rheumatic disease, family history of rheumatic illness, and treatment history with ART. A detailed general and systemic examination was performed and rheumatic symptoms guided appropriate investigations were carried out on as required basis.

Results: 879 confirmed HIV cases were evaluated for rheumatic manifestations during the study period. Of these 499 cases were newly detected HIV cases and the rest 380 were old cases on follow up. Rheumatic disorders were diagnosed in 16 cases (1.82%). Spondyloarthopathy was the commonest presentation i.e. 5 out of 16 cases (31.25 % of the rheumatic disorders). Mean age was 37 years (range 27-52 yrs). 2 patients of the study group had the rheumatic illness prior to detection of HIV. Psoriatic Arthritis (0.114 %) was seen in 1 patient who was HLA B-27 negative. Reactive arthritis (0.227 %) was noted in 2 patients. 1 patient had cutaneous small vessel vasculitis (0.114 %), whereas 1 of the patient developed DLE (0.114 %) over neck. HIV related non specific polyarthritis (0.114 %) of the large joints was noted in 1 patient who was RF negative, while polyarthralgia (0.340 %) was noted in 3 patients. 10 patients (60 %) had CD 4 count < 200 cells/µL, whereas 6 patients had a CD 4 count between 200 and 500 cells/µL. 13 out of 16 patients detected to have rheumatic illnesses were on ART.

Conclusion: With the advent of ART, the clinical spectrum of HIV infection is changing as a chronic treatable disease. Present study consisting mainly adult males, showed only 1.82 % prevalence of rheumatic disorders in HIV infection. Early diagnosis, availability of ART and prompt treatment of opportunistic infections have changed the clinical profile of HIV patients. Impact of ART in producing and affecting the clinical spectrum of rheumatic disease has to be kept in mind while treating HIV-infected patients.

Introduction

Immuneologic and rheumatic disorders are uncommon in patients with Human Immunodeficiency Virus (HIV) infection. The occurrence of rheumatic manifestations is an apparent paradox in the setting of the profound immunodeficiency and immunosuppressed state associated with HIV infection. These may range from excessive immediate type hypersensitivity reactions to an increase in the incidence of some usual conditions like reactive arthritis, and some unusual conditions like diffuse infiltrative lymphocytosis syndrome. In addition, following the initiation of antiretroviral therapy (ART), a variety of exaggerated immune responses to existing opportunistic infections referred to as immune reactivation syndromes may also be seen.1

Rheumatic manifestations associated with HIV infection presenting as the first manifestation of the disease in some patients have also been recognized of late. Musculoskeletal manifestations can occur at any phase of the infection, though they are much more prevalent in the late phases.2 With the rising global epidemic of HIV infection, the knowledge of spectrum of rheumatic disorders associated with this disease is gradually expanding.

The rheumatic manifestations can be attributed to direct and indirect effects of the HIV virus with genetic and environmental factors playing a key role.2 Some of these conditions are HIV specific, like painful articular syndrome, HIV-associated arthritis and diffuse infiltrative lymphocytosis syndrome. The virus may cause abnormal polyclonal B cell activation and polyclonal hypergammaglobulinemia.3 The viral infection may resemble an autoimmune disorder, as suggested by the possible role of intact CD4+ T cell limb in the pathogenesis of these conditions. The two common autoimmune diseases, namely systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) have been reported to improve when CD4 count decreases in HIV infection.4

In this study, we report our experience on rheumatic manifestations in HIV infected patients. Majority of our patients were healthy, young, sexually active males.

Aim and objectives of the study:
(i) To assess the type and frequency of rheumatic manifestations among patients followed at an HIV clinic of a tertiary care hospital in northern India. (ii) To determine the prevalence and clinical spectrum of rheumatic manifestations in those HIV infected patients.

Patients and Methods

The study was conducted at an HIV clinic of a tertiary care hospital in northern India over a period of four years and six months. Any patient presenting to the hospital’s outpatient department (OPD) clinics or those inpatients, who were detected to be HIV positive on routine serological screening test by enzyme linked immunosorbent assay (ELISA) were referred to the HIV clinic. The diagnosis of HIV infection was then confirmed by Western Blot test. Detailed history and clinical examination findings were noted, and the prevalence and characteristics of any rheumatic manifestations found in these patients were recorded. They were further evaluated with routine and other relevant special investigations if indicated. Standard criteria were used to classify the rheumatic and inflammatory joint diseases seen during the study period.

All patients with HIV infection (confirmed by Western Blot) were studied after obtaining written informed consent. Most of the patients enrolled for the study were sexually active young males, who were newly diagnosed with HIV infection. Patients who had been diagnosed with HIV infection in recent past and were on regular OPD follow up during the study period were also included. All these patients were then evaluated for rheumatic disorders as per study protocol. The patients who were detected to be HIV positive by ELISA test, but were then found to be negative by Western Blot test were excluded from the study. Few female HIV positive patients were followed up on OPD basis and were excluded from the study, as their regular follow up at the same centre could not be ensured, while some patients refused to give consent.
Clinical and laboratory evaluation

The history of the enrolled study subjects was recorded in detail including the date of seropositivity, symptoms of rheumatic disease i.e. history of diffuse or localised muscular pains, joint pains, restricted joint mobility, early morning stiffness, swelling of joints, oral ulcers, rashes, skin involvement, eye involvement or kidney involvement. Doses and duration of ART received if any, and family history of rheumatic illness was also elicited.

A detailed general and systemic examination was performed including examination of musculoskeletal system, joints, skin and eyes.

The serological investigations were carried out on as required basis for the confirmation of diagnosis of rheumatic disorder as per standard criteria. CD4 and CD8 counts were done by flowcytometry. Erythrocyte sedimentation rate (ESR) was performed by Westergren’s method, rheumatoid factor (RF) done by latex agglutination method, anti nuclear antibody (ANA) done by ELISA, and HLA B-27 was performed by flowcytometry. Anti double stranded antibody (anti ds DNA), anti-cyclic citrullinated peptide (CCP) were done where indicated. Liver function tests, renal function tests, hepatitis B surface antigen (HBsAg), anti Hepatitis C virus antibody (Anti HCV) were done for all patients. The imaging studies, including ultrasonography of joints and needle aspiration cytology were performed if indicated.

Results

879 confirmed HIV positive male patients were evaluated for rheumatic manifestations during the study period. As the study was conducted at a defence hospital mandatory screening medical evaluation and regular follow up helped in enrolling large number of patients. Of these 499 cases were newly detected HIV cases and the rest 380 were old cases on follow up. Heterosexual promiscuity was the commonest mode of infection in these patients, though a large number of patients (20%) denied history of high risk behaviour. Intravenous drug abuse, blood transfusion and occupational exposure were the other modes of infection in these patients. About 30% of the newly detected patients were asymptomatic and were diagnosed during blood donation or mandatory HIV screening medical evaluation. Forty one patients expired during study period.

Rheumatic disorders were diagnosed in 16 cases (1.82 %). The details of the type of rheumatic disorder seen in these HIV positive patients and relative percentages of each are as given in Table 1. Non specific complaints like myalgia and arthralgia were not taken into consideration due to lack of specificity and varying nature of complaints by the patients. Two patients of the study group had a diagnosed rheumatic illness prior to detection of HIV. One had ankylosing spondylitis, while the other had gout. HLA B-27 was positive in the former. One patient was detected to have seronegative spondyloarthropathy; HLA B-27 and RF were negative. Psoriatic arthritis was seen in one patient who was HLA B-27 negative. Reactive arthritis (0.227 %) was noted in two patients amongst whom one had diarrhea and the other

<table>
<thead>
<tr>
<th>Rheumatological disorder</th>
<th>No (n=16) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous Vasculitis</td>
<td>1 (0.114)</td>
</tr>
<tr>
<td>Gout</td>
<td>1 (0.114)</td>
</tr>
<tr>
<td>Discoid Lupus Erythematosus</td>
<td>1 (0.114)</td>
</tr>
<tr>
<td>Spondyloarthropathy</td>
<td>1 (0.114)</td>
</tr>
<tr>
<td>Ankylosing Spondylitis</td>
<td>1 (0.114)</td>
</tr>
<tr>
<td>Reactive Arthritis</td>
<td>2 (0.227)</td>
</tr>
<tr>
<td>Psoriatic Arthritis</td>
<td>1 (0.114)</td>
</tr>
<tr>
<td>Non Specific Polyarthritis</td>
<td>1 (0.114)</td>
</tr>
<tr>
<td>Septic Arthritis</td>
<td>1 (0.114)</td>
</tr>
<tr>
<td>Necrotising Fascitis</td>
<td>1 (0.114)</td>
</tr>
<tr>
<td>Chronic Nonspecific Synovitis</td>
<td>1 (0.114)</td>
</tr>
<tr>
<td>Polyarthralgia</td>
<td>3 (0.340)</td>
</tr>
<tr>
<td>Adhesive Capsulitis</td>
<td>1 (0.114)</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>1.1 (0.4)</td>
</tr>
<tr>
<td>Reactive arthritis</td>
<td>11.2 (0.96)</td>
</tr>
<tr>
<td>Septic arthritis</td>
<td>- (0.98)</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>- (2.9)</td>
</tr>
<tr>
<td>Polyarthralgia</td>
<td>- (3.4)</td>
</tr>
<tr>
<td>Adhesive Capsulitis</td>
<td>- (3.4)</td>
</tr>
</tbody>
</table>

Table 1: Rheumatological disorders in 16 HIV patients (study group – 879 patients)

<table>
<thead>
<tr>
<th>Manifestations</th>
<th>Berman A et al1</th>
<th>Munoz FS et al a</th>
<th>Achutan K et al a</th>
<th>Krishnan KK et al a</th>
<th>Narayanan et al a</th>
<th>Present Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>N=89</td>
<td>N=556</td>
<td>n=102</td>
<td>n=29</td>
<td>n=704</td>
<td>n=879</td>
</tr>
<tr>
<td>Undifferentiated Spondyloarthropathy</td>
<td>2.2 (0.2)</td>
<td>0.2 (1.96)</td>
<td>24.1 (0.6)</td>
<td>0.114</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reactive arthritis</td>
<td>11.2 (0.4)</td>
<td>1.96 (17.2)</td>
<td>0.3 (0.227)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>1.1 (0.4)</td>
<td>0.98 (3.4)</td>
<td>0.15 (0.114)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ankylosing Spondylitis</td>
<td>- (0.98)</td>
<td>-</td>
<td>-</td>
<td>0.114</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV associated Arthralgia</td>
<td>26 (1.6)</td>
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<td>0.15 (0.340)</td>
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<td>HIV associated Arthritis</td>
<td>5 (0.4)</td>
<td>-</td>
<td>3.4 (0.6)</td>
<td>0.227</td>
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<td></td>
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<tr>
<td>Septic arthritis</td>
<td>- (0.98)</td>
<td>-</td>
<td>3.4 (0.114)</td>
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<tr>
<td>Vasculitis</td>
<td>- (2.9)</td>
<td>10.4 (0.114)</td>
<td></td>
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<tr>
<td>Gout</td>
<td>- (3.4)</td>
<td>-</td>
<td></td>
<td>0.114</td>
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<tr>
<td>DLE</td>
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<tr>
<td>Necrotising Fascitis</td>
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<tr>
<td>Pyomyositis</td>
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<td>-</td>
<td></td>
<td>0.114</td>
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Table 2: Comparative study of rheumatic manifestations (%)
had urethritis prior to developing arthritis. One of these patients had cutaneous small vessel vasculitis (0.114 %), whereas one patient developed discoid lupus erythematosus (DLE) (0.114 %) over neck. HIV related non specific polyarthritis (0.114 %) of the large joints was noted in one patient amongst the sixteen who was RF negative, while polyarthralgia (0.340 %) was noted in three patients. One of the patient developed adhesive capsulitis (0.114 %) of the right shoulder joint which responded to non steroidal anti inflammatory drugs (NSAIDs) and physiotherapy. One of the study group patients had monoarthritis of the right elbow joint which on biopsy was reported to be chronic nonspecific synovitis (0.114 %) with negative RF, ANA and HLA B-27. Amongst the infective complications were septic arthritis (0.114 %) of the left knee joint and necrotising fascitis (0.114 %) of the left leg. All patients were managed with non steroidal anti inflammatory drugs (NSAIDs).

Mean age of all the HIV patients with rheumatic manifestations was 37 years (Range 27-52 yrs). Most patients belonged to the age group 36-40 years, followed by the age group 31-35 years. The detailed age wise distribution is shown in Figure 1.

The most common mode of transmission of HIV in the patients with rheumatic manifestations was by heterosexual exposure to commercial sex workers (CSW), n= 11 (68.75 %). There was one case of transmission through intravenous drug abuse (IVDU), n= 1 (6.25 %) and one case of transmission through blood transfusion, n= 1 (6.25 %). Mode of transmission was unknown in three of these patients, n = 3 (18.75 %). The details are as depicted in Figure 2.

The Erythrocyte Sedimentation Rate by Westergren’s method was assessed. The mean ESR was 42.1 mm fall after first hour with a range of maximum 82 mm and minimum 16 mm. The details are as depicted in Figure 3.

CD 4 and CD 8 counts of the study patients were as depicted in Figure 4. Mean CD 4 count was 223 cells/µL with a range of maximum as 498 cells/µL and minimum as 103 cells/µL. Mean CD 8 count was 920 cells/µL with a range of maximum as 1513 cells/µL and minimum as 350 cells/µL. Ten patients (60 %) had CD 4 count < 200 cells/µL had features of clinical acquired immunodeficiency syndrome (AIDS) when the rheumatic manifestations occurred, whereas six patients had a CD 4 count between 200 and 500 cells/µL.

There were no cases of polymyositis, myopathy, rheumatoid arthritis, systemic lupus erythematosus, painful articular syndrome or Sjogren’s syndrome in our series. Thirteen out of sixteen patients detected to have rheumatic illnesses were on ART. Ten patients with CD 4 count < 200 cells/ cumm were on ART, whereas three out of six patients with CD 4 count of 200-500 cells/ cumm were receiving ART due to any of the AIDS defining illness occurring during the course of their disease.

