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Omicron: Is its Bark Worse than its Bite?

Rajeev Soman¹, Sujata Rege²

SARS CoV2 is here to stay, continues to evolve and to spring surprises. We need to watch it, literally, with bated breath. Predictions about where do we go from here, while needed, are at best educated guesses and in dealing with this virus, science along with a liberal measure of humility is essential. India is currently witnessing a surge in COVID-19 cases in many states, and is in the midst of the third wave of the pandemic. The Omicron variant is in community transmission and has elbowed out previous variants in India and worldwide. India’s daily cases breached the 1 lakh mark far faster than the previous two waves.¹

Omicron (B.1.1.529 lineage) was identified and sequenced in South Africa in November 2021. It was initially detected only in international travelers and later in those without any travel history. There are 3 important sub-lineages of Omicron. BA.1 has 13 unique spike mutations, BA.1+R346K has 14, and BA.2 has 8 unique mutations while lacking the 13 ones in BA.1.² As per COVID-19 genomic surveillance in India, BA.2 strain of Omicron is currently the predominant circulating strain as compared to BA.1.³ However the existence of these variants poses therapeutic dilemmas due to differing resistance to neutralization by antibodies following prior infection, vaccination and the monoclonal antibodies.

Emerging data on Omicron variant has highlighted the following features seemingly unique to this variant.⁴

1. Omicron has 3 times higher secondary attack rate within close contacts as compared to alpha and delta variants.

2. It has a shorter incubation period which is typically 3 to 5 days.

3. It shows immune evasion by escaping the humoral and cellular immunity induced by prior infection or vaccines, leading to higher risk of infection in vaccinated individuals and those previously infected with a different strain.

4. It is more likely to produce an illness like a ‘cold’ confined to upper respiratory tract along with mild fever and bodyache. Severe disease with pulmonary involvement, systemic complications, hospitalization and death with omicron is less likely.

5. Diagnostic difficulties in identification of Omicron were circumvented by finding S gene target failure (SGTF) which could be used because of the large number of mutations in the S gene. However, BA.2 strain of Omicron does not often lead to SGTF, prevents using SGTF as a screening test. Antigen testing, which relies on nucleocapsid protein, can detect all variants including Omicron but with a lower sensitivity and cannot positively identify the variant as Omicron. The new locally developed kit Omisure is likely to be useful and has been approved by ICMR for diagnosis of Omicron infection.⁵

6. Omicron escapes neutralization by casirivimab-imevimab, bamlanivimab-etesevimab and regdanvimab, and hence these monoclonal antibodies are not useful in the current pandemic, especially where Omicron is suspected on clinical and epidemiologic features. Genomic sequencing is unfortunately unavailable for variant identification of most patients and in a suitable time frame. Sotrovimab has a good activity against the original omicron variant, but is unavailable in India as of now. However recent data has shown that Sotrovimab, which retained good activity against BA.1, showed hardly any against BA.2 lineage.⁶ Cilgavimab + Tixagevimab has activity against BA.2 but is not yet authorized for treatment.⁶

The emergence of Omicron is a reminder of the raw and restless power of the microbes. Viruses replicate very rapidly and in stupendous numbers. Each time that SARS CoV2 RNA is copied, errors occur due to lack of ‘proof reading enzymes’. Some of these errors (mutations) may be recipes for disaster for monoclonal antibodies as well as for the antibodies and cell mediated defenses generated due to previous infection or vaccination. Substitutions in the antigenic structure, deletions, insertions, changes in gyrations of protein structures reduce the affinity and binding to antibodies several fold. Some of these alterations may reduce the fitness or replication capacity, but the virus can accumulate compensatory mutations which restore fitness to previous levels. On the other hand, viral mutations around the receptor binding sites can increase its affinity to cellular receptors. However excessively tight receptor binding can compromise intracellular entry and the subsequent release of progeny virus. These mechanisms may possibly explain why Omicron has a higher transmissibility, escapes neutralization by humoral and cellular mechanisms, but has lesser cytopathic effects and ability to spread to other cells. It has been found to be about 75% as likely as delta to cause severe disease in unvaccinated and previously uninfected persons.⁷ We must realize, against all hope, that evolution simply selects variants that excel at multiplying and not necessarily those that are less virulent. Since the major transmission of this virus occurs before the illness becomes severe, reduced virulence is not a characteristic that is specifically selected. Besides, as mutants circulate between immune and naïve hosts, viruses with the full repertoire of both immune evasive and virulence mechanisms will dominate from time to time.⁸

Most of the western guidelines on treatment have been formulated during the delta wave or earlier, wherein use of monoclonal antibody, remdesivir and

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certain oral antivirals like nirmatrelvir-ritonavir and molnupiravir were advised. Extrapolation of the guidance is now needed to the current situation in India where a different vaccine has been used, number of doses/boosters received and time since vaccination is variable, hosts are ethnically different, herd immunity due to recognized and unrecognized infection is considerable and the virus itself has changed in its properties. In the third wave the aim is mainly prevention of clinical deterioration and hospitalization, as most patients will likely develop a mild illness and be managed as out patients. Trial data which is usually presented as relative risk reduction is misleading in this situation because it heightens the perception of therapeutic efficacy. Since the absolute risk of severe disease and hence the reduction in it with therapy is very small, it raises questions about whether the therapy is really worth the inconvenience and expense in all patients. Patient selection is therefore paramount to prioritize treatment to those at the highest risk of poor outcome. These groups are immunocompromised patients unable to mount a good immune response to vaccines, elderly unvaccinated individuals with comorbidities, elderly vaccinated individuals with uncontrolled comorbidities. As with other diseases, the co-existence of multiple co-morbidities may augment the risk and enhance the need for treatment. The omicron wave brought on certain critical changes to the treatment paradigm, with removal of monoclonal antibody use due to lack of efficacy. Nirmatrelvir-ritonavir (unavailable in India), Sotrovimab (unavailable in India, but already found to be ineffective for BA.2) and 3-day course of IV remdesivir all had similar clinical efficacy and relative risk-reduction ranging from 85-88% in hospitalizations and deaths. Molnupiravir, recommended only in adults ages 18 and above, showed 30% risk-reduction in hospitalizations and death in unvaccinated adults. It may be accepted for use in high-risk individuals, if the other 3 choices are not available. Choosing a regimen for COVID-19 needs consideration of efficacy, drug availability, adverse effects, interactions and ease of drug delivery (iv vs oral). Viral resistance cannot be far behind as more patients receive anti-viral drugs and transmit resistant strains. Drugs that increase viral mutagenesis may hasten this phenomenon and have the potential to add fuel to the fire.

Omicron seems to have a bark that is worse than its bite. A ‘cold’ is only a ‘cold’, except when it is not. To trivialize it and get on with ‘omicron parties’ rather than vaccination as a means of attaining individual or herd immunity is dangerous. Results do not show that immunity acquired by infection is longer lasting or superior to that by vaccination. The only thing we are certain of about this virus, is that its behavior is unpredictable. It produces long term sequelae including Alzheimer-like changes in the brain and others that will show-up as time passes. High risk individuals are still at risk of severe disease owing to their comorbidities. Even if the individual risk for severe disease is lower due to the omicron variant, the sheer number of cases can result in increase in hospitalizations, coupled with affected healthcare workers, adding to our overburdened healthcare system.

Universal masking and isolation of affected individuals remain the cornerstones for controlling the pandemic although at the moment of writing, there is a push to do away with many of these. It is now more important than ever to have a modern data gathering system, agile evidence based policy changes and better public health implementation infrastructure. Completion of vaccination and booster doses at the earliest cannot be overemphasized. Vaccine updates based on circulating strains, mucosal vaccines, optimum combinations and boosting schedules will be needed. Eradicating the virus does not now seem to be a tangible goal. The ‘new normal’ of living peacefully with the virus will be reached when the aggregate viral respiratory infections, hospitalizations and deaths are not significantly higher than what typically occurred during pre-COVID-19 times. Till then masking, distancing, patience and loads of common sense will serve us in good stead.

References

4. Singhal T. The Emergence of Omicron: Challenging Times Are Here Against India / Pediatr 2022; 1-7
In hypertension management

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

In T2DM patients
ADD

Glimy
Glimepiride 1/2/3/4 mg Tablets

The Patient Friendly Glimiepride

T2DM: Type 2 diabetes mellitus; BP: blood pressure.
Sure-Shot BP Drop: Nearly 80% patients treated with Olmesartan 40 mg reached target blood pressure < 130/80 mm Hg.


Images used are for illustration purposes only.
Extra-pulmonary Manifestations of COVID-19 in Western India

Sudhir Bhandari¹, Govind Rankawat²*, Mangesh Diwakar³, Vishal Gupta⁴

Abstract
Background: SARS-CoV-2 is well known disorder to affect respiratory system, although it can also influence several extrapulmonary organs through variety of pathological mechanism. In this study, we aimed to discuss the prevalence of atypical and/or extrapulmonary manifestations in COVID-19, therefor action for early isolation and diagnosis can be initiated to prevent spread of infection.

Methods: This retrospective observational study included 4200 admitted COVID-19 patients. The patient’s data concerning medical history, clinical symptoms at presentation and during course of hospitalization, laboratory and radiological diagnosis and underlying chronic medical illness were extracted from their medical records. Data of extrapulmonary and/or atypical presentations of COVID-19 were compiled and tabulated to know prevalence of these manifestations.

Results: In this study, 1260 patients (30%) had symptomatic presentation. Major extrapulmonary clinical manifestation includes fatigue in 72.22% patients, impaired sense of taste (ageusia) in 58.73%, loss of appetite in 52.78%, impaired sense of smell (anosmia) in 46.83%, palpitation in 33.33%, headache in 33.17%, nausea/vomiting in 31.43%, diarrhoea in 25.40% patients. Among symptomatic COVID-19 patients, 95.56% patients had sinus tachycardia, 38.49% had lymphocytopenia, 36.83% had hepatitis, 35.48% had leukopenia, 27.83% had gastroenteritis, 22.22% had sepsis, 20.87% had proteinuria, 17.30% had lymphocytopenia, 36.83% had hepatitis, 35.48% had leukopenia, 27.83% had coronary artery disease and 16.34% had acute kidney injury in decreasing order. Prevalence of coagulation defect associated disorder were found to be deep venous thrombosis in 15.56%, patients, acute coronary syndrome in 7.78%, brain infarct in 6.35%, pulmonary artery thrombosis in 3.25% and SMA thrombosis in 0.32% of symptomatic patients.

Conclusion: Patients of SARS-CoV-2 had widespread organ-specific manifestations with involvement of almost all organ system of body. Clinicians must have knowledge of these extrapulmonary symptoms or atypical presentations of COVID-19 as it assists in early diagnosis, isolation of suspected patients and limit the transmission of infection in the hospital settings.

Introduction
The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is responsible for the disease COVID-19 (coronavirus disease 2019). The clinical manifestations of SARS-CoV-2 infection vary widely, from asymptomatic infection to severe pneumonia with respiratory failure and even death. Symptomatic presentation of confirmed COVID-19 patients is fever, dry cough, sore throat, dyspnea, fatigue and myalgia. However, patients with confirmed COVID-19 might present with non-specific or extrapulmonary symptoms, which may delay testing, diagnosis and isolation. Our clinical experience and the emerging literature suggest that the hematologic, cardiovascular, renal, gastrointestinal, hepatobiliary, endocrinologic, neurologic, ophthalmologic, and dermatologic systems can all be affected by COVID-19. The coronavirus spike protein facilitates entry of the virus into target cells by engaging ACE2 (angiotensin-converting enzyme 2). In addition, cell entry requires priming of the spike protein by the cellular serine protease TMPRSS2 or other proteases. Co-expression on the cell surface of ACE2 and TMPRSS2 is required for the completion of this entry process. Major pathophysiological mechanism of multi-organ dysfunction secondary to infection with SARS-CoV-2 include direct viral toxicity, endothelial cell damage, thrombo-inflammation, dysregulation of the immune response and dysregulation of the renin–angiotensin–aldosterone system (RAAS). Few studies proposed that cerebrovascular and neurological symptoms could be explained by hypercoagulability in patients with COVID-19, leading to thrombi formation in the vessels. ACE2-mediated entry of SARS-CoV-2 in endothelial cells damage it and subsequently produces inflammation and generate prothrombotic milieu. Infection-mediated endothelial injury and endothelialitis, found in multiple vascular beds including the lungs, kidney, heart, small intestine and liver in patients with COVID-19. This produces excessive thrombin, inhibit fibrinolysis and activate complement pathways, initiate thromboinflammation and ultimately leading to microthrombi deposition. Hypoxia-mediated hyper viscosity and upregulation of the HIF-1 (hypoxia-inducible factor 1) signaling pathway, subsequent to acute lung injury may also contribute to the prothrombotic state. Higher serum levels of the cytokine IL-6 have also been linked to a worse prognosis and have been found to correlate with fibrinogen levels in patients with COVID-19. It is important that healthcare professionals to be aware of...
The present retrospective observational study was conducted on 4,200 COVID-19 positive patients, admitted to S.M.S. Medical College and Attached Hospitals, Jaipur, India till 20th July 2020. This study was approved by the Institutional Ethics Committee of our institution. In this study we included RT-PCR positive patients for SARS-CoV-2 and data regarding their clinical symptoms at presentation especially extrapulmonary symptoms and diagnosis was collected retrospectively in order to anaylization and interpretation of these data.

**Data Collection**

COVID-19 were diagnosed based upon World Health Organization interim guidance. The patient information regarding clinical symptoms and diagnosis were extracted from medical records for data analysis. All COVID-19 positive patients screened for their clinical symptoms at onset of disease and during course of disease especially in the form of body system, then compiled for evaluation. Data regarding diagnosis of associated disease during course of hospitalization were also collected and compiled for analysis.

**Statistical analysis**

Quantitative data was expressed as mean and standard deviation. Qualitative data was expressed as proportions.

### Results

A total of 4,200 COVID-19 patients were included in this study. The mean age of SARS-CoV-2 infected patients enrolled in study were 40.16 year with male preponderance (63.25% male and 36.75% female). In our study 1260 patients (30%) were symptomatic during course of illness while remaining 70% patients did not develop any symptoms.

### Clinical presentation (Table 1)

Out of symptomatic 1260 patients, major extrapulmonary clinical manifestation includes fatigue in 72.22% patients, impaired sense of taste (ageusia) in 58.73%, loss of appetite in 52.78%, impaired sense of smell in 46.83%, palpitation in 33.33%, headache in 33.17%, nausea/vomiting in 31.43%, diarrhoea in 25.40% patients and other minor symptoms. All major extrapulmonary clinical features were found to be new onset in most of patient. However, some clinical symptoms also exist previously like gastrointestinal bleed in 41.9% of symptomatic patients, dizziness in 40.3%, headache in 27.3%, seizure in 39.6%, haematuria in 42.9%, maculopapular rashes in 29.1% of symptomatic patients.

### Clinical diagnosis (Table 2)

Most of Moderate to severe and critical ill patients of COVID-19 presented with radiographic evidence of COVID-19 related pneumonia. However, extrapulmonary entity of COVID-19 also established in most of patients which includes sinus tachycardia in 95.56% patients, lymphocytopenia in 38.49%, hepatitis in 36.83%, leukopenia in 35.48%, gastroenteritis in 27.38%, sepsis in 22.22%, proteinuria in 20.87%, coronary artery disease (CAD) in 17.30%, acute kidney injury (AKI) in 16.34%, deep venous thrombosis (DVT) in 15.56%, cardiomyopathy in 12.22%, metabolic acidosis in 11.75%, hyperkalaemia in 9.84%, cutaneous manifestation in 9.84%, cerebrovascular accident (CVA) in 9.05%, acute on chronic kidney disease in 8.10%, acute coronary syndrome (ACS) in 7.78%, sinus bradycardia in 7.78%, hypokalaemia in 6.98%, requirement of renal replacement therapy in 6.67%, brain infarct in 6.35%, thrombocytopenia in 6.03%, hyponatremia in 5.63%

<table>
<thead>
<tr>
<th>Table 1: Extra pulmonary manifestation in COVID-19 (N=4200)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical manifestation</strong></td>
</tr>
<tr>
<td><strong>Number of patients</strong></td>
</tr>
<tr>
<td><strong>% Among symptomatic patients (1260)</strong></td>
</tr>
<tr>
<td><strong>% Among total patients (4200)</strong></td>
</tr>
<tr>
<td><strong>New onset symptoms</strong></td>
</tr>
<tr>
<td><strong>Pre-existing symptoms</strong></td>
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<td>------------------------------------------------------------</td>
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</tbody>
</table>

The possibility of COVID-19 presenting with non-specific and/or atypical symptoms. In this study, we aimed to find out prevalence of extrapulmonary and atypical manifestations of COVID-19 to facilitate early isolation and diagnosis to prevent spread of infection.

### Methods

#### Study Design

The present retrospective observational study was conducted on 4,200 COVID-19 positive patients, admitted to S.M.S. Medical College and Attached Hospitals, Jaipur, India till 20th July 2020. This study was approved by the Institutional Ethics Committee of our institution. In this study we included RT-PCR positive patients for SARS-CoV-2 and data regarding their clinical symptoms at presentation especially extrapulmonary symptoms and diagnosis was collected retrospectively in order to anaylization and interpretation of these data.

#### Data Collection

COVID-19 were diagnosed based upon World Health Organization interim guidance. The patient information regarding clinical symptoms and diagnosis were extracted from medical records for data analysis. All COVID-19 positive patients screened for their clinical symptoms at onset of disease and during course of disease especially in the form of body system, then compiled for evaluation. Data regarding diagnosis of associated disease during course of hospitalization were also collected and compiled for analysis.

#### Statistical analysis

Quantitative data was expressed as mean and standard deviation. Qualitative data was expressed as proportions.
Table 2: Extrapulmonary Diagnosis of COVID-19 (N=4200)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of patients</th>
<th>% Among symptomatic patients (1260)</th>
<th>% Among total patients (4200)</th>
<th>New onset symptoms</th>
<th>Pre-existing symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal System</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis</td>
<td>464</td>
<td>36.83%</td>
<td>11.05%</td>
<td>398 (85.8)</td>
<td>66 (14.2)</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>345</td>
<td>27.38%</td>
<td>8.21%</td>
<td>320 (92.8)</td>
<td>25 (7.2)</td>
</tr>
<tr>
<td>SMA Thrombosis</td>
<td>4</td>
<td>0.32%</td>
<td>0.1%</td>
<td>4 (100)</td>
<td>0</td>
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<tr>
<td>Cardiovascular system</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sinus Tachycardia</td>
<td>1204</td>
<td>95.56%</td>
<td>26.67%</td>
<td>1176 (97.7)</td>
<td>28 (2.3)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>218</td>
<td>17.30%</td>
<td>5.19%</td>
<td>98 (45)</td>
<td>120 (53.0)</td>
</tr>
<tr>
<td>Deep Venous Thrombosis</td>
<td>196</td>
<td>15.56%</td>
<td>4.67%</td>
<td>162 (82.7)</td>
<td>34 (17.3)</td>
</tr>
<tr>
<td>Cardiomyopathy and cardiac failure</td>
<td>154</td>
<td>12.22%</td>
<td>3.67%</td>
<td>46 (29.9)</td>
<td>108 (70.1)</td>
</tr>
<tr>
<td>Acute Coronary Syndrome</td>
<td>98</td>
<td>7.78%</td>
<td>2.33%</td>
<td>98 (100)</td>
<td>0</td>
</tr>
<tr>
<td>Sinus Bradycardia</td>
<td>98</td>
<td>7.78%</td>
<td>2.33%</td>
<td>52 (33.1)</td>
<td>46 (46.9)</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>63</td>
<td>5.00%</td>
<td>1.50%</td>
<td>5 (7.9)</td>
<td>58 (92.1)</td>
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<tr>
<td>QTc Prolongation</td>
<td>61</td>
<td>4.84%</td>
<td>1.45%</td>
<td>33 (54.1)</td>
<td>28 (45.9)</td>
</tr>
<tr>
<td>Pulmonary Artery Thrombosis</td>
<td>41</td>
<td>3.25%</td>
<td>0.98%</td>
<td>39 (95.1)</td>
<td>2 (4.9)</td>
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<td>Neurological System</td>
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<td>CVA</td>
<td>114</td>
<td>9.05%</td>
<td>2.71%</td>
<td>78 (68.4)</td>
<td>36 (31.6)</td>
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<td>Infarct</td>
<td>80</td>
<td>6.35%</td>
<td>1.90%</td>
<td>62 (77.5)</td>
<td>18 (22.5)</td>
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<tr>
<td>Encephalitis</td>
<td>41</td>
<td>3.25%</td>
<td>0.98%</td>
<td>35 (85.4)</td>
<td>6 (14.6)</td>
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<tr>
<td>ICH</td>
<td>22</td>
<td>1.75%</td>
<td>0.52%</td>
<td>18 (81.8)</td>
<td>4 (18.2)</td>
</tr>
<tr>
<td>GBS</td>
<td>20</td>
<td>1.59%</td>
<td>0.48%</td>
<td>18 (90.0)</td>
<td>2 (10.0)</td>
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<tr>
<td>SAH</td>
<td>12</td>
<td>0.95%</td>
<td>0.29%</td>
<td>12 (100)</td>
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<td>Renal System</td>
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<tr>
<td>Proteinuria</td>
<td>263</td>
<td>20.87%</td>
<td>6.26%</td>
<td>140 (53.2)</td>
<td>123 (46.8)</td>
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<tr>
<td>Metabolic acidosis</td>
<td>148</td>
<td>11.75%</td>
<td>3.52%</td>
<td>148 (100)</td>
<td>0</td>
</tr>
<tr>
<td>Hyperkalaemia</td>
<td>124</td>
<td>9.84%</td>
<td>2.95%</td>
<td>68 (54.8)</td>
<td>56 (45.2)</td>
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<tr>
<td>AKI</td>
<td>206</td>
<td>16.34%</td>
<td>4.90%</td>
<td>206 (100)</td>
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<tr>
<td>Acute on CKD</td>
<td>102</td>
<td>8.10%</td>
<td>2.43%</td>
<td>0</td>
<td>102 (100)</td>
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<tr>
<td>Hypokalaemia</td>
<td>88</td>
<td>6.98%</td>
<td>2.10%</td>
<td>68 (77.3)</td>
<td>20 (22.7)</td>
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<tr>
<td>Dialysis</td>
<td>84</td>
<td>6.67%</td>
<td>2.00%</td>
<td>29 (34.5)</td>
<td>55 (65.5)</td>
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<tr>
<td>Hyponatremia</td>
<td>71</td>
<td>5.63%</td>
<td>1.69%</td>
<td>58 (81.7)</td>
<td>13 (18.3)</td>
</tr>
<tr>
<td>Hypermotremia</td>
<td>19</td>
<td>1.51%</td>
<td>0.45%</td>
<td>19 (100)</td>
<td>0</td>
</tr>
<tr>
<td>Hematologic System</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>447</td>
<td>35.48%</td>
<td>10.64%</td>
<td>435 (97.4)</td>
<td>12 (2.6)</td>
</tr>
<tr>
<td>Lymphocytopenia</td>
<td>485</td>
<td>38.49%</td>
<td>11.54%</td>
<td>464 (95.7)</td>
<td>21 (4.3)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>280</td>
<td>22.22%</td>
<td>6.67%</td>
<td>251 (89.6)</td>
<td>29 (10.4)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>76</td>
<td>6.03%</td>
<td>1.81%</td>
<td>53 (69.7)</td>
<td>23 (30.3)</td>
</tr>
<tr>
<td>Neutrophilia</td>
<td>52</td>
<td>4.13%</td>
<td>1.24%</td>
<td>38 (73.1)</td>
<td>14 (26.9)</td>
</tr>
<tr>
<td>Cutaneous manifestation</td>
<td>124</td>
<td>9.84%</td>
<td>2.95%</td>
<td>80 (64.5)</td>
<td>44 (28.7)</td>
</tr>
</tbody>
</table>

atrial fibrillation (AF) in 5.00%, QTc prolongation in 4.84%, neutrophilia in 4.13%, pulmonary artery thrombosis in 3.25%, encephalitis in 3.25%, intracranial haemorrhage (ICH) in 1.75%, Guillain berry syndrome (GBS) in 1.59%, hyponatremia in 1.51%, Subarachnoid haemorrhage (SAH) in 0.95% and superior mesenteric artery thrombosis (SMAT) in 0.32% in decreasing order. Most of extrapulmonary COVID associated disorders were found to be new onset at the time of presentation which includes SMA thrombosis (100%), acute coronary syndrome (100%), SAH (100%), metabolic acidosis (100%), AKI (100%), hyponatremia (100%), sinus tachycardia (97.7%), leukopenia (97.4%), pulmonary artery thrombosis (95.1%), gastroenteritis (92.8%), GBS (90%) etc.

**Disorders associated with coagulation defect**

In our cohort, among symptomatic COVID-19 patients, ischaemic disorders as a consequences of coagulation defect were found as deep venous thrombosis in 15.56% patients, acute coronary syndrome in 7.78%, brain infarct in 6.35%, pulmonary artery thrombosis in 3.25% and SMA thrombosis in 0.32% patients. In our cohort 86 patients required renal replacement therapy (RRT) among them 26 patients (30.23%) had been associated with clotting of RRT circuit with hypercoagulable state.

**Discussion**

In the present study, we evaluated the extrapulmonary manifestation of COVID-19. Although COVID-19 predominantly affects the respiratory system, there is involvement of multiple organs, such as the gastrointestinal system, the cardiovascular system, neurological system, hematological system, endocrine system as well as renal system. The virus SARS-CoV-2 is known to enter human lung cells by binding to angiotensin-converting enzyme 2 (ACE2). In the multiorgan involvement of SARS-CoV-2 has linked to the wide distribution of ACE2 in the body; the highest expression of ACE2 is found in the ileum and kidneys. These multiple organ disturbances may then interact with each other, which correlates with the severity of the disease.