**Discussion**

In the past, many physicians, rheumatologists and immunologists have documented rheumatic manifestations resulting from HIV infection such as spondyloarthopathy, HIV associated arthralgia, HIV associated arthritis, painful articular syndrome, septic arthritis, pyomyositis, vasculitis, etc.5

The specturm of rheumatic manifestations seen in HIV patients in the present study are compared with other series (Table 2). The difference in the prevalence of rheumatic diseases in the Chennai study7 from those in other studies is because they studied HIV positive patients with definite rheumatic manifestations referred from other centres, while in other studies including the present study, all HIV patients were screened for rheumatic manifestations.

Arthritis may manifest during any stage of HIV infection and sometimes may be the initial manifestation.10 In the present study non specific polyarthritis (0.114 %) was seen in one patient, monoarthritis (0.114 %) was observed in another patient whose synovial biopsy from the joint suggested chronic synovitis. HIV associated polyarthritis (0.340 %) was seen in three patients. Narayanan et al, reported only 3 % of AIDS patients with arthritis who had low CD4 count.4 Vaidya et al, reported rheumatological complaints in the form of arthralgias and bone pains in 4 % cases among HIV patients.11 Many earlier studies from west reported the incidence of unexplained arthralgia to be as high as 45%.12 Recent reviews of soft-tissue symptoms, arthralgias, and nonspecific arthritis have attributed most of these symptoms to initiation or change in ART.13

Spondyloarthopathy was the commonest form of inflammatory arthritis seen in HIV infection and in the Chennai study it was 44.8%.7 In our study, 5 of the 16 cases (31.25 %) were diagnosed as spondyloarthopathy (1- undifferentiated spondyloarthopathy, 1-ankylosing spondylitis, 1-psoriatic arthritis, 2-reactive arthritis). Four of these five had CD 4 count < 200/cumm and therefore had AIDS. Achuthan et al have reported this in 2 out of 5 case.4 In HIV infected individuals, there is not only an exacerbation of psoriatic skin lesion but also an increased incidence of psoriatic arthritis.3 The epidemic of HIV infection in sub-saharan Africa in recent years however, has been associated with a dramatic upsurge in the prevalence of spondyloarthropathies other than ankylosing spondylitis, primarily reactive arthritis and undifferentiated forms of the disease, and less often psoriatic arthritis. HIV infection is increasingly showing such a strong association with reactive arthritis, psoriatic arthritis, and undifferentiated spondyloarthropathies in sub-saharan african populations that any patient with acute or chronic inflammatory arthritis may need to be tested for possible HIV infection.3,14

Reiter’s syndrome was the first arthritis described in HIV infection, with a reported prevalence of zero to 10%.15 The increased frequency of Reiter’s syndrome is possibly due to the sexually active nature of the population at the highest risk for HIV infection and the secondary infection in the gastrointestinal and genitourinary tract due to arthritogenic organisms.15 For more than 10 years, HIV has been predominantly associated with an increased incidence of reactive arthritis and psoriatic arthritis.16 As the CD4 cell count recovers with ART, patients with reactive arthritis tend to improve their reactive symptoms.7,10 Although reactive arthritis can develop at any time during the course of HIV infection, it tends to develop more often later in the course of the disease.7,15

One patient had septic arthritis (0.114 %) and another patient with necrotising
fascitis (0.114 %) was seen in the present study. It is not unusual to see septic arthritis associated with an immunosuppressed disorder such as HIV infection. The most common infectious agent is staphylococcus aureus. However, extension to the muscle and soft tissues is a common sequelae.17

Inflammatory vascular disease involving small, medium and large vessels has been described in HIV infection. Gherardi et al reported vasculitis in 34 (23%) of 148 symptomatic HIV positive patients studied.18 In the present series, one (0.114 %) of 16 patients with rheumatic manifestations out of a total of 879 HIV patients studied, presented with cutaneous small vessel vasculitis. There was one patient each who had DLE (0.114 %), adhesive capsulitis (0.114 %) and gout (0.114 %) in the present study. In contrast to increase in frequency of spondyloarthropathy in HIV infection, a few rheumatic diseases such as SLE and RA can go into amelioration.5 HIV-related immuno-suppression improves SLE symptoms, but ART may lead to an autoimmune disease flare subsequent to the increase in circulating CD4 cell count.19

The non-infectious musculoskeletal conditions associated with HIV infection and AIDS include polymyositis, drug-induced myopathy, myositis ossificans, adhesive capsulitis, avascular necrosis, bone marrow abnormalities, and hypertrophic osteoarthropathy.19 Painful articular syndrome is unique to HIV patients, characterized by extremely painful, self limiting condition lasting for less than 24 hours. It has mainly been reported from USA and Africa. None of patients in the present study or those reported by Achuthan et al20 had this syndrome. Pyomyositis has been reported from Africa.20 There was no patient with pyomyositis in the present study. There was no case of sjogren-like syndrome or diffuse infiltrative lymphocytosis syndrome (DILS) in the present study.

Conclusion
In our study, 16 (1.82 %) out of 879 males enrolled with HIV infection had features of rheumatic disorders. Spondyloarthropathy was the commonest presentation seen in 5 out of 16 cases (31.25 % of the rheumatic disorders). 2 cases had rheumatic disorders prior to their detection of HIV infection (ankylosing spondylitis and gout). The most common mode of transmission among these patients was unprotected sexual exposure to commercial sex workers. 13 of these 16 patients were receiving ART. Most of these patients had relief of their rheumatic symptoms with NSAIDs in addition to ART. With the advent of ART, HIV infection has become a chronic disease which can be well managed and hence we may expect a different pattern of rheumatic disorders in future.

Initial reports of the rheumatic symptoms seen in acutely infected HIV patients may have been nothing more than an exaggerated form of the arthralgias and myalgias associated with acute viremia that is well known in clinical medicine. Early diagnosis, availability of effective ART drugs and prompt treatment of opportunistic infections have changed the clinical profile of HIV patients. The increased frequencies of reactive arthropathies, especially those associated with overt infectious episodes, are coupled with clear evidence for the higher susceptibility of HIV patients to secondary infections. Early recognition and treatment of opportunistic infections is of paramount importance as they can be the inciting agents for rheumatic disorders. It also suggests that HIV and its effects on immune surveillance may have more to do with the seronegative spondyloarthropathies and reactive arthropathies than the classic autoimmune disorders. The understanding of interface of HIV with the immune system and clinical manifestations of rheumatic and autoimmune disorders is important, as HIV infection per se can alter the clinical presentation and course in these patients. The pathogenesis of these rheumatic manifestations which is still not well understood will improve further as the research on HIV associated rheumatic disorders continues. Treatment of HIV infection is part of the management when rheumatic disorders co-exist with HIV infection or disease. Anti-viral effects of drugs like indomethacin and hydroxychloroquine, and impact of ART in modulating the clinical spectrum of rheumatic disease has to be kept in mind while treating HIV-infected patients. Early understanding and treatment of rheumatic diseases will go a long way in reducing physical, mental, social, and economic burden in these HIV-infected patients.

References
## Key Parameters of Combination

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<th>Parameter</th>
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<td>HTH safety data (Sedation)</td>
<td>9.6%</td>
<td>23.2%</td>
<td>No HTH data</td>
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2. This dissolution study compares Allegra M, Allegra, Singular and one Fexofenadine + Montelukast fixed dose combination available as a microencapsulated tablet in India. Data on File, 2012 (b)
3. Concomitant bilastine and montelukast as additive therapy for seasonal allergic rhinoconjunctivits and mild-to-moderate asthma. The SKY study. 2019

Expert Opinion on P2Y12 Inhibitors Use in Management of Acute Coronary Syndromes: Focus on Ticagrelor

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Abstract
Ticagrelor is a potent, oral P2Y12 inhibitor used as a part of dual antiplatelet therapy (DAPT) in acute coronary syndromes (ACS). New evidence has emerged for its use in ACS, which may be crucial for the Indian context. This brought together nearly 150 experts in ACS management across the country who reviewed the current evidence and discussed the same through a series of 10 meetings on an online platform. With all experts’ agreement, the key expert opinions for the P2Y12 inhibitors use in ACS management were finalized. These include the following. In ACS patients aged <75 years, with diabetes, a history of stroke/transient ischemic attack, and chronic kidney disease, ticagrelor may be preferred over other P2Y12 inhibitors. It may also be preferred in the elderly above 75 years with clopidogrel is a suitable alternative in patients at high-risk of bleeding. Rates of stent thrombosis are lower with ticagrelor than clopidogrel. In patients managed with fibrinolysis, use ticagrelor after 48 hours if streptokinase was the fibrinolytic agent or it can be used after 12 to 24 hours if fibrin-specific fibrinolytic was used. Rates of major bleeding in patients treated with fibrinolysis are similar to clopidogrel. Prehospital administration may be preferred over in-hospital administration with expected bleeding rates similar to clopidogrel. Switching among P2Y12 inhibitors should be done with due consideration of their pharmacodynamics. At present, DAPT should be continued for 12 months with discontinuation after three to six months in patients with high bleeding risk. The use of low dose ticagrelor may be considered in cases with high-bleeding risk. DAPT or ticagrelor continuation beyond one year should be individualized considering ischemic and bleeding risks. Dyspnea is a common, mild, and transient and does not necessitate ticagrelor discontinuation. Severe dyspnea should be investigated thoroughly. In conclusion, ticagrelor (180 mg, 90 mg, and 60 mg doses), a potent antiplatelet is expected to reshape the antiplatelet use in the management of ACS.

Introduction
Antiplatelets are central to the management of acute coronary syndromes (ACS) for the prevention of atherothrombotic complications.1 Dual antiplatelet therapy (DAPT) incorporating aspirin and a P2Y12 inhibitor (P2Y12i) is recommended in the management of ST-elevation myocardial infarction (STEMI), non-ST-elevation MI (NSTEMI), and stable coronary artery disease (CAD) whether managed medically or with interventions such as percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).2-6 In managing these clinical situations, physicians are faced with challenges such as the selection of a P2Y12i, efficacy in reducing ischemic events and stent thrombosis, risk of bleeding and duration of DAPT, etc. These are critical in secondary prevention of major adverse cardiovascular (CV) events (MACE) in CAD patients.7 The subtle differences in P2Y12i may cause variations in their clinical efficacy and safety. In ACS, newer P2Y12 inhibitors such as ticagrelor (TICA), prasugrel (PRASU) are significantly more effective in the prevention of MI and CV death than clopidogrel (CLOPI).8 Their superiority in significantly reducing MACE and MI in NSTEMI patients is also proven.9 However, the risk of major and minor bleeding is higher with newer P2Y12i.8,9 Efficacy of the TICA and PRASU, is equivalent but the risk of bleeding is higher with PRASU.10 In recent years, TICA has been evaluated widely across the ACS spectrum. In patients with a MI more than one year previously, the PEGASUS-TIMI 54 trial demonstrated TICA in a dose of either 90 mg or 60 mg twice daily was superior in reducing the composite outcome of
Table 1: Expert opinions

Choice of P2Y12 inhibitor

- In ACS patients aged <75 years without comorbidities, preference to TICA should be given over CLOPI and PRASU.
- TICA can be preferred over other antiplatelet agents across age groups, including the elderly above 75 years. CLOPI is a suitable alternative in patients at high risk of bleeding.
- In patients with diabetes with ACS, TICA may be preferred over other P2Y12i such as CLOPI or PRASU.
- In patients of ACS with a history of stroke or TIA, TICA may be preferred over other P2Y12i to reduce the mortality and stroke outcomes.
- In patients of ACS with CKD, TICA may be preferred over other P2Y12i to prevent MACE and reduce mortality. In end-stage kidney disease, choices may vary depending on the individual experiences of the treating physicians.
- The use of TICA as part of DAPT is associated with lower rates of stent thrombosis compared to CLOPI and is similar to that of PRASU.
- In fibrinolytic-treated patients with STEMI, defer administration of TICA till 48 hours when streptokinase is used or the fibrinolytic agent is not known. In the case of fibrin specific fibrinolytic, TICA may be administered within 12 to 24 hours. The rates of TIMI major bleeding including fatal and intracranial bleeding, at day 30 are similar to CLOPI. PRASU should be avoided in such patients as coronary anatomy is not known.

Prehospital or In-hospital administration

- TICA prehospital compared to in-hospital administration may be preferred in STEMI patients undergoing PCI. Bleeding risk is comparable to that of CLOPI. CLOPI is a suitable alternative if prior loading has been done in the periphery or in patients with high bleeding risk.

Switching among P2Y12i

- Switching among P2Y12i is common in a clinical setting. Pharmacodynamics of the P2Y12i should be correctly recognized to appropriately switch from one P2Y12i to the other. De-escalation in cases with high rates of bleeding and escalation in high ischemic risk may be an appropriate strategy.

Duration of DAPT

- At present, we consider that DAPT should be continued for 12 months after an index procedure as a standard of care. In high bleeding risk patients, discontinuation of DAPT at 6 months followed by TICA 90 mg BD should be considered. Continuation of DAPT or individual P2Y12i beyond one year should be individualized. Use of TICA in low dose i.e. 60 mg dose after one year of DAPT may be considered especially in those with high bleeding risk.

Adverse effects

- Major bleeding risk of TICA is similar to that of CLOPI, but minor bleeding events are common with TICA. In high-bleeding risk patients, strategies such as short DAPT duration, use of low dose TICA can be adapted to minimize the bleeding complications. Fatal and intracranial bleeds are rare with TICA. In urgent CABG, discontinue DAPT as soon as possible and operate without waiting for recovery of full platelet function. In elective CABG, discontinue TICA at least 3 days before whereas stop CLOPI and PRASU before 5 days and 7 days of surgery.

- Dyspnea is commonly observed with TICA treatment. In majority cases, dyspnea is mild, transient, and requires no specific treatment. Severe dyspnea may require discontinuation of TICA which should only be done after excluding other causes of dyspnea.

- Bradycardhythmias are asymptomatic, transient, which are common in the first month of ACS and are observed with equal frequency in TICA and CLOPI treatments.

P2Y12i resistance

- CLOPI resistance is common worldwide which may lead to nonresponsiveness. Shift to TICA is the optimal strategy in ACS patients identified to have CLOPI resistance.

Ticagrelor formulation

- In routine clinical practice, one must prefer a generic TICA formulation that is bioequivalent to the innovator formulation.

CV death, MI, or stroke than placebo. The Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study (THEMIS) trial also demonstrated superior efficacy of ticagrelor plus aspirin DAPT over aspirin alone in reducing ischemic events among patients with stable CAD and diabetes without a history of MI or stroke. The TWILIGHT trial showed that in patients undergoing complex PCI, the continuation of TICA monotherapy after initial three months of DAPT (TICA plus aspirin) had lower bleeding rates without any increase in the risk of ischemic events compared to continuing DAPT after three months. These pieces of evidence indicate that antiplatelet therapy in the management of ACS/CAD is reshaping with TICA. However, in India, CLOPI is the widely used P2Y12i either alone or as part of DAPT. Therefore, it is important to determine the role of TICA in the ACS spectrum especially in the Indian setting. In this article, we discuss the current place of antiplatelets focusing on TICA and provide expert opinion for the use of antiplatelets in the management of ACS in the Indian context.

Approach to the Expert Opinion

Across India, 150 experts in the field of Cardiology participated in ten advisory board meetings conducted on an online platform. Each meeting was of nearly two hours’ duration. In each meeting, two experts presented the clinical evidence on the choice of P2Y12i, timing of administration, switching among the different P2Y12i, duration of DAPT, tolerability, resistance, and ticagrelor formulation (generic alternatives). Each of these critical points were discussed in detail. After the discussion, an expert opinion was formulated with the agreement of all the experts in each meeting. All the expert opinions were recorded in a systematic way and opinions from each meeting were collated to derive final expert opinion statements. After the last meeting, the final expert opinion statements were shared with all the experts for their review and comments. The expert opinions across different areas of ACS management are presented in below sections. Table 1 enlists the expert opinions formulated for P2Y12i use in ACS.

Choice of P2Y12i in ACS

In patients of STEMI and NSTEMI as well as in stable CAD; CLOPI, TICA, and PRASU are recommended by different guidelines with a preference to TICA or PRASU over CLOPI. Among the two, PRASU has limitations for its use. PRASU has a high risk of major bleeding compared to TICA and CLOPI, is prohibited for use without knowing coronary anatomy, contraindicated in patients with stroke / transient ischemic attack, in elderly patients (aged ≥ 75 years) and in those with a body-weight < 60 kg. A caution for its use in CABG is also advised. Thus, in patients who are <75 years of age, TICA is a choice of P2Y12i for DAPT after ACS.

Expert opinion: In ACS patients aged <75 years without comorbidities, preference to TICA should be given over CLOPI and PRASU.

Elderly (aged 75 years and above): Despite current guidelines advising TICA or PRASU in all patients with an ACS, clopidogrel still represents the most used P2Y12i in the elderly. This is probably because of the lower rate of bleeding events than the more potent TICA and PRASU. However, high on-clopidogrel platelet reactivity rates are significantly higher compared with younger patients, which may result in poor outcomes in elderly patients with ACS. The PLATO trial findings in the elderly indicate a significant reduction in ischemic endpoints with TICA at the expense of increased bleeding.
ticagrelor (37.3% versus 30.6%). Contrastingly, a propensity score-matched study from Schmucker et al. reported that in elderly patients with STEMI, compared with clopidogrel, ticagrelor reduced MACE as well as cerebrovascular events without a significant increase in bleeding events within one year. They observed significantly higher net adverse clinical events clopidogrel than ticagrelor (37.3% versus 30.6%).

**Expert opinion:** TICA can be preferred over other antiplatelets across age groups including the elderly above 75 years. CLOPI is a suitable alternative in patients at high risk of bleeding.

**Diabetes:** In the PLATO trial, the benefits of ticagrelor in the diabetic subgroup were consistent with the overall cohort. No heterogeneity in relation to diabetes was seen. In patients with poor metabolic control (HbA1c ≥7%), there was a 20% reduction in the primary endpoint, 22% reduction in all-cause death, a 48% reduction in stent thrombosis with TICA compared to CLOPI. There was no increase in the risk of major bleeding (8.4% vs. 8.2%). In the PEGASUS TIMI 54 trial, compared to non-diabetic individuals, relative risk reduction in MACE with TICA (pooled dose effect) was 14% in the diabetic subgroup. Ticagrelor reduced CV death by 22% and CAD death by 34%. In patients with diabetes and stable CAD, a recent THEMIS trial demonstrated the clinical efficacy of TICA when added to aspirin compared to aspirin alone.

**Expert opinion:** In patients with diabetes with ACS, TICA may be preferred over other P2Y12i such as CLOPI or PRASU.

**Stoke/Transient Ischemic Attack (TIA):** Past intracranial hemorrhage is a contraindication for TICA and PRASU. Additionally, PRASU is contraindicated in patients with ischemic stroke or TIA. In the PLATO substudy, an analysis of patients with a history of stroke or TIA was done. At 1-year, total mortality (7.9% versus 13.0%) but not the primary composite outcome (19.0% versus 20.8%) was significantly lower with TICA than CLOPI respectively. Simultaneously, the overall PLATO-defined bleeding rates were similar (14.6% versus 14.9% respectively). Thus, compared to CLOPI, TICA may have favorable net benefit mainly derived from mortality reduction in patients with ACS with stroke/TIA. Henriksen et al. in a Swedish cohort of patients with acute MI who had a previous ischemic stroke observed that administration ticagrelor was associated with lower rates of a stroke at 1 year than clopidogrel (8.6% versus 12.1%). In a similar cohort of Korean patients aged <75 years, Kim et al. demonstrated that TICA had significant reduction of all-cause death and stroke with no increase in bleeding risk. In nearly 30% of patients switching from ticagrelor to different P2Y12i, an increase in the number of clinical adverse events including MI, stroke, and bleeding was reported.

**Expert opinion:** In patients of ACS with a history of stroke or TIA, TICA may be preferred over other P2Y12i to reduce the mortality and stroke outcomes.

**Chronic kidney disease (CKD):** The PLATO substudy in patients with CKD (creatinine clearance <60 mL/min; n=3237) showed significant superior efficacy of ticagrelor over clopidogrel for the reduction in both primary end-point (17.3% vs. 22.0%) and total mortality (10.0% versus 14.0%). The absolute risk reduction was greater in CKD patients compared to those with normal renal function (7.9% versus 8.9%). There were no significant differences in rates of major bleeding (15.1% vs. 14.3%), fatal bleeding (0.34% vs. 0.77%), and non-coronary bypass-related major bleedings (8.5% vs. 7.3%).

The evidence for use of P2Y12i in end-stage renal disease or in patients on maintenance hemodialysis is lacking. However, CLOPI is observed to be used more frequently probably attributable to its large experience in routine clinical practice. The TROUSER trial, a prospective, controlled, multicenter, randomized trial to investigate the optimal P2Y12 antagonist (ticagrelor versus clopidogrel) in CKD patients with ACS is currently underway. The primary endpoint is the rate of MACE, including death, MI, urgent revascularization, and stroke at 1 year.

**Expert opinion:** In patients of ACS with CKD, TICA may be preferred over other P2Y12i to prevent MACE and reduce mortality. In end-stage kidney disease, choices may vary depending on the individual experiences of the treating physicians.

**Stent thrombosis:** Based on time elapsed, stent thrombosis is defined as acute, subacute, late, and very late as <24 hours, 1 to 30 days, >30 days, and >12 months post stent implantation. The occurrence of stent thrombosis is determined by multiple factors such as procedure and lesion-related parameters (e.g. multiple stents, long, calcified lesions, bifurcation lesions, etc.), patient comorbidities (e.g. diabetes) and antiplatelet therapy (e.g. inadequate intensity, premature cessation, non-compliance). A study from Chaudhary et al. reported early stent thrombosis in 1% of patients undergoing PCI. Another Indian real-world study involving 1000 patients receiving Everolimus stent (XIENCE V®) reported stent thrombosis in 0.51% of patients at the end of 1-year. The composite endpoint of cardiac death and any MI at 1, 2, and 3 years was reported in 1.9%, 2.7%, and 3.1% of patients respectively. Analysis of PLATO data revealed that compared to clopidogrel, ticagrelor reduced stent thrombosis across all definitions i.e. definite (1.37% versus 1.93%); definite or probable (2.21% versus 2.87%) and definite, probable, and possible (2.94% versus 3.77%). The effect was consistent regardless of ACS type, presence of diabetes, stent type, CYP2C19 genetic status, a loading dose of aspirin, dose of clopidogrel before randomization, and use of glycoprotein IIb/IIIa inhibitors at randomization. A meta-analysis of 11 clinical studies from Fan et al. reported significantly lower rates of stent thrombosis with TICA compared to CLOPI (odds ratio 0.74, 95% confidence interval 0.59–0.93; P=0.009). In a meta-analysis of 9 studies with 21360 patients of ACS, Watt et al. observed similar rates of stent thrombosis with TICA and PRASU (0.6% vs. 0.3% respectively).

**Expert opinion:** The use of TICA as part of DAPT is associated with lower rates of stent thrombosis compared to CLOPI and is similar to that of PRASU.

**After fibrinolysis:** In ACS patients who are treated with fibrinolysis, there is a conservative use of TICA because of the risk of major bleeding such as intracranial or fatal bleeding. The CLARITY-TIMI 28 and COMMIT trials established that DAPT with aspirin and clopidogrel reduces MACE
in fibrinolytic-treated patients with STEMI. To evaluate the safety of ticagrelor in this clinical setting, the TREAT trial was conducted with the primary outcome of TIMI major bleeding through 30 days. At 30 days, there was no significant difference in TIMI major bleeding among patients receiving TICA and CLOPI (0.73% vs. 0.69% respectively). Rates of major bleeding (1.20% vs. 1.38%), intracranial bleeding (0.42% vs. 0.37%) and fatal bleeding (0.16% vs. 0.11%) were also similar with TICA and CLOPI. However, minor bleeding rates were higher with TICA. The effect on composite outcome (CV death, MI, or stroke) was also similar in the two groups (4.0% vs. 4.3%). Thus, in STEMI patients aged <75 years managed with fibrinolysis, administration of TICA is not associated with an increase in TIMI major bleeding compared to CLOPI and had a similar effect on outcomes.

A critical point is the timing of the administration of TICA in these patients. In the TREAT trial, randomization to the treatment was after a median of 11.4 hours (interquartile range, 5.8-18.2 hours) of fibrinolytic therapy. We consider this duration is further dependent on the type of fibrinolytic agent used. In the TREAT trial, tenecteplase (39.6% vs 39.8%), alteplase (19.7% vs 19.2%) and reteplase (16.8% vs 16.6%) were major fibrinolytic agents in both groups with streptokinase (5.7% vs 5.6%) being used in a minority of patients. Thus, when fibrin specific fibrinolytic agent is used, TICA may be administered after 12 to 24 hours of fibrinolysis. In patients treated with streptokinase, which is a common scenario in the Indian setting, the administration of TICA may be delayed until 48 hours.

Expert opinion: In fibrinolytic-treated patients with STEMI, defer administration of TICA till 48 hours when streptokinase is used or the fibrinolytic agent is not known. In the case of fibrin specific fibrinolytic, TICA may be administered within 12 to 24 hours. The rates of TIMI major bleeding including fatal and intracranial bleeding at day 30, are similar to CLOPI. PRASU should be avoided in such patients as coronary anatomy is not known.

Prehospital or Cath-lab Administration

Prehospital or Cath-lab administration of DAPT in STEMI patients is subject of great interest. In a Swedish STEMI patient cohort undergoing PCI, Koul et al. reported no difference in the composite endpoint of all-cause mortality or MI or stent thrombosis or its individual components at 30 days when ticagrelor pre-hospital treatment versus administration the Cath-lab.

The ATLANTIC trial wherein TICA administration compared in pre-hospital (in the ambulance) and hospital (in Cath-lab) settings. The coprimary endpoints (proportion of patients who did not have a 70% or the greater resolution of ST-segment elevation before PCI and the proportion of patients who did not have TIMI flow grade 3 in the infarct-related artery at initial angiography) did not differ significantly. The major reason could be the very short time duration between the two treatments (median time difference between the two treatment strategies was 31 minutes). Rates of MACE at 30 days did not differ in the two groups, but rates of stent thrombosis were significantly lower in the pre-hospital group (0.2% vs. 1.2%). Rates of major bleeding events were low and similar in the two groups. In a separate multivariate analysis of data from the ATLANTIC trial, pre-hospital ticagrelor resulted in significantly lower rate of new MI or definite stent thrombosis ( Odds ratio 0.43, 95% CI 0.20-0.92, P = .031), or definite ST (OR 0.26, 95% CI 0.07-0.91, P = .036) at 30 days. In assessing 1-year mortality, Danchin et al. in a propensity-matched cohort reported lower mortality rates in the prehospital compared to in-hospital administration of DAPT (93.9% versus 90.3%).

Bleeding risk may be a concern feared by some physicians with prehospital administration of TICA. However, the ATLANTIC trial observed no significant increase in bleeding events with prehospital administration. In a retrospective registry data, Bergmeijer et al. compared prehospital initiation clopidogrel and ticagrelor. During an average hospital stay of 5.9 days after PCI for STEMI, there was no significant difference in any bleeding in the two groups (17.8% with CLOPI vs. 20.1% with TICA). Also, there was no significant difference (6.3 vs. 4.9%) in composite thrombotic endpoint (all-cause mortality, spontaneous MI, definite stent thrombosis, stroke, or TIA). All-cause mortality was comparable (3.3 vs. 3.2%). Rates of definite stent thrombosis and stroke or TIA were numerically lower in the ticagrelor-treated patient group.

Expert opinion: TICA prehospital compared to in-hospital administration may be preferred in STEMI patients undergoing PCI. Bleeding risk is comparable to that of CLOPI. CLOPI is a suitable alternative if prior loading has been done in the periphery or the patients has a high bleeding risk.