**Cardiovascular manifestations**

ACE2 has high expression in cardiovascular tissue, including cardiac myocytes, which support for a possible mechanism of direct viral injury. Viral myocarditis is a presumed etiology of cardiac dysfunction either direct invasion as reported in a few autopsy studies or by inflammatory infiltrates. Moreover, isolated right ventricular dysfunction may occur as a result of elevated pulmonary vascular pressures secondary to ARDS or pulmonary thromboembolism. Risk of acute coronary syndrome may be exaggerated in patients with COVID-19, as a consequence of disproportionately increased hypercoagulability in affected people. SARS-CoV-2 can cause both direct and indirect cardiovascular sequelae, including myocardial injury, acute coronary syndromes (ACS), cardiomyopathy, acute Cor-pulmonale, arrhythmias and cardiogenic shock as well as the aforementioned thrombotic complications. In our study most prevalent arrythmia in symptomatic COVID-19 patients was sinus tachycardia (95.56%) while least common arrythmia observed was sinus bradycardia (7.78%) and atrial fibrillation (5.00%). In a multicenter New York City cohort, 6% of 4,250 patients with COVID-19 had prolonged QTc (corrected QT; >500 ms) at the time of admission. Our study showed that 61 patients had QTc prolongation during course of disease out of them 12 patients developed QTc prolongation after hospitalization most probably as an impact of medicine. In our study 98 patients out of 4100, were diagnosed as acute coronary syndrome among
which 76 patients had STEMI. Acute coronary events precipitated by viral inflammation and hypercoagulable state in COVID-19 patients. The level of D-dimer in COVID-19 was higher in severe disease compared with mild disease which could indicate that D-dimer has a prognostic value. Therefore, patients with COVID-19 are at higher risk to develop venous thrombo-embolic (VTE) events. In our cohort 196 patients out of 4200, who had complaint of lower limb pain with swelling and diagnosed as deep venous thrombosis of lower limbs with raised D-dimer level. Among available computed tomography pulmonary angiogram (CTPA), 41 patients of our cohort recorded pulmonary artery thrombosis during course of hospitalization. In our study 154 patients were diagnosed as cardiomyopathy or cardiac failure as a result of direct myocyte injury or ischemic cardiac damage. However, only 30% patients had newly diagnosed cardiomyopathy or heart failure while 70% patients had pre-existing cardiac failure.

**Gastrointestinal manifestations**

The incidence of gastrointestinal manifestations has ranged from 12% to 61% in patients with COVID-19. The pathophysiology of gastrointestinal damage in COVID-19 is multifactorial, mostly via virus-mediated direct tissue damage, given the presence of ACE2 in intestinal glandular cells or the visualization of viral nucleocapsid protein in gastric, duodenal, and rectal epithelial cells, and glandular enterocytes. Liver damaged either from direct binding of SARS-CoV-2 to ACE2 on cholangiocytes or hyperinflammation seen with cytokine storm and hypoxia-associated metabolic derangements. In our cohort, out of total 4200 COVID-19 positive patients, 15.83% patients had anorexia, 9.43% had nausea/vomiting, 7.62% had diarrhea, 5.43% had pain abdomen and 0.74% had gastrointestinal bleeding. In critically ill patients with COVID-19 a hepatocellular injury is seen in 14–53% of hospitalized patients. In our cohort 464 patients out of 4200, were diagnosed as hepatitis during course of hospitalization. However, 66 patients had pre-existing history of liver damage and/or hepatitis. A beccarra et al showed that abdominal CT scan of a COVID-19 patient showed arterial thrombosia of vessels efferent of the superior mesenteric artery with bowel distension. In our cohort four patients had been diagnosed as superior mesenteric artery thrombosis who had presented with acute pain abdomen with hypercoagulable state.

**Neurological manifestations**

SARS-CoV-2 may access the central nervous system via the nasal mucosa, lamina cribrosa, and olfactory bulb or via retrograde axonal transport and directly invades the neural parenchyma. Because of highest expression of ACE2 in nasal epithelial cells sense of smell and taste altered in COVID-19 patients. The proinflammatory and prothrombotic cascade in the wake of cytokine storm affects brain vasculature and the blood–brain barrier. In our cohort, out of symptomatic 1260 patients, 72.22% patients had fatigue, 58.73% had loss of taste, 46.83% had loss of smell, 33.17% had headache, 15.56% had dizziness, 10.79% had altered mental status, 9.05% had hemiplegia, 8.41% had seizures, 7.78% had myalgia and 2.78% had paraparesis. Yaghi S. et al. showed that COVID-19 manifested as acute stroke in 6% patients of severe illness with varying arterial and venous mechanisms and confusion or impaired consciousness in 8–9% of patients. In our cohort 6.35% of symptomatic patients presented with cerebrovascular infarct with hypercoagulable state, among them 22.5% patients had pre-existing history of cerebrovascular infarct.

**Renal manifestations**

SARS-CoV-2 either directly infect renal cells via the presence of ACE2 receptors or renal microvascular dysfunction, secondary to endothelial damage and cytokine storm, which leads to clinical ‘viral sepsis’ and multiple-organ dysfunction, including AKI. In patients with COVID-19, Transient heavy albuminuria might occur secondary to endothelial dysfunction or direct podocyte injury which results in the observed instances of proteinuria. In China, the reported incidence of AKI in hospitalized patients with COVID-19 ranged from 0.5% to 29% and occurred within a median of 7–14 days after admission. In our cohort 206 patients (16.34% among symptomatic patients) had AKI during course of hospitalization. However, 102 patients developed AKI as a sequel of chronic kidney disease. About one fourth symptomatic patients had complaint of decrease urine output while 6.67% of symptomatic patients had hematuria. In our study 302 patients (about one fourth of symptomatic patients) had electrolyte disturbance among them 9.84% of symptomatic patients had hyperkalemia, 6.98% had hypokalemia, 5.63% had hyponatremia and 1.51% had hypernatremia, 84 patients (6.67% of symptomatic patients) were needed renal replacement therapy and 11.75% of symptomatic COVID-19 patients had metabolic acidosis.

**Endocrinologic manifestations**

While patients with pre-existing endocrinologic disorders may be predisposed to more-severe presentations of COVID-19, including worsened hyperglycemia and ketosis. Elevated cytokine levels in SARS-CoV may lead to impairments in pancreatic β-cell function and consequently, decreased insulin production. In addition, direct binding of SARS-CoV-2 to ACE2 on β-cells might contribute to insulin deficiency and hyperglycemia. Non-specific factors in COVID-19 patients with diabetes and infections include increase in counter-regulatory hormones that promotes hepatic glucose production, decreased insulin secretion, ketogenesis, and insulin resistance. In a report from the US Centers for Disease Control, 24% of hospitalized patients and 32% of patients admitted to the ICU who had underlying diabetes had hyperglycemia. Similar observations were made in our study that 38.10% patients who had symptomatic COVID-19 disease presented with hyperglycemia. However, out of 480 hyperglycemic patients, 334 patients (69.6%) had underlying history of diabetes mellitus while remaining 30.4% patients presented with new onset hyperglycemia. Moreover, patients hospitalized with COVID-19 have exhibited a range of abnormalities of glucose metabolism, including worsened hyperglycemia, euglycemic ketosis, and classic diabetic ketoacidosis. In our study, 68 patients (5.40% of symptomatic patients) presented with ketosis and 30 patients (2.38%) had diabetic coma as a consequences of complicated diabetes mellitus.

**Hematologic manifestations**

SARS-CoV-2 have cytotoxic effect associated with ACE2-
dependent or ACE2-independent entry into lymphocytes apoptosis-mediated lymphocyte depletion and inhibitory effects of lactic acid on lymphocyte proliferation which leads to lymphocytopenia. Leukocytosis (especially neutrophilia) is thought to be a consequence of a hyperinflammatory response to infection with SARS-CoV-2 and/or secondary bacterial infections. Lymphopenia, a marker of impaired cellular immunity, is a cardinal laboratory finding reported in 67–90% of patients with COVID-19, with prognostic association in the vast majority of studies published so far. In our study 485 patients (38.59% of symptomatic patients) had lymphopenia in their hemogram, suggestive of COVID-19 related lymphocyte destruction proportional to severity of disease. Thrombocytopenia, although often mild (in 5–36% of admissions), is associated with worse patient outcomes. In our study 76 (6.03% of symptomatic patients) patients had thrombocytopenia. 280 patients of our study (22.2% of symptomatic patients) had septicemia as COVID-19 induced and/or secondary infection.

**Dermatological manifestations**

Potential mechanisms for COVID-19-related cutaneous manifestations include an immune hypersensitivity response to SARS-CoV-2 RNA, cytokine-release syndrome, deposition of microthrombi, and vasculitis. Approximately 20% of hospitalized patients had cutaneous findings including erythematous rash, urticaria, and chickenpox-like vesicles during the course of their illness. In our study 124 patients (9.84% of symptomatic patients) had dermatological manifestation including maculopapular rashes in 110 patients. However, among these patients, 32 patients (29.1%) had pre-existing rashes over skin.

**Conclusion**

Patients of SARS-CoV-2 mostly presented with life threatening pulmonary complication. Moreover, widespread organ-specific manifestations of COVID-19 are increasingly being appreciated. For better clinical practice of SARS-CoV-2, it is mandatory to development of a comprehensive understanding of the common and organ-specific pathophysiology and clinical manifestations of this multi-system disease. Extrapolmonary presentations of COVID-19 can be the only symptoms during hospital visit. Clinicians must consider these symptoms as COVID-19 manifestations to avoid misdiagnosis or delayed diagnosis. Therefore, the knowledge of these clinical manifestations of COVID-19 is important as it assists in early diagnosis, isolation of suspected patients and limit the transmission of infection in the hospital settings. Interestingly, other routes of infection, such as fecal-oral transmission and transmission of infection through body fluids can be explained by these unusual clinical presentations of COVID-19. Furthermore, multiple sites other than throat can also be used to take specimen for testing of SARS-CoV-2.

**Ethical approval**

This study approved by ethical and research committee of SMS medical college and Hospital, Jaipur, India.

**Author contributions**

S. Bhandari and G. Rankawat formulated the research questions, designed the study, developed the preliminary search strategy, and drafted the manuscript. G. Rankawat and V. Gupta collected the data for study and write the manuscript. S. Bhandari and M. Divakar conducted the quality assessment. All authors critically reviewed the manuscript for relevant intellectual content. All authors have read and approved the final version of the manuscript.

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**Availability of data and materials**

Available from corresponding author upon reasonable request.

**Declaration of competing interest**

All authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential.

**References**


2. Eidarppuli SD, Venkatesh A. Atypical symptoms in COVID-19: the many guises of a common culprit. 2020 Apr 22; Available from: https://www.bmj.com/content/369/bmjm1375/nr-12


Study of Clinical Spectrum of Severe COVID-19 Infection in Elderly Patients and its Outcome-A Major Mumbai Tertiary Care Hospital Observations

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Abstract

Background: At 140 million, India has the second largest population of old people in the world, as per the 2011 census.1 The covid 19 pandemic has wreaked havoc in millions of lives. Elderly are especially vulnerable to COVID-19 and experience high morbidity and mortality as a result of immunosenesence. Age is independently linked with mortality, but age alone does not adequately capture the robustness of older adults who are a heterogeneous group. The current research was done in a tertiary healthcare hospital in Maharashtra to understand the clinical profile and factors that affected the outcome of elderly during the second wave of the COVID pandemic.

Method: This was a single centre retrospective observational study done in a tertiary hospital which was admitting both covid and non-covid patients during the time of this study. All elderly patients admitted with COVID 19 disease in Covid ward and covid ICU (Intensive care unit) were included in the study. Their Demographic details, duration of illness, vital parameters, oxygen saturation, partial pressure of arterial oxygen compared to fraction of inspired oxygen (PaO2-FiO2 ratio) were recorded and also relevant investigations such as complete blood count, kidney function tests, liver function tests, arterial blood gases, chest X-ray and ECG (Electrocardiogram), CT scan of the brain, CSF (cerebrospinal fluid) studies and other tests where relevant were recorded. Inflammatory markers such as C-Reactive Protein (CRP), Ferritin, D-Dimer and Chest CT scan were noted. Clinical profiles and outcomes were noted till discharge or death.

Results: Among 231 patients that were included in this study, 81 (35%) were female and 150 (65%) were male. Ninety-two patients died (39.8%) while 139 patients (60.2%) survived in our study. Majority of our patients (211; 91.3%) presented in category E (pneumonia with respiratory failure) or category F (pneumonia with respiratory failure and multiorgan dysfunction syndrome). Factors which had a major impact on mortality were - a low PaO2-FiO2 ratio on admission, high C-Reactive Protein (CRP) levels, high d-dimer levels, a finding of bilateral ground glass opacities on x-ray, and need for invasive ventilation on admission.

Conclusions: Elderly remain vulnerable to severe consequences of COVID-19 infection owing to the increasing comorbidities and immunosenesence in them. Prolonged oxygen therapy and intensive respiratory rehabilitation are the mainstays of effective management. Given the constant threat of mutating virus, masking, maintaining hand sanitization, vaccination and also caring for our elders while still maintaining social distance are our best bet against a fatal third wave.
the T cell diversity repertoire. When infected by SARS-CoV-2, young people present with a milder disease as they frequently clear the virus through an efficient adaptive immune response. In contrast, the elderly are more prone to an uncontrolled activation of innate immune response that leads to cytokine release syndrome and tissue damage.

Not only the outcome but also the clinical presentation of the elderly shows some differences as compared to the younger population. The most common symptom of COVID-19 infection is fever. However, elderly patients frequently had a low intensity of fever or no fever, even in severe cases in some studies. Atypical clinical manifestations include anorexia, myalgia, asthenia, headache, anosmia, diarrhoea, and cardiovascular complications. Elderly patients often present with atypical and non-specific manifestations, making diagnosis difficult. The severity of disease is generally higher as reflected by the CRP levels and CTSI (CT Severity Index) scores. The co-occurrence of chronic diseases in elderly such as diabetes, hypertension, atherosclerotic cardiovascular diseases is a common problem and a further challenge in their treatment.

In spite of the towering mortality rates, the number of elderly patients who have recovered has also been impressive. Thus, understanding factors beyond age which affect prognosis is crucial to prevent morbidity and mortality in this age group.

The current research was done in a tertiary healthcare institute in Maharashtra to understand the clinical profile and factors that affected the outcome of elderly during the second wave of the COVID pandemic among people aged 60 and above during the months of April 2021 till July 2021.

**Aims and Objectives of the Study**

1. To study demographics, clinical profile, biochemical (Inflammatory markers) and radiological features of elderly patients admitted with moderate and severe category Covid 19 disease.

2. To study various complications of Covid-19 infection and need of ventilator requirement in Moderate to Severe Category Covid 19 elderly patients.

3. To study the outcome of admitted geriatric patients with COVID 19 disease

**Materials and Methods**

This was a prospective observational study done in a tertiary care hospital in Mumbai over a period of 4 months from April 2021 till July 2021.

Patients satisfying following inclusion criteria were included in the study.

**Inclusion Criteria**

1. Age > 60yrs

2. Confirmed COVID-19 by positive nasopharyngeal or throat swab by antigen test/RT-PCR or CBNAAT (Cartridge Based Nucleic acid amplification test) or CORAD (Covid-19 reporting and data system) score of 4 or 5 in absence of swab positivity

3. Moderate to severe category patients

4. Patients/relatives giving consent for study

**Exclusion Criteria**

Patients and relatives not willing to participate in the study or transferred to other hospital or withdrawal of consent were excluded from study

**Study Procedure**

A detailed history including demographic details, duration of illness, vital parameters, Spo2(saturation of oxygen) were recorded and also relevant investigations such as CBC(Complete blood counts), LFT(Liver function tests), RFT(renal function tests), RBS(random blood sugar), ABG(arterial blood gas) Chest X-ray, ECG(electrocardiogram) were recorded.

Inflammatory markers such as CRP(C-reactive protein), D-Dimer and Chest CT scan with other investigations like CT scan brain, CSF, tests for co-existing infections like malaria, leptospirosis, dengue, sepsis were recorded when relevant and available.

These patients were monitored in ward with their follow up on day 3, day 7 and day 28 (personally or telephonically as per feasibility) for outcome, oxygen requirement and development of any complications. Severity grading as per Maharashtra state COVID-19 task force guidelines was done as follows:


2. Category B-Symptomatic/URTI (Upper respiratory tract infection) without comorbidity

3. Category C -Symptomatic/URTI with comorbidity

4. Category D-Pneumonia (LRTI) (Lower Respiratory tract infection) without respiratory failure

5. Category E-Pneumonia (LRTI) with respiratory failure

6. Category F-Pneumonia (LRTI) with respiratory failure with sepsis/ septic shock/ multi-organ dysfunction syndrome.

All patients received standard treatment as per established protocols including antibiotics, steroids, anticoagulation, management of coexistent comorbidities and oxygen supplementation. Remdesivir, Tocilizumab and Ilotizumab were given to patients after expert opinion on a case-to-case basis as per availability.

Outcomes were measured as primary-survival and secondary-duration of hospitalization, ICU requirement, change in oxygen saturation and need of oxygen supplementation/mechanical ventilation and new onset organ failure. Patients were followed up daily till hospitalization and their clinical profile-symptoms, improvement/deterioration of respiratory failure, mode of oxygen supplementation, need of HFNO(High flow nasal oxygen), ventilation (non-invasive or invasive), need of ICU care, development of complications, concomitant medications like antibiotics, anticoagulants, tocilizumab, steroids, need of other organ support, and complications were studied. Surviving patients were followed up on day 28 of initiation of therapy for dependence on oxygen and complications if any.

**Statistical analysis**

All data was entered into Microsoft Excel (Windows 7, Version 2007) and analysis was done using the Statistical Package for Social Sciences (SPSS) for Windows software (version 22.0; SPSSInc., Chicago). Continuous variables were summarized using summary statistics (number of observations, mean and standard deviation). Categorical values were summarized...
The association between variables was analyzed by using Chi-Square test for categorical variables. Level of significance was set at 0.05.

Results

A total of 891 covid positive patients were admitted to our hospital during the study period. Out of these, 231 patients satisfied the inclusion criteria and were studied in detail. Among these, 81 patients (35%) were female whereas 150 patients (64%) were male. Age of the patients ranged from 60 to 98 years with maximum number of patients (133; 57%) between 60-70 years of age. The age distribution of the study group was as shown in Figure 1. The most common symptoms were fever (209; 90.5%), cough (200; 86.5%) and breathlessness (196; 85.2%). Atypical presentations like stroke (20; 8.6%), myocardial infarction (10; 4.2%), conjunctivitis (3; 1.2%) and skin rash (2, 0.8%) were also found in decreasing order in our study. Only two patients did not have any comorbidity in our study. The most common comorbidity was hypertension which was found in 179 (77%) of patients. Other comorbidities such as diabetes mellitus (140; 60.6%), obesity (82; 35.5%), ischemic heart disease (2410.4%), obstructive airway disease (12; 5.2%), chronic liver disease (12; 5.2%), hypothyroidism (10; 4.3%), pulmonary Koch’s (8; 3.3%), cerebrovascular accident (8; 3.5%) and chronic kidney disease (4; 1.7%) were also common in our study (Figure 2). Forty patients (17.3%) had more than one comorbidity. Majority of the patients had not received any vaccination in (177; 76%) with only minority (54; 23%) having received at least one dose with a meagre (5; 2%) having taken both doses. One hundred and forty-seven patients (63%) presented within one week of onset of symptoms while 84 (36%) of the patients presented after one week of symptoms out of which 31 (13.4%) had a very late presentation (>10 days) to our hospital. Respiratory distress as evidenced by tachypnea (respiratory rate >20 breaths/min) and hypoxia (oxygen saturation <90%) was found in 207 patients (89%). Severity grading of the patients was done as per Maharashtra Covid-19 task force guidelines and is shown in Figure 3.

Primary and secondary outcomes were noted as follows. Ninety two patients (39.8%) died in our study while 139 patients (60.2%) survived. During the same period, the overall mortality rate for covid patients of all age groups admitted to this hospital was 34.9%.

Table 1: Comparison of the patients who were discharged and died

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Discharged (n=139)</th>
<th>Death (n=92)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (F/M)</td>
<td>45/94</td>
<td>36/56</td>
<td>0.624</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>87</td>
<td>46</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>70-79</td>
<td>44</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>80-89</td>
<td>8</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>90-99</td>
<td>0</td>
<td>2</td>
<td></td>
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<tr>
<td>Vaccination history</td>
<td>Not vaccinated</td>
<td>67</td>
<td>110</td>
</tr>
<tr>
<td></td>
<td>One dose</td>
<td>29</td>
<td>25</td>
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<tr>
<td></td>
<td>Two doses</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Number of Comorbidities</td>
<td>&lt;2</td>
<td>38</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>≥3</td>
<td>42</td>
<td>45</td>
</tr>
<tr>
<td>HTN</td>
<td>Yes</td>
<td>87</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>15</td>
<td>37</td>
</tr>
<tr>
<td>DM</td>
<td>Yes</td>
<td>55</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>47</td>
<td>43</td>
</tr>
<tr>
<td>Saturation on room air at presentation</td>
<td>&lt;60</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>60-80</td>
<td>2</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>80-90</td>
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<td>35</td>
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<tr>
<td></td>
<td>90-95</td>
<td>65</td>
<td>18</td>
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<tr>
<td>Respiratory rate</td>
<td>10-20</td>
<td>30</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>20-30</td>
<td>100</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>&gt;30</td>
<td>9</td>
<td>72</td>
</tr>
<tr>
<td>Category on presentation</td>
<td>category d</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>category e</td>
<td>103</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>category f</td>
<td>18</td>
<td>37</td>
</tr>
<tr>
<td>Mode of oxygenation at presentation</td>
<td>No supplemental oxygen</td>
<td>19</td>
<td>02</td>
</tr>
<tr>
<td></td>
<td>nasal prongs</td>
<td>60</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>NRBM</td>
<td>41</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>NIV</td>
<td>17</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>Invasive ventilation</td>
<td>02</td>
<td>39</td>
</tr>
<tr>
<td>Chest X-ray findings</td>
<td>Bilateral consolidation</td>
<td>57</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Unilateral consolidation</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>GGO</td>
<td>62</td>
<td>44</td>
</tr>
</tbody>
</table>

Table 2: Comparison between laboratory parameters in both groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Discharged (n=139)</th>
<th>Death (n=92)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>&lt;12</td>
<td>80</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>≥12</td>
<td>59</td>
<td>38</td>
</tr>
<tr>
<td>WBC or Leucocytosis</td>
<td>up to 150000</td>
<td>128</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>&gt;150000</td>
<td>11</td>
<td>45</td>
</tr>
<tr>
<td>Platelets</td>
<td>&gt;150000</td>
<td>118</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>≤150000</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td>CRP</td>
<td>77 (1.8-342)</td>
<td>117 (1-510)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>D-dimer</td>
<td>1531 (200-5478)</td>
<td>2230 (122-8878)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>N/L ratio</td>
<td>2.3 (1.2-7.6)</td>
<td>4.5 (1-9)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Serum Creatinine</td>
<td>up to 1.2</td>
<td>108</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>&gt;1.2</td>
<td>31</td>
<td>24</td>
</tr>
<tr>
<td>PaO2-FiO2 ratio</td>
<td>&gt;200</td>
<td>66</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>100-200</td>
<td>63</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>≤100</td>
<td>10</td>
<td>27</td>
</tr>
<tr>
<td>Serum glutamate oxalate transaminase</td>
<td></td>
<td>52</td>
<td>61.8</td>
</tr>
<tr>
<td>Random blood sugar</td>
<td>165</td>
<td>206.7</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Fig. 1: Age-wise distribution of patients
Thirty-four (14.7%) of patients died within three days from admission. The mean duration of hospital stay among patients that died ranged from less than 24 hours to 32 days with a mean duration of 6 days. The average hospital stay was 10 days for those discharged without oxygen (95;41.1%) whereas it was much higher at around 20 days for those discharged on short term oxygen therapy (44;19%). Sixty six (28.6%) patients were admitted directly to the Intensive care unit on the day of presentation, however 105 patients (45.4%) needed to be shifted to the intensive care unit by day 5 of admission.

Table 1 shows comparison of demographic and clinical characteristics among patients who were discharged and those who died in the study. An advanced age (>80 years), presence of Diabetes Mellitus, respiratory rate >30 breaths/min, SpO2 (Saturation of oxygen) <60% on room air, Category E and F on presentation and need for invasive ventilation were associated with higher mortality.

Laboratory parameters including complete blood count (CBC), kidney function tests and liver function tests were done for all patients. Inflammatory markers such as C-reactive protein (CRP), D-Dimer and Neutrophil-Lymphocyte ratio (NLR) were also studied in all patients. A comparison between laboratory parameters among the patients who survived versus those who died is shown in Table 2. As shown in Table 2, the mean CRP levels, mean D-dimer levels and N/L ratio was much higher in the patients who died as compared to those who survived in our study. The mean random blood sugar on admission was much higher among those patients that died as compared to the survivors.

Radiological investigations included chest X-ray which was done for all patients and CT pulmonary angiography. The commonest findings on X-ray were bilateral ground glass opacities (106;45.8%), bilateral consolidation (97;41.9%) and unilateral consolidation (28;12.1%). High resolution Computer Tomography (HRCT) was done in 69 (29.8%) of the patients. CT-Severity Index scores ranged from 4 till 20 with a mean score of 16. The average CTSI score was higher (18.6) among those who died than those who survived (CTSI-13). Seventeen patients (7.4%) had a pulmonary thromboembolism on CT-Pulmonary Angiography (Figure 4) out of which 7(3%) died whereas 10(4.3%) survived.