Switching Among P2Y12 Inhibitors

Switching among the three oral P2Y12i may vary in acute and chronic settings. Due consideration of the pharmacodynamics of each P2Y12i is necessary before switching among them.

Escalation (Switch from CLOPI to TICA or PRASU)

In the acute phase, the escalation from CLOPI should be done with a loading dose of TICA and PRASU, i.e., 180 mg and 60 mg respectively. It can be done irrespective of the timing last dose of CLOPI. In the chronic setting, however, escalation to routine dose, i.e., 90 mg BD and 10 mg regimen. It should be done at a scheduled dose of CLOPI i.e. 24 hours after the last dose of CLOPI.

De-escalation (Switch from TICA or PRASU to CLOPI)

In an acute setting, switching from PRASU to CLOPI may be done with a 600 mg loading dose of CLOPI as the onset of effect is variable, unpredictable, and often delayed. The administration should be done at the next scheduled dose of PRASU i.e. after 24 hours. In the chronic setting, a routine maintenance dose of 75 mg is used at the next scheduled time i.e. 24 hours after stopping PRASU. However, when de-escalating from TICA, a 600 mg dose of CLOPI is necessary for acute as well as chronic settings. CLOPI should be given after 24 hours of TICA discontinuation. A dose of 75 mg of CLOPI may be considered in cases where de-escalation from TICA is because of bleeding.

Change (Switch between PRASU and TICA)

When switching from TICA to PRASU either in an acute or chronic setting, a loading dose of 60 mg should always be used. It should be done after 24 hours of the last dose of TICA. However, switch from PRASU, there is a need for a loading dose of TICA in
Table 2: Strategies of switching among P2Y12i

<table>
<thead>
<tr>
<th>Switch</th>
<th>Setting</th>
<th>Dose strategy</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>C to T or P</td>
<td>Acute</td>
<td>Loading – T (180 mg) and P (60 mg)</td>
<td>Irrespective of the timing of the last dose of C</td>
</tr>
<tr>
<td></td>
<td>Chronic</td>
<td>Routine – T (90 mg BD) and P (10 mg)</td>
<td>After 24 hours of the last dose of C</td>
</tr>
<tr>
<td>T to C</td>
<td>Acute / Chronic</td>
<td>Loading – C (600 mg)</td>
<td>After 24 hours of the last dose of T</td>
</tr>
<tr>
<td></td>
<td>Due to bleeding</td>
<td>Routine – C (75 mg)</td>
<td>After 24 hours of the last dose of T</td>
</tr>
<tr>
<td>P to C</td>
<td>Acute</td>
<td>Loading – C (600 mg)</td>
<td>After 24 hours of the last dose of P</td>
</tr>
<tr>
<td></td>
<td>Chronic</td>
<td>Routine – C (75 mg)</td>
<td>After 24 hours of the last dose of P</td>
</tr>
<tr>
<td>P to T</td>
<td>Acute</td>
<td>Loading – T (180 mg)</td>
<td>After 24 hours of the last dose of P</td>
</tr>
<tr>
<td></td>
<td>Chronic</td>
<td>Routine – T (90 mg BD)</td>
<td>After 24 hours of the last dose of T</td>
</tr>
</tbody>
</table>

T: Ticagrelor; P: Prasugrel; C: Clopidogrel

Table 3: Duration of DAPT in ACS managed by three different strategies

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>PCI</th>
<th>CABG</th>
<th>Medical Therapy</th>
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</thead>
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<td>12 months*</td>
<td>6 months</td>
<td>12 months*</td>
</tr>
<tr>
<td>BR: High</td>
<td>6 months</td>
<td>12 months</td>
<td>12 months*</td>
</tr>
<tr>
<td>ACC/AHA</td>
<td>12 months*</td>
<td>6 months</td>
<td>12 months*</td>
</tr>
</tbody>
</table>

* May be extended up to 30 months, taking into consideration the ischemic and bleeding risk

Switching among oral P2Y12i is an important consideration in the management of ACS. In a study from Li et al. involving 653 Chinese STEMI patients, 48.6% de-escalated from TICA to CLOPI for the main reason of financial burden. Such de-escalation was associated with a significant increase in secondary ischemic events compared to the continuation of TICA (15.1% vs. 5.6%). However, the rates were still lower in the de-escalated group compared to those who received CLOPI (15.1% vs. 24.6%). No difference in bleeding rates was reported in the three groups. A meta-analysis of 14 studies observed no significant differences in MACE for any comparison of switching among P2Y12i in an acute setting. The risk of bleeding was significantly increased among switched patients overall and in the escalation group. Therefore, it is important to select initial P2Y12i based on ischemic and bleeding risks in the index patient. This will help minimize the switching during hospitalization and in the first 30 days.

Expert opinion: Switching among P2Y12i is common in a clinical setting. Pharmacodynamics of the P2Y12i should be correctly recognized to appropriately switch from one P2Y12i to the other. De-escalation in cases with high rates of bleeding and escalation in high ischemic risk may be an appropriate strategy (Table 2).

Duration of DAPT

Duration of DAPT after the index procedure is dependent on various factors such as type of ACS, type of stent, and bleeding risk. Table 3 provides a guideline-recommended duration for ACS managed with PCI, CABG, or medical therapy. In patients with no or low bleeding risk, DAPT should be continued until 12 months irrespective of the type of ACS treatment strategy. The decision to continue DAPT beyond 12 months should be based on ischemic and bleeding risk. Guidelines recommend DAPT may be continued until 30 months. In high bleeding risk, the recommended DAPT duration is six months. The PEGASUS-TIMI 54 trial demonstrated that compared to the placebo, the continuation of TICA in a dose of 90 mg BD or 60 mg BD after 1 year of DAPT significantly reduced composite endpoint of CV death, MI, and stroke (9.04% vs 7.8% and 7.77%, respectively). TIMI major bleeding rates were significantly higher with both 90 mg (2.60%), and 60 mg (2.30%) doses of TICA than placebo (1.06%). However, rates of fatal and intracranial bleeding did not differ between the groups. The Median follow-up of patients was 33 months with an interquartile range of 28 to 37 months. These findings substantiate the continuation of DAPT till three years after the index event reduces the ischemic events albeit at an increased rate of bleeding. The major takeaway from PEGASUS TIMI 54 trial is that in a lower dose of 60 mg BD, TICA achieved a similar reduction in composite events as compared to the 90 mg BD dose with slightly lower rates of bleeding. Thus, TICA at 60 mg BD can be considered as part of DAPT even after a year of index event and procedure.

The SMART-DATE trial compared 6-month DAPT to 12 months DAPT. Clopidogrel was the major P2Y12i as part of DAPT in two groups (79.7% vs. 81.8%). The primary endpoint (composite of all-cause death, MI, or stroke at 18 months) event rate did not differ in the two groups (4.7% vs. 4.2%). The rates of MI, however, were significant in 6-month than 12-month DAPT groups (1.8% vs. 0.8% respectively). Rates of BARC 2-5 bleeding rates did not differ significantly (2.7% vs. 3.9%). Authors suggested prolonged DAPT in patients with ACS without excessive risk of bleeding should remain the standard of care.43 However, a recent TWILIGHT trial involved patients with complex PCI (3-vessels treated, >3 lesions treated, total stent length >60 mm, bifurcation with two stents implanted, atherectomy device use, left main PCI, surgical bypass graft or chronic total occlusion as target lesions). Compared to the continuation of TICA and aspirin DAPT, the continuation of TICA alone after initial 3 months of DAPT was associated with significantly lower bleeding rates (4.2% vs 7.7%) with no difference in the composite outcome of death, MI, or stroke (3.8% vs. 4.9%) or stent thrombosis. Such results were also consistent in non-complex PCI.13 Similarly, the TICO trial demonstrated TICA alone after 3 months of DAPT compared to TICA-based DAPT for 12 months had a significant reduction in the net adverse clinical event (composite of major bleeding and MACE [death, MI, stent thrombosis, stroke, or target-vessel revascularization]). Major bleeding was also lower with TICA alone group compared to DAPT continuation to 12 months (1.7% vs. 3.0%). The RESET trial from Kim et al. also replicated similar results. Patients with coronary artery stenosis were randomized to 3-month DAPT following Endeavor zotarolimus-eluting stent (E-ZES) implantation (E-ZES + 3-month DAPT) versus 12-month DAPT following the other DES implantation (standard therapy). Primary composite endpoint (CV death, MI, stent thrombosis, target vessel revascularization, or bleeding) at one year was similar in two groups (4.7% in both). It proved the non-inferiority of short term DAPT with
Continuation of DAPT between 3 to 12 months should be individualized, taking into consideration the ischemic and bleeding risks. DAPT (aspirin plus TICA 60 mg BD) continuation until three years may be appropriate for patients with multiple stents, diffuse disease, long-standing diabetes, high risk of ischemic events.

**Expert opinion: At present, we consider that DAPT should be continued for 12 months after an index procedure as a standard of care. In high bleeding risk patients, discontinuation of DAPT at 3 to 6 months followed by TICA 90 mg BD should be considered. Continuation of DAPT or individual P2Y12i beyond one year should be individualized considering ischemic and bleeding risks. Use of TICA in a low dose i.e. 60 mg dose after one year of DAPT may be considered especially in those with high bleeding risk.**

### Adverse Effects

#### Bleeding

Bleeding is an inevitable complication with an antithrombotic drug. Compared to a single antiplatelet agent, DAPT has a higher risk of bleeding. Compared to clopidogrel, newer P2Y12i have a higher risk of bleeding in both NSTEMI and STEMI patients. 8,9 Analysis of data from the PLATO trial revealed that at 30 days, rates of PLATO major bleeding (11.6 vs. 11.2%), TIMI major bleeding (7.9 vs. 7.7%), and GUSTO severe bleeding (2.9 vs. 3.1%) are similar in TICA and CLOPI treatments respectively. However, non-CABG major bleeding (4.5 vs. 3.8%) and non-procedure-related major bleeding (3.1 vs. 2.3%) were more common in ticagrelor-treated patients. 45 A large, observational study from India reported bleeding in 1.1% of patients and TICA discontinuation due to bleeding in 0.6% of patients. 46

Emerging evidence indicates lower bleeding events with the continuation of P2Y12i alone after three months of DAPT than DAPT for 12 months. This strategy is associated with a nearly 40% reduction in the risk of bleeding. 52 Also, the use of a lower dose of TICA reduces bleeding tendencies significantly. A metaanalysis from Chen et al. involved 16 trials that compared a low-dose of TICA to standard-dose clopidogrel in ACS patients. Compared to standard-dose clopidogrel, low dose TICA (45 mg BD, 60 mg BD, 90 mg OD) significantly reduced MACE (odds ratio 0.39, 95% CI 0.26, 0.58). For major bleeding events, there was no difference between the two groups (odds ratio 1.16, 95% CI 0.43, 3.08). Platelet reaction units were also significantly lower with low dose TICA than standard-dose clopidogrel. 53 The use of such strategies needs to be adopted to lower the incidence of bleeding complications with more potent TICA without increasing the risk of ischemic events.

In patients who received DAPT, discontinuation may be necessary if urgent or elective CABG is required to reduce the bleeding complications. In patients at high risk of recurrent ischemic events (i.e., eminent large myocardial loss due to critical stenosis, recurrent ischemia) or who develop hemodynamic deterioration, DAPT should be discontinued and the patient should be operated on as soon as possible without waiting for the full recovery of platelet function. For non-urgent CABG, discontinue TICA, CLOPI and PRASU at least 3 days, 5 days, and 7 days before surgery, respectively. 2 GP IIb/IIIa inhibitors are to be used only for a bailout if there is evidence of no-reflow or a thrombotic complication. 4,6

**Expert opinion: Major bleeding risk of TICA is similar to that of CLOPI, but minor bleeding events are common with TICA. In high-bleeding risk patients, strategies such as short DAPT duration, use of low dose TICA may be adopted to minimize the bleeding complications. Fatal and intracranial bleeds are rare with TICA. In urgent CAGB, discontinue DAPT as soon as possible and operate without waiting for recovery of full platelet function. In elective CABG, discontinue TICA at least 3 days before whereas stop CLOPI and PRASU before 5 days and 7 days of surgery.**

#### Dyspnea

Dyspnea is one of the common symptoms in ACS patients. The use of TICA has been reported to be associated with an increased incidence of dyspnea. This dyspnea is not associated with wheezing, orthopnea, paroxysmal nocturnal dyspnea, chest tightness, or pain. It usually occurs at rest. There is no relation to exertion and does not limit exercise capacity. Though the exact mechanism is not known, few hypotheses are suggested. TICA is associated with increased levels of extracellular adenosine because of the antagonism of adenosine reuptake via equilibrative nucleoside transporter-1 (ENT-1). This increased adenosine stimulates pulmonary vagal C fibers and causes dyspnea. Another suggested mechanism is the inhibition of P2Y12 receptors located on C fibers of sensory neurons. 42 Analysis of data from the PLATO study showed that 14.5% of ticagrelor-treated patients and 8.7% of clopidogrel-treated patients had dyspnea after randomization. The dyspnea associated with TICA was mild to moderate in intensity but did not affect efficacy and safety outcomes. 42 Sawhney et al. reported dyspnea of mild, moderate, and severe degree in 1.1%, 0.8%, and 0.4% of TICA treated Indian patients. 46

**Expert opinion: Dyspnea is commonly observed with TICA treatment. In the majority of cases, dyspnea is mild, transient, and requires no specific treatment. Severe dyspnea may require discontinuation of TICA which should only be done after excluding other causes of dyspnea.**

#### Bradycardia

Bradycardia and bradycardia may occur after TICA treatment which is caused due to the rise in adenosine leading to the slowing of cardiac conduction. Analysis of PLATO data revealed that ventricular pauses ≥3 seconds were significantly more frequent with TICA than CLOPI (5.8% vs. 3.6%) at one week of randomization. But, at one month, the frequency was similar between the two treatments (2.1% vs. 1.7%). It was concluded that ventricular pauses remained asymptomatic, had a sinoatrial nodal origin, were nocturnal, and more frequent in the acute phase of ACS. 43 A population-based, nested case-control study found no significant association
between bradycardia and exposure to ticagrelor relative to clopidogrel in the previous 90 days prior to the index date.22

Expert opinion: Bradycardia is asymptomatic, transient, which are common in the first month of ACS and are observed with equal frequency in TICA and CLOP treatments.