Treatment for all patients was as per established protocols. All patients received anticoagulation and steroids unless contraindicated in cases where bleeding (2.6.8%) or additional immunocompromised state (5.2.1%) or active pulmonary Koch’s (8;3.4%) complicated the picture. In such cases, clinical decision was taken after deliberation to ensure best possible outcome for patients. As shown in Table 3, Remdesivir (186;80%) was given to all patients who had hypoxia or persistent fever and presented within 10 days of onset of symptoms. Tocilizumab or Itolizumab was given to far fewer patients (21;9.09%) as per availability after expert opinion. As per standard guidelines, low dose steroids (methyl prednisolone at 1mg/kg) was given to all hypoxic patients (216;93.5%) however it was avoided in 15 patients due to complications like gastrointestinal bleeding or immunocompromised state or active pulmonary Koch’s.

Respiratory Support

As shown in Table 4, the mode of oxygenation on day 1 and day 5 were noted. The need for increased oxygen support on day 5 as compared to day 1 was associated with a poor prognosis. While 43 out of 92 patients who died required higher oxygen support on day 5 as compared to day 1, only 12 out of 139 patients who survived required higher oxygen support on day 5 as compared to day 1 (p value <0.05).

The most common complications were sepsis (72;31%) and renal failure (23.8%). We also noted 9 cases (3.8%) of mucormycosis in this study. They were present on admission in some cases (5.2.1%) or developed as a complication (4.1.7%) during prolonged stay in the hospital in some cases. Six of these patients (2.6%) died whereas 3 were discharged.

Discussion

Several studies have been done till date to study the outcome of elderly in Covid. However, studies done during the second wave of the pandemic in India are scarce at the time of writing this article. In our study, the elderly accounted for 25% (231 out of 891) of all patients admitted for covid in our hospital. This was in keeping with the study done by Vijay Kumar Jain et al which concluded that the second wave affected the young more than the elderly. Females accounted for just 35% of cases whereas males
accounted for 65% of cases which was consistent with other studies from India. Fever remained the most common symptom followed by cough and breathlessness as in other similar studies. Thromboembolic phenomena including stroke (20;8.6%) myocardial infarction (10;4.3) and pulmonary thromboembolism (17.7.36%) were also encountered by us in our study. A study done by Tan et al11 found high incidence of venous thromboembolic events (7.8%) and arterial thromboembolic events (3.9%) in COVID 19 infection. The most common comorbidities were hypertension and diabetes, just as in other studies.12 We reported a large number of patients with obesity (82;35.5%). This reflects the ongoing pandemic of obesity all over the world including India as reported in the study by KY Santhosh Kumar et al.13 Obesity is reported to be associated with increased severity of illness and poor outcomes as observed in various studies. The Indian government started vaccination programme for senior citizens on 1st March 2021. As our study duration was from April 2021 till July 2021, only 5 patients in our study had been vaccinated with both doses of either vaccines available in India. Out of these patients 1 died however the patient had not completed 15 days since vaccination. These numbers are too small to judge efficacy of vaccine.

Our hospital being a tertiary referral centre with strict admission policy, the majority (210;91%) of our patients belonged to severe categories i.e. Category E and Category F. A study done by Singhal et al14 found that severe disease is two-three times higher in elderly as compared to younger population. However, in the serious and critical group the mortality was around 50% in most studies. We reported 39.8% mortality in our study. Given that we had a very high proportion of severely sick elderly, we believe that our mortality was kept in check because of increased awareness of the disease and its treatment. Late presentation, ignorance and lack of knowledge in people of suburban and rural areas which constituted major proportion of patients in our hospital added to the increased mortality seen in our study. The elderly accounted for 25% of all cases and they accounted for 29.6% of all the deaths due to covid across all age groups reported during the same time period.

A wide variety of laboratory derangements were noted in our study. We found an association of high CRP levels, D-dimer levels, total white blood cell counts and neutrophil-lymphocyte ratio with mortality. A study done by Stringer et al15 found higher mean levels of CRP in those who died (118 mg/dl) as compared to those who survived (67mg/dl) which was quite similar to our study (117 mg/dl Vs 77 mg/dl).Higher D-dimer levels in those who died as compared to survivors was found in many studies. High white blood cell counts with a high neutrophil-lymphocyte ratio16 are also cheap and readily available indicators of poor prognosis. We also found the random blood sugar on admission to be much higher among those who died as compared to the survivors. A study by Aggarwal et al17 found that admission hyperglycemia, even in the absence of diabetes mellitus was a predictor of poor prognosis.

A chest X-ray and HRCT (High resolution CT scan) of the chest and CTPA (CT-pulmonary angiography) were the only major radiological investigations performed in most cases. The portable X-ray chest was easily available to all patients however the image qualities were limited by poor patient position in some cases along with over exposure in most cases. Though CT scans could clearly define the pathology, there posed multiple problems in getting CT scans for our patients because of the time required for them, high oxygen requirements of our patients with increased tachypnea and limited resources to provide oxygen during transport along with a limited time slot for covid patients to get CT scans due to the need for isolation and cleaning of equipment. Despite these limitations, 69 of our patients underwent a HRCT chest along with 40 patients undergoing CTPA. The CTSI score was higher among those who died (18) as compared to the survivors (13). The study done by Francone et al19 found a score of greater than 18/25 to be associated with poor prognosis. We also used the CT scan to diagnose COVID 19 cases in which the RT-PCR was not available or negative despite high clinical suspicion. The presence of pulmonary thromboembolism was noted in 17 patients however no association was noted with mortality probably due to the use of heparin in all patients as per learnings from the first wave. We found that the need for increased oxygen support on day 5 as compared to day 1, along with a need for high oxygen at admission was a poor prognostic indicator. A study done by Somers et al19 highlights the vicious circle where hypoxia worsens lung damage by viral replication and hypoxic pulmonary vasoconstriction causing further hypoxia leading to poor prognosis.

We found sepsis and renal failure to be the most common complications as

<table>
<thead>
<tr>
<th>Table 3: Treatment modalities and outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td>Inj Remdesivir Given</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Inj Tocilizumab/ Htolizumab Given</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Inj Methylprednisolone Given</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4: Mode of oxygenation on day of admission and day 5 from admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of oxygenation</td>
</tr>
<tr>
<td>No supplemental oxygen</td>
</tr>
<tr>
<td>Nasal prongs</td>
</tr>
<tr>
<td>Hudson mask</td>
</tr>
<tr>
<td>NRBM</td>
</tr>
<tr>
<td>NIV</td>
</tr>
<tr>
<td>Invasive ventilation</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Fig. 4: CT pulmonary angiography showing thrombus in the right pulmonary artery
should prompt early and intensive therapy and death in many cases. Raised inflammatory markers with severe hypoxia on admission, in the first wave. Late presentation to COVID-19 in the second wave as a major factor. Though a comprehensive study of all elderly admitted in the wards as well as ICUs was a major strength of our study, we had many limitations including:

1. There was no comparison between young and elderly or mild cases with severe cases
2. This being a cross-sectional study with limited time frame, long term effects of COVID-19 infection could not be studied in detail.

Conclusion
Elderly remained highly vulnerable to COVID 19 in the second wave as in the first wave. Late presentation with severe hypoxia on admission, uncontrolled sugars and presence of multiple comorbidities resulted in prolonged stay, requirement of intensive therapy and death in many cases. Raised inflammatory markers should prompt early and intensive treatment.

References
1. Census of India Website : Office of the Registrar General & Census Commissioner, India.

**CHALLENGES IN THE EPIDEMIC - A MULTI-DISCIPLINARY APPROACH**

*Editors: Joseph Varon, Paul Marik, Jose Iglesias, Christopher de Souza*

*Published by: Theme Medical and Scientific Publishers Private Limited*

COVID-19 - the unexpected pandemic that hit the world in early 2020 with its accompanying rapid and unprecedented evolution in the field of medical science, has left a profound impact in the history of mankind.

With over 90,000 papers having been published on the subject, many of which were contradictory or later withdrawn, the management of COVID-19 has been uncertain and by far one of trial and error. The need for a reliable book that explored and analysed this vast database and put it together in an easy-to-understand format was very much felt. Thus was born “Challenges in the epidemic - A multidisciplinary approach”, a unique book put together by world renowned doctors with the common aim of giving physicians a proper direction in the management of the disease. The entire spectrum of COVID-19 from epidemiology to etiopathogenesis, case appropriate testing modalities, clinical/ laboratory/radiologic findings, treatment strategies to a broad coverage on vaccines - every topic is extremely well explored. Each chapter is contributed by experts in their respective fields and award winning, world leaders in their work for COVID-19 like Dr Joseph Varon.

This one-of-a-kind book caters to everyone’s requirements - from medical students to resident doctors to physicians, and to consultants.

Barring the research published on COVID-19 post August, 2021 - which included trials on Molnupiravir, booster doses of vaccines and the Omicron variant - this is an outstanding book which will enrich the knowledge of medical professionals all over the world and help them in decreasing the overall morbidity and mortality of patients.

*Dr. Pralhad Prabhudesai*

Consultant Chest Physician, Lilavati Hospital, Mumbai
Prevalence of Urinary Tract Infection among Hospitalized Covid 19 Patients: A Study in Eastern India

Sanjeev Das1, Jayashree Konar2, Abhra Banerjee3, Manas Talukdar4*

Abstract

COVID-19 is the disease caused by SARS-CoV-2. The present hospital based study was performed to find out prevalence of Urinary Tract Infection among COVID 19 patients. The cross sectional study was performed with seven hundred fifty three laboratory confirmed COVID 19 cases over six months (from 1st July to 31st December, 2020). Urine samples collected from laboratory confirmed COVID-19 cases in appropriate sterile manner and were screened for pus cells and bacteria. This was followed by plating on Mac-conkey’s agar media and 5% Sheep Blood agar media. Inoculated plates were incubated overnight in aerobic condition at 37°C. Discrete colonies were further studied by Gram staining, tests for motility, battery of biochemical tests. Antibigram was performed by disk diffusion method as per CLSI guidelines. Species confirmation and MIC (Minimum Inhibitory Concentration) values of the tested antibiotics were detected by automation. Results were analyzed according to standard statistical methods. Ninety urine samples were culture positive (11.95%). Escherichia coli was found to be the commonest pathogen, isolated in forty three cases (47.78%) followed by Enterococcus faealis in twenty nine cases (32.22%). Enterococcus faealis isolates were sensitive to Vancomycin, Linezolid and Nitrofurantoin and isolates were resistant to fluoroquinolones (65.51%). Majority of the Gram Negative isolates were susceptible to nitrofurantoin (80.32%) where as fifteen carbapenemase producers, thirteen AmpC Betalactamase producers and twenty one Extended Spectrum Beta Lactamase (ESBL) producers have been recorded. Constant awareness regarding the antibiotic guidelines for COVID-19 cases is the need of the hour.

Introduction

COVID-19 is the disease caused by a new coronavirus called SARS-CoV-2. WHO first learned of this new virus on 31 December 2019, following a report of a cluster of cases of ‘viral pneumonia’ in Wuhan, People’s Republic of China. The most common symptoms of COVID-19 are a triad comprised of fever, dry cough and fatigue. Other less common symptoms include loss of taste or smell, nasal congestion, conjunctivitis (also known as red eyes), sore throat, chills or dizziness, headache, muscle or joint pain, different types of skin rashes, nausea or vomiting and diarrhea. Symptoms of severe COVID-19 disease include High temperature (above 38 °C) with or without shortness of breath, loss of appetite, confusion and persistent pain or pressure in the chest. Other less common symptoms of severity are irritability, confusion, reduced consciousness (sometimes associated with seizures), anxiety, depression and sleep disorders. More severe and rare neurological complications such as strokes, brain inflammation, delirium and nerve damage are also manifested in some cases. People of all ages may experience fever with or without cough associated with shortness of breath, chest pain or loss of speech or movement.

On the other hand, Urinary tract infection (UTI) is a collective term that describes any infection involving any part of the urinary tract, namely the kidneys, ureters, bladder and urethra. The urinary tract can be divided into the upper (kidneys and ureters) and lower tract (bladder and urethra). Uncomplicated lower UTI remains one of the most commonly treated infections in primary care. The urinary tract is a common source of infection in children and infants and is the most common bacterial infection in children < 2 years of age, both in the community and hospital setting. During the first six months of life, UTIs are more common in boys. The outcome is usually benign, but UTIs can progress to renal scarring in early infancy, especially when associated with congenital anomalies of the urinary tract. Renal scarring may lead to complications in adulthood including hypertension, proteinuria, renal damage and even chronic renal failure, which requires dialysis treatment. Few reports are emerging with urinary symptoms amongst SARS-CoV2 or COVID 19 cases.

The present study was performed to find out prevalence of Urinary Tract Infection among COVID 19 patients.

Objective(s)

1. Estimation the prevalence of Urinary Tract Infection among COVID 19 patients.

2. Identify the pathogenic bacteria to cause Urinary Tract Infection among COVID 19 patients.

Material and Methods

The cross sectional study was performed with seven hundred fifty three laboratory confirmed COVID 19...
cases over six months (from 1st July to 31st December, 2020) in a COVID hospital of Eastern India. Urine samples were screened from laboratory confirmed COVID 19 cases with symptoms of Urinary Tract Infection. Urine samples collected in appropriate sterile manner were screened for pus cells and bacteria. This was followed by plating on Macconkey’s agar media (differential as well as selective media for Gram Negative bacteria) and 5% Sheep Blood agar media (Enriched media, aids to isolate both Gram Negative and Gram Positive bacteria. Inoculated plates were incubated overnight at 37°C. Discrete colonies were further studied by Gram staining, tests for motility, battery of biochemical tests and by VITEK 2 Microbial identification system (bioMerieux) with “Advanced Expert System” (AES) to confirm the speciation.

Antibiogram was performed by disk diffusion method (modified Kirby-Bauer technique) on Muller-Hinton agar and blood agar media. MIC (Minimum Inhibitory Concentration) values of the tested antibiotics were detected by VITEK 2 with “Advanced Expert System” (AES) as per CLSI guidelines with its ability to provide accurate “fingerprint” recognition of bacterial resistance mechanisms and phenotypes. Results were analyzed according to standard statistical methods.

**Discussion and Conclusion**

Hospitalized COVID-19 patients have been reported to suffer from superinfection such as Ventilator Associated Pneumonia (VAP) and UTI. Similarly, in this present study, out of seven hundred and fifty three total samples, ninety were culture positive (11.95%) UTI cases. On the other hand, few studies have documented the fact that patients admitted with COVID-19 did not have any lower urinary tract symptoms. Moreover, AJB Marand et al (2021) concluded that hematuria, pus cells and SARS-CoV-2 virus in urine, were found to be strong negative prognostic factors in admitted COVID-19 patients. However, several other studies such as the study performed by Sara M Karaba et al (2021)have noted that the most common urinary pathogens were *Escherichia coli* along with *Proteus* spp. and *Klebsiella* spp.

Similarly, in the present study, *Escherichia coli* was found to be the commonest pathogen, isolated in forty three cases (47.78%) followed by *Enterococcus faecalis* in twenty nine times (32.22%). *Klebsiella pneumoniae subsp. pneumoniae* was isolated in eighteen occasions (20%). No other isolate was identified. Regarding antimicrobial susceptibility pattern, all the *Enterococcus faecalis* isolates were sensitive to Vancomycin, Linezolid and nitrofurantoin. Out of twentynine isolates, nineteen isolates were resistant to fluoroquinolones (65.51%). Majority of the Gram Negative isolates were susceptible to nitrofurantoin (49 out of 61, i.e., 80.32%) as fifteen carbapenemase producers, thirteen AmpC Betalactamase producers and twentyone Extended Spectrum Beta Lactamase (ESBL) producers have been recorded (Figure 1).

**References**

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One for the Day!
Clinico-immunological Profile of Systemic Lupus Erythematosus: An Observational Study

Gotur Amrita Jagdish¹, Londhey VA²*, Kini Seema H³

Abstract

Background: SLE is a common connective tissue disease in Indians (mostly women) which is frequently underdiagnosed due to limited awareness and knowledge regarding the disease.

Methods: This is a retrospective observational study conducted in a tertiary care hospital in Western India among patients of SLE attending outpatient Rheumatology Clinic and inpatient admissions of Topiwala Medical College and BYL Nair Charitable Hospital, Mumbai. Sixty patients were recruited based on inclusion and exclusion criteria.

Results: In clinical profile, arthralgia was the most common manifestation seen in 53 patients (88.3%) followed by alopecia in 46 patients (76.7%). In systemic involvement, CNS lupus was the most common manifestation seen in 27 patients (45%) followed by renal involvement in 13 cases (21%). Pulmonary hypertension (PH) was another noticeable finding seen in 24 cases (40%) of which 18 (75%) had mild PH, 6 (25%) patients had severe PH. The mean SLEDAL score was 11.85 at baseline which reduced to 2.65 at 6 months and remained 3.65 at the end of 3 years of the study.

In immunological profile, ANA was positive in all patients. Speckled pattern of ANA was the most common pattern seen in 34 patients (56.7%). A titre of above 1:100 was noted in 53 patients (88.3%). ds DNA was positive in 26 patients (43.3%). Anti Ro/La was positive in 3 patients (5%) and U1RNP in 2 patients (3.3%). Autoimmune hemolytic anemia (AIHA) was the most common autoimmune association seen in 25 patients (41.7%), antiphospholipid antibody(APLA) was seen in 15 patients (25%), 7 patients (11.6%) were anti TPO antibody positive, 3 patients (5%) were Ro/La positive while only 2 patients(3.3%) were U1RNP positive.

Conclusion: Clinical profile and immunological patterns of SLE are diverse. A systematic work up is needed to identify the multisystem involvement and asking for specific antibody tests to identify common autoimmune associations is recommended.

Introduction

Systemic lupus erythematosus (SLE) is a multysystem autoimmune disease characterised by a relapsing and remitting course with a highly variable prognosis. Immunologic abnormality is characterized by antinuclear antibodies (ANAs) that form immune complexes that mediate pathogenesis by tissue deposition or cytokine induction.¹ The clinical course of SLE is variable and may be characterized by periods of remissions and chronic or acute relapses. Women, especially in their 20s and 30s, are affected more frequently than men.² Various studies across the country and all over the world have evaluated clinical and immunological profile of SLE patients. We conducted our study in a tertiary care hospital in Western India with the purpose of studying the characteristics in our cohort and compare the findings with previous studies.

Objective

To study clinical and immunological profile of SLE patients.

Methods

This is a retrospective observational study conducted in a tertiary care centre in Western India. Between August 2014 and August 2015. Sixty patients of SLE attending outpatient department and inpatient admissions from department of General Medicine, TNMC and BYL Nair Charitable hospital, Mumbai who had 3 year follow up were enrolled.

Inclusion criteria

1. Adults (Male or female) who were diagnosed as SLE either in OPD or as inpatients by ACR diagnostic criteria (1997 update) in last 8 years with records of investigations and treatment available for 3 consecutive years since the date of diagnosis.

Exclusion criteria

1. Those patients whose records are not available or incomplete in rheumatology clinic.
2. Those patients who failed to follow up for 3 continuous years.

Written informed consent in the language the patient /relative best understands i.e. English/ Marathi/ Hindi was taken. Data of the following investigations was collected from patient case record files in Rheumatology outpatient department. Complete blood count, liver and kidney function tests, erythrocyte sedimentation rate, urine routine and microscopy, C reactive protein, rheumatoid factor, thyroid function test, chest X ray, Electrocardiogram, ultrasound abdomen, Complement

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Received: 04.08.2021; Revised: 31.12.2021; Accepted: 18.01.2022
Table 1: Clinical profile

<table>
<thead>
<tr>
<th>Age</th>
<th>Mean (SD)</th>
<th>Range (10-55 years)</th>
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<tbody>
<tr>
<td>Gender</td>
<td>Number Male</td>
<td>58</td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
<td>3.3%</td>
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Clinical Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>No. of Cases (N = 60)</th>
<th>Percentage (%)</th>
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<tbody>
<tr>
<td>Malar rash</td>
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<td>28.3</td>
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<tr>
<td>Vasculitic rash</td>
<td>34</td>
<td>56.7</td>
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<tr>
<td>Arthralgia</td>
<td>53</td>
<td>88.3</td>
</tr>
<tr>
<td>Oral ulcer</td>
<td>37</td>
<td>61.7</td>
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<tr>
<td>Photosensitivity</td>
<td>38</td>
<td>63.3</td>
</tr>
<tr>
<td>Alopecia</td>
<td>46</td>
<td>76.7</td>
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<tr>
<td>Myositis</td>
<td>2</td>
<td>3.3</td>
</tr>
<tr>
<td>Chest pain</td>
<td>02</td>
<td>3.3</td>
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<tr>
<td>Breathlessness</td>
<td>10</td>
<td>16.7</td>
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<tr>
<td>Headache</td>
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<tr>
<td>Seizures</td>
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<td>Altered sensorium</td>
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<td>Psychosis</td>
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<tr>
<td>Vasculitic neuropathy</td>
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<td>0.67</td>
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<tr>
<td>Fever</td>
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<td>68.3</td>
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<td>Raynauds phenomenon</td>
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<td>13.3</td>
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<tr>
<td>Spontaneous abortion</td>
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<td>11.7</td>
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<td>Renal involvement</td>
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<td>Dry eyes/dry mouth</td>
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<td>0.5</td>
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<td>CNS Lupus</td>
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<td>45.0</td>
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<td>Autoimmune hypothyroidism</td>
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<td>11.7</td>
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<tr>
<td>Pulmonary HTN</td>
<td>24</td>
<td>40.0</td>
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Table 2: Immunological profile

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. of Cases (%)</th>
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<tbody>
<tr>
<td>ANA profile (N = 60)</td>
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</tr>
<tr>
<td>Homogenous</td>
<td>20</td>
</tr>
<tr>
<td>Nucleolar</td>
<td>02</td>
</tr>
<tr>
<td>Speckled</td>
<td>34</td>
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<tr>
<td>Cytoplasmic</td>
<td>04</td>
</tr>
<tr>
<td>ANA titre (1:100 and above)</td>
<td>53</td>
</tr>
<tr>
<td>dsDNA positivty rate</td>
<td>26</td>
</tr>
<tr>
<td>Low C3/C4</td>
<td>18</td>
</tr>
<tr>
<td>Anti TPO positivity</td>
<td>7</td>
</tr>
<tr>
<td>Direct Coombs test</td>
<td>25</td>
</tr>
<tr>
<td>Ro / La positivity rate</td>
<td>3</td>
</tr>
<tr>
<td>U1RNP</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 3: Secondary outcome: Association with common autoimmune diseases

<table>
<thead>
<tr>
<th>Autoimmune disease</th>
<th>Number (n=60)</th>
<th>Percentage (%)</th>
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<tr>
<td>Hypothyroidism</td>
<td>7</td>
<td>11.6</td>
</tr>
<tr>
<td>Sjogren’s syndrome</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>APLA</td>
<td>15</td>
<td>25</td>
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<tr>
<td>Overlap syndrome (SLE with myositis)</td>
<td>2</td>
<td>3.3</td>
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Table 4: Secondary outcome

<table>
<thead>
<tr>
<th>Number</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>Death</td>
<td>5</td>
</tr>
<tr>
<td>Relapse</td>
<td>5</td>
</tr>
<tr>
<td>Remission</td>
<td>55</td>
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</tbody>
</table>

Results

Clinical profile (Table1)

The mean age in our study population was 25 years (SD 9.92), 24 patients (40%) were between 21-30 years of age. 35 patients (58.3%) had a mean duration of SLE less than 5 years. 58 out of 60 patients (96.7%) were female. Arthralgia was the most common manifestation noted in 53 patients (88.3%). CNS lupus was noted in 27 patients (45%). Serositis was seen in 11 patients (19.3%). Seizures were the most common manifestation seen in 10 patients (16.7%). Renal involvement and pulmonary hypertension was noted in 13 patients and 24 patients (21.7 % and 40 % respectively). Autoimmune hemolytic anemia was the most common immune disorder noted in 25 patients (41.7%).

9 patients underwent kidney biopsy out of which 5 (8.3%) had stage IV glomerulonephritis, 2 had class III and 2 had class V. 4 patients had denied biopsy and were treated like class IV.

The mean SLEDAI (Systemic lupus erythematosus disease activity index) dropped from 11.85(+/-.67) at baseline to 3.65(+/-.4.76) at 36 months of treatment. (p<0.001) (Figure 1). A sharp drop was noted 6 months following initiation of treatment; which persisted throughout 3 years of follow up.

Immunological profile (Table 2)

The immunofluorescence pattern of ANA was analysed in all patients. Speckled was the most common pattern noted in 34 patients (56.7 %). dsDNA was positive in 26 patients (46.3%).
Table 5: Comparison with other Indian studies

<table>
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<td>4</td>
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</tr>
</tbody>
</table>

Among the autoimmune associations noted in secondary outcome (Table 3), association with antiphospholipid antibody syndrome was most common noted in 15 patients (25%).

Patient outcome (Table 4)

There were 5 deaths; of which 4 (6.6%) were SLE related. 1 death was due to tuberculous meningitis with military TB. Relapse was noted in these 4 patients who succumbed to SLE Flare. 55 patients (88%) remained in remission.