P2Y12 Resistance

The prevalence of clopidogrel resistance varied from 5% to 44%. Increasing the loading dose to 600 mg or shifting to TICA helps in overcoming the non-responsiveness.23 The RESPOND study demonstrated that TICA overcomes nonresponsiveness to clopidogrel, and its antiplatelet TICA overcomes nonresponsiveness.24

Cornerstone in ACS management, for P2Y12i. As these drugs are the cornerstone in ACS management, ticagrelor fairs well providing favorable net clinical benefit and thus is the most appropriate P2Y12 inhibitor in all ACS patients.

References


Amilodipine Induced Gingival Hyperplasia

Sankar J¹, Sunil Bennur², NS Taneja³

3 year old female, known case of primary hypertension on tab Amilodipine 10 mg once daily for last 7 years, presented with severe gingival hyperplasia (Figure 1). Oral and maxillofacial surgeon consultation was taken and amilodipine induced gingival hyperplasia was suspected. Amilodipine was discontinued and she underwent external bevel gingivectomy and advised proper oral hygiene. Post operative follow up showed resolution of gingival hyperplasia and no recurrence was noted for 1 year. Histological assessment of biopsy specimen revealed non specific inflammation and connective tissue proliferation (Figure 2). Clinical and histological findings were consistent with amilodipine induced gingival hyperplasia. The most common drugs causing gingival hyperplasia are cyclosporine, phenytoin and calcium channel blocker, especially nifedipine.¹ Treatment includes discontinuation of the drug and most cases have required surgical intervention.² Amilodipine induced gingival hyperplasia, even though known is a rare entity. Physicians should also think of amilodipine as a cause of gingival hyperplasia since it is one of the commonly used antihypertensive drug.

References


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Double Right Coronary Artery

Rajeev Bhardwaj

2 years male presented with angina on exertion for 2 yrs. Angina was initially of walking about half a kilometre. It gradually increased in severity and now he had angina on walking a few steps. He was taken for coronary angiography and was found to have three vessel disease. He had two right coronaries (RCA) arising from right coronary sinus. One RCA showed diffuse disease, with total occlusion after right ventricular branch (Figure 1). There was retrograde filling of this artery.
Fig. 3: Retorograde filling of occluded RCA from normal RCA

RCA from the other RCA (Figure 3). Other RCA was normal (Figure 2).

Coronary anomalies are incidentally detected during routine coronary angiography. Congenital coronary anomalies are seen in approximately 1% of adult patients. Double RCA is a very rare type of coronary abnormality. There was no mention of this anomaly in a series of 126,595 patients who underwent coronary angiography.

The first report about double RCA anomaly in the literature was by Barthe et al. The true definition and correct diagnosis of this uncommon anomaly remain controversial. Some authors have claimed that it is very difficult to distinguish double RCA with single orifice, from RCA which has a high take-that off of a large right ventricular artery, solely by coronary angiography. Nevertheless, they have mentioned that right anterior oblique (RAO) view provides better demonstration of artery courses and may be helpful in differentiating double RCA from a large right ventricular branch. In their study, Sato et al. have proposed that double RCAs are defined when they supply the blood to the inferior left myocardium, thus both of the RCAs should course downwardly to reach the interventricular sulcus whether or not they cross the crux. In recent papers multidetector computed tomography (MDCT) was offered as an alternative or adjunctive imaging method. MDCT allows 3D comprehension of the coronary artery system, and it is extremely useful to identify congenital coronary anomalies such as anomalous origin of the RCA. MDCT might also be useful to differentiate double RCA from high take off of a large branch.

References

OBITUARY

‘The life given to us by nature is short, but the memory of a life well spent is eternal’

Such was the life of Prof. Radharaman Jiban Dash, who is regarded as the legend and patriarch of Indian Endocrinology. He had an extraordinary existence in the medical fraternity, especially in endocrinology. Hailing from Cuttack, Odisha, his humble beginnings did not deter him from pursuing his higher education. Later, he embarked upon a long journey in medicine, starting with the MBBS degree from SCB Medical College, followed by MD (Medicine) and DM (Endocrinology) from PGIMER, Chandigarh, making him the first DM across all superspeciality disciplines in the country. His journey in PGIMER, Chandigarh culminated with him heading the department of endocrinology for well over two decades. Even though he was an ‘incidental endocrinologist’ being called upon to develop the specialty of endocrinology in India, his commitment to the development of the subject was intentional. In his glorious years of service at PGIMER, he trained nearly 70 DM residents, who currently hold prestigious positions at various institutes in India and abroad.

He has several firsts to his credit; the first DM in the country, the first DM in endocrinology, the first dean (research) of the institute and the youngest professor in the institute. His professional contributions were rewarded in the form of several awards of national and international repute, including the prestigious Dr. B C Roy award for developing the specialty of endocrinology in the country. His citation by the Fellowship of the Royal College reads ‘Prof Radharaman Jiban Dash, Senior Prof Endocrinology from PGIMER, Chandigarh, India is ahead of his times. ….. In honoring him, RCP London is honoring itself’.

Prof. Dash achieved what he was destined to. He was an astute clinician, avid reader, and researcher. He is regarded as the ‘teacher of teachers’ and is credited with advancing the first radioimmunoassay in the country in the discipline of endocrinology. He was a visionary, intending to create and nurture the department both in the clinical and research/laboratory aspects. His gesture of generous donations to the local newspaper ‘Samaja’ on various occasions is proof of his gratitude and philanthropy. He was instrumental in organising numerous collaborative efforts with the US and other countries leading to enhanced bilateral ties. These traits evaled him to the position of eminence not only in the country but also overseas, having been chosen to be the visiting professor to nearly 30 universities in the US, UK, Australia, New Zealand, and Bahrain.

In Prof. Dash’s own words (when he offered his tribute to his mentor, Prof. G K Rastogi) ‘great men never die as they live in the hearts of their followers’. Prof. R J Dash lived a life that was distinguished by his simplicity even in the most complex of situations. He achieved several milestones in the professional and personal spheres and his life and journey are for us to strive to emulate. Sunit, Goldie and Puchi’s Bapi and Prof. PN Chuttani’s Dr. Dash………ssh is and will be immortal.

Pinaki Dutta1, Liza Das1, Surjit Singh2

1Department of Endocrinology, 2Former Head, Department of Internal Medicine, PGIMER, Chandigarh
Statin Induced Rhabdomyolysis

Sampath Kumar¹, Shefali Anne², Hari krishna B²

Table 1: Daily variabilities of biochemical parameters and hemodialysis sessions

<table>
<thead>
<tr>
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<th>Day 10</th>
<th>Day 11</th>
<th>Day 12</th>
<th>Day 13</th>
<th>Day 16</th>
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Abstract
Statins are group of medicines that lower the level of low-density lipoprotein (LDL) cholesterol. They may exert toxic effects on skeletal muscle ranging from simple muscle pain to life-threatening complications such as rhabdomyolysis. We report a case of 74-year-old male who was prescribed statins along with other drugs for treatment of coronary artery disease (CAD) and developed rhabdomyolysis which lead to acute renal failure. We report this case as statin induced rhabdomyolysis is very rare.

Introduction
Statins have been shown to improve lipid blood levels and reduce atherosclerotic coronary artery disease (CAD) risk, resulting in reduced CAD morbidity and mortality, and in several studies, reduced overall (“all-cause”) mortality.1 Statin therapy has been proven both safe and well tolerated in millions of patients over nearly 15 years of clinical use. The main adverse effects of statins include dyspepsia, gastrointestinal disturbances, headaches, myalgia, central nervous system disturbances, and sleep disorders. The more clinically significant adverse events that deserve attention include hepatotoxicity and skeletal muscle abnormalities like rhabdomyolysis.2

Case Report
A 74 yr old man admitted with complaint of breathlessness, sudden in onset of one day duration which was present even on walking for a short distance (NYHA III). There was no history of chest pain, palpitations or any syncope. He reported that he was known diabetic for past fifteen years and was on treatment with oral hypoglycemic agents (not specified). There were no other co-morbid illnesses and no prior history of similar complaints in the past. He did not report history of any substance abuse.

On examination, there were no signs of pallor, cyanosis or edema. His vitals were essentially normal. There was a gallop rhythm on auscultation of heart and further examination of chest revealed bibasilar crepitations. His electrocardiogram showed normal axis and a pathological ‘q’ wave in inferior leads along with T wave inversions. On further evaluation, two dimensional echo was consistent with ECG findings and showed a regional wall motion abnormality in RCA and LAD territory (anterior wall, mid basal inferior wall hypokinetic). He had mild LV dysfunction and his left ventricular ejection fraction was 45%. These findings were further confirmed by angiography.

His biochemical profile was normal other than his glucose levels which showed elevated fasting and post prandial values. Hemogram and other investigations were in normal range.

Patient was started on anticoagulants, antiplatelets and atorvastatin 80mg on first day of his presentation. Later atorvastatin was reduced to 40mg. On day 8 of his stay in hospital he became drowsy and complained of not passing urine for a duration of six hours. He also complained of generalized myalgia and it was observed that his urine was reddish brown in color. Creatinine phosphokinase (CPK) was 8190 IU/L (reference upper limit of normal range-170 IU/L). His blood urea and serum creatinine were increased compared to the baseline values.

Based on these findings a diagnosis of rhabdomyolysis secondary to statin usage was established. Statins were stopped immediately and he was started on hemodialysis. There was dramatic improvement in his CPK levels, renal profile (Table 1) and his urine output. He was discharged a few days later with prescription of ezetimibe 10 mg.

Discussion
Myalgia is the most common side effect of statin use, with documented rates from 1-10%. Whereas, rhabdomyolysis is the most serious adverse effect from statin use, though it occurs quite rarely (less than 0.1%).3

Rhabdomyolysis is a clinical syndrome that results from severe and widespread injury to skeletal muscle and the subsequent accumulation of toxic muscle products in the blood and urine. It is accompanied by findings such as myoglobinuria, myoglobinemia, and evidence of target-organ damage, such as decreased renal function or acute renal failure.4

The mechanism by which statins cause myopathy is not completely understood. Evidence from well-designed randomized controlled trials shows that myopathy correlates most closely with dose of statins and is independent of reductions in low density lipoprotein cholesterol.5 Several risk factors have been proposed that associate with statin induced myopathy.

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like, elderly, low body mass index, alcohol intake, vigorous exercise, associated drug usage (fibrate, azoles, amiodarone, calcium channel blockers), genetic factors.

Since their introduction for the treatment of hypercholesterolemia in 1987, the use of statins has grown to over 100 million prescriptions per year. Lovastatin was the first commercial statin which was given FDA approval in September 1987. The reported rates of serious adverse events (SAEs) among statins as a class have been very low (<1%).

The US Food and Drug Administration Adverse Event Reporting System database reports rates of statin-induced rhabdomyolysis of 0.3–13.5 cases per 1,000,000 statin prescriptions. Although initially defined by the US Food and Drug Administration (FDA) as a CK level greater than 10 000 U/L, more recently rhabdomyolysis has been defined by the FDA as an appropriate diagnosis only when organ damage (typically renal insufficiency) occurs in association with elevated CK levels. In this case CPK was elevated to 8190 IU/L (nearly 50 times) which did not satisfy the early criteria for rhabdomyolysis, but there was evidence of organ damage in the form of acute kidney injury which was satisfying recent definition as per FDA.

Drug-drug interactions with statins are significantly more likely to be associated with myopathy this is because statins are extensively metabolized via cytochrome P450 (CYP) pathways. Lovastatin, simvastatin, atorvastatin, and cerivastatin use mainly the CYP3A4 pathway. The concurrent use of statins that are recognized by CYP3A4 and other agents that are potent inhibitors or substrates of this enzyme—in particular, the azole antifungals, some macrolide antibiotics, and cyclosporine lead to increased toxicity of the drugs. However, it should be noted that the risk for myopathy also appears to increase when statins are combined with drugs that may not be metabolized via the CYP3A4 pathway, such as fibrates and niacin. This interaction was unlikely in our case as there was no concomitant use of above mentioned drugs.

The time between initiation of statin to onset of rhabdomyolysis was 8 days in this case which is similar to a case series with a mean duration of 9 days. Acute kidney injury is a potential complication of severe rhabdomyolysis, and the prognosis is substantially worse if renal failure develops. Although the exact mechanisms by which rhabdomyolysis impairs the glomerular filtration rate are unclear, experimental evidence suggests that intrarenal vasoconstriction, direct and ischemic tubule injury, and tubular obstruction all play a role. Development of acute kidney injury was very rapid in our case occurring almost simultaneously with myalgia.

The standards of care for rhabdomyolysis-induced acute kidney injury include, aggressive intravenous fluids until myoglobinuria is cleared, urine alkalization if urine pH<6.5, maintaining urine output at rate of 200ml/hour and renal-replacement therapy if there is oliguria or anuria, symptomatic hyperkalemia, volume overload and resistant metabolic acidosis. Continuous venovenous hemofiltration or hemodiafiltration has shown some efficacy in removing myoglobin. The use of antioxidants and free-radical scavengers (e.g., pentoxifylline, vitamin E, and vitamin C) may be justified in the treatment or prevention of myoglobinuric acute kidney injury, but controlled studies evaluating their efficacy are lacking.

Conclusion

Statin-associated myopathy should be suspected when a statin-treated patient complains of unexplained, generalized muscle pain, tenderness, or weakness. Likewise, patients should be taught to recognize symptoms of myopathy and report them promptly. If myopathy is suspected, statin therapy should be discontinued and serum CK levels should be monitored. Early diagnosis and treatment of symptomatic CK elevations, including cessation of drug therapies potentially related to myopathy, can prevent the progression to rhabdomyolysis.