Discussion

The clinical and immunological profile of 60 Indian patients in our study is as shown in Tables 1 and 2. Arthralgia was the most common manifestation in our study (88.3%) which is similar to the observation in the paper by Madhavan et al14 (81.4%), Binoy et al17 (89.3%), Renu Sehgal et al18 (86.7%). Cutaneous manifestations were the next most common presentation in our study (85%) which is similar to the study by Talukdar et al (87.59%). Cardiovascular, renal, pulmonary, hematologic and CNS lupus are the major systemic manifestations noted in our study which is comparable to the findings of other Indian studies. Serositis was found in our study in 19.3% (11 patients), which was found in 32 % percent patients in the study by Santhanam et al.3

Neuropsychiatric lupus was the major systemic involvement in our study (45%) which is similar to the findings of Santhanam et al4 (45%). Seizure was the most common CNS manifestation, others being headache, psychosis, altered sensorium and peripheral neuropathy. This is consistent with the findings of the Iranian study by Haghighi et al.5 It is necessary to be aware of various neuropsychiatric manifestations in order to have a high index of suspicion of SLE. Autoimmune haemolytic anaemia was the next most common manifestation (41.7%) which is lower than that found in the study by Talukdar et al6 (61.24%).

We noted pulmonary hypertension (PH) on 2 D Echo in 24 (40 % percent) patients; of which 17 patients (i.e. 70 %) had mild PH. This is a new finding in our study unlike previous studies. This could be because we performed 2D Echo as a routine test at the end of 3 years. Comparison of our data with other Indian studies is

A recent meta-analysis of six studies encompassing 323 lupus patients with PAH demonstrated that the pooled 1-, 3-, and 5-year survival were 88%, 81% and 68 % respectively.11 Hence, prompt recognition and treatment is necessary. Our patients showed good response to cyclophosphamide in controlling pulmonary hypertension.

All our patients were ANA positive which is similar to the findings of Santhanam et al.4 Speckled pattern was the most common pattern in our study as compared to homogenous pattern in the study by Kosaraju et al.19 43.3% of our patients were dsDNA positive which is lower than all other Indian series. 30 % of our patients had low C3, C4 which is lower than that found by Santhanam et al2 (72%). Ro/La and U1RNP positivity rate was 5% and 3.3% respectively in our study which is lower than that found by Santhanam et al (47% and 42% respectively). This could be because of our smaller sample size and all the patients were not having active disease when the complements were checked. Anti-phospholipid antibody syndrome, autoimmune hypothyroidism and overlap syndrome were other autoimmune associations noted in our study found in 25% and 11.6% and 2 % respectively. This association with SLE has not been discussed in previous studies. Interestingly, renal involvement (21.7%) was lower than other Indian studies. This could possibly be because many of our patients were diagnosed early in the course of the disease and promptly started on treatment.

dsDNA is known to correlate with renal involvement.13 21 % patients in our study had renal involvement; while 43 % patients were ds DNA positive. The discrepancy between these two results can be explained by the fact that those with dsDNA positivity can have renal involvement in future and should be closely followed up.

The significant decline of SLEDAI within 3 months of treatment suggested that our patients responded well to treatment. IV Methylprednisolone pulse for 3 -5 days and /or IV Cyclophosphamide pulse was given for CNS and Renal lupus followed by tapering oral steroids and Azathioprine/ Mycophenolate mofetil for maintenance therapy. These patients had no relapse at the end of 3 years. Comparison of our data with other Indian studies is
As shown in Table 5.

Limitations

Our study is not without limitations. First of all, our sample size was small since it was a single centre study. Secondly, this is a retrospective observational study. A prospective observational study would have helped to follow up patients over long-term for development of complications. Other antibodies such as anti Smith, anti nuclease which are specific to SLE and their correlation with organ specific complications were not studied. Though we wanted to evaluate association with polymyositis in secondary outcome, our patients refused muscle biopsy. Also, since SLE itself can cause myositis, the association noted in the study could be a confounder. Lastly, we used a screening test i.e. echocardiogram to diagnose PH amongst our patients. Definitive test i.e. right heart catheterisation was not done to confirm the PH.

Data from our study can be added to meta-analysis of studies addressing clinical and immunological profile of SLE patients. This would help us understand regional differences and similarities among patients of SLE across the globe.

Conclusion

SLE commonly presents among young females in the second decade of life. CNS lupus is the most common systemic complication noted in our study. Mild pulmonary arterial hypertension is a common finding among these patients to be watched for. Autoimmune hypothyroidism, autoimmune haemolytic anaemia and antiphospholipid antibody syndrome are other common autoimmune associations.

References

5. Talukdar. The clinical and immunological profiles of systemic lupus erythematosus patients from Assam, North-East India [Internet]. [cited 2021 Mar 7]. Available from: https://www.indianrheumatol.org/article.asp?issn=0973-3698;year=2002;volume=15;issue=5;spage=181;epage=186;aulast=Talukdar

Effect of Supplementation of Vitamin C and Thiamine on the Outcome in Sepsis: South East Asian Region

Gayathri Ranie AP1, Mradul Kumar Daga2, Govind Mawari1, Bidhan Chandra Koner3, Vijay Kumar Singh3, Naresh Kumar4, Ishan Rohatgi1, Rashmi Mishra1

Abstract

Introduction: The global burden of sepsis is overwhelming and novel therapeutic agents is the need of the hour. The present study was designed to understand the role of Malondialdehyde as a marker of the oxidative stress in sepsis, as well as the effect of supplementation of Vitamin C and Thiamine in patients of sepsis.

Methods: 80 patients of sepsis were randomly divided into 4 groups of 20 each. Twenty age-sex matched healthy volunteers were chosen as controls. The first group received Vitamin C, the second group received Thiamine, the third group received both and the fourth group received neither. Vitamin C (2g 8 hourly) and Thiamine (200 mg 12 hourly) were given intravenously for five days. The outcome was recorded in terms of mortality in the various groups as well as by the improvement in SOFA.
scores (ΔSOFA). The serum levels of Vitamin C, Thiamine and Malondialdehyde were estimated.

Results: Among the 80 patients, 17 (21%) were in septic shock. The mortality rate was 10% overall, and 47% among patients of septic shock. No additional mortality benefit was observed in the groups supplemented with Vitamin C and Thiamine. However, the ΔSOFA score in patients who received both Vitamin C and Thiamine was significantly higher as compared to the other groups. The mean malondialdehyde level was higher in patients of sepsis (1.81±1.18 µmol/l) as compared with healthy controls (0.78 ± 0.36 µmol/l). The Vitamin C level and Thiamine level (estimated indirectly by TPP effect), at presentation were 5.14±4.19 ng/ml and 52.99±28.45 % in patients of sepsis, which was significantly lower than that in healthy controls, in whom the levels were 14.64±5.51 ng/ml and 27.55±13.67% respectively.

Conclusion: Vitamin C and Thiamine supplementation is a cost-effective approach with a good safety profile. Additional studies including a larger population is required to study the mortality benefits and reaffirm our findings.

Introduction

Sepsis is a common, complex and often fatal syndrome, representing a major public health problem. Estimates of the incidence of sepsis ranges from 66 to 300 per 100,000 population in the developed world. The incidence is increasing, driven by an ageing population with multiple comorbidities, increased use of immunosuppressive therapy and high-risk interventions. Mortality estimates for sepsis range from 27% to 36%.

Oxidative stress has been postulated as a mechanism of organ dysfunction in sepsis. Modulators of antioxidant/oxidant state could be used as a new class of drugs for the treatment of sepsis. Vitamin C is a potent antioxidant which efficiently detoxifies the various free radicals that are formed in the body. Recent studies have confirmed that as many as 30% of the critically ill patients present with significantly low plasmatic levels of vitamin C. Septic patients are particularly at risk, with an incidence rate of 40%. Deleterious sequelae from thiamine deficiency include lactic acidosis, hypotension, and death. Septic shock is a metabolically demanding state that possesses a clinical presentation very similar to thiamine deficiency. Several studies have shown metabolic support with intravenous thiamine to be associated with decrease mortality in critically ill patients with septic shock.

Supplementation of Vitamin C and Thiamine in patients with sepsis remains an attractive therapeutic target, considering the potential benefits, low costs and favourable safety profile. Hence the present study was planned to see the role of MDA as a marker of the oxidative stress and the effect of supplementation of Vitamin C and Thiamine in patients of sepsis.

Method

This study is a randomised controlled study conducted in the Lok Nayak Hospital, New Delhi, India, over a period of one year. 80 patients of sepsis, admitted in the medical wards of our hospital during this period were selected, as defined by the Sepsis 3 guidelines. We excluded patients with chronic kidney disease, chronic alcoholics and immunocompromised patients. The 80 patients were divided randomly into 4 groups of 20 each and were followed through till discharge or death. Apart from the standard treatment of sepsis, Group 1 received intravenous supplementation of VITAMIN C at a dose of 6 grams per day, as 2g, 3 times a day, for 5 days. Vitamin C was administered as an infusion over 30 to 60 minutes, mixed in a 100 mL solution of either dextrose 5% in water (D5W) or normal saline. Group 2 received intravenous supplementation of 200 milligrams of THIAMINE per day, 12 hourly, for 5 days. Group 3 received the combination of Vitamin C and Thiamine in the same doses and duration as mentioned. Group 4 received only the standard treatment of sepsis and no additional supplementation.

Blood samples were drawn on the day of admission from all 4 groups for routine investigations, to determine the SOFA score on Day 1. The samples for estimation of Vitamin C, Thiamine and Malondialdehyde were stored appropriately at – 80 degree Celsius. The serum samples for vitamin C estimation required addition of 10% Metaphosphoric acid, to prevent oxidation. 20 healthy age-sex matched volunteers were selected to act as controls for the comparison of these levels. Blood samples for the estimation of Vitamin C and Thiamine were collected on Day 6 following supplementation, from groups 1 and 2 respectively. Day 6 estimation of both Vitamin C and Thiamine was done for patients in group 3. Day 6 SOFA scores of all patients as well as the difference between Day 6 and Day 1 SOFA scores (ΔSOFA score) were calculated. The outcome was recorded in terms of mortality in the various groups as well as the clinical improvement observed in terms of improvement in SOFA scores. The outcomes of groups 1, 2 and 3 were compared with that of group 4 to study the effect of supplementation of Vitamin C and Thiamine.

The estimation of Vitamin C was done using commercially available ELISA kits, procured from SINCERE BIOTECH. Thiamine deficiency state was assessed from Erythrocyte Transketolase Activity and TPP Effect by modified Smeets, Mueller and De Wael method. MDA analysis was done by TBARS assay.

Results

The age of patients in our study ranged from 18 to 78 years with mean being 52.35 ± 13.73 years in the case group. In healthy controls, the mean age was 48.35 ± 11.19 years (Table 1). 52 were male (65%) and 28 were female (35%), in the case population. Among the healthy controls, 16 were males (80%) and 4 were females (20%). The Respiratory tract (47%) was the most common source of sepsis in our patients, followed by the Urinary

Table 1: Age distribution of cases and controls

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<thead>
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<th>Age</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
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<td>18 to 30 years</td>
<td>10 (12.5%)</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>31 to 50 years</td>
<td>19 (23.8%)</td>
<td>6 (30%)</td>
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<td>51 to 70 years</td>
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<td>71 to 90 years</td>
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</tr>
<tr>
<td>Total</td>
<td>80 (100%)</td>
<td>20 (100%)</td>
</tr>
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</table>
tract (36%). Of the 80 patients in our study, 17 patients overall were found to be in septic shock. Among the 80 patients, 58.75% of the patients had Diabetes Mellitus type II, 37.5% had Hypertension, 12.5% had underlying Coronary Artery Disease and 11.25% had Hypothyroidism as underlying systemic comorbidity.

**Malondialdehyde**

The MDA levels of patients with underlying comorbid conditions were compared with those who have none. 59 patients in our study had various underlying comorbid conditions while 21 patients had none. The MDA level was 1.96 ± 1.28 µmol/l in patients with comorbid conditions. In patients having no underlying comorbid illness, the MDA level was 1.36 ± 0.71 µmol/l. This difference is statistically significant, with a p value of 0.046.

When we compared the MDA levels of sepsis patients who had no underlying comorbidities (1.36 ± 0.71 µmol/l) with healthy controls (0.78 ± 0.36 µmol/l), the difference was statistically significant (p value =0.013). A positive correlation was established between MDA levels and SOFA scores on Day 1 and Day 6. The mean Malondialdehyde level was 1.63 ± 1.057 µmol/l in the patients who survived and 3.33 ± 1.22 µmol/l in the patients who succumbed to the disease. The significant difference observed indicates that Malondialdehyde levels correlate well with the severity of the disease.

**Vitamin C**

The normal range of Vitamin C according to the ELISA kit used in our study was 4.4 to 14.4 ng/ml. We observed that the baseline Vitamin C level was significantly lower in the patients of sepsis (5.1±4.19 ng/ml) than in healthy controls (14.6±5.51 ng/ml).

The baseline Vitamin C levels of the groups 1, 2, 3 and 4 were 5.16 ± 0.36, 3.15 ± 0.44, 6.51 ± 0.51 and 3.08 ± 0.39 ng/ml respectively. The baseline Vitamin C levels showed significant variation, p <0.002.

In groups 1 and 3, Vitamin C was supplemented for 5 days, and the Vitamin C level on Day 6 was estimated. The Day 6 Vitamin C level of groups 1 and 3 were 4.01±2.12 ng/ml and 8.11±11.5 ng/ml. There was no significant variation in the levels of Vitamin C post supplementation.

**TPP Index**

The TPP INDEX was assessed as a measure of Thiamine deficiency state. The TPP index of the patients was 52.99±28.45 % in cases of sepsis while in controls, the TPP index was 27.55±13.67 %. The p value was found to be <0.001.

As TPP index denotes the increase in transketolase activity with thiamine stimulation, a greater value denotes deficiency state.

The baseline TPP effect of the groups 1, 2, 3 and 4 were 47.10±30.58%, 64.05±27.02%, 54.95±24.82% and 45.85 ± 29.61% the baseline values showed no significant variation. In groups 2 and 3, Thiamine was supplemented, and the day 6 TPP index of groups 2 and 3 showed significant variation, p <0.002.
were 46.40±22.47 % and 45.40±17.40 %. Comparing the TPP effect on Day 1 and Day 6, there is no significant variation in the TPP effect post supplementation of Thiamine.

**Mortality**

Of the 80 patients, 8 patients expired and 72 patients survived. Among the 80 patients, 17 patients were in septic shock and all the 8 patients who expired were in septic shock. In our study, the mortality rate among patients of septic shock was 47 %. The overall mortality rate was 10 %.

Comparing the outcome of groups 1, 2 and 3 with group 4, there is 10 % mortality in groups 1 and 3 while it is 15 % and 5 % in groups 2 and 4 respectively (Figure 2). The p values on comparison of groups 1, 2 and 3 with 4 are 0.548, 0.292 and 0.548 respectively, denoting that there is no significant difference in the mortality among the groups.

The distribution of patients with septic shock among the groups gives a better picture of the mortality rate between the groups. In group 1, there were 7 patients of septic shock, of whom, 2 patients survived. There is a 28.5 % mortality in group 1. In group 2, out of the 5 patients in septic shock, 3 patients expired, amounting to a mortality rate of 60 %. Similarly, in group 3, it is 50% whereas in group 4 there was one patient of septic shock who expired, with a mortality of 100 % (Figure 3).

The MDA, Vitamin C level and TPP index was compared between the survivors and non survivors who were in septic shock. There was no statistically significant difference in the variables between the two subgroups.

**Sofa Score**

The mean SOFA score at presentation of the patients in our study was 7.37 with a standard deviation of 2.20. There was no statistically significant difference in the SOFA score at presentation among patients of the four groups (p=0.056).

The mean SOFA score of patients of sepsis at presentation was 7.04 ± 2.05 in the survivor group and 10.38 ± 1.41 in the non- survivor group. The difference in the score is statistically significant with a p value of <0.001. Similarly, the Day 6 SOFA score (2.26 ± 1.85 in the survivor group and 8.12 ± 2.10 in the non- survivor group) showed statistically significant difference (p value <0.001).

The difference in SOFA scores on Day 1 and Day 6, ΔSOFA was calculated. The ΔSOFA values of patients in groups 1, 2, 3 and 4 were 4.70±2.47, 4.25 ± 1.68, 5.45±1.54, 3.85±1.79 respectively. Comparing the ΔSOFA of groups 1, 2 and 3 each against that of group 4, it was observed that there was a statistically significant difference between the ΔSOFA value of group 3 (5.45±1.54) and group 4 (3.85±1.79), with p value <0.046.

**Discussion**

In our study, we explored the role of oxidative stress in sepsis, by the quantitative analysis of Malondialdehyde as the marker, as well as attempted to establish the importance of Vitamin C and Thiamine in the treatment of sepsis. The malondialdehyde levels was significantly higher in the patients of sepsis as compared to the control group. Further, the MDA level in patients who expired was significantly higher than that of the patients who survived. A positive correlation was observed between serum MDA level and SOFA scores on Days 1 and 6. These results are consistent with the study conducted by Lorente and colleagues, a multi-centre study conducted in six Spanish Intensive Care Units, in which the serum level of MDA was found to be higher in severe septic patients (2.06–4.86 µmol/l) than in healthy controls (0.78–1.51 µmol/l). Also, a significant positive correlation was established between MDA level and SOFA scores in this study.

Several studies have shown increase in plasma MDA in conditions like Diabetes mellitus type II, hypothyroidism, Coronary Artery Disease etc. Among the 80 patients of sepsis in our study, we observed that, the MDA level in patients who had underlying comorbid conditions was significantly higher in comparison to those who had no underlying comorbidities. However, when we compared the MDA levels of patients who had no underlying comorbidities with healthy controls, the difference was statistically significant (p value =0.013). The serum MDA level is thus increased in sepsis, even in the absence of comorbid conditions.

Although the TBARS assay employed in our study has several limitations (non-specificity of TBA reactivity on MDA, low stability of MDA in biological samples etc.), the high sensitivity, rapidity, ease of use and cost of this assay justified the use of this method. Vitamin C and thiamine supplementation in sepsis

Critically ill patients have either low or undetectable vitamin C levels (normal serum levels, 40-60 mM). To achieve normal serum vitamin C levels in critically ill patients, a daily dose of more than 3 g is required. In the study by Paul E. Marik and colleagues, Vitamin C was given intravenously at a dose of 1.5 g every 6 h for 4 days or until ICU discharge and thiamine was given intravenously 200 mg every 12 h for 4 days or until ICU discharge.

**Vitamin C level in sepsis**

Vitamin C estimation was done using ELISA kits in the present study. The normal range of Vitamin C according to the ELISA kit used was 4.4 to 14.4 ng/ml, the detection range being 0.615 to 40 ng/ml. We observed that the Vitamin C level, at presentation, in patients of sepsis was found to be significantly less compared to the levels in healthy controls, demonstrating deficiency of Vitamin C in patients of sepsis. Similar results have been obtained in a study done by Paul E. Marik and colleagues, where baseline vitamin C levels in patients of sepsis was found to be 14.1 ± 11.8 mM (normal, 40-60 mM), with no patient having a normal level. The prevalence of Vitamin C deficiency is about 13 % in the U.S population (serum concentrations < 11.4 µmol/l) and 16 to 26% in the United Kingdom. In a study conducted by Ravinder et al, the prevalence of Vitamin C deficiency in India ranged from 46 % (South India) to 74 % (North India). Haptoglobin polymorphisms might also explain in part the lower levels of vitamin C reported in South Asians. Also, Vitamin C levels were lower in men, in tobacco users, those with indices of poor nutrition, lower socioeconomic status and had an inverse association with age. Although we recruited age and sex matched control population for comparison of Vitamin C levels, the vast majority of the patients as well as controls belonged to the fifth to seventh decade of life. The prevalence of Vitamin C deficiency in this age
group ranged from 68.7% to 79% in the study conducted by Ravinder et al.\textsuperscript{14} The socio-economic status of our patients was not assessed objectively using any available scales, yet it could be surmised that a large proportion of the patients belonged to a lower socio-economic status. The ubiquitous usage of tobacco products also warrants mention. Vitamin C is extremely sensitive to oxidation, hence all necessary precautions were taken in collection, preservation and storage of samples to minimize their impact on Vitamin C levels.\textsuperscript{3} Vitamin C levels are considered adequate at a level > 28 \(\mu\)mol/l (>4 mg/dl), sub-optimal in the range of 11–28 \(\mu\)mol/l (1.5 to 4 mg/dl) and deficient when the levels are < 11 \(\mu\)mol/l (<1.5 mg/dl).\textsuperscript{15} As the normal range of Vitamin C detected by our kit varied from the reference range of general population, the absolute level of Vitamin C could not be determined in our study. Low dietary Vitamin C intake during the period of illness also contributes to the deficiency of Vitamin C in critical illnesses. Despite the various factors which influenced the Vitamin C levels, we observed that the Vitamin C levels of the healthy controls fell in the normal range and the values of the patients of sepsis was significantly lower when compared with them.

### TPP effect

The TPP effect of the patients compared with the healthy controls ascertained that there exists a state of Thiamine deficiency in patients of sepsis. The reference range for TPP effect in healthy individuals varies slightly among the various studies, depending on the method. The mean TPP effect determined by ETKA in the various studies are 0 to 53% (Markkanen et al), 6 to 22% (Baker et al) and 2 to 20% (Brin et al).\textsuperscript{6} In a study conducted by Camilo M.E, the reference range for the TPP index in healthy individuals was found to range from 3.5% to 40%.\textsuperscript{16}

In a two-centre, randomized, double-blind trial comparing thiamine supplementation versus placebo in adult patients (n=88) with septic shock, conducted by Donnino et al, 35% of the patients were found to be thiamine deficient at baseline. 10% had absolute Thiamine deficiency upon presentation; and an additional 20% of patients of sepsis developed Thiamine deficiency within 72 hours of presentation.\textsuperscript{17} In another study, Costa et al showed that the incidence of thiamine deficiency was 71.3% in septic shock patients.\textsuperscript{18} Though the methods used in these studies for Thiamine estimation differed from our study, the results were comparable to our study, reinforcing the finding of Thiamine deficiency in sepsis.

It was observed that there is no significant difference in the TPP index between survivors and non survivors in our study. In an Australian cohort study of 129 patients, Corcoran et al showed that thiamine admission levels in patients who had not received thiamine supplementation prior to admission to the ICU did not differ between those patients who died (264nmol/l) and those who survived (268nmol/l) (normal range: 190–400 nmol/l), the \(p\) value was 0.891.\textsuperscript{19} The erythrocyte transketolase activity (ETKA) assay is a traditional and most widely used method which indirectly assesses thiamine status. Apart from thiamine deficiency, other factors which influence erythrocyte transketolase activity are, advancing age, poor inter-assay precision, difficulty in standardization, defects in the transketolase apoenzyme.\textsuperscript{5}

### Outcome

In our study, the primary outcome was recorded in terms of mortality in the various groups as well as the clinical improvement observed in terms of improvement in SOFA scores. While recording the outcome, group 4, in which patients received no additional supplementation of Vitamin C or Thiamine, apart from the standard treatment of sepsis, was taken as the control group. The outcomes of groups 1, 2 and 3 were compared with that of group 4 to study the effect of supplementation of Vitamin C and Thiamine. **Mortality** Out of the 80 patients in our study, 8 patients expired. The overall mortality rate in our study was 10%.

Among the 80 patients, 17 patients were in septic shock and all the 8 patients who expired were in septic shock. In our study, the mortality rate among patients of septic shock was 47%. This is comparable with mortality rates in previous studies; in the study conducted by Chatterjee and colleagues, the mortality rate of severe sepsis patients was 56%.\textsuperscript{20} In the INDICAP study, the mortality rate in patients of severe sepsis was 34%.\textsuperscript{21} Comparing the mortality in groups 1, 2 and 3 (where patients received Vitamin C and Thiamine supplementation alone or in combination) with group 4 (no supplementation of Vitamin C and thiamine), there was no significant difference in mortality among the 4 groups.

However, In a retrospective before-after clinical study conducted by Paul E. Marik, where Vitamin C and Thiamine supplementation was given in 47 patients of severe sepsis and septic shock, it was observed that early treatment with vitamin C, thiamine, and hydrocortisone saw a reduction of mortality in patients with severe sepsis and septic shock. There was a significant reduction in mortality in the treatment group (8.5%) as compared to the control group (40.4%) \(p < 0.001\).\textsuperscript{15} Fowler et al observed that supplementation of Vitamin C caused a reduction in the incidence of progressive organ failure in sepsis, though the mortality benefits were not recorded.\textsuperscript{22} Zabet and colleagues demonstrated a reduction of norepinephrine requirement and decrease in mortality in patients of sepsis treated with vitamin C.\textsuperscript{22}

Donnino et al found that administration of thiamine did not improve lactate levels, mortality or ICU length of stay in patients with septic shock.\textsuperscript{17} The difference in outcomes between our study and pre-existing studies could be explained by the smaller sample size in each group (n=20), a smaller number of patients in septic shock (n=17) and the unequal distribution of patients in septic shock among the four groups. **SOFA score** The mean SOFA score of the patients in our study was 7.37 ± 2.2 at presentation. The SOFA score of the non survivors was higher than that of the survivors. The \(\Delta\)SOFA score of patients who received the combination of Vitamin C and Thiamine was significantly higher as compared to the group of patients who received neither of them. Also, the SOFA score in patients who received Vitamin C / Thiamine supplementation showed an improving trend and there was no new onset organ dysfunction during the course of stay, in the patients who
in the sequential organ failure assessment score was 4.7 in the intervention group and 4.1 in the placebo group over 72 hours. As opposed to our study, in patients with septic shock, the combination of ascorbic acid, corticosteroids, and thiamine, compared with placebo, did not result in a statistically significant reduction in SOFA scores during the first 72 hours after enrollment.23

Conclusion

The findings in our study emphasize the role of oxidative stress in the pathophysiology of sepsis, reflected by an increase in MDA levels. The deficiency of Vitamin C and Thiamine in patients of sepsis could be due to their role as an antioxidant per se, as well as the various risk factors associated with sepsis. Our study has several limitations, including a smaller sample size and a smaller proportion of patients having septic shock. Though the antioxidant role of Vitamin C is well established by in vitro studies, the practical benefits in vivo are yet to be explored. Larger randomized control trials are necessary to establish the role of Vitamin C and Thiamine supplementation in sepsis.