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Thrombotic Thrombocytopenic Purpura in a Patient with Brucella Infection

Atul Bhasin¹, RK Singal², Dharma Chaudhary³, Sanjeev Kr Sharma⁴, Saurabh Arora⁵, Rasika Setia⁶, Jai Khullar⁷, Gagan Anand⁸

Abstract

Thrombotic thrombocytopenic purpura (TTP) is characterized by disseminated thrombotic occlusions in the microcirculation and a syndrome of microangiopathic hemolytic anemia (MAHA), thrombocytopenia, fever, renal and neurologic abnormalities. Several factors such as viral and bacterial pathogens, pancreatitis, drugs, collagen-vascular diseases, cancers, and pregnancy have been reported to cause TTP. Brucellosis is an exceptional cause of this disorder. We present a case of a 33 year old male who was found to have Brucella antigen (IgG) positivity who responded well to antibiotic therapy directed to Brucella infection. He subsequently reported back with B/L diminution of vision, fever and was found to have severe thrombocytopenia. Ophthalmology opinion revealed retinal hemorrhages. In view of severe thrombocytopenia with a normal coagulogram, raised LDH, renal azotemia and peripheral blood smear showing fragmented RBCs he was diagnosed to have Thrombotic Thrombocytopenic Purpura (TTP) secondary to Brucellosis. He was immediately treated with Plasma exchange; however, he relapsed after initial cycles. He underwent further plasma exchanges with unsatisfactory response, thus was eventually started on Rituximab to which he responded well.

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a coagulation disorder which causes micro thrombi formation in small blood vessels leading to extensive ischemic damage to organs. We present here a case of Secondary TTP due to Brucellosis requiring plasma exchange and rituximab.

Case Summary

33 years old male, presented in ER with chief complaints of high grade fever with chills, itching all over body, poor oral intake, weight loss and pain abdomen on and off 3-4 months. On examination patient was febrile, temperature rising up to 104.4°F and had generalized lymphadenopathy. He was earlier evaluated elsewhere where he was thoroughly examined and investigated. Whole body PET scan revealed mildly FDG avid and non FDG avid bilateral cervical, axillary, abdominal and inguinal lymph nodes with mildly FDG avid hepatosplenomegaly suggestive of infective / inflammatory etiology. He was empirically treated with anti tubercular four drug combination and discharged.

He remained symptomatic with fever and was brought to our hospital, where he was re investigated for Pyrexia of Unknown Origin. Bone marrow aspiration, biopsy and culture were performed which showed significant eosinophilia with mild prominent of histiocytes, while lymphnode biopsy was suggestive of reactive eosinophilic reaction and sinus histiocytes. Brucella antigen (IgG) was positive, so treatment as combination therapy of Rifampicin and Doxycycline were initiated. Patients fever responded well to the given treatment and he was discharged. During follow up two weeks later he developed B/L blurring of vision and was found to have severe thrombocytopenia on investigation. He was evaluated by ophthalmologist and was found to have best corrected visual acuity (BCVA) of 5/60 in right eye (RE) and 6/12 in left eye (LE). Fundus examination clinically revealed cotton wool spots in both eyes predominantly at posterior pole along with cystoid macular edema which was documented on Optical coherence tomography (OCT) (Figures 1, 2, 3). A relapse of Brucellosis was thought and he was hospitalized again for further investigations. He was found to have normal coagulogram, raised LDH with renal azotemia. The clinical and Laboratory findings were consistent with Brucella associated TTP findings.¹ He was immediately started on Plasma exchange (Figure 4). He was initially given five cycles over a period of 10 days to which he responded well (Platelet counts raised and LDH levels decreased). While on therapy he developed fever and was treated on lines of CRBSI (Catheter related blood stream infection) and his central line was removed and antibiotics upgraded for CRBSI Sepsis. Patients count normalized and he became afebrile. Repeat blood counts again revealed thrombocytopenia and raised LDH levels, suggesting relapse of TTP. Seven more cycles of plasma exchange were carried to which he responded inadequately. He was given Rituximab at a dose of 375 mg / meter²for relapsed TTP. An Intravenous dose of 700 mg was given, divided over four doses, on weekly interval over next 4 weeks. He was also given simultaneous RE Intra vitreal triamcinolone acetate followed by LE Intra vitreal triamcinolone acetate and ranibizumab after 2 weeks. His BCVA improved to 6/12 in RE and 6/9 in LE at 3 months after treatment. To this local and systemic therapy the patient responded well. He has been on regular follow and has partial restoration of vision and normal blood
counts with no fever.

Discussion

Brucellosis is a systemic disease transmitted through ingestion of raw milk, meat or by direct contact with infected animals. It usually presents with multisystem involvement. Symptoms may be nonspecific like fever, headache, malaise, arthralgia, anorexia, and hematological manifestations. Hematological abnormalities such as pancytopenia, thrombocytopenia, leucopenia, DIC or rarely TTP are seen. Despite being described as benign disorder with favorable outcomes, there are no strict treatment guidelines for complicated infections. Eye involvement in brucellosis occurs usually during the chronic phase and patients often present with bilaterally diminished vision. Ocular manifestations include conjunctivitis, dacroyoadenitis, episcleritis, nummular keratitis, cataract, glaucoma, multifocal choroiditis, exudative retinal detachment and maculopathy and majority showing posterior uveitis.

The pathogenesis in ophthalmic disease includes immune complex mediated disease as well as presence of brucellae in the intraocular fluids.

Thrombotic thrombocytopenic Purpura (TTP or Moschcowitz syndrome) is a hematological disorder recognized by thrombocytopenia, microangiopathic hemolytic anemia, neurological abnormalities, renal failure and fever. TTP can be seen in many infections due to viruses, bacteria, mycobacteria or non infectious diseases like connective tissue diseases, drug reactions, or solid tumors. Endothelium damage by bacterial antigen, and cross-reactive antibodies between Brucella antigen and the VWF-cleaving metalloprotease have been reputed to cause this hematological phenomenon.

Our patient had hemolytic anemia, thrombocytopenia, schistocytes in the blood smear, reticulocytosis, increased serum LDH, fever and renal impairment.

TTP is a disorder which is cascaded by aggregation of platelets and activation of coagulation proteins in blood vessels leading to binding of vWF. These platelet-vWF complexes formed, cause micro thrombi formation and lead to shearing of red blood cells thus causing erythrocyte rupture and hemolysis. Micro thrombosis in vessels leads to ischemia of end organs especially kidneys, heart and brain. There are three types of TTP, they are Idiopathic, Secondary and Inherited form (deficiency of ADAMTS13), also known as the Upshaw-Schülman syndrome. The mechanism of secondary TTP is poorly understood, and is primarily linked to endothelial damage. Other factors responsible in pathogenesis of Pancytopenia in brucellosis are immunologically mediated bone marrow suppression, hypersplenism, granulomatous bone involvement, hemophagcytosis and sometimes due to disseminated intravascular coagulation.

Being a zoonotic disease and Brucellae being facultative intracellular pathogen, it is resistant to various antibiotic therapies. Therefore necessitating multiple drug’s for a longer period of duration. World Health Organization recommends a combination of rifampicin 600 to 900mg and doxycycline100mg twice daily in adults for a minimum of six weeks. Few studies have documented a combination of streptomycin (1 g/day for 2-3 weeks) and tetracycline (2 g/ day for 6 weeks), with fewer relapses. Trimethoprim- sulmefamoxole (TMP/SMX) can be added to above regimes in case triple drug combination is contemplated in endemic areas, relapses, neurobrucellosis, brucellar endocarditis. Rifampicin-containing regimes are avoided in areas where tuberculosis is endemic primarily to avoid developing of its resistance. Corticosteroids are reserved for resistant and relapsed cases. Patients diagnosed to have TTP require plasmapheresis. Plasmapheresis is now considered as mainstay therapy in removing antibodies against the VWF cleaving metalloprotease.

Rationale behind Plasma infusion and exchange is to restore an enzyme that by modulating protease activity of vWF factor prevents fragmentation of the molecule. Treat ing infection with antibiotics in addition with plasma exchange was successful in TTP secondary to brucellosis. Large-volume exchange leads to removal and reduction of immunoglobulins and immune complexes from the blood.

Patients suffering with TTP who are not responding to corticosteroids and Plasmapheresis, are recommended to be treated with Rituximab. Monoclonal
antibody, Rituximab, targets CD20 molecule on B lymphocytes in cases of TTP. Laboratory monitoring of LDH, platelet Count and schistocytes on Peripheral blood smear are monitored for progression or remission of TTP. We did not measure ADAMTS13 activity, which should be measured if possible.

Prevention of this zoonotic infection from transmission, by avoiding unpasteurized dairy products, control infection in goats and sheep, regularly screen bulls and their semen for brucellosis while performing artificial insemination are some of the methods.

**Conclusion**

This case highlights the management of Brucella infection with TTP requiring aggressive and early plasmapharesis and Rituximab. TTP is one of the few diseases requiring plasmapharesis, as treatment of choice in primary management.

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**Fig. 2:** FFA of Both eyes showing blocked fluorescence corresponding to areas of multiple cotton wool spots, splinter hemorrhages with late diffuse maculopathy and diffuse ooze around peri-papillary area at presentation.

**Fig. 3:** OCT of Both eye showing spongy thickening R>L with right eye sub foveal detachment, at presentation and complete resolution of edema with foveal thinning in both eyes after 3 months post ocular / systemic treatment (3b Right and Left).
World’s First Hospital Train

Jayant Pai-Dhungat¹, Aparna Verma²

World’s first hospital train, Lifeline Express or Jeevan Rekha Express started in India from Mumbai 29 years ago with three wooden coaches. It now has seven steel coaches, two of which were added recently to serve as a Cancer Coach and the other, dedicated to Family Health Services.

It started with a simple idea to: take the hospital to the people, especially people of the most remote parts of rural India, who remain poorly serviced by healthcare facilities. The Impact India Foundation (IIF), an NGO, proposed the idea to the Ministry of Railways. Shortly after, the Indian Railways and IIF signed a MoU under which the Railways would provide a three-coach train with water, electricity, and maintain it, and the NGO would operate the medical services.

Today, seven coaches of the Lifeline Express have state-of-the-art facilities with operation Theatres, a pathology Lab, a mammography unit, a gynecology examination Room, dental Unit, Pharmacy, Consultation Cubicles, X-RAY, among others.

The train is Wi-Fi enabled with which a doctor can consult concerned specialist sitting in a metropolitan city and seek opinion on x-ray, ECG and other images.

The train has made a health impact both in India, as well as around the world where it has inspired similar initiatives. In fact, such has been the impact of the train that at least two countries have replicated the idea. China has four and South Africa has two such trains. Concept is also adopted by Bangladesh and Cambodia which have made Riverboat hospitals.

In the 1990s the train provided treatment primarily for cataract and polio but, over the years it has provided, many cleft palate and other plastic surgeries, dental surgeries, epilepsy services, cancer treatment.

For surgeries - disability data, vital health indicators and the facilities are available in the district are assessed and report for the location is first prepared. This is followed by a preliminary screening of the patients at the local primary health centre or community health centre and a list of those who require surgeries is prepared.

Till now, nearly 2,00,000 medical professionals from India and around the world have rendered their services to the train. The Lifeline Express has travelled across 19 states, covering 201 rural locations in 138 districts providing medical treatment to 12.32 lakh patients, including 1.46 lakh cases of surgery. It has also entered into a MOU with Tata cancer Memorial Hospital; among its other sponsors are Mahindra and Mahindra, Tata Chemicals, Tata Steel, Tata Trust, Emirates Airlines and SBI.

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Aspiring Doctors Cognizance on Organ Donation – A Reflection

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Sir,

There has always been a dearth of donor organs be it stem cells to heart-lung. Though the need for organs is ever-growing, the rate at which organs are donated remains very meagre. People’s misconceptions, cultural and religious beliefs along with inadequate knowledge among the doctors and public, the array of ethical concerns contribute to present state of organ donation and transplantation across the globe. We attempted to analyze the knowledge, attitude and perceptions about organ donation and transplantation among medical students at various levels of their academic career, to see if knowledge impacted their attitude and perceptions as they form the future generation of treating doctors.

A questionnaire-based study was conducted involving 520 students, with 320 students pursuing undergraduate degree (M.B.B.S.) - 100 students pursuing the first year, 110 students amongst the fourth year and 110 students at internship while 100 students each from the medical and surgical postgraduate specialties. They were assessed on their demographic outline, knowledge, attitude and perception about organ donation and transplantation and the impact of the course on these aspects.

We had 247 respondents in the age group of 21-24 years with 48.1% males and 51.9% females. 94.2% of the study respondents were residing in India of whom 85.4% were practicing Hinduism. The attitude of the respondents was graded as agreeable, equitable and disagreeable. Both gender and religion did not influence any of these aspects of study. A linear relationship between knowledge and academic career, agreeable attitude of the participants and their academic career and a statistically significant increment in attitude was seen as the students progressed through medical education.

Most of the participants had acquaintance with the terms of organ donation, living donor and cadaveric donor as shown in previous studies conducted by Deepthi et al. Post graduate students were found to have better knowledge about donor eligibility and matching (96%) as against 71% among undergraduates. The importance of right attitude and knowledge possessed by the doctors in encouraging organ donation has been reinforced at multiple occasions. We observed an encouraging attitude towards organ donation among the students. Most of the respondents were willing to be donors (91%) and were confident about discussing the same with their families. Almost everyone felt organ donation as a praiseworthy act (94%). A sizeable number supported monetary benefits to donors (58%). Despite the reassuring response to deter organ trafficking (77.3%), it came with a warning of 8% expressing support. 29.4% of the respondents considered organ donation unfair and unclear displaying lack of trust in the prevailing system. Atamanuk AN et al observed mistrust in the system and attributed the same to lack of knowledge. Despite showcasing adequate knowledge, the participants had clearly expressed their suspicion about the transparency of organ donation which raises an alarm, highlighting the existing trust levels on the system and is a vital aspect in decision making among them.

Knowledge and attitude of medical students across wide range of medical career has shown satisfactory results with progressing knowledge and attitude with every progressing stage of academics. Changes in the medical curriculum in the form of early clinical rotations to transplant units, wiser application of social media in understanding these concepts could bring in better perception and adaptability towards organ donation and transplantation.