Declarations

- Ethics approval: This study was conducted only after approval from the institutional ethical committee Maulana Azad Medical College & with the aid of informed consent from all the patient participants.
- Funding: No organised funding source was used in study conduction.
- Conflict of interests: The authors declare that they have no conflict of interest.

References


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Dr. Mangesh Tiwaskar
Hon. General Secretary
Clinical Outcome of Idiopathic Membranous Nephropathy-A Single Centre Study

Muruganantham B1*, Gopalakrishnan N2, Dinesh Kumar T3, Dhanapriya J3, Sakthirajan R3, Malathy N3

Abstract

Introduction: Idiopathic Membranous nephropathy (IMN) is one of the most common causes of adult onset nephrotic syndrome worldwide. About 50% will slowly progress to renal failure if untreated.

Methods: We did a retrospective study in patients with Idiopathic membranous nephropathy who were on follow-up between 2016-2018 at Madras medical college, Chennai. Clinical records, investigations, treatment and treatment response were analyzed. Risk stratification was done according to urine protein estimation, Modified Ponticelli regimen was administered in patients with high risk of renal failure and those with complications. They were followed up 6-12 months.

Results: Among 61 patients with IMN, 37 were treated with Modified Ponticelli regimen after 6months of supportive treatment. Spontaneous remission was 14%, after mean follow up of 3.14 yrs total remission was 64.86 % (CR-43.24%; PR-21.62%) and 35.14% had no remission. Three patients progressed to CKD. Tacrolimus was initiated in non responders to IST. Analysis between IST responders and non responders shows those who presented with lesser proteinuria had statistically better outcome.

Conclusion: This retrospective study of IMN showed a reasonably better outcome. Seventeen per cent of patients had spontaneous remission and 64.86% achieved remission with Modified Ponticelli regimen.

Introduction

Idiopathic Membranous nephropathy (IMN) is one of the most common causes of adult onset nephrotic syndrome worldwide. Membranous nephropathy (MN) is characterised by uniform thickening of glomerular basement membrane resulting from sub-epithelial immune complex deposits and granular staining for IgG and complement C3 along the glomerular capillary wall. Based on the recent detection, in plasma, of antibody to a podocyte antigen, M-type phospholipase A2 receptor (M-PLA2R). IMN is considered as a kidney-specific autoimmune disease. In about 60%-70% of MN is idiopathic. Infections like hepatitis C and B virus, autoimmune diseases, drugs and malignant tumours are important secondary causes. Outcome of IMN is varied; about 30%-50% will go for spontaneous remission, whereas about 50% will slowly progress to renal failure if untreated. Supportive therapy consists of angiotensin converting enzyme inhibitors (ACE inhibitors) or angiotensin II receptor blockers (ARB) combined with low salt diet and statins. Those not responding to supportive therapy will be given immunosuppressive therapy including alkylating agents with steroids or calcineurin inhibitors. In this retrospective study, the clinical course and outcome of IMN were studied in a tertiary care centre in South India.

Material and Methods

Subjects

All patients with idiopathic membranous nephropathy who were on follow-up between 2016-2018 at Madras medical college, Chennai were studied.
in maximally tolerated doses. For treatment purpose patients were classified according to quantum of proteinuria (<4 G/day, 4-8 G/day, >8 G/day) and patients having < 4 G and 4-8 G proteinuria/day received conservative therapy for 6 months. Immunosuppressive therapy (Modified Ponticelli regimen) was initiated for those who did not respond to conservative therapy even at 6 months, those with proteinuria >8 G/day, life threatening complications and those at high risk of renal failure. Modified Ponticelli regimen (IST) is a six-month course consisting of intravenous methylPrednisolone 1 gm/day for 3 consecutive days followed by oral prednisone 0.5 mg/kg/day for the remaining 27 days during 1st, 3rd and 5th months and oral Cyclophosphamide 2 mg/kg/day during 2nd, 4th and 6th months. Calcineurin inhibitor (CNIs) Tacrolimus at 0.05-0.07mg/kg/day were given in patients who did not achieve either complete or partial remission at 12 months after completion of modified Ponticelli regimen. None of our patients received rituximab.

Follow Up

In each visit, blood pressure, body weight and physical examination were performed. Serum creatinine, albumin, urine spot protein-creatinine ratio (PCR) and complete blood counts were analysed. Complete remission was defined as uPCR <0.3g/dl confirmed by two values at least 1 week apart, accompanied by normal serum albumin and normal serum creatinine. Partial remission was defined as uPCR <3.5g/dl and 50% or greater reduction from peak values confirmed at least 1 week apart with normal serum albumin and stable serum creatinine.

Table 1: Baseline characteristics of study population (mean±standard deviation or median)

- Total number of patients: 61
- Male/Female ratio: 33(55%)/28(45%)
- Mean age: 44±13.8 yrs
- Median S.creatinine(mg/dl): 1
- Mean e GFR (CKD-EPI,ml/min): 71.19±27.1
- Mean u PCR(mg/mg): 5.19±2.5
- Mean S.albumin(gm/dl): 2.7±0.5
- Mean BP systolic(mmHg): 121±18
- Mean BP diastolic(mmHg): 85±11
- ACEi/ARB treatment: 61(100%)
- Statin treatment: 61(100%)
- Mean follow up period(months): 3.41 yrs

Table 2: Clinical presentations of study population (n=61)

- Nephrotic syndrome: 31(51%)
- Sub nephrotic proteinuria: 15(25%)
- Renal failure with proteinuria: 14(22%)
- RPRF: 1(2%)

Table 3: Baseline characteristics of three ‘risk stratification’ groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>&lt; 4 gms/day (low risk)</th>
<th>4-8 gms/day (moderate risk)</th>
<th>&gt;8 gms/day (high risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no of patients (n=61)</td>
<td>20</td>
<td>32</td>
<td>9</td>
</tr>
<tr>
<td>Median S. creatinine (mg/dl)</td>
<td>1.05</td>
<td>1.07</td>
<td>1</td>
</tr>
<tr>
<td>Mean e GFR (CKD-EPI,ml/min)</td>
<td>73.65±24.2</td>
<td>70.12±22.03</td>
<td>70.77±47.82</td>
</tr>
<tr>
<td>Mean S.albumin (gm/dl)</td>
<td>2.9±0.47</td>
<td>2.6±0.46</td>
<td>2.3±0.35</td>
</tr>
<tr>
<td>Mean u PCR (mg/mg)</td>
<td>2.79±0.96</td>
<td>5.61±1.03</td>
<td>9.8±2.3</td>
</tr>
</tbody>
</table>

Table 4: Clinical Response to immunosupression (IST)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Complete remission</th>
<th>Partial remission</th>
<th>Total remission</th>
<th>No response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Ponticelli regimen (n=37)</td>
<td>16(43.24%)</td>
<td>8(21.62%)</td>
<td>24(64.86%)</td>
<td>13(35.14%)</td>
</tr>
<tr>
<td>Tacrolimus (n=11)</td>
<td>2(5.40%)</td>
<td>2(5.40%)</td>
<td>4(10.80%)</td>
<td>7(18.91%)</td>
</tr>
</tbody>
</table>

Fig. 1: Flow chart showing clinical response to treatment

Biopsy proven
MN at our hospital (n=94)

Conservative
management
(n=52)

Spontaneous
remission
(n=9)

High risk
group (n=9)

Modified Ponticelli regimen administered (n=37)

1. On conservative treatment (n=8)
   2. CKD (n=1)

1. Lost follow up (n=4)
   2. CKD (n=2)

1. Complete remission-16 (43.24%)
   2. Partial remission-8(21.62%)
   3. Total remission (CR+PR)-24(64.86%)

1. Complete remission-2(5.40 %)
   2. Partial remission-2(5.40%)
   3. Total remission (CR+PR)-4(10.80%)

No remission-
(n=7)

Tacrolimus initiated
(n=11)

1. No remission 13(35.14%)

Results (Figure 1)

A total of 94 patients with membranous nephropathy were treated at our centre during 2016-2018. Sixty one (64.90%) patients had idiopathic
primary membranous nephropathy; of them, 31 (51%) had nephrotic syndrome, 15 (25%) had sub-nephrotic proteinuria, 14 (23%) had renal failure with proteinuria and one patient (2%) had rapidly progressive renal failure (RPRF) as initial presentation [Table 2]. Forty three (70.49%) patients tested positive for M-PLA2R antibody. Sixty one patients with IMN were classified according to quantum of proteinuria <4 G/day (n=20), 4-8 G/day (n=32) and >8 G/day (n=9). The baseline characteristics are shown in Table 1.

Among the study population, 9 (14.75%) had hypertension, 7 (11.4%) had diabetes mellitus, and 5 (8.19%) had hypothyroidism. Basic characteristics differences between three groups of patients at the time of initial presentation are given in Table 3. Supportive treatment was initiated in low risk group (proteinuria <4 gm/day and 4-8 gm/day) patients and observed for 6 months. Those in high risk group early initiation of immunosuppression (IST) was done. The mean follow up was 3.41 yrs.

Response to Treatment (Figure 1)

Among the 61 patients, 52 were on supportive treatment and 9 patients were started on modified Ponticelli regimen as they belonged to high risk group. After 6 months of supportive treatment 9/52 patients (17%) attained spontaneous remission and among the remaining 43/52patients, eight were on conservative treatment, one had chronic kidney disease (CKD). Four patients in high risk group were lost to follow up, and two developed chronic kidney disease (CKD). A total of 37 patients were initiated on modified Ponticelli regimen and followed up. After 6-12 months of follow-up complete remission was observed in 43.24% (16/37), partial remission in 21.62% (8/37) (Table 4). There can be ‘time lag’ between remission of the disease and disappearance of proteinuria in some patients. Hence, remission status was assessed up to 6 months after completion of IST.

Among 13/37 (35.14%) who had persistent proteinuria, 11/13(84.61%) were initiated on Tacrolimus (CNIs). After 12 months of treatment, 2 each had complete remission and partial remission (Table 4).

Complications

Leucopenia occurred in three patients, two patients developed sepsis due to pulmonary infection, two patients developed type 2 diabetes mellitus, three developed chronic kidney disease (CKD) and no mortality occurred. Thrombotic complications were present at the time of presentation in five patients (4-DVT, 1- IVC thrombosis) 8.19%. Three patients had cellulitis leg.

Discussion

Idiopathic membranous nephropathy is considered as a kidney specific autoimmune disease on the basis of M-PLA2R antibody detection by indirect immunofluorescence reported by Becks et al in 2009. A study previously published by our centre has shown the prevalence of M-PLA2R antibody in IMN to be 70%, which is similar to Western data. In IMN risk of ESRD is 14% at 5 year, 35% at 10 years and 41% at 15 years. KDIGO recommends the Modified Ponticelli regimen for patients at risk of renal failure or those who present with complications. The original Ponticelli regimen by Ponticelli et al, first published in 1995, consisted of methylprednisolone and chlorambucil for 6 months, alternating with each other every other month. Later chlorambucil was replaced by cyclophosphamide due to drug toxicity and risk of neoplasia. In 1998 Claudio Ponticelli et al compared two regimens based on 6 months of treatment (methylprednisolone and chlorambucil/ methylprednisolone and cyclophosphamide) and remission rates were similar but a smaller number of patients stopped treatment because of side effects in Cyclophosphamide group compared to chlorambucil. This study was conducted in European population with a follow up of 42 months. 43 patients were included, with mean proteinuria 2.11±2.89 g/day, and 93% achieved total remission.

Ilan Rozenberg et al in a retrospective study of IMN in Caucasians (n=37), reported a total remission of 81% with modified ponticelli regimen. In India a prospective randomized controlled study by Jha et al in 2007 compared modified ponticelli regimen with supportive treatments in adult IMN. A total of 93 patients were included, with 47 patients receiving immunosuppression and 46 in the control group, with a follow-up of 10 years. 34 patients (73%) achieved remission and treated patients showed significant reduction in the risk of renal failure. Another Indian study by Raja Ramachandran et al in 2017 compared outcomes of modified ponticelli regimen and Tacrolimus with corticosteroids in IMN. Seventy patients were enrolled in this RCT, and followed up for 24 months after treatment. At 18 and 24 months 60% and 80% of cases were in remission in the Tacrolimus and modified ponticelli group respectively. At 2 yrs relapse rates were higher in Tacrolimus group compared to modified ponticelli regimen.

In our study, total remission was achieved in 24 (64.86%) patients, and 3 (4.91%) patients progressed to CKD over a mean follow up of 3.41 yrs. Among the patients males were predominant, and the mean age among IST responders was 45.41±10.81. Tacrolimus was initiated in IST nonresponders at 0.05-0.07mg/kg/day and C0 level was monitored and total remission 10.80% achieved. However, in our study, Tacrolimus was not offered to treatment naive individuals, but only given to those who failed to achieve remission to IST. Hence we cannot compare this figure of 10.8% total remissions to other studies. Analysis between IST responders and non responders shows those who presented with lesser proteinuria had statistically better outcome (Table 5).
study were similar to other published studies. In our study, patients in ‘low risk’ and ‘moderate risk’ groups had statistically better outcome in terms of reduction of proteinuria, improvement in renal function and achievement of sustained remission. M-PLA2R antibody monitoring during follow up was not done due to financial issues. Hence, correlation between immunological and clinical remission could not be done. This is the largest south Indian cohort of IMN patients. Strength of our study is significant duration of follow-up (mean of 3.41 years). Limiting factors of the study are retrospective design and lack of serial monitoring of M-PLA2R antibody titres during follow up.

Conclusion
This retrospective study of IMN showed a reasonably better outcome. Seventeen per cent of patients had spontaneous remission and 64.86% achieved remission with modified Ponticelli regimen. Modified Ponticelli regimen was well tolerated.

References
10. KDIGO Guidelines 2012 chapter 7; Treatment of idiopathic membranous nephropathy.

Incidence and Correlates of Early Cognitive Impairment following Intracerebral Haemorrhage

Ravi Shukla1*, Lt. Col. Shaman Gill2, Col. Pawan Dhull3, Anjali Tripathi3

Abstract
Objectives: To determine the incidence of early cognitive impairment following intracerebral haemorrhage.
Methods: A total of 30 adult patients (>18 years) with intracerebral hemorrhage were enrolled in the study. Demographic profile, clinical and radiological profile of the patients was noted. Cognitive status at discharge was assessed using Montreal Cognitive Assessment (MoCA). Data was analyzed using Chi-square and independent samples 't'-test.
Results: Mean age of patients was 63.53±12.11 years. Majority of patients were males (56.7%). At discharge, all the patients had cognitive impairment - majority (76.7%) had moderate cognitive impairment followed by severe impairment (16.7%) and mild impairment (6.7%) respectively. Among different clinicodemographic and radiological factors, only history of tobacco use showed a significant association with severe cognitive impairment.
Conclusions: At discharge mild to moderate cognitive impairment is quite frequent among intracerebral hemorrhage patients irrespective of the demographic, clinical and radiological profile. Further studies on a larger sample size are recommended.

Introduction
Intracerebral hemorrhage (ICH) is the second most common subtype of stroke after ischemic stroke and accounts for approximately 10% to 20% of all strokes. It has an overall incidence of 24.6 per 100,000 person-years and is associated with a high case fatality. With increasing life expectancy, the burden of stroke is likely to increase worldwide. Middle and low income countries have particularly witnessed this phenomena more lucidly.

The classic presentation of ICH is sudden onset of a focal neurological deficit that progresses over minutes to hours with accompanying headache, nausea, vomiting, decreased consciousness, and elevated blood pressure. Rarely patients present with symptoms upon awakening from sleep. Neurologic deficits are related to the site of parenchymal hemorrhage. Thus, ataxia is the initial deficit noted...
in cerebellar hemorrhage, whereas weakness may be the initial symptom with a basal ganglia hemorrhage. Early progression of neurological deficits and decreased level of consciousness can be expected in 50% of patients with ICH. The progression of neurological deficits in many patients with an ICH is frequently due to ongoing bleeding and enlargement of the hematoma during the first few hours.\(^5\)

It must be noted that intracerebral hemorrhage is accompanied with vascular dysfunction too. Cerebral amyloid angiopathy (CAA) is primarily responsible for cognitive dysfunction\(^6,7\) and causes brain edema and/or secondary ischemia. Presence of subarachnoid hemorrhage and involvement of hippocampal and frontotemporal regions\(^8,9\) also lead to vascular cognitive impairment which affects the visuospatial memory and language deficits.\(^10\) It is postulated that in such a case vascular cognitive impairment occurs in response to the impact of subdural membrane on dural lymphatic drainage.\(^11\)

The neurological deficits in ICH patients are often reflected as cognitive impairment. Interestingly cognitive decline is observed in both before- and after-ICH\(^12\). In a systematic review the prevalence of cognitive impairment has been reported to range between 9-29% for pre ICH and from 14-88% for post-ICH\(^13\). The variability in prevalence of cognitive impairment in different studies might be dependent on the patient characteristics as well as on the measuring method, time of measurement, follow-up period and frequency of measurements. The prevalence of post-ICH mild cognitive disorders has been reported to be as high as 87.5% while major cognitive disorders have been reported to affect nearly 2.5% of the patients followed up to a median period of 4 months.\(^12\) Even studies focused on early cognitive impairment (within 30 days) following have reported significant cognitive impairment in almost one-third ICH patients.\(^14\)

Considering the interrelationship between loss of cognitive function immediately after the ICH or after some time and its impact on physical and functional ability ultimately has an influence on the overall quality of life of patient. Hence, the present study was carried out with an aim to determine the early cognitive impairment in patient with ICH at a tertiary care centre in North India.

**Material and Methods**

The present study prospective observational study was carried out at Department of General medicine, Command Hospital (CH), Central Command (CC), Lucknow, Uttar Pradesh after getting approval from Institutional Ethics Committee and after obtaining informed consent from the patients/caregivers to patients. The study included a total of 30 adult patients (>18 years) with parenchymal hemorrhage on computed tomography (CT). The sample size projections were based on feasibility based on previous hospital trends. Patients with Pure intraventricular hemorrhages, ICH resulting from intracranial vascular malformation, intracranial venous thrombosis, oral anticoagulants, head trauma or tumor, those with Hemorrhagic transformation within an infarct or those who were lost to follow-up, not been able to assess cognitive status at discharge (including mortalities) were excluded from the study.

Demographic details such age, sex, place of residence, occupation and education were noted. Presence of vascular risk factors according to the medical history was enquired. History of previous stroke or transient ischemic attack (TIA) and atrial fibrillation was asked for. Brain computed tomographic scans was performed at admission in all the patients. Computed tomographic scans were reviewed by a senior stroke specialist.

The location of the ICH, volume of bleed, GCS were considered as

1. Lobar (frontal, temporal, parietal, and occipital; when the origin appeared to be in the cerebral hemispheres superficial to the deep gray matter structures)
2. Nonlobar (deep; when the hemorrhage originated from lenticular or caudate nucleus, thalamus, internal or external capsule, or in the posterior fossa and when the hemorrhage originated from the brain stem or cerebellum).
3. Undetermined in cases of large ICH.

The volume of the hemorrhage was calculated according to the validated AxBxC/2 method.

ICH scores (Table 1) were calculated by taking into account GCS at admission, ICH volume, presence of intraventricular hemorrhage, infratentorial origin of ICH and age of patient using the following criteria:\(^15\)

At discharge, cognitive assessment
of patients was done using Montreal Cognitive Assessment (MoCA). The tests were performed by a trained research assistant. MoCA is highly validated for use in adults and displays excellent psychometric properties.\textsuperscript{16–18} MoCA items address orientation, drawing figures, processing speed, naming objects, memory, recall, attention, vigilance, repetition, verbal fluency, and abstraction. The MoCA adds one point for those whose educational level is 12 or fewer years. Mild cognitive impairment was defined by the MoCA score between 18 and 26; moderate cognitive impairment between 10 and 24; mild cognitive impairment - majority (76.7%) patients were illiterate. There were only 5 (16.7%) females. Sex ratio of study population was 1.31. Maximum number of patients were housewives (n=13; 43.3%) followed by farmers (n=11; 36.7%) and urban patients. More than three-fourth (83.3%) of patients were from rural areas (83.3%). There were only 5 (16.7%) serving servicemen and 2 (6.7%) ex-servicemen. Majority of patients were from rural areas (83.3%). There were only 5 (16.7%) urban patients. More than three-fourth (76.7%) patients were illiterate. There were only 7 (23.3%) literates. All the patients were married and belonged to middle socio-economic class. At discharge, all the patients had mild cognitive impairment (p=0.009) (Table 3).

Table 3: Association of Early Cognitive Status with Demographic Profile

<table>
<thead>
<tr>
<th>No. (%)</th>
<th>Total (N=30)</th>
<th>Mild-Mod (n=25)</th>
<th>Severe (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- Midline shift 15</td>
<td>12 (48)</td>
<td>3 (60)</td>
<td>0.240 0.624</td>
</tr>
<tr>
<td>Mean ShiftSD (mm) 30</td>
<td>3.04±4.08</td>
<td>2.56±3.27</td>
<td>- -</td>
</tr>
<tr>
<td>2- Hydrocephalus 0</td>
<td>0</td>
<td>0</td>
<td>- -</td>
</tr>
<tr>
<td>3- Herniation 1</td>
<td>1 (44)</td>
<td>0</td>
<td>- -</td>
</tr>
<tr>
<td>4- Subarachnoid 2</td>
<td>1 (26)</td>
<td>0</td>
<td>0.207 0.649</td>
</tr>
<tr>
<td>5- Intraventricular 1</td>
<td>1 (44)</td>
<td>0</td>
<td>0.429 0.513</td>
</tr>
<tr>
<td>6- ICH Score 4.440</td>
<td>0.109</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7- ICH Volume 56.46±34.54</td>
<td>48.20±17.91</td>
<td>2.45±2.49</td>
<td>-0.516 0.610</td>
</tr>
<tr>
<td>8- Hospital Stay 7.80±4.87</td>
<td>6.20±1.10</td>
<td>2.10±0.52</td>
<td>-0.722 0.476</td>
</tr>
</tbody>
</table>

Discussion

In present study, at discharge all the patients of intracerebral hemorrhage showed cognitive impairment with majority showing moderate cognitive impairment (76.7%), followed by severe impairment (16.7%). Only 2 (6.7%) patients had mild cognitive impairment. On reviewing the literature, we did not come across any study evaluating cognitive function at this early stage. In fact, discharge events took place at a mean delay of 7.5±2.4 days only after the stroke which is too early a time to measure the cognitive function ever use of tobacco was significantly associated with severe cognitive impairment (p=0.009) (Table 3).

No significant association of at discharge cognitive status was observed with any of the radiological features and duration of hospital stay (Table 4).

No significant correlation of age, ICH volume or duration of hospital stay was observed with early cognitive score (MoCA). However, ICH score and GCS showed a mild significant correlation with early cognition score. The correlation between GCS and MoCA scores at discharge was near moderate and positive in direction (r=0.480; p=0.007) whereas ICH scores showed a mild negative correlation with MoCA scores at discharge (r=-0.450; p=0.013) (Table 5).

Table 5: Correlation of Early Cognitive Score

<table>
<thead>
<tr>
<th>Variable</th>
<th>‘r’</th>
<th>Level of correlation</th>
<th>‘p’</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.042</td>
<td>No/Weak</td>
<td>0.827</td>
<td>NS</td>
</tr>
<tr>
<td>ICH Vol</td>
<td>-0.450</td>
<td>Mild</td>
<td>0.013</td>
<td>Significant</td>
</tr>
<tr>
<td>ICH Score</td>
<td>0.480</td>
<td>Mild</td>
<td>0.007</td>
<td>Significant</td>
</tr>
<tr>
<td>GCS</td>
<td>-0.094</td>
<td>No/Weak</td>
<td>0.621</td>
<td>NS</td>
</tr>
</tbody>
</table>
given the fact that most of the patients are still convalescing and owing to within ICU/hospital environment had a disorientation of time and space that must have been affecting their cognitive function too. In the previous study conducted among critically ill patients admitted to ICU even among non-stroke or brain injury patients too have shown high prevalence of cognitive impairment at discharge along with depressive symptoms. Similar to findings of present study, Tembo who conducted their assessment in ICU patients found that even 15 days after discharge there was some form of cognitive impairment in all the patients. They also reported that at this early stage, most of the patients felt of 'Being in Limbo' with three major themes of 'Being Disrupted', Being Imprisoned' and 'Being trapped'. The major themes 'Being Disrupted and 'Being Trapped' highlighted the prevalence of cognitive impairment. Considering the fact that intracerebral hemorrhage is an acute event following which there is an all of a sudden change in patient’s physical as well as psychological status, moreover by the time of discharge most of the patients are on psychotropic, analgesic, sedative support which also have their impact on neurocognitive functions and as such cognitive functions are not deemed to be normal at this early stage in almost all the patients and as depicted in present study too. In present study, all the patients had cognitive impairment at discharge, and majority of them had moderate cognitive impairment. This coincides with the observation of Tembo and shows a combined effect of ICH induced morphological changes in brain as well as the impact of in-hospital experience. Owing to these issues, the attempts to measure cognitive impairment in stroke patients, particularly ICH patients are made at a sufficient time gap after hospital discharge in order to rule out the impact of change in environment, post-critical illness psychological stress and hospital related depression and anxiety.

A high prevalence of cognitive impairment in present study is comparable to observation made by Planton et al. who reported cognitive impairment in 90% of ICH patients after a median delay of 4 months. Similar to present study they also reported this cognitive impairment to be generally of mild order (87.5%) and reported severe impairment in only 1 (2.5%) patient. In present study too, we found that the 3-month cognitive impairment was dominated by mild impairment only (73.3%) and only 1 (3.3%) patient had severe impairment. A high prevalence of cognitive impairment following spontaneous ICH was also reported by Banerjee et al. who reported impairment of at least one cognitive domain in as many as 84% of their patients.