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Computerized Prescription

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Sir,

Prescription errors are common medical errors. Computerized prescribing is a change that is overdue. Most Indian Doctors are not computer savvy and are not willing to leave the traditional way of writing prescriptions. Medication errors are many including mistakes by the pharmacist incorrectly interpreting illegible handwriting. Adverse drug reactions can be minimized by eliminating errors of prescription writing. Significant barriers to implementation include cost, lack of provider support, patient privacy, system errors etc. Computerized prescription is being used in many Corporate, Government hospitals and private clinics in most metros. In the recent pandemic there is sudden spurt in computerized /online prescription. Most developed countries are already generating Electronic Prescription “e-prescription”. E-prescription is a distant dream, so we focus on “computerized prescription” only.

Computerised prescriptions can be easily generated on your desktop, laptops or smartphone. Software can be tailor made and personalized. One has to pay yearly maintenance. Cloud based software are more prevalent. Doctor can access it from anywhere. One need not burden the computer with extra storage of data. New softwares are using artificial intelligence (AI). With this software one writes with a ‘special or electronic pen’ on prescription pad and the patient gets a WhatsApp and digital copy.

Benefits of Computerised Prescription
1. Computers maintain personal details of the patients including mobile numbers, address, weight, height, age, patient’s diagnosis, current
medications, for drug-drug interactions, drugs-allergy, other allergies etc. and personal habits including alcohol intake or smoking also.

2. With advancing age the handwriting gets more illegible and the memory weakens. With computerized prescription one gives a clear prescription and directions on every aspect.

3. The prescription can be designed to highlight abnormal findings and reports. At one click, one can recheck any drug formulation, its safety profile, contraindications before prescribing. It can flag lethal dosages and combinations of drugs. One can incorporate known side effects of the drugs. Common errors like ‘mg’ and ‘ug’ are reduced.

4. Illegibility and oral miscommunications regarding prescriptions can be reduced. Computerized prescriptions can reduce the volume of chemist’s call-back, decreasing the amount of time wasted on the phone. It should be in readable format meaning using “ALL CAPS” letters, as per the Government’s directive.

5. The MCI in its 2016 notification asked the medical practitioners to prescribe generic medicines to the patients, so the patients can buy cheaper medicine with the same formulation. It is not humanly possible to remember and write generic names because of combination of multiple salts in “polypills” and their lengthy names. Most software have generic names.

6. Doctors have all the records and can verify from the records date and purpose of the consultation. If a patient loses the prescription, you have all the details. Doctor can just copy, edit and paste prescription. If you do not want to repeat the same medicines, you can change and avoid repetition.

7. Neat and tidy prescriptions give a good feeling to patients and satisfaction to doctors.

8. One can make templates of investigations, diseases, medicines, advice etc. With one click one can reproduce the same in another patient. It saves on time and reduces the chances of missing a medicine, instructions or investigation.

9. Language of the prescription can also be changed. It helps patients who do not understand English. Moreover patients feel happy when they get the prescription in their native language.

10. Date of subsequent visit is also printed. So the patient’s excuses of jumping the date of visit are minimized. A reminder mail or message for the next appointment or any information can be send by using the saved numbers.

11. It also generates bills and invoices, so no need to maintain a separate bill book.

12. Investigations are also listed for advice. A comparative chart can be made regarding progress of disease and effect of treatment. With the data collected one can write research papers.

13. Prescriptions can be printed or emailed or texted (saves on paper). It can be directly sent to laboratory and/or pharmacy.

14. As per law one has to maintain OPD register. If you have daily data in electronic form, then there is no need to maintain a separate register.

15. Many a times patients insist to issue a back dated prescription. One can excuse oneself that it cannot be generated in back date, as the computer does not accept any backdate entry.

16. One can feed medical/fitness certificate, education material, diet and vaccination charts, for giving to patients.

17. In the computer there are certain findings stored in the data, which only the doctor can see. This aids in maintaining the confidential information of the patient that is of importance to the doctor for patient management.

18. Most software are linked to OPD register. If you have daily data in electronic form, there is no need to maintain a separate register.

19. In the computer there are certain findings stored in the data, which only the doctor can see. This aids in maintaining the confidential information of the patient that is of importance to the doctor for patient management.

20. Most software are linked to OPD register. If you have daily data in electronic form, there is no need to maintain a separate register.

21. A doctor can generate or renew “online prescriptions” from anywhere.

22. Some softwares have alert popups for drug interactions, drug reactions etc.

**Disadvantage**

1. Choosing the right hardware and software applications can be a difficult. The doctors generally struggle with how to get started, appropriate vendor selection, cost and functions of the whole system.

2. One has to invest in computer, printer, software; training of staff and upgrading from time to time etc. The cost associated with purchasing, implementing and supporting may be a barrier. Maintenance of equipment (Annual Maintenance Contract) is expensive.

3. System is dependent upon electricity, Internet connection, machines etc. Difficulties may arise due to network, hardware failure or loss of electricity. When the system is down, work is stuck and one has to fall back on other procedures or one should have standby equipment.

4. Your data or patient’s information can be used, misused, stolen or hacked by anyone including the provider. If provider shuts shop all your data is lost. Loss of data is of grave concern for the prescriber and the patients. Privacy of patient information is also a concern. Instances of negligence may arise, where employees may forward prescriptions to organizations outside its intended use. Data is to be protected with firewalls, use strict computer permission settings and remain vigilant towards any intrusion.

5. Accidental data entry errors, selecting the wrong patient or clicking on the wrong choice may occur. Patients with similar names should be cross checked with mobile numbers. Efforts has to be made to verify the trade name and the correct generic contents of formulations. The list of medicines should be updated frequently.

6. The doctor should have knowledge about computers and typing. If the doctor is slow then the patient feels irritated.

7. Many patients do not carry the prescription and feels it is doctor’s responsibility to save and reproduce the prescription. Even the insurance companies come asking for the old records, which can be denied until it is legally required.

8. The software having lack of alert specificity causes multiple alerts, thus leading to alert fatigue. So prescriber tend to ignore the alerts, thus missing a important alert.

Computerized prescription reduces errors while simultaneously reducing the risks of liability. It decreases the work needed to execute a prescription. It improves medication compliance by patients. It reduces the work and call back from the dispensing chemists. It helps in reducing the cost by
 offering a substitute or generic drugs. Computerized prescription is a baby step and we are waiting for the whole nation to be united with e-prescription.

References


Left Atrial Volume Index (LAVI): An Important Parameter for Risk and Stroke Subtype Prediction

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Sir,

Cerebrovascular stroke constitutes a global health epidemic and is the leading cause of sustained disability. It is important to be able to identify and differentiate stroke subtypes since therapeutic decisions may differ.

Since the left Atrium is not a symmetrically shaped three-dimensional structure and its enlargement does not occur uniformly, measurement of LAVI (Left atrial volume index) provides a more accurate and reproducible estimate of left atrial enlargement than measuring the left atrial size only. LAVI can be calculated by measuring the Left Atrial volume by 2d echocardiography and indexing it to Body surface area. In this study, we determined the association between LAVI and the risk of ischemic stroke along with its association with various ischemic stroke subtypes.

The study included 100 patients with ischemic stroke who were admitted at Rajendra Institute of Medical Sciences, over one year. Patients with hemorrhagic stroke or a history of stroke were excluded. Stroke subtypes were divided into atherothrombotic stroke, cardioembolic stroke, and lacunar infarct based on the TOAST classification.1 LAVI was calculated by measuring Left atrial volume by 2D echocardiography using the Biplanar area length method2 and indexing it to body surface area. A value of 22 ± 6 ml/m² was taken as the normal range as per recommendations of ASE (American Society of Echocardiography) and left atrial enlargement was identified if LAVI >28ml/m².

Out of 100 patients with ischemic stroke, 35% had cardioembolic and atherothrombotic stroke each, and 30% had a lacunar stroke. 76% of the patients with ischemic stroke had increased LAVI >28 ml/m² with a mean LAVI of 32.8 (±2.96) ml/m². Mean LAVI in the cardioembolic stroke patients was significantly higher than the atherothrombotic and lacunar infarct groups ((34.05±3.7) vs 31.4±3.04) and 28.16 (±2.2)) ml/m² respectively, p<0.001. Moreover, majority of the patients with cardioembolic stroke had LAVI>32ml/m² as compared the lacunar and atherothrombotic groups (51.4% vs 10% and 20%, p<0.001).

Left atrial dilatation promotes stasis of blood, resulting in an increased propensity for thrombus formation and hence ischemic stroke. Moreover, left Atrial Enlargement is a potent risk factor for the development of atrial fibrillation as seen in the Framingham Study where every 5 mm increment in Left Atrial size increased the risk of atrial fibrillation by 39%,3 thus explaining the association between cardioembolic stroke and increased LAVI.

The increase in LAVI in atherothrombotic stroke can be postulated to be due to hypertension mediated left atrial enlargement as hypertension leads to left atrial enlargement by increasing left ventricular filling pressure. This is also supported by the fact that the majority of the atherothrombotic patients in our study had hypertension (82.9%) as compared to the cardioembolic patients (68.6%).

Thus, increased LAVI is associated with risk of ischemic stroke and LAVI correlates with stroke subtype as at mild increases in left atrial volume indices (28-32 ml/m²) there were more atherothrombotic strokes patients but at higher left atrial volume index (32-36 ml/m² and >36 ml/m²) there was more cardioembolic stroke. Hence, LAVI can be a very useful parameter to identify people in the normal population who are at risk of ischemic stroke and differentiate stroke subtypes, which is very important as identification of ischemic stroke subtype affects the management.

Prevalence of Thyroid Disorders (TD) in Newly Diagnosed Type 2 Diabetes Mellitus Patients – A Cross Sectional Study

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Sir,

Prevalence of thyroid disorder (TD) and diabetes mellitus (DM) is high in India.1 Around 42 million people in India are currently suffering from various TD and is more in female and older patients. According to International Diabetes Federation estimates, around 463 million people had DM in 2019 and it is expected to rise to 700 million by 2045. It is more in obese, sedentary people and genetically predisposed patients. Since both are two most common endocrine problems so the prevalence of TD in diabetic patient would be expected to be as high as in general population. But a meta-analysis of 36 articles concluded that prevalence of TD is more in diabetic patients than in general population. Various studies from India also prove that prevalence of TD is more in diabetic patients than non-diabetes population.2,3 In type 1 DM prevalence of TD is high because of autoimmune nature of disease and we know that when there is one organ specific autoimmunity there is high chance of another autoimmune disease. Prevalence of TD is high in Type2 DM because thyroid hormone (TH) induces IR (insulin resistance) and IR causes thyromegaly and other TD.

There is a two-way relationship between TD and DM. DM affects the thyroid hormone (TH) level and TH also affects the DM. In DM
Hyperinsulinemia of DM causes peripheral insulin resistance due to various mechanisms. On peripheral tissue it causes increase glucose uptake, lipolysis and lipogenesis through central and hepatic conversion of T4 to T3.4 It also suppresses insulin secretion.

T3 exerts its effects on glucose and lipid metabolism through central and hepatic conversion of T4 to T3.4 It also suppresses insulin secretion. T3 exerts its effects on glucose and lipid metabolism through central and peripheral pathways. T3 has got insulin antagonistic effects on liver and insulin synergistic role on peripheral tissue such as fat and muscle cells.4 T3 act on liver and causes increase in HGP, lipolysis and lipogenesis through various mechanisms. On peripheral tissue it causes increase glucose uptake but in thyrotoxic patient there is peripheral insulin resistance due to increase in cytokines (TNFa, IL6). T3 is important for islet cell development. It improves the beta cell maturation, beta cell proliferation and insulin secretion.4 Both hyperthyroidism and hypothyroidism cause IR through various mechanisms. Besides this TD worsen the micro and macro vascular complication of DM. TD is also known to adversely affect the metabolic control.5 So, control of TD is important in diabetes patients for holistic management. Since the actual prevalence TD in newly diagnosed Type 2 DM patient is scanty and non-existing in this area so we conducted this study. The aim of this present study was to determine the prevalence of TD in newly onset Type 2 DM and to study the effect of glucose on thyroid hormone level.

During the study period 276 patients were enrolled and examined. Total T3(TT3) between 5.5 to 20 µIU/ml and normal TT3 and TT4. Overt hypothyroidism (OH) was defined as TSH > 20 µIU/ML and or low TT3 and TT4. Subclinical hypothyroidism was defined as low TSH and normal TT3 and TT4 and overt hyperthyroidism was defined as low TSH and high TT3 and TT4. Student’s t-test and Chi-Square test were used to determine statistical difference between variables. Results were considered significant if P value were <0.05.

In the study 196(71.01%) were male patients and 80(28.99%) were female patients. Prevalence of TD was 20.29%. This shows a high prevalence of TD in a diabetic patient. In various studies it ranges from 10.8% to 51.6%. Low incidence of TD in our study as compared to study by Celani et al, Udiong et al, Uppal et al, Pimenta et al and Deshmukh et al is due to low number of female patients in our study. Other reasons of low incidence were due to lower age of patients and exclusion of type 1 patients in our study. In Pimenta et al study very high prevalence was due to inclusion of colloid goiter in their study.3 Prevalence of TD in various studies varies due to various reasons such as different criteria used for diagnosis, different sensitivity of TSH assay, population diversity, different intake of iodine etc. In our study prevalence of TD in male was 16.84% while in female patients it was 28.75%. This was also seen in other studies.

In our study hypothyroidism and hyperthyroidism was seen in 18.48% and 1.81% of all patients respectively (Table 1). In TD patients, hypothyroidism and hyperthyroidism was seen in 91.07% and 8.93% respectively. So, hypothyroidism was more common than hyperthyroidism and this is also seen in other studies. In our study prevalence of subclinical hypothyroidism, overt hypothyroidism, subclinical hyperthyroidism and overt hyperthyroidism was presents in 62.5%, 28.57%, 5.36% and 3.57% of all TD patients while in Smithson et al study it was 36%, 45.46%, 9.09% and 9.09% respectively.6

Uncontrolled diabetes is considered as a low T3 state. Our study also shows the same. Euthyroid diabetic patients were stratified into 4 groups based on glyA1c level. TT3 was significantly low (P<0.05) in highly uncontrolled (HbA1c >12%) euthyroid diabetic patient as compared to controlled(HbA1c <7%) euthyroid diabetic patients (Table 2). Low TT3 is due to reduced peripheral and hepatic conversion of T4 to T3.4

For TT3, TT4 and TSH, P value between group A and group D is <0.05,<0.988 and <0.191 respectively.