In fact there seems to be extreme variability in prevalence of post-ICH cognitive impairment in different studies. Donnellan and Werring too in a recent systematic review revealed that this prevalence ranged from 14-88% in 11 studies reviewed by them.

In present study, no significant association of mean MoCA scores at discharge was observed with age, gender, occupation, place of residence, literacy status, presence of risk factors like hypertension, diabetes, dyslipidemia, tobacco use, smoking, alcohol use and previous history of stroke. Among different demographic, clinical and history factors, tobacco use history was seen to be significantly associated with severe grade of cognitive impairment. Angiotensin II blockers use was significantly associated with higher MoCA scores while use of any medication was seen to be significantly associated with better cognitive status. The association between tobacco use and cognitive impairment is well established even in young adults.

Compared to present study, Douiri et al. reported that older age, ethnicity and socioeconomic status have a significant association with prevalence of cognitive impairment. In contrast, in present study, majority of patients were >60 years old (60%) belonged to only one ethnicity and had no socioeconomic differences as all of them hailed from middle class, hence these differences could not be elucidated as significant factors associated with cognitive impairment.

In another study, Mellon et al. found a significant association of cognitive impairment with female sex and history of cerebrovascular disease. In present study, no significant association of sex with cognitive impairment was observed. As far as history of cerebrovascular disease was concerned, it was positive in only two cases and did not hold relevance from the statistical point of view. However, they also found that increasing number of total prescribed medications was moderately associated with poorer cognitive impairment whereas in present study we found that use of medications for hypertension or diabetes had a positive impact on cognitive functions. The difference might be owing to difference in severity of disease and type of medications. In present study, hypertension was the most common disease affecting 22 patients, apart from these only 5 patients each had diabetic or dyslipidemic history and were present as comorbid condition with hypertension only. As such none of the patients had any other serious ailment such as history of heart disease. Previous history of stroke was positive in only two patients, hence most of the patients were on prescription drugs for one ailment only.

In another study, You et al. also found that among demographic factors - older age and female sex, prior history of stroke and higher mean systolic blood pressure had a significant association with cognitive impairment. In another study, Biffi et al. found educational level to be significantly associated with cognitive impairment. But in present study, we did not find these associations to be significant. One of the reasons for absence of most of the relationships in present study is small sample size. While present study included only 30 patients of ICH, most of the previous studies evaluating this relationship had a much larger sample size. In fact, the findings of Douiri et al. are based on data of 271817 stroke cases. Mellon et al. in their study had 256 stroke patients and Biffi et al. and You et al. had 738 and 231 ICH patients respectively in their studies. Compared to these studies, the present study could be perceived as only a pilot study verifying trends reported in previous studies and also trying to establish some new trends rather than establishing them.

Not much significance to demographic and clinical factors has been given by previous workers while studying the problem of post-ICH cognitive impairment but the focus of their assessments has been on radiological features. In present study, within a restricted sample size limitation, we also intended to explore...
this relationship. The radiological features in present study were not much diversified. Firstly owing to sample size and secondly owing to the exclusion criteria in which we ruled out inclusion of patients with pure intraventricular hemorrhage and other conditions. Owing to sample size limitation, we were unable to find any patient with radiological feature of herniation, hydrocephalus or vasospasm. There was only one case with subarachnoid bleed and two cases with intraventricular bleed. Most of the other radiological features of interest were absent in the spectrum of radiological findings in a limited sample of our study. The only features of interest were thus midline shift, extent of midline shift and hematoma size. But none of these features were found to be significantly associated with level and severity of cognitive impairment.

In other studies among ICH patients, radiological features like cortical involvement,25,26 hydrocephalus,27 hematoma size24 and lobar location of ICH24 have been stated to be significantly associated with cognitive function. However, within the limited sample size of present study, a number of these features could either not be seen in any patient or were present in only few patients to hold any statistical relevance.

Nevertheless, in present study, we found that a combined association of radiological as well as clinodemographic factors, as projected by ICH score was significantly associated with cognitive function, thus showing that radiological features in combination with clinodemographic factors play a dominant role in determining the prevalence and extent of cognitive impairment in post-ICH patients. As such multifactoriality of cognitive impairment following stroke is accepted by almost all the workers. As such multifactoriality of cognitive impairment following stroke is accepted by almost all the workers. This relationship was more prominent in patients with subarachnoid hemorrhage.

The findings of present study showed that post-ICH cognitive impairment is quite prevalent, however, its relationship with different clinic-demographic and radiological features could be elucidated in a larger sample size. Post-stroke cognitive impairment should be considered as a multifactorial problem in which both clinic-demographic variables and radiological features seem to have their independent as well as mutual roles which could be illustrated with the help of a scoring system like ICH that incorporates the both. Further studies on a larger sample size with diversified radiological features could help in understanding the independent role of different radiological features in a better way.

Conclusion

Early mild to moderate cognitive impairment is quite frequent among intracerebral hemorrhage patients irrespective of the demographic, clinical and radiological profile. Further studies on a larger sample size are recommended.

References

Predictors of Outcome in Acute Respiratory Distress Syndrome in Acute Febrile Illness in Medical Intensive Care Unit

Anwitha Varmudy¹, Archana Sonawale²*, Vishal A Gupta², Niteen D Karnik³

Abstract

Aims: Acute Respiratory Distress Syndrome (ARDS) is a known complication of acute febrile illness (AFI). The in-hospital mortality rate of ARDS is between 35-44%. Our study aimed to identify the different parameters that could be used to detect patients at higher risk of poor outcome in AFI complicated by ARDS.

Methods: 130 patients with AFI complicated by ARDS as per Berlin definition, admitted at the Medical Intensive Care Unit of Seth GS Medical College & KEM Hospital Mumbai, were studied over a period of 18 months. Investigations done during the course of MICU stay were noted. From the reports, SOFA score, delta SOFA score, Lung Injury Score (LIS), Disseminated Intravascular Coagulation (DIC) score (by ISTH scoring system) were also calculated. Main outcome was recorded as transfer out from the MICU or death.

Results: Etiology of the 130 patients of AFI with ARDS was as follows: dengue 32 patients (24.6%), H1N1 31(23.8%), undifferentiated fever 30 (23.1%), leptospirosis-22 (16.9%), malaria-15 (11.5%). Our study had a mortality rate of 25.4% (n=33). 40.8% of the study population required invasive ventilation at admission. SOFA score at admission and 48 hours, delta SOFA score, PaO2/FiO2 ratio at admission and 48 hours, Blood Urea Nitrogen (BUN), creatinine, bicarbonate and albumin were the significant predictors of overall outcome. Hemoglobin, platelets and leukocyte counts, pH, pO2, pCO2 at admission and 48 hours, Lung Injury Score (LIS) and DIC score were not significant predictors of outcome.

Conclusion: SOFA score at admission and 48 hours, delta SOFA score and PaO2/FiO2 ratio were significant predictors of outcome in patients of AFI complicated by ARDS. LIS and DIC score were not significant predictors of outcome.

Introduction

Acute febrile illness (AFI) also known as acute undifferentiated fever has been defined as fever of two weeks or shorter in duration.1,2 In India AFI is an important cause of hospitalization, especially between the months of June to September.3 The underlying etiology of AFI as per different studies have been reported as follows - malaria in 5 to 50% cases, Rickettsial fevers/scrub typhus in 4 to 49% cases, enteric fever in 7 to 30% cases, dengue in 4 to 19% cases, leptospirosis in 3 to 10% cases and influenza in 8 to 12% of cases.4 The common complications associated with AFI are hypotension, acute kidney injury, acidosis, superimposed bacterial infections, acute respiratory distress syndrome (ARDS), thrombocytopenia, acute liver failure or DIC, depending on the underlying etiology of AFI.

Currently, ARDS is being defined as per Berlin definition5 to better the reliability and predictive value as compared to AECC (American-European Consensus Conference) definition. The in-hospital mortality rate is estimated to be between 34 and 55%.6,7 Most ARDS-related deaths are due to multiorgan failure. Refractory hypoxemia accounts for only 16% of ARDS-related deaths.8

The Sequential Organ Failure Assessment (SOFA) score is an objective score which calculates severity of organ dysfunction in six organ systems (liver, cardiovascular, renal, neurologic, respiratory, coagulopathy). It can measure individual or aggregate organ dysfunction.9,10

SOFA score has been studied in critically ill elderly patients.11 However, Indian literature assessing the prognostic value of SOFA score in patients of AFI complicated by ARDS is limited. Hence we here present the findings from our study assessing the clinical profile of and utility of SOFA score, Lung Injury Score (LIS), Disseminated Intravascular Coagulation (DIC) score and Arterial Blood Gas (ABG) parameters in patients with AFI complicated by ARDS in the medical intensive care unit.

Materials and Methods

This prospective observational study was performed on 130 patients at the Medical Intensive Care Unit of Seth GS Medical College & KEM Hospital Mumbai, over a period of 18 months from March 2016 to August 2017 after obtaining the permission of Institutional Ethics Committee. Patients diagnosed with ARDS as per Berlin definition were included in the study. The study included those diagnosed with an existing diagnosis of ARDS upon admission into the ICU, provided they survived the initial 24 hours of the ICU stay. Informed consent was taken from the study participants or their legal guardians. Patient details were noted in a proforma. Laboratory reports obtained at and after 48 hours of admission into the MICU were noted, consisting of ABG, complete
blood counts, liver and renal function tests and DIC profile. For fever, along with blood culture, the following tests were done - fever profile consisting of Dengue NS1 antigen assay, Dengue IgM and IgG antibodies, Leptospira IgM antibody, peripheral smear for malaria and malarial antigen test (MAT), RT PCR on throat swab for H1N1 virus and chest radiograph. PCR studies for Dengue and Leptospirosis were done in patients with strong clinical suspicion having negative Dengue NS1/IgM and negative Leptospira IgM reports respectively.

From the above reports SOFA score, Lung Injury Score (LIS), DIC score (by ISTH scoring system) were calculated. Delta SOFA score was calculated as the change in SOFA score over 48 hours (T0 SOFA score – T48 SOFA score). During the MICU stay, the mode of ventilatory support needed and treatment given to each patient was noted. Main outcome measure was recorded as transfer out from MICU or death. Criteria for transfer out from MICU to the ward were as follows- lack of the need for invasive mechanical ventilation, CPAP support or NRBM support along with hemodynamic stability. The patients were not followed up for readmissions for the purpose of this study.

### Statistical analysis

Descriptive statistics were used for summarising the results of the study. Statistical significance was tested by using the Student’s t-test for comparing numerical data and the Chi-square test for comparing categorical data. The significance level was set at p < 0.05. Statistical analysis was carried out using Stata 15.1.

### Table 1: Etiology of AFI with ARDS with mortality (n=130)

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Number of patients</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dengue</td>
<td>32</td>
<td>12.5% (n=4)</td>
</tr>
<tr>
<td>H1N1</td>
<td>31</td>
<td>16.1% (n=5)</td>
</tr>
<tr>
<td>Undifferentiated fever</td>
<td>30</td>
<td>46.7% (n=14)</td>
</tr>
<tr>
<td>Leptospirosis</td>
<td>22</td>
<td>45.4% (n=10)</td>
</tr>
<tr>
<td>Malaria</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>130</td>
<td>33 (25.4%)</td>
</tr>
</tbody>
</table>

### Table 2: Parameters and their significance in Acute Febrile Illness (AFI) with ARDS for outcome prediction (n=130)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Category of patient</th>
<th>N</th>
<th>Mean</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>Survivors</td>
<td>97</td>
<td>10.856</td>
<td>0.755</td>
</tr>
<tr>
<td></td>
<td>Non-survivors</td>
<td>33</td>
<td>10.733</td>
<td></td>
</tr>
<tr>
<td>Platelet count (/mm3)</td>
<td>Survivors</td>
<td>97</td>
<td>122.958</td>
<td>0.080</td>
</tr>
<tr>
<td></td>
<td>Non-survivors</td>
<td>33</td>
<td>920.967</td>
<td></td>
</tr>
<tr>
<td>Total leucocyte count (/mm3)</td>
<td>Survivors</td>
<td>97</td>
<td>8377.94</td>
<td>0.3640</td>
</tr>
<tr>
<td></td>
<td>Non-survivors</td>
<td>33</td>
<td>9381.82</td>
<td></td>
</tr>
<tr>
<td>Blood Urea Nitrogen (mg/dL)</td>
<td>Survivors</td>
<td>97</td>
<td>22.422</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td></td>
<td>Non-survivors</td>
<td>33</td>
<td>46.669</td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>Survivors</td>
<td>97</td>
<td>1.464</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td></td>
<td>Non-survivors</td>
<td>33</td>
<td>2.557</td>
<td></td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>Survivors</td>
<td>97</td>
<td>1.414</td>
<td>0.045*</td>
</tr>
<tr>
<td></td>
<td>Non-survivors</td>
<td>33</td>
<td>2.439</td>
<td></td>
</tr>
<tr>
<td>Direct bilirubin (mg/dL)</td>
<td>Survivors</td>
<td>97</td>
<td>0.743</td>
<td>0.051</td>
</tr>
<tr>
<td></td>
<td>Non-survivors</td>
<td>33</td>
<td>1.463</td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase (AST) (IU/L)</td>
<td>Survivors</td>
<td>97</td>
<td>99.280</td>
<td>0.016*</td>
</tr>
<tr>
<td></td>
<td>Non-survivors</td>
<td>33</td>
<td>322.575</td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase (ALT) (IU/L)</td>
<td>Survivors</td>
<td>97</td>
<td>53.715</td>
<td>0.063</td>
</tr>
<tr>
<td></td>
<td>Non-survivors</td>
<td>33</td>
<td>183.879</td>
<td></td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>Survivors</td>
<td>97</td>
<td>3.101</td>
<td>0.001*</td>
</tr>
<tr>
<td></td>
<td>Non-survivors</td>
<td>33</td>
<td>2.921</td>
<td></td>
</tr>
<tr>
<td>PaO2/FiO2 at admission (0 hours)</td>
<td>Survivors</td>
<td>97</td>
<td>239.16</td>
<td>0.002*</td>
</tr>
<tr>
<td></td>
<td>Non-survivors</td>
<td>33</td>
<td>231.33</td>
<td></td>
</tr>
<tr>
<td>PaO2/FiO2 at 48 hours</td>
<td>Survivors</td>
<td>97</td>
<td>363.87</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td></td>
<td>Non-survivors</td>
<td>33</td>
<td>210.82</td>
<td></td>
</tr>
<tr>
<td>SOFA score at admission (0 hours)</td>
<td>Survivors</td>
<td>97</td>
<td>4.78</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td></td>
<td>Non-survivors</td>
<td>33</td>
<td>7.97</td>
<td></td>
</tr>
<tr>
<td>SOFA score at 48 hours</td>
<td>Survivors</td>
<td>97</td>
<td>3.21</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td></td>
<td>Non-survivors</td>
<td>33</td>
<td>10.00</td>
<td></td>
</tr>
<tr>
<td>Delta SOFA score</td>
<td>Survivors</td>
<td>97</td>
<td>1.577</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td></td>
<td>Non-survivors</td>
<td>33</td>
<td>-2.030</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>Survivors</td>
<td>97</td>
<td>7.397</td>
<td>0.361</td>
</tr>
<tr>
<td></td>
<td>Non-survivors</td>
<td>33</td>
<td>7.412</td>
<td></td>
</tr>
<tr>
<td>PaO2 (mmHg)</td>
<td>Survivors</td>
<td>97</td>
<td>51.867</td>
<td>0.200</td>
</tr>
<tr>
<td></td>
<td>Non-survivors</td>
<td>33</td>
<td>50.333</td>
<td></td>
</tr>
<tr>
<td>PaCO2 (mmHg)</td>
<td>Survivors</td>
<td>97</td>
<td>35.021</td>
<td>0.550</td>
</tr>
<tr>
<td></td>
<td>Non-survivors</td>
<td>33</td>
<td>33.969</td>
<td></td>
</tr>
<tr>
<td>HCO3- (meq)</td>
<td>Survivors</td>
<td>97</td>
<td>21.887</td>
<td>0.001*</td>
</tr>
<tr>
<td></td>
<td>Non-survivors</td>
<td>33</td>
<td>18.333</td>
<td></td>
</tr>
<tr>
<td>Lung Injury Score (LIS) at admission (0 hours)</td>
<td>Survivors</td>
<td>97</td>
<td>1.704</td>
<td>0.078</td>
</tr>
<tr>
<td></td>
<td>Non-survivors</td>
<td>33</td>
<td>1.833</td>
<td></td>
</tr>
<tr>
<td>DIC score at admission (0 hours)</td>
<td>Survivors</td>
<td>97</td>
<td>0.92</td>
<td>0.357</td>
</tr>
<tr>
<td></td>
<td>Non-survivors</td>
<td>33</td>
<td>1.06</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05; significant

### Table 3: Disease-wise prognostic value of SOFA scores at admission (0 hours) and at 48 hours in ARDS due to Acute Febrile Illness (AFI) (n=130)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Survivor status</th>
<th>No. of patients (N)</th>
<th>Mean SOFA score at admission (0 hours)</th>
<th>Mean SOFA score at 48 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dengue</td>
<td>Survivor</td>
<td>28</td>
<td>5.64</td>
<td>4.04</td>
</tr>
<tr>
<td></td>
<td>Non-survivor</td>
<td>4</td>
<td>7.00</td>
<td>7.00</td>
</tr>
<tr>
<td>H1N1</td>
<td>Survivor</td>
<td>26</td>
<td>3.12</td>
<td>1.73</td>
</tr>
<tr>
<td></td>
<td>Non-survivor</td>
<td>5</td>
<td>5.60</td>
<td>6.80</td>
</tr>
<tr>
<td>Undifferentiated fever</td>
<td>Survivor</td>
<td>16</td>
<td>4.00</td>
<td>2.38</td>
</tr>
<tr>
<td></td>
<td>Non-survivor</td>
<td>14</td>
<td>6.07</td>
<td>6.64</td>
</tr>
<tr>
<td>Leptospirosis</td>
<td>Survivor</td>
<td>12</td>
<td>6.92</td>
<td>4.50</td>
</tr>
<tr>
<td></td>
<td>Non-survivor</td>
<td>10</td>
<td>12.20</td>
<td>14.70</td>
</tr>
<tr>
<td>Vivax malaria</td>
<td>Survivor</td>
<td>11</td>
<td>5.36</td>
<td>4.55</td>
</tr>
<tr>
<td></td>
<td>Non-survivor</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Falciparum malaria</td>
<td>Survivor</td>
<td>4</td>
<td>4.75</td>
<td>2.75</td>
</tr>
<tr>
<td></td>
<td>Non-survivor</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*p < 0.05; significant

### Table 4: Disease-wise prognostic value of mean PaO2/FiO2 ratio at admission (0 hours) and at 48 hours in ARDS due to Acute Febrile Illness (AFI) (n=130)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Survivor status</th>
<th>No. of patients (N)</th>
<th>Mean PaO2/FiO2 ratio at admission (0 hours)</th>
<th>Mean PaO2/FiO2 ratio at 48 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dengue</td>
<td>Survivors</td>
<td>28</td>
<td>245.36</td>
<td>386.82</td>
</tr>
<tr>
<td></td>
<td>Non-survivors</td>
<td>4</td>
<td>229.50</td>
<td>234.75</td>
</tr>
<tr>
<td>H1N1</td>
<td>Survivors</td>
<td>26</td>
<td>234.58</td>
<td>356.62</td>
</tr>
<tr>
<td></td>
<td>Non-survivors</td>
<td>5</td>
<td>218.40</td>
<td>197.60</td>
</tr>
<tr>
<td>Undifferentiated fever</td>
<td>Survivor</td>
<td>16</td>
<td>254.63</td>
<td>359.88</td>
</tr>
<tr>
<td></td>
<td>Non-survivors</td>
<td>14</td>
<td>208.64</td>
<td>262.36</td>
</tr>
<tr>
<td>Leptospirosis</td>
<td>Survivors</td>
<td>12</td>
<td>214.08</td>
<td>339.67</td>
</tr>
<tr>
<td></td>
<td>Non-survivors</td>
<td>10</td>
<td>210.90</td>
<td>135.70</td>
</tr>
<tr>
<td>Vivax malaria</td>
<td>Survivor</td>
<td>11</td>
<td>234.64</td>
<td>333.45</td>
</tr>
<tr>
<td></td>
<td>Non-survivor</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Falciparum malaria</td>
<td>Survivor</td>
<td>4</td>
<td>251.50</td>
<td>422.50</td>
</tr>
<tr>
<td></td>
<td>Non-survivor</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*p < 0.05; significant
study. Data was analyzed by $X^2$ test and multivariate logistic regression. Analysis of significance was done using computer-based program SPSS version 17; $p$ value of <0.05 was considered as significant.

**Results**

Total admission in MICU during our study period was 999, out of which 13.01% (n=130) had AFI complicated by ARDS thus constituting our study population. Mean age of the study population was 39.4+/-13.4 years, with majority of them belonging to the age group of 26-45 years (49.2%, n=64). The distribution of patients among the other age groups was as follows: 14-25 years-18.5% (n=24), 46-60 years-22.3% (n=29), 61-80 years-10% (n=13). Males constituted 53.8% (n=70) and females constituted 46.2% (n=60) of the study population. The major comorbidities in this study were diabetes mellitus (18.5%) and hypertension (16.9%). The common presenting symptoms were fever (100%), cough (83.8%), breathlessness (86.2%), myalgia (60%) and vomiting (52.3%). Majority (n=117, 90%) of the study population was symptomatic for a period of 1-6 days prior to presentation to the hospital with ARDS. Table 1 gives underlying etiology of ARDS with mortality. The etiologies were as follows: Dengue-24.6% (n=32), H1N1-23.8% (n=31), undifferentiated fever 23.1% (n=30), leptospirosis-16.9% (n=22), vivax malaria-8.5% (n=11), falciparum malaria-31% (n=4). The overall mortality rate was 25.4% (n=33). Among non-survivors, 69.7% (n=23) were males and 30.3% (n=10) were females, with this gender disparity being statistically significant (Pearson Chi-square=4.471, $p$ value 0.034). Hypotension was seen at presentation in 30% of the study population. Among the non survivors, 42.4% of them were hypotensive on admission and this was found to be statistically significant (Pearson Chi-square=3.251, $p$ value= 0.046). The presence of comorbidities i.e. hypertension and diabetes mellitus did not have any significant correlation with the disease outcome. Highest mortality rate in AFI complicated by ARDS was seen amongst patients with undifferentiated fever (46.7%), followed by leptospirosis (45.4%), H1N1 (16.1%) and dengue (12.5%). Malaria associated ARDS showed 100% survival rate (Table 1). The modes of ventilation used on admission in our study were invasive ventilation in 40.8% (n=53), non invasive ventilation in 59.2% (n=77). The criteria used for patient selection for non invasive ventilation were hemodynamically stable patients and patients who tolerated non invasive ventilation (NIV) mask well and were compliant to it. Out of the patients intubated at admission, only 37.7% of the patients survived whereas 96.1% of the patients ventilated non-invasively at presentation survived the MICU stay. The mean duration of ventilatory support received in the survivors was 5.23 +/- 3.70 days while that among non-survivors was 4.39 +/- 1.92 days ($p$=0.185). The duration of MICU stay among survivors was 7.10 +/- 4.68 days and among non survivors was 5.12 +/- 3.25 days ($p$=0.187).

Table 2 shows the correlation of different investigation parameters with outcome of ARDS in AFI. The laboratory parameters having significant outcome predictive value were BUN, creatinine, bicarbonate, total bilirubin, AST and albumin. The PaO2/FiO2 ratio was significant both on admission (0 hours) and at 48 hours. The scores having significant outcome predictive value were SOFA score at admission and 48 hours, delta SOFA score. LIS and DIC score at admission were not found to have significance for outcome prediction. Table 3 shows disease-wise analysis of SOFA score at 0 hours and at 48 hours. It had significant outcome prediction value for H1N1, leptospirosis and undifferentiated fever but was not significant for Dengue ($p$=0.192 and $p$=0.101 respectively). Delta SOFA score (difference of SOFA scores at 0 hours and 48 hours) showed a fall in SOFA score by 2.6 +/- 2.67 in non-survivors as compared to a rise in SOFA score of 1.577 +/- 1.847 in survivors (Table 2). ANOVA showed a $p$ value of <0.001. Hence delta SOFA score had a significant association with outcome. Mean PaO2/FiO2 at admission and at 48 hours values (Table 2) was found to be statistically significant in determining overall outcome in AFI with ARDS ($p$=0.002 and $p$<0.001 respectively). Table 4 shows disease-wise analysis of PaO2/FiO2 at 0 hours and at 48 hours. PaO2/FiO2 at admission was a significant outcome predictor only in leptospirosis and undifferentiated fever whereas at 48 hours was significant in all etiologies of ARDS due to AFI. Analysis of DIC score as an outcome predictor in individual diseases (Table 5) showed statistical significance only in H1N1 ($p$=0.001). However, DIC score as an overall predictor of outcome in AFI with ARDS has no statistical value ($p$=0.357, Table 2). Table 6 shows that LIS had no statistically significant outcome prediction value in any of the diseases.