In conclusion, our study shows that there is a high prevalence of Thyroid Disorder in newly diagnosed Type-2 diabetic patients from this geographical area, especially in females. So thyroid function should be tested routinely in diabetic patients. This study also shows that uncontrolled diabetes is associated with low TT3 so TT3 might be used as a potential marker of control of diabetes mellitus.

References

Acute Pancreatitis in a Patient with Coronavirus Disease 2019 (COVID-19) Pneumonia

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1PG Resident, 2Professor, 3Professor and Head, Department of General Medicine, 4Senior Resident, Department of Radiology, Mahatma Gandhi Medical College and Hospital, Jaipur, Rajasthan Sir,

The ongoing COVID-19 pandemic has led to an explosion of scientific literature on COVID-19, and while gastrointestinal manifestations of COVID-19 (diarrhea, pain abdomen and nausea/vomiting) occur in 15-20% patients,1 there have not been many reports on acute pancreatitis in COVID-19 patients. Even though the expression of ACE-2 is very high in pancreas, it is mainly localized to endocrine pancreas. We highlight the case of a young female with COVID-19, who developed acute pancreatitis in the absence of other known risk factors for pancreatitis.

A 25-year old Indian female with no co-morbidities, presented to the emergency department with history of fever, sore throat, dry cough and loss of taste sensation for 9 days; and severe, dull-aching epigastric pain radiating to the back, with vomiting for 2 days. Her COVID RT-PCR was positive on the second day of illness. On admission, her serum amylase and serum lipase levels were elevated >3 times the upper limit of normal (1814 U/L and 1920 U/L respectively), and D-dimer (3627 ng/ml) were also highly elevated. The CECT abdomen showed a diffusely bulky pancreas without parenchymal necrosis, with soft tissue stranding and inflammatory changes in peripancreatic and mesenteric fat, which was suggestive of acute interstitial pancreatitis, with mild ascites (CT severity index - 6). HRCT chest showed ground glass opacities consistent with COVID-19 infection (CO-RADS 6, CT Severity Score 3/25). Thus, the diagnosis of COVID-19 with acute pancreatitis was confirmed. Other common causes of acute pancreatitis (biliary tract disease, alcohol intake, hyperglycemia, hypercalcemia, developmental anomalies of pancreas, tumors, history of surgical procedures/ERCP on pancreas, etc.) were ruled out. The patient was managed conservatively, made a full recovery and was consequently discharged on day 9 of admission.

The temporal presentation of pancreatitis with COVID-19 of our case (in the 2nd week of the illness) matches that of a case reported by Anand et al., however a serum amylase level was not performed in their case. Another case of acalculous acute pancreatitis on the 11th day of COVID-19 illness was reported by Meireles et al.3 Both these reports did not find an explanation as to why the patient with SARS-CoV-2 infection developed pancreatitis.

The factors determining the spread of SARS-CoV-2 outside the respiratory tract are still under evaluation. One possible hypothesis was the level of expression of ACE-2 (host receptor of SARS-CoV-2) in tissues, however, the expression of ACE-2 in pancreas is mainly localised to endocrine pancreas, whereas the exocrine pancreas has weak expression. Thus the pancreatic injury has been attributed to be either due the immune-mediated inflammatory response, or due to the direct cytopathic effect of SARS-CoV-2.

Viruses such as mumps virus, cossackie virus CMV, EBV and others are already among the most common infectious causes of acute pancreatitis, and the addition of SARS-CoV-2 to this list might be warranted. The development of this complication could also potentially depend upon several other factors (route of transmission, host genetic factors, TMRPRSS2 expression/polyorphism, cellular receptor status, etc.). Respiratory, cardiac, renal involvement and multi-organ failure with thrombosis are already well established causes of mortality in COVID-19 patients, and it might be prudent to add acute pancreatitis to the list of potentially life threatening complications to look for in SARS-CoV-2 infection.

Fungal Co-infections in Pregnant Women with COVID-19: A Potential Challenge?

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1Scientist C, 2Scientist D, Department of Molecular Immunology and Microbiology, ICMR-NIRRH, Parel, Mumbai, Maharashtra Sir,

At present, India is in the terminal stage of the second wave of SARS-CoV-2 infection, with 43,654 new cases and 640 deaths on July 28th, 2021. In addition, the increased prevalence of mucormycosis in patients with COVID-19 poses a formidable challenge to the already burdened health system.

In India, the first case of mucormycosis associated with COVID-19 was reported in December 2020, and an upsurge of cases was noticed during April-May 2021. In May 2021, mucormycosis was declared as a notifiable disease in India. Till 20th July 2021, more than 45,400 people have been infected with mucormycosis across India, and 4,252 (9.3%) died as per the data of the Union Health Ministry. Based on a systematic review on mucormycosis associated with COVID-19, more than two-thirds (29/41, 71%) of the patients reported, were from India, and 98% of them had a severe COVID-19. A large-scale meta-analysis study among pregnant women with COVID-19 revealed that diabetes mellitus (18%; 95% CI 11–27) was the most common comorbid condition, followed by gestational diabetes (10%; 95% CI 7.5–13.5). A significant proportion of viral (14%; 95% CI 7.5–25) and bacterial co-infections (16%; 95% CI 2.5–61) were also observed among pregnant women with COVID-19 compared to non-pregnant women with COVID-19. In another review article among 145 pregnant women, the usage of antibiotics, antivirals and corticosteroids during the treatment of COVID-19 was about 44.1%, 27% and 8.2% respectively.

At present, conventional methods such as potassium hydroxide staining and microscopy, histopathology of debrided tissue, and culture are being used for diagnosis. The lack of awareness as well as the low sensitivity of these existing methods suggest that reported cases of mucormycosis may not reflect the real disease
burden. Recently, RT-PCR tests (PN-700 MucorGenius® real-time PCR and Redclife Lifetech) have been launched in India for the detection of mucormycosis. However, the wider use of the RT-PCR tests for mucormycosis in low and middle-income countries like India is challenging.

To the best of our knowledge, there is no data available on mucormycosis in pregnant women with COVID-19. Since 88% of pregnant women are reported to be asymptomatic during and post COVID-19 infection, identification and association of rare, opportunistic infections in pregnant women with COVID-19 is a major challenge considering the limitations of available diagnostic tools as well as the limited awareness about this condition. Adequate follow-up is essential in pregnant women for detection of mucormycosis post-COVID-19. Appropriate diagnostic tools including molecular diagnosis for other fungal pathogens such as Candida, Aspergillus, etc. also need to be optimized for early diagnosis and provision of suitable antifungal treatment to manage the patients.

On 18th May 2021, Indian Council of Medical Research, released guidelines on the management of mucormycosis in COVID-19 patients.6 Given, the rapid spread of the SARS-CoV-2 in India, acquisition of fungal co-infections such as mucormycosis in vulnerable populations such as pregnant women seems to be highly probable. In view of this, there is a need for greater emphasis and appropriate guidelines for early diagnosis and treatment of mucormycosis in pregnant women with COVID-19. Timely identification and appropriate management of fungal co-infections such as mucormycosis, Candida infections as well as other antifungal resistant infections is likely to reduce mortality from COVID-19 among pregnant women.

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Contributions

IKC and VB: Conceptualization and manuscript preparation. Both the authors reviewed the manuscript.

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Table 1: Treatment Seeking Behaviour of the patients

| Variables | Number of participants (%)
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Seeking during Lockdown</td>
<td>N=380</td>
</tr>
<tr>
<td>Consult A Doctor</td>
<td>240 (63.2)</td>
</tr>
<tr>
<td>Self-Medicating</td>
<td>132 (34.7)</td>
</tr>
<tr>
<td>No Treatment</td>
<td>8 (2.1)</td>
</tr>
<tr>
<td>Mode of Seeking Treatment during Lockdown</td>
<td>N=240</td>
</tr>
<tr>
<td>Govt Clinic/Primary Health Care Centre</td>
<td>19 (8)</td>
</tr>
<tr>
<td>On Call</td>
<td>89 (37)</td>
</tr>
<tr>
<td>Online Consulting</td>
<td>9 (3.7)</td>
</tr>
<tr>
<td>Private Clinic</td>
<td>108 (45)</td>
</tr>
<tr>
<td>Private Hospital</td>
<td>14 (5.8)</td>
</tr>
<tr>
<td>Reasons for Seeking Treatment during Lockdown</td>
<td>N=230</td>
</tr>
<tr>
<td>Routine OPD check-up for chronic illness</td>
<td>135 (58.7)</td>
</tr>
<tr>
<td>OPD check for new onset symptoms</td>
<td>87 (37.8)</td>
</tr>
<tr>
<td>Emergency</td>
<td>21 (9.1)</td>
</tr>
<tr>
<td>For medical tests, scans and reports</td>
<td>21 (9.1)</td>
</tr>
<tr>
<td>Pregnancy Check-up and Delivery</td>
<td>15 (6.5)</td>
</tr>
<tr>
<td>Surgery</td>
<td>4 (1.7)</td>
</tr>
<tr>
<td>Treatment Seeking Behaviour before the Lockdown</td>
<td>N=380</td>
</tr>
<tr>
<td>Consult A Doctor</td>
<td>347 (91.3)</td>
</tr>
<tr>
<td>Self-Medicating</td>
<td>30 (7.9)</td>
</tr>
<tr>
<td>No Treatment</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Reasons for Not Seeking Treatment during the Lockdown</td>
<td>N=140</td>
</tr>
<tr>
<td>Fear of Catching COVID-19</td>
<td>77 (55)</td>
</tr>
<tr>
<td>Strict Rules of Lockdown</td>
<td>79 (56.4)</td>
</tr>
<tr>
<td>Nearby Healthcare Facility Closed</td>
<td>19 (13.6)</td>
</tr>
<tr>
<td>Insufficient Money</td>
<td>4 (2.8)</td>
</tr>
<tr>
<td>Mild Symptoms</td>
<td>73 (52.1)</td>
</tr>
</tbody>
</table>

Participants were allowed to choose more than one reason for seeking and not seeking treatment during the lockdown

Sample size of 380 participants residing in the Naigaon locality of Dadar, who were recruited by systematic random sampling. Individual who had suffered from any acute or chronic illness or were pregnant between March 2020 to October 2020 were included, while those diagnosed with COVID-19 or under the age of 18 were excluded.

The mean age of the participants was 53 ± 15.7 years. Proportion of females (58.4%) was slightly more than that of the males (41.6%). Based on Kuppuswamy classification majority of the participants belonged to the lower middle socio-economic class (42.4%). The types of diseases were classified as Acute only (28%), Chronic only (61%), Acute on Chronic (7%) and Pregnancy (4%). The most reported chronic illnesses were hypertension (46%) followed by diabetes mellitus

Treatment Seeking Behaviour & Perceived Quality of Healthcare among Non-COVID-19 Patients of Mumbai during the COVID-19 Lockdown

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Sir,

National Health Mission data from March 2020 onwards suggested that medical treatment, whether as inpatients, outpatients, or emergencies fell for both communicable and non-communicable non-COVID-19 diseases. However, this might not have been due to reduced number of cases, but due to reduced number of patients reaching the healthcare facilities. With an aim to assess the ways through which non-COVID-19 patients sought medical treatment and the perceived quality of healthcare received by them, a retrospective questionnaire-based study was conducted between December 2020 to January 2021 in a...
(35%), while among the acute illnesses common cold (14%) & viral fever (10%) were most common. The treatment seeking behaviour of the patients was found to be as depicted in Table 1. When asked about their approach before the lockdown for similar symptoms, an additional 28% said they would have sought medical attention. This difference in treatment seeking behaviour was significant (p<0.01).

The median perceived quality score was 5 out of 5(IQR 0.5, 95% CI [4.5-4.7]). However, the scores of those who developed acute complications(7%), sought emergency medical care (8.7%) or were denied treatment at the first centre (7.1%) were significantly poor (p<0.01). In terms of medication practices, majority were able to keep with their prescribed schedule for which they either bought the medications regularly (88.3%) or had them stored in bulk (23%). Amongst those who self-medicated, cough cold medication, antipyretics and pain killers were used once to occasionally, while the participants said that they consumed, multivitamins, AYUSH medications & Home remedies like kadha frequently to almost daily to boost their immunity.

The COVID-19 lockdown negatively influenced the treatment seeking behaviour of the patients which led to more patients indulging in self-medication, mostly by consuming home remedies. Such patients with flu like symptoms could have contributed to early spread COVID-19 in the locality, while those with hypertension & diabetes who didn’t go for routine check-ups were amongst those patients who reached the emergency facility with acute complications like heart attack, diabetic foot, deep vein thrombosis etc.

It has been estimated that, between January to May 2020 over 24 lakh non-COVID-19 deaths have occurred, almost 100 times greater than those accounted due to COVID-19 during that period. About five lakhs out of these could have been prevented provided we had a stronger health system. With an anticipated third wave around the corner, it’s time we realise that COVID-19 containment is critical but healthcare for others can no longer be ignored. The emergency facilities need to be strengthen & telemedicine has to be encouraged via government advertisements so as to manage the burden of COVID-19 & non-COVID-19 patients more efficiently and hence provide a satisfactory quality of healthcare to all.

References


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\text{Olmesar-A} & : & \text{Olmesartan Medoxomil} & + & \text{Amlopril 5 mg Tablets} & : & \text{A-20/40} & : & 12.5 \\
\text{TriOlmesar-CH} & : & \text{Olmesartan Medoxomil} & + & \text{Amlodipine 5 mg} & + & \text{Chlorthalidone 12.5 mg Tablets} \\
\text{Olmesar-M} & : & \text{Olmesartan Medoxomil} & + & \text{Moxisylyte 10 mg} & + & \text{Moxisylyte 12.5 mg Tablets} \\
\end{align*}
\]

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