**Discussion**

Patients with ARDS constituted approximately 13.01% (130/999) of the total admissions in MICU during our study period of 18 months. The mortality rate in our study was similar (25.4%) to the mortality in ARDS Network study done in 2003 (N-91) and 2005 (N-487), where the mortality was 29% and 26% respectively. A few studies have described gender differences in the occurrence of sepsis and ARDS and in the outcomes of patients with those conditions, with a higher incidence and poorer outcomes in men compared to women. Our study showed revealed poorer outcome in men as compared to women. This is probably explained by the immunomodulatory role of sex hormones as reports have shown that female sex hormones are immunostimulatory, whereas male sex hormones are immunosuppressive. According the literature review conducted by Zambon M and Vincent J L, investigators reported improved survival with shortened duration of mechanical ventilation by means of lung protective ventilation and conservative fluid management as suggested by NIH-NHLBI ARDS Network trial. In our study, the 77 patients who could be ventilated by non-invasive ventilation on admission had a survival rate of 96.1%. Of the patients requiring invasive ventilation on admission had a survival rate of 96.1%. Of the patients requiring invasive ventilation on admission had a survival rate of 96.1%. Of the patients requiring invasive ventilation on admission had a survival rate of 96.1%. Of the patients requiring invasive ventilation on admission had a survival rate of 96.1%. Of the patients requiring invasive ventilation on admission had a survival rate of 96.1%. Of the patients requiring invasive ventilation on admission had a survival rate of 96.1%. 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Of the patients requiring invasive ventilation on admission had a survival rate of 96.1%. Of the patients requiring invasive ventilation on admission had a survival rate of 96.1%. Of the patients requiring invasive ventilation on admission had a survival rate of 96.1%. Of the patients requiring invasive ventilation on admission had a survival rate of 96.1%. Of the patients requiring invasive ventilation on admission had a survival rate of 96.1%. Of the patients requiring invasive ventilation on admission had a survival rate of 96.1%. Of the patients requiring invasive ventilation on admission had a survival rate of 96.1%. Of the patients requiring invasive ventilation on admission had a survival rate of 96.1%. Of the patients requiring invasive ventilation on admission had a survival rate of 96.1%.
present on admission, that the Δ-SOFA score can demonstrate the degree of dysfunction or failure developing during an ICU stay, and that the total maximum SOFA score can represent the cumulative organ dysfunction experienced by the patient. They also demonstrated a strong correlation of all these parameters with mortality. SOFA score has been validated in the SOFA score Male, gender APACHE II, APACHE III, Pre-existing comorbidities Surgery prior to onset of ARDS

Table 6: Disease-wise prognostic value of Lung Injury Score (LIS) in ARDS due to Acute Febrile Illness (AFI) (n=130)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Survivor status</th>
<th>No. of patients (N)</th>
<th>Mean Lung Injury score at admission (0 hours)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dengue</td>
<td>Survivor</td>
<td>28</td>
<td>1.607</td>
<td>0.920</td>
</tr>
<tr>
<td></td>
<td>Non-survivor</td>
<td>4</td>
<td>1.625</td>
<td></td>
</tr>
<tr>
<td>HIN1</td>
<td>Survivor</td>
<td>26</td>
<td>1.685</td>
<td>0.656</td>
</tr>
<tr>
<td></td>
<td>Non-survivor</td>
<td>5</td>
<td>1.760</td>
<td></td>
</tr>
<tr>
<td>Undifferentiated fever</td>
<td>Survivor</td>
<td>16</td>
<td>1.738</td>
<td>0.390</td>
</tr>
<tr>
<td></td>
<td>Non-survivor</td>
<td>14</td>
<td>1.864</td>
<td></td>
</tr>
<tr>
<td>Leptospirosis</td>
<td>Survivor</td>
<td>12</td>
<td>1.792</td>
<td>0.473</td>
</tr>
<tr>
<td></td>
<td>Non-survivor</td>
<td>10</td>
<td>1.910</td>
<td></td>
</tr>
<tr>
<td>Vivax malaria</td>
<td>Survivor</td>
<td>11</td>
<td>1.718</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Non-survivor</td>
<td>0</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Falciparum malaria</td>
<td>Survivor</td>
<td>4</td>
<td>2.075</td>
<td>-</td>
</tr>
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<td></td>
<td>Non-survivor</td>
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<td>-</td>
<td></td>
</tr>
</tbody>
</table>

*P <0.05; significant

Table 7: Comparison of prognostic factors determined by our study with that of similar studies

<table>
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<tr>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>130</td>
<td>58</td>
<td>180</td>
<td>150</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td>25.4%</td>
<td>57%</td>
<td>47.8%</td>
</tr>
<tr>
<td>SOFA score-outcome</td>
<td></td>
<td>Yes</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>PaO2/FiO2 ratio-outcome predictive value</td>
<td>No</td>
<td>Yes</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>PaO2/FiO2 ratio-outcome predictive value</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Other adverse outcome predictors</td>
<td>Delta SOFA score</td>
<td>Hypotension on admission, albumin, creatinine, acidosis, Failure</td>
<td>Sepsis, acidosis, hypotension, multiorgan failure</td>
<td>Delta SOFA score</td>
</tr>
<tr>
<td></td>
<td>MAE</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

similar result (p=0.49).20

Limitations

The data in our study may be applicable only to the critically ill patients of AFI since the study was conducted at a tertiary referral center where the most sick of the patient population gets referred. We also did not include patients who succumbed within the first 48 hours of admission as we needed SOFA score at 48 hours for data and analysis

Conclusion

AFI complicated by ARDS was associated with a mortality rate of 25.4%. SOFA score and PaO2/FiO2 at admission and at 48 hours, delta SOFA score, serum albumin, bicarbonate levels BUN and creatinine levels were significant predictors of outcome in the patients in our study.

References


A Study of ICU Outcome and Long-Term Quality of Life in ICU Survivors in Central India

Tanuja Manohar¹, Hemant Waghmare²*, Pranjalee Bhagat Waghmare³

Abstract

Background: Patient surviving in the ICU may have to undergo physical and mental sufferings after the discharge from the ICU. Health Related Quality of Life (HRQoL) of such patients post discharge has been addressed mostly in developed countries, however in developing countries the data is insufficient. Thus, in this study we have aimed to assessed the HRQoL of such patients.

Objectives: To evaluate the HRQoL of critically ill survivors in Central India

Methodology: It was a prospective, observational study conducted on the 82 patients of an ICU of central India. APACHE II and SOFA score were calculated after the admission of the patient and a Short Form Health Survey (SF-36) was conducted at 1st, 3rd and 6th month by telephonic interview after the discharge of the patient.

Result: APACHEII and SOFA score was found significantly associated with the mortality outcome of the patient (p<0.0001). HRQOL improved in survivor patients progressively after hospital discharge and was maximum at 6 months (p<0.0001).

Conclusion: The APACHE II score and SOFA score were able to predict the mortality of the patients, and the HRQOL was improved significantly over a period of 6 months post discharge.

Introduction

Since the establishments of first ICU in the 1950s we can clearly see the difference that has been created by the technology in conveying the diagnostic, monitoring and investigational devices at patient’s bedside. The main outcome of ICU admission is either survivor or death. With the advancement in the technology and development of new drugs, the percentage of patients surviving during the treatment in the ICU has increased. Though the number of survivors are increasing following treatment in the ICU, the patient may experience the lifelong complications. The complications can be the result of disease pathology, treatment adverse effects, prolonged stay in ICU, prolonged mechanical ventilation.

WHO defines Quality of Life as an individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. The quality-of-life post discharge from the ICU is assessed with the help of questionnaire-based studies. The questionnaire is developed depending on the domain of assessment. The 36-Item Short Form (SF-36), and 12-Item Short-Form Health Survey (SF-12) are the most widely used instruments for assessing HRQOL after the discharge of the patient from the ICU. The SF – 36 consist of 36 questions which measures 8 scales, PF – Physical Functioning, BP – Bodily Pain, RP – Role Physical, RE- Role Emotional, EWB – Emotional Well Being, SF – Social Functioning, E/F – Energy/Fatigue, GH – General Health.

Various studies have been conducted to assess the HRQOL of patients after ICU discharged in developed countries but the data regarding HRQOL post ICU discharge is lacking in developing country, thus we have taken an initiative through this study to assess the HRQOL of ICU patients after their discharge from the ICU.

Aims and Objectives

Primary

To evaluate the QOL in critically ill ICU survivors in central India after the
hospital discharge.

Secondary
1. To study the outcome of critically ill patients admitted in the ICUs.
2. To assess the influence of clinical variables on quality of life.

Material and Methods

It was a prospective longitudinal study conducted in the ICU of NKP Salve Medical College and Hospital, Nagpur. The study was initiated after taking the approval from institutional ethics committee.

Inclusion criteria: Patients more than 18 years of age.

Exclusion criteria: Patients with
1. Previous cognitive deficit, aphasia, neurological deficit
2. Tracheostomy
3. Neurological deficit at ICU discharge
4. Amputation of limbs
5. Surgical Problems
6. Head Injury

After getting written informed consent from the patient or their relatives, patients admitted to the ICU were enrolled in the study. The patients were divided in to Sepsis, Cardiac, Respiratory Neurological, Intoxication and Others disorders.

The disease severity score – APACHE II (Acute Physiology and Chronic Health Evaluation) score was calculated on admission of the patients and SOFA (Sequential Organ Failure Assessment) score was evaluated on daily basis. Duration of Mechanical Ventilation, ICU length of stay were noted during the ICU stay of the patient.

After the discharge of the patients the Health-Related Quality of Life (HRQOL) was assessed with the help of Short Form Health Survey (SF – 36). The SF -36 survey was conducted at 1st, 3rd and 6th month. Patient were contacted telephonically and were asked for each of the components of the SF -36 form. Routine follow-up as per clinical condition were done by the treating Clinician. If on telephonic call patient appears unduly unfit, they were called in between for the evaluation and investigations. Mortality, Readmissions, Dropouts, over the period of six months were recorded.

Data collection: The data was collected in an electronic proforma on a link provided to the individual intensivists.

Statistical Analysis

Categorical variables were described as numbers (percentages) and continuous variables as mean (± Standard deviation) if normally distributed, or median if not normally distributed. The length of stay (LOS) was expressed in terms of medians and quartiles. The Mann-Whitney U-test was applied for continuous variables and the χ2 test for the categorical variables. Longitudinal data was analysed using Repeated Measures ANOVA. Survival analysis was performed to analysed time to event (morbidity and mortality) data resulting from 6 months follow-up of survivors and non-survivors.

Results

Total 87 patients were screened out of which 82 patients were enrolled in our study. The 5 patients were excluded as 2 of them were of head injury and 3 were having neurological deficit at the time of discharge. Out of total 82 patients enrolled 60.97 % (50 patients) were male and 39.02 % (32 patients) were female. The mean age of the patient is 47.81 ± 17.29 yrs. (Figure 1).

As depicted in Figure 2, eighteen percent of patients were between 51 – 60 years, 19 % of patients were between the age group of 18 – 30 years, 20 % of patients were between 61 – 70 years, 21 % of patients were between 31 -40 years and 22% of patients were between 41 – 50 years.

Out of 82 patients 6 patients expired post discharge from the ICU. Two patients expired within the first month of the discharge, one patient expired at the end of 2nd month, two patients expired at the end of 4th month and one patient expired at the 6th month, post discharge from the ICU.

Six patients lost to follow up as they did not receive the call during the post discharge telephonic assessment for SF-36 score.

The Mean ± SD age of survivor patient was 46.75 ± 16.57 years, non-survivor patient was 60.66 ± 14.17 years and for lost to follow up patient was 70.5 ± 3.93 years.

The survivor patients were diagnosed with Intoxication (27.14%), Respiratory diseases (25.71%), Cardiac diseases (14.28%), Neurological diseases (11.42%), Others (14.28%) and sepsis (7.14%).

The non-survivor patients were diagnosed with Intoxication (4.28%),

<table>
<thead>
<tr>
<th>APACHE II score</th>
<th>Non-Survivor (N = 6)</th>
<th>Survivor (N = 70)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 5</td>
<td>0</td>
<td>7 (10)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>6 - 10</td>
<td>0</td>
<td>13 (18.57)</td>
<td></td>
</tr>
<tr>
<td>11 - 15</td>
<td>1 (16.66)</td>
<td>25 (35.71)</td>
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<tr>
<td>16 - 20</td>
<td>3 (50)</td>
<td>20 (28.57)</td>
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<tr>
<td>21 - 25</td>
<td>2 (33.33)</td>
<td>5 (7.14)</td>
<td></td>
</tr>
<tr>
<td>25 – 30</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Number of Patients

Fig. 1: Gender Wise Distribution of Patients in the Study

<p>| Table 1: Correlation of APACHE II score with mortality outcome of patient |
|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>APACHE II score</th>
<th>Non-Survivor (N = 6)</th>
<th>Survivor (N = 70)</th>
<th>P value</th>
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<tbody>
<tr>
<td>0 - 5</td>
<td>0</td>
<td>7 (10)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>6 - 10</td>
<td>0</td>
<td>13 (18.57)</td>
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<tr>
<td>11 - 15</td>
<td>1 (16.66)</td>
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<td>16 - 20</td>
<td>3 (50)</td>
<td>20 (28.57)</td>
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<tr>
<td>21 - 25</td>
<td>2 (33.33)</td>
<td>5 (7.14)</td>
<td></td>
</tr>
<tr>
<td>25 – 30</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Statistical Analysis

<p>| Table 2: Correlation of SOFA Score with mortality outcome of patient |
|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>SOFA score</th>
<th>Non-Survivor (N = 6)</th>
<th>Survivor (N = 70)</th>
<th>P value</th>
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<tbody>
<tr>
<td>1 - 6</td>
<td>0</td>
<td>29 (41.42)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>7 - 12</td>
<td>1 (16.66)</td>
<td>28 (40)</td>
<td></td>
</tr>
<tr>
<td>13 - 18</td>
<td>3 (50)</td>
<td>9 (12.85)</td>
<td></td>
</tr>
<tr>
<td>19 - 24</td>
<td>2 (33.33)</td>
<td>5 (7.14)</td>
<td></td>
</tr>
</tbody>
</table>
The PCs (Physical component score) and MCs (Mental component score) Component were improved over a period of 6 months. (p < 0.0001)

Role emotional was the most affected and least improved while role physical, physical functioning and bodily pain has shown a significant improvement over the period. The MCs component was less improved as compared to the PCs and 6th month. We have noticed a significant rise in the SF-36 score at 1st, 3rd and 6th month for 70 survivor patients. The HRQoL of life was assessed on the basis of SF – 36 score at 1st, 3rd and 6th month for 70 survivor patients. All the scores of physical and mental components of the SF-36 questionnaire were compromised post discharge from the ICU. We have noticed a significant rise in the SF-36 score at 1st, 3rd and 6th month. As shown in the Fig 3 (Radar chart) and Table 3 all the components were significantly improved over a period of 6 month. Role emotional was the most affected and least improved while role physical, physical functioning and bodily pain has shown a significant improvement over the period of 6 months. (p < 0.0001)

The PCS (Physical component score) and MCS (Mental component score) Component were improved over a period of 6 months and a strong significant improvement in score was seen from 1st to 6th month in the survivor patient (p<0.0001). The MCS component was less improved as compared to the PCS component over the period of 6 months from the time of discharge of patient from the ICU.

**Table 3: HRQOL of ICU patients after discharge from ICU by using SF – 36 at 1st, 3rd and 6th month**

<table>
<thead>
<tr>
<th>Component of SF – 36</th>
<th>1st month</th>
<th>3rd month</th>
<th>6th month</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF</td>
<td>32.12 ± 25.15</td>
<td>43.73 ± 34.12</td>
<td>79.41 ± 34.45</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>BP</td>
<td>32.12 ± 34.18</td>
<td>58.61 ± 12.12</td>
<td>81.43 ± 10.09</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>RP</td>
<td>23.41 ± 12.81</td>
<td>46.51 ± 27.98</td>
<td>75.09 ± 34.60</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>RE</td>
<td>18.12 ± 32.12</td>
<td>38.43 ± 66.71</td>
<td>46.24 ± 56.12</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>EWB</td>
<td>20.21 ± 54.24</td>
<td>39.47 ± 16.12</td>
<td>50.47 ± 72.02</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>SF</td>
<td>28.19 ± 64.16</td>
<td>49.33 ± 34.90</td>
<td>71.11 ± 42.26</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>E/F</td>
<td>23.11 ± 54.52</td>
<td>49.01 ± 40.65</td>
<td>69.12 ± 70.12</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>GH</td>
<td>16.49 ± 11.3</td>
<td>39.33 ± 55.11</td>
<td>64.90 ± 66.46</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>PCS</td>
<td>25.63 ± 4.66</td>
<td>44.40 ± 4.44</td>
<td>74.19 ± 3.52</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>MCS</td>
<td>23.85 ± 4.93</td>
<td>42.60 ± 4.07</td>
<td>69.37 ± 3.27</td>
<td>&lt; 0.0001*</td>
</tr>
</tbody>
</table>

**Post ICU Discharge HRQoL Assessment**

The HRQoL of life was assessed on the basis of SF – 36 score at 1st, 3rd and 6th month for 70 survivor patients. All the scores of physical and mental components of the SF-36 questionnaire were compromised post discharge from the ICU. We have noticed a significant rise in the SF-36 score at 1st, 3rd and 6th month. As shown in the Fig 3 (Radar chart) and Table 3 all the components were significantly improved over a period of 6 month. Role emotional was the most affected and least improved while role physical, physical functioning and bodily pain has shown a significant improvement over the period of 6 months. (p < 0.0001)

The PCS (Physical component score) and MCS (Mental component score) Component were improved over a period of 6 months and a strong significant improvement in score was seen from 1st to 6th month in the survivor patient (p<0.0001). The MCS component was less improved as compared to the PCS component over the period of 6 months from the time of discharge of patient from the ICU.

**Correlation of Age, APACHE II and SOFA score with PCS and MCS**

A significant correlation was found between Age/APACHE II score/SOFA score/ICU stay/MV at 3rd month and 6th month and PCS. No significant correlation was found between Age/APACHE II/SOFA score and MCS.

**Discussion**

Patient surviving in the ICU have a compromised quality of life as compared to the normal person. Some of the studies has mentioned the quality of life has returned to normal in a year. As we have conducted the study for 6 months, our findings suggest improvement in the QOL but has not reached to the population norms.

The mean age of patients admitted to the ICU in our study was 47.81 ± 17.29 years. In a study conducted by Fildissis et al., Langerud A et al., Mafra J et al the mean age of patients was 58.2, 55.1 and 50.2 respectively. The mean age of the patient in our study is less than the Fildissis G et al and Langerud A et al but it coincides with the study conducted by Mafra J et al. In a study conducted by Mafra J et al 38% of patients were > 60 years of age, where as mechanical ventilation while 3 out of the 6 non survivor were on mechanical ventilation.

**Disease Severity Score**

The severity of disease score was assessed with the help of APACHE II score and SOFA score. The APACHE II score > 15 was seen in 83% of non-survivor patients and in 35 % of survivor patients. The SOFA score > 12 was seen in 83.3% of non-survivor and 20% of survivor. There was a strong significant association seen between the APACHE II score and SOFA score with the mortality outcome of the patient (p < 0.0001) (Tables 1 and 2).
in our study it was 20%. The difference can be because of the sample size of our study was smaller as compared to their study.

In our study the Mean ± SD of APACHE II score was 12.08 ± 4.40 which coincides with the findings of Chen CY et al. There was a strong correlation of the APACHE II score with the mortality outcome of the patient, > 80% of the non-survivor patient in our study had the APACHE II score > 15 which is compatible with the study done by Daly et al. The APACHE II and SOFA score have a significant correlation with the PCS.

In our study both physical and mental components of SF-36 improved significantly over time after hospital discharge, which is in accordance with the study conducted by Cuthbertson et al and Rai R et al. Age of the patients is the most influencing factor affecting the Physical component, this coincides with the studies conducted by Cuthbertson BH et al, Eddleston J et al and Pettila V et al. The MCS score has shown a less improvement as compared to the PCS score at 1st, 3rd and 6th month assessment, but it was not influenced by age, APACHE II score and SOFA score.

In some of the previous studies, higher APACHE II score, longer length of stay in the ICU, and prolonged mechanical ventilation have been found to significantly affect the HRQoL after the ICU discharge.

After the discharge of the patients, they were contacted telephonically, most of the patients responded to the telephonic communication but still it was a very challenging task to reach out to the patients telephonically which leads to the lost to follow up of 6 patients during the study.

Conclusion

Our study suggests that there is a strong correlation between the age/APACHE II score/SOFA score/ICU stay/Mechanical ventilation duration with the physical component score after the discharge of patient. The PCS and MCS score significantly improved over a period of 6 months duration. This study contributes the HRQoL after ICU discharge in an Indian population which can be used to draw up the normative data in the developing countries.

Limitations of the study

Many patients were excluded because of the exclusion criteria – tracheostomy, neurological deficit on discharge and head injury.

References

7. WHOQoL: Measuring Quality of Life. https://www.who.int/tools/whoqol
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Microalbuminuria: As an Indicator of Sepsis and to Predict Mortality in Patients Admitted to Intensive Care Unit

CL Nawal1, Sagar Barasara2, Radhey Shyam Chejara3*, PD Meena4, Aradhana Singh3, Vinay Kumar Meena5

Abstract

Background: Sepsis is an important healthcare concern in India as well as globally. This study shows how the level of microalbuminuria predict mortality of patients diagnosed with sepsis and those without sepsis.

Methods: In this study total 150 patients of which 75 patients belonging to each sepsis and non-sepsis group, with age >15 years admitted in Medical Intensive Care Unit (ICU) were enroled. Microalbuminuria levels were analyzed at admission and after 24 hours after admission.

Results: Microalbuminuria levels were significantly high in patients with sepsis as compared to non sepsis. Microalbuminuria has highest sensitivity of 90 % and specificity of 98 % to differentiate between sepsis and non sepsis in comparison to APACHE II and SOFA scores.

Conclusion: Serial monitoring of bedside urine albumin-creatinine measurement might help in the early identification of patients with sepsis that requires early targeted therapy. The 24-hour ACR assessment predicts ICU survival and may have the potential to monitor the efficacy of therapeutic interventions delivered, such as fluid resuscitation, appropriate antibiotics, vasopressors, and ionotropes that affect the endothelium.

Introduction

Sepsis is still an important healthcare concern in India as well as globally, despite all the advances that have been made in medical therapeutics.1,2 Because of frequent delay in diagnosis, targeted therapies do not remain as effective.3,4 There is no standard method to diagnose sepsis early in patients who are critically ill. Sepsis is characterized by host defense response in which a variety of inflammatory mediators are released in the circulation.5 Increased capillary permeability leading to loss of barrier function is an important early event.6 In the kidneys, this is manifested by the glomeruli in the form of increased albuminuria.7 This study was conducted with the objective of assessing the difference between levels of microalbuminuria in sepsis and non sepsis patients. The change in the levels in the first 24 hours were also compared with two scores of sepsis i.e. APACHE II (Acute physiology and chronic health evaluation) and SOFA (Sequential Organ Failure Assessment) scores for the prediction of morbidity and mortality.

Material and Methods

75 patients of sepsis and 75 patients of non-sepsis admitted in ICU of SMS hospital were taken for study after applying inclusion and exclusion criteria.

Inclusion Criteria
- Patient admitted in Medical Intensive Care Unit (ICU) with age >15 years.

Exclusion Criteria
- Patient with anuria, macroscopic hematuria
- History of preexisting Chronic Kidney Disease (CKD) (patients on long-term renal replacement therapy, and/or sonologic features of chronic damage and/or history of glomerular filtration rate of <30 ml/min)
- Female patients with menstruation or pregnancy
- Patients with macroalbuminuria (more than 1+ protein on dipstick) due to renal and post renal causes, for example urinary tract infection
- New infection after 48 hours of ICU admission, i.e., nosocomial infection will be excluded.
- Known case of diabetes and hypertension

Comparison of SOFA score and APACHE score with Microalbuminuria within 6 hour of admission (ACR1), Micro albuminuria at 24 hour of admission (ACR2) and ∆ACR (ACR1-ACR2) was done between sepsis and non-sepsis group.

Results

We enrolled total 150 patients of which 75 patients belonged to sepsis group (Group A) and 75 in non-sepsis group (Group B). Mean age of group A was 50.90 ± 13.32 year and mean age of group B was 47.37 ± 14.37 year. In group A, there were 28 female and 47 male patients, mean SOFA score and mean APACHE II was 7.97 ± 3.802 and 14.53 ± 6.98 respectively. In group B, there were 24 females and 51 male patients and mean SOFA score and mean APACHE II was 5.23 ± 2.84 and 8.71 ± 5.18 respectively (Table 1).

Regarding mortality, out of 75 patients, 24 died in group A comparing with group B in which only 15 patients were succumbed to
does not correlate with the severity is nonspecific, takes time to rise and infections. C-Reactive Protein (CRP) in infectious inflammatory conditions for systemic infections, but it is also used conventionally to identify sepsis. Appropriate lifesaving therapy. There management and early initiation of sepsis early for optimum patient death. Microalbuminuria at 24 hour of admission (ACR2) and ∆ACR (ACR1-ACR2) between sepsis and non-sepsis group. In sepsis group mean SOFA score was 7.97 ± 3.802 and in non-sepsis group was 5.23 ± 2.84 and it was statistically significant (p value = 0.0001). In sepsis group mean APACHE II score was 14.53 ± 6.98 and in non-sepsis group was 8.71 ± 5.18 and it was statistically significant (p value = 0.0001).

In sepsis group initial level of microalbuminuria (ACR1) was 152.01 ± 25.62 mg/g which increased to 156.77 ± 58.64 mg/g (ACR2) after 24 hours of admission. Mean ∆ACR was -4.76 ± 36.69 mg/g in sepsis group. In non-sepsis group initial level of microalbuminuria (ACR1) was 81.4 ± 18.63 mg/g which decreased to 71.13 ± 28.601 mg/g after 24 hours of admission. Mean ∆ACR was 10.27 ± 14.35 mg/g in non-sepsis group. This difference of ACR1, ACR2 and ∆ACR was statistically significant (p value = 0.0001, 0.0001, 0.00012 respectively) (Table 2).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>Mean differences</th>
<th>P value</th>
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<tr>
<td>SOFA score</td>
<td></td>
<td></td>
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<tr>
<td>Sepsis</td>
<td>7.97</td>
<td>3.802</td>
<td>2.75</td>
<td>0.0001(s)</td>
</tr>
<tr>
<td>Non-sepsis</td>
<td>5.23</td>
<td>2.84</td>
<td></td>
<td></td>
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<tr>
<td>APACHE II score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>14.53</td>
<td>6.98</td>
<td>5.76</td>
<td>0.0001(S)</td>
</tr>
<tr>
<td>Non-sepsis</td>
<td>8.71</td>
<td>5.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>152.01</td>
<td>25.62</td>
<td>70.61</td>
<td>0.0001(S)</td>
</tr>
<tr>
<td>Non-sepsis</td>
<td>81.4</td>
<td>18.63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>156.77</td>
<td>58.64</td>
<td>85.64</td>
<td>0.0001(S)</td>
</tr>
<tr>
<td>Non-sepsis</td>
<td>71.13</td>
<td>28.601</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>-4.76</td>
<td>36.69</td>
<td>-15.02</td>
<td>0.0012(S)</td>
</tr>
<tr>
<td>Non-sepsis</td>
<td>10.27</td>
<td>14.35</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Above table shows comparison of SOFA score, APACHE score, Microalbuminuria within 6 hour of admission (ACR1), Micro albuminuria at 24 hour of admission (ACR2) and AACR (ACR1-ACR2) between sepsis and non-sepsis group.

### Discussion

It is important to diagnose sepsis early for optimum patient management and early initiation of appropriate lifesaving therapy. There are several markers that have been used conventionally to identify sepsis. Procalcitonin (PCT) has been used as a sensitive and specific marker for systemic infections, but it is also known to increase in other non-infectious inflammatory conditions and may remain normal in localized infections. C-Reactive Protein (CRP) is another marker which is used but it is nonspecific, takes time to rise and does not correlate with the severity of the disease. As compared to PCT and CRP, levels of microalbuminuria increase within hours of inflammatory injury.

In our study, patients were divided into two groups: Patients without sepsis and patients with sepsis. In both groups, patients were comparable with respect to their demographic parameters.

In our study, in sepsis group 24 out of 75 patients died. Low mortality and low median APACHE II score in sepsis group in our study as compared to C Grion et al (32% vs 71% mortality, mean APACHE II score 14.53 ± 6.98 vs 24.4 ± 7.7) (Table 1). Bhadade RR et al had mortality and APACHE II score similar to our study.

In the current study, the mean levels for ACR1 in sepsis group was 152.01 mg/g with standard deviation (SD) of 25.62 and in non-sepsis group mean level of ACR1 was 81.4 mg/g with SD of 18.63. The levels of microalbuminuria were significantly high among the patients with sepsis at admission as compared to those without sepsis.

In our study, the microalbuminuria levels after 24 hours (ACR 2) and mean ∆ACR levels were found to decrease significantly among the patients with sepsis [ACR2-156.77 ± 58.64 mg/g, ∆ACR= -4.76 ± 36.68mg/g] as compared to the patients without sepsis [ACR2-71.13 ± 28.60, ∆ACR= 10.26 ± 14.34]. After 24 hours, the decline in microalbuminuria could be attributed to the effect of treatment, protecting the glycocalyx layer and preventing rise in capillary permeability. From these observations one could infer that microalbuminuria can be used as a diagnostic tool as well as to check the efficacy of treatment. Singh A et al used microalbuminuria to document the effect of N-Acetyl cysteine and Hydrocortisone in severe sepsis.

In the current study, the area under curve (AUC) of Receiver Operating Characteristics (ROC) curve for differentiating sepsis and non-sepsis was highest for ACR1 (0.994) followed by ACR2 (0.919) and ∆ACR (0.553) (Figure 1).

ACR1 was found to have a differentiating value between sepsis and non-sepsis. In this current study, based on the area under ROC curve, the ability to distinguish between sepsis and non-sepsis was highest for ACR1 at a cutoff of >118.5 mg/g with a sensitivity of 90 % and specificity of 98 %. In our sepsis group the survivors had a mean ACR1 of 138.41 ± 17.65 mg/g which decreased to a value of 121.86 ± 28.34 mg/g after 24 hours with a mean ∆ACR value of 15.55 ± 16.38 mg/g. On the other hand, those who expired had a mean ACR1 of 180.92 ± 12.38 mg/g which increased to 230.96 ± 28.73 mg/g after 24 hours with a mean ∆ACR value of -50.04 ± 23.84 mg/g (Figure 2). Similar findings were found in studies done in past by Basu et al and Bhadade RR et al.

Our study has demonstrated using the area under the ROC curves for
prediction of mortality in sepsis group was highest for APACHE II score (0.993) and ACR2 (0.983) followed by ACR1 (0.969), ∆ACR (0.961) and SOFA score (0.957) (Figure 2). Bhadade RR et al found ACR2 significantly better than APACHE II score for mortality prediction.15,19 Gosling et al had found that ACR2 was as good as APACHE II for mortality prediction.15,19 Gosling et al had found ACR1 as good a predictor of mortality as APACHE II among surgical patients but not medical patients.20

In our study, APACHE II has the highest value among all for predicting mortality. In our study, comparison of ROC of ACR2 APACHE II in sepsis group demonstrate that difference in AUC is 0.0102, Standard error-0.0179 with 95 % confidence interval = -0.0249 to 0.0453, Z value = 0.570 and P value = 0.5689. This finding suggest that there is no significant difference in predicting mortality by ACR2 and APACHE II score and ACR2 is as good as APACHE II score for prediction of mortality in patient of sepsis group.

This can be explained by the presence of ongoing inflammatory processes among those who expired and hence the higher levels of ACR2 among them. On the other hand, a lower level of ACR2 might indicate decrease in the inflammatory activity and explain the improved survival.

In our study for mortality prediction of sepsis group, ∆ACR performed better than SOFA score but not better than APACHE II score. Still, there is no significant difference observed between mortality prediction by APACHE score, SOFA score and ∆ACR (Figure 2).

A similar logic explains the better ability of ∆ACR in prediction of mortality where an increasing trend predicts a poorer outcome, whereas a decreasing trend predicts a better outcome. Abid ET al and Bhadade RR ET al had also found a higher mortality among patients with increasing microalbuminuria levels.15,21

In the past, studies done by Gosling, Gopal and Bhadade RR et al found microalbuminuria as a good marker in the prediction of mortality in sepsis patients.15,22,23

Limitation of study

We have excluded diabetic and hypertensive patient because they have pre-existing microalbuminuria. So our study population is less representative of real life scenario. Further studies will be required to determine effects of illness on pre-existing microalbuminuria. Critically ill patients with urinary tract infections and chronic renal insufficiency were excluded from the study, which may be a limitation to the universal applicability of microalbuminuria as a diagnostic tool.

Many conditions such as age (>40 years), smoking, alcohol, BMI (Body mass index) are independent causes of microalbuminuria in the general population, these patients were included in our study. During the course of treatment, certain nephrotoxic antibiotics were used within creatinine clearance range, thereby limiting kidney injury and ACR levels.

Conclusion

Several potential applications of microalbuminuria measurement in the critically ill are suggested by this study. Urine ACR is significantly higher in the sepsis group in comparison to non-sepsis group. Serial monitoring of bedside urine albumin-creatinine measurement might help in the early identification of patients with sepsis that requires early targeted therapy. The 24-hour ACR assessment predicts ICU survival and may have the potential to monitor the efficacy of therapeutic interventions delivered, such as fluid resuscitation, appropriate antibiotics, vasopressors, and inotropes that affect the endothelium.

References

Prevalence of Glucose Metabolism Disorder in Liver Cirrhosis and its Correlation with Risk Factors of Diabetes Mellitus: A Hospital-Based Cross Sectional Observational Study from New Delhi

Prashasti Gupta¹, Aparna Agrawal²*, Jayashree Bhattacharjee³

Abstract

Objectives: Association between liver cirrhosis (LC) and glucose intolerance has been known since long. This study was carried out to (1) determine the proportion of LC patients having insulin resistance and glucose metabolism disorder (GMD) which includes pre-diabetes (pre-DM) and diabetes mellitus (DM) and (2) study the correlation between GMD and the presence of risk factors (RF) for DM in patients with LC.

Methods: 100 patients with LC admitted in medical wards were studied and tested with fasting plasma glucose (FPG), 2 hours post-75 gram oral glucose load plasma glucose (PPG), glycosylated hemoglobin (HbA1c) and fasting plasma insulin. They were also evaluated for the presence or absence of RF for DM and groups of LC patients with and without GMD were compared.

Results: Out of the 100 patients, 77% were males and 76% were between 30-59 years of age. Insulin resistance (IR) was found in 26% and GMD in 39% (pre-DM 13% & DM 26%). Certain RF for DM like advanced age, positive family history (F/H) of DM, high body mass index (BMI), hypertension, high triglycerides, history of CAD/ CVA/ PVD showed positive correlation with the occurrence of GMD in LC; advanced age, hypertension and high triglycerides had a significant correlation with occurrence of IR.

Conclusion: GMD was prevalent in about a third and IR in about a quarter of patients with LC. Traditional risk factors of DM increase the chances of an individual with LC having GMD. IR increased with advanced age, the presence of hypertension and high triglycerides and did not always predate GMD.

Introduction

Glucose metabolism disorders (GMD) refer to a spectrum of abnormalities in glucose tolerance and their association with liver cirrhosis (LC) is known since long. It includes not only patients of LC developing GMD but also known diabetics developing liver disease progressing to cirrhosis known as non-alcoholic fatty liver disease (NAFLD). World over, GMD has been identified in 44-96% of patients with LC,¹² overt diabetes mellitus (DM) in 13-71% of LC patients³⁴ and pre-diabetes mellitus (pre-DM) in 13-59%.¹⁴ Though LC is a major problem in our country, the prevalence of GMD in LC in Indian settings is not fully known. Also, there is conflicting data on the role of various risk factors (RF) for DM in increasing GMD in LC. Hence, this study was planned to find out more about this association and the likely RF for its occurrence.

Table 1: WHO criteria for diagnosis of DM and Pre-DM

<table>
<thead>
<tr>
<th>Glycemic status</th>
<th>FPG (mg/dL)</th>
<th>PPG (mg/dL)</th>
<th>HbA1c (%)</th>
</tr>
</thead>
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<td>Normoglycemia</td>
<td>&lt; 110</td>
<td>&lt; 140</td>
<td>&lt; 6.0</td>
</tr>
<tr>
<td>Pre-DM</td>
<td>≥ 110 and &lt; 126 and/or ≥ 140 but &lt; 200</td>
<td>6.0-6.4</td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>≥ 126 and/or ≥ 200</td>
<td>≥ 6.5</td>
<td></td>
</tr>
</tbody>
</table>

Materials and Methods

This was a hospital-based cross sectional observational study conducted in the General Medicine Department, Lady Hardinge Medical College and Smt. Sucheta Kriplani Hospital, New Delhi from November 2015 to April 2017. A total of 100 adult (≥ 18 years) patients diagnosed with LC by a combination of clinical/biochemical/ radiological findings, willing to participate and not having the exclusion criteria (on or received corticosteroids within the last 48 hours, suffering from hepatocellular carcinoma, acute/chronic pancreatitis/ pancreatic cancer/post pancreatectomy or endocrinopathies such as Cushing’s syndrome, acromegaly, glucagonoma, pheochromocytoma, polycystic ovarian syndrome) were enrolled into the study after obtaining a written informed consent. All the study patients were subjected to fasting plasma glucose (FPG) and 2 hours post-75 gram oral glucose load plasma glucose (PPG) by glucose oxidase-peroxidase method. Glycosylated hemoglobin (HbA1c) was done by latex agglutination method (NGSP certified) using the D-10 instrument in patients with newly diagnosed hyperglycemia. GMD was diagnosed if the patient was a known diabetic/pre-diabetic or was detected to have DM/pre-DM after entering the study. World Health Organization (WHO) diagnostic criteria were used (Table 1).

Those with symptoms suggestive of diabetes and one abnormal fasting or postprandial value were
Insulin resistance (IR) was found in 26% of patients.

Etiology of Liver Cirrhosis

Majority (71%) patients had chronic alcohol abuse as the cause of liver cirrhosis and rest had other causes such as Hepatitis B (9%), Hepatitis C (3%) NAFLD (5%), and other causes (12%). As shown below, neither GMD, Pre DM nor DM were significantly associated with any particular cause of liver cirrhosis (Table 2).

Risk Factors for DM

Table 3 gives the detailed analysis of all the patients with different risk factors for DM and the prevalence of GMD, Pre-DM and DM in them.

1. Age > 45 years: A total of 37 patients were above 45 years of age, out of which 22 had GMD (14 DM and 8 Pre-DM). Association with GMD was highly significant (p value = 0.001). It was also significantly associated with both pre-DM (p value = 0.039) and DM (p value = 0.049).

2. Sex: 30% (13% pre-DM, 17% DM) of females and 42% (13% pre-DM, 29% DM) of males had GMD, however the frequency of GMD, pre-DM or DM was statistically not significant in either of the sexes.

3. Positive F/H of DM: 21 patients had a positive F/H, out of which 14 had GMD (12 DM & 2 Pre-DM). It was significantly associated with GMD (p value = 0.001) and DM (p value = 0.003) and DM (p value = 0.003).

4. Hypertension (≥ 140/90 mm Hg): 7 patients were hypertensive; all had GMD (14 DM and 8 Pre-DM). It was significantly associated with both pre-DM (p value = 0.039) and DM (p value = 0.049).

5. Smoking: There was no significant association of smoking with GMD (p value = 0.501), DM (p value = 0.155) or pre-DM (p value = 0.549).

6. Low serum HDL-cholesterol: 100% patients had a low HDL. So, no inference could be drawn.

7. High serum triglycerides (> 150 mg/dL): 13 patients had high triglyceride levels out of which 12 had diabetics (13%). Insulin resistance (IR) was found in 26% of patients.

Results

Mean age of the cases was 44.03 ± 12.20 years (range 18-75 years). Male: female ratio was 77:23.

GMD was present in 39%, cases including diabetics (26%) and pre-diabetics (13%). Insulin resistance (IR) was found in 26% of patients.
High serum triglycerides (>150 mg/dL) were found significant RF factors, positive F/H of DM and high abnormalities, as illustrated in the following table (Table 4).

### Table 4: Correlation between number of R/F for DM and GMD

<table>
<thead>
<tr>
<th>GMD</th>
<th>IR</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>1.93± 0.87</td>
<td>3.13± 1.26</td>
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</tbody>
</table>

GMD. It showed highly significant association with both GMD (p value < 0.0001) and DM (p value < 0.0001).

8. High serum total cholesterol: Single patient had a high total cholesterol level. Though he was a diabetic, again no significant inference could be drawn because of small sample.

9. CAD/CVA/ PVD: Total 6 patients had this RF, out of which 4 had GMD (all 4 had DM). A significant association with DM was demonstrated (p value = 0.038).

10. None of our patients had acanthosis nigricans and none of our 23 female patients gave history of Gestational DM or birth of a large weight baby.

### Correlation with Mean Age and Mean Number of RF for DM

Mean age of LC patients with GMD (49.5 ± 13.0 years) (p value = 0.0001), DM (51.2 ± 14.0 years) (p value = 0.001) as well as IR (50.3 ± 11.7 years) (p value = 0.002) was significantly more as compared to LC patients without GMD (40.5 ± 10.3 years). Likewise, the number of RF for DM was also significantly more in LC patients with GMD (p value < 0.0001), DM (p value < 0.0001) as well as IR (p value = 0.026) as compared to LC without these abnormalities, as illustrated in the following table (Table 4).

After adjusting for confounding factors, positive F/H of DM and high triglycerides were found significant RF for GMD as well as DM, whereas, high BMI was also found to be significant RF for GMD (Table 5).

Note: Since all the 7 patients with hypertension had GMD, multivariate logistic regression could not be applied because of zero in the contingency table.

After adjusting for confounding factors, no RF was found to be significant for pre-DM.

### Discussion

#### Demographic Characteristics of Cirrhotics

In our study, the mean age of 100 studied patients was 44.0 ± 12.2 years; 77% being males. 60% of total cases were from the 30-49 years age group. In a prospective cross-sectional study of 158 cirrhotic patients from Chennai, India, the overall mean age was 53.3 ± 11.5 years; majority (93.7%) were men. The mean age was similar to this in the study by Garcia-Compean D et al (56%), cryptogenic (51%), hepatitis C (32%), or alcoholic (27%) cirrhosis. In yet another study, overt DM was found to be highest among those with chronic hepatitis C (36.4%) and those with chronic hepatitis B (20%) and alcoholism (20%). 33.8% of our alcohol induced LC patients had GMD with 9/71 (12.68%) having overt DM.

#### Frequency of GMD in LC

Prevalence of GMD in our study was 39% including 11% (all DM) were already known cases whereas 28% (15 DM & 13 pre-DM) were newly diagnosed. Reported prevalence among the studies performed in the past varies from 44%-96%.1,2,7,13 Our results (39%) are matching with the study by Hu L et al (44%).

In our study, the prevalence of diabetes was 26%; the literature reveals a wide range of 13-71%.1,3-7,11,13 Our results were comparable with the studies by Islam MK et al (21.67%), Garcia-Compean D et al (26%), Hu L et al (31.25%) and a systematic review and meta-analysis by Lee WG et al (31%). A higher proportion (64.5%) found by Braganca ACC et al was probably because the study included decompensated cirrhosis cases awaiting orthotopic liver transplantation.

In our study pre-DM was 13%. Comparing with available literature, prevalence varies from 13-59%.1,4,6,8,15 Higher prevalence (59.3%) in the study by Custro N et al is probably explained by the fact that 121 out of the total 145 patients with LC were hepatitis C virus related.

#### Prevalence of IR in LC and GMD and its Correlation with Etiology of LC and RF for DM

In our study, IR was 26% (HOMA-IR ≥2.5) and age (≥ 45 years), hypertension (≥ 140/90 mm Hg) and high serum triglycerides (> 150 mg/dL) were
A positive correlation. However, no study could be found on the correlation of hypertension as RF for GMD in LC. Correlation with smoking was not found as significant. Also, no major study in the past has studied this factor. High triglycerides were found to be significantly associated in present study however, no major study has studied lipids as a risk factor of GMD in LC. We could not assess the role of low LDL as all our patients had a low HDL. A significant association with CAD/CVA/PVD and DM was found in present study, however, no older studies was available for comparison.

Strength of this study lies in the fact that GMD was established after repeating FPG and PPC values in all asymptomatic patients to confirm the abnormality. Also, all risk factors of DM were studied and correlated individually with the risk of GMD/DM/pre-DM. One important limitation of the study was that certain confounders could not be avoided like presence of ascites and pedal edema on BMI, effect of use of diuretics on BMI, low blood pressures in the study group (e.g. constitutionally due to splanchic vasodilatation, use of diuretics for treatment, etc.), false low values of HbA1c in patients of cirrhosis.

Conclusion
It was found that GMD was prevalent in about a third of patients with LC. Thus, it is recommended to screen and monitor glycemic status in all patients with LC. Traditional RFs of DM like advancing age, positive F/H of DM, high BMI, hypertension, high triglycerides and a history of CAD/CVA/PVD were found to increase the chances of an individual with LC having GMD. In our study, IR was found in about one-fourth of total patients and advancing age, hypertension and high serum triglycerides were found significant risk factors associated with IR.

The effect of preventive measures for controlling the modifiable RF for DM in reducing the occurrence of GMD in LC needs to be studied.

Acknowledgements
We would like to express our thanks to Miss Bhawna, who helped us with the data analysis and technical assistance.

References
### EVIDENCE | TRUST | CREDIBILITY

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### Allegra-M

**Rich evidence in Indian patients with proven clinical superiority vs other combinations**

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<th>Fexofenadine + Montelukast</th>
<th>Levocetizine + Montelukast</th>
<th>Bilastine + Montelukast</th>
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<td>23.2%</td>
<td>No data</td>
</tr>
</tbody>
</table>

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**Your trusted choice for managing Allergic Rhinitis**

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**Reference**

1. Walekar A, Chodankar D, Naqvi M, Trivedi C: Assessment of Bioequivalence of Fexofenadine and Montelukast Fixed Dose Combination Tablet Versus Separate Formulations of the Individual Components at the Same Dose Levels. Indian journal of pharmacy sciences, 2016, 78(5), 65656
4. Concomitant bilastine and montelukast as additive therapy for seasonal allergic rhinoconjunctivitis and mild-to-moderate asthma. The SKY study. 2019

Study of Correlation of CD4, CD8 Count with Tuberculous Pneumonia and Non Tuberculous Bacterial Pneumonia in Type-2 Diabetes Mellitus

Surendra Kumar¹, Rajkumar Lakiwal², Chandreshwar Pratap Singh², Chandra Shekar Bhandiwad², Nitin Sharma², Vipin Singhal², Ashish Chakranarayan²

Abstract

Aim: Type-2 DM patients are susceptible for various types of infections. Long standing Type-2 DM patients have strong predilection for tuberculosis as seen in various studies. Here, we aimed to study susceptibility of tuberculosis as compared to other non tuberculous pneumonia in type-2 DM on the basis of CD markers.

Material and Methods: A case control study on 150 subjects was conducted in S.P. Medical College and Associated Group of P.B.M. Hospitals, Bikaner. Subjects were divided into 3 groups each of 50 type-2 diabetic patients having tuberculosis pneumonia, of 50 type-2 diabetic patients having non tuberculosis pneumonia and 50 patients of type 2 diabetes as a control group attending Medical Outdoor and those Admitted in Hospital IPD Wards. All participants were subjected to detailed clinical examination and relevant investigations. Flow cytometry was used for CD4 and CD8 count.

Results: Diabetic patients with tuberculous pneumonia have significantly (p-value <0.05) elevated numbers of CD4 and CD8 cell count in comparison of both controls and nontuberculous pneumonia. Diabetic patients with non tuberculous pneumonia have significantly (p-value <0.05) lower CD4 and CD8 cell count in comparison of diabetic controls and diabetic patients with tuberculosis pneumonia.

Conclusion: DM is associated with an alteration in the immune response to tuberculosis, leading to a induction of CD4 and CD8 mediated cellular responses and likely contributing to increased immune pathology in M. tuberculosis infection. Our study also provides an impetus to perform longitudinal studies examining the role of immunological biomarkers in the development of tuberculosis in diabetic patients.

Introduction

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system. Based on the current trends, International Diabetic Federation projects that 438 million individuals will have Diabetes by 2030.¹ Type 2 diabetes mellitus (T2DM) is the predominant form of diabetes worldwide, accounting for 90% of cases globally.² There are around 62 million people living with diabetes and the estimated prevalence of diabetes in India was 10.4% in 2011.³ Type 2 diabetes mellitus is a metabolic disorder characterized by peripheral insulin resistance and reduced insulin production. Type 2 DM has been viewed in the past as a disorder of ageing, with an increasing prevalence with age. This remains true today. However, a disturbing trend has become apparent in which the prevalence of obesity and T2DM in children is rising dramatically. Chronic complications can be divided into vascular and nonvascular complications. The vascular complications of DM are further subdivided into microvascular (retinopathy, neuropathy, and nephropathy) and macro vascular complications [coronary heart disease (CHD), peripheral arterial disease (PAD), cerebrovascular disease].¹,⁶ Nonvascular complications include problems such as gastroparesis, infections, and skin changes.

Diabetes affects the immune system in different ways and if the immune system is suppressed, the risk of contracting various infections increases like urinary tract infections, respiratory tract infections, genital infections, skin infections and predilections to other septic foci. Among respiratory tract infections diabetes may lead to tuberculous and other infectious pneumonia (eg-pneumococcal).

Tuberculosis is a chronic bacterial infection caused by Mycobacterium Tuberculosis usually characterized pathologically by the formation of granulomas.⁴ The most common site of infection is the lung, but other organs may be involved. Most infections do not have symptoms; in which case it is known as latent tuberculosis. About 10% of latent infections progress to active disease which, if left untreated, kills about half of those infected. A number of factors make people more susceptible to TB infections. The most important risk factor globally is HIV. Tuberculosis is closely linked to both overcrowding and malnutrition, making it one of the principal diseases

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of poverty. Certain medications such as corticosteroids and infliximab and other disease states can also increase the risk of developing tuberculosis. These include chronic lung diseases (like Silicosis) and diabetes mellitus. Patients with diabetes are at greater risk of contracting TB and diabetes can worsen the course of TB. TB can worsen glycemic control in patients with diabetes.

CD4 and CD8 cells are type of blood cells that are part of our immune system. They are type of white blood cell (lymphocyte), called as T-cells. Most CD4+ T cells function as cytokine secreting helper cells that assist macrophages and B lymphocytes to combat infections. Most CD8+ cells function as cytotoxic (killer) T lymphocytes (CTLs) to destroy host cells harboring microbes. CD4+ and CD8+ T-cells shares several effector functions that mediate anti-mycobacterial activities and CD8+ T-cells responses should as well are stimulated to provide protective immunity. Response by helper and cytotoxic cells is well regulated to combat infections. In our study, we just want to find out response of these CD markers in diabetic patient when patient infected with TB or other non-tuberculous bacterial pathogen causing pneumonia.

**Methods**

A case control study was conducted from June 2017 to December 2017 in S.P. Medical College and Associated Group of P.B.M. Hospitals, Bikaner after clearance from institutional ethical committee to find out “Correlation of CD4 and CD8 count with tuberculous pneumonia and non tuberculous (bacterial) pneumonia in type 2 diabetes mellitus”. It included 150 subjects, which includes a group of 50 type-2 diabetic patients having tuberculous pneumonia, a group of 50 type-2 diabetic patients having non tuberculosis pneumonia and 50 patients of type 2 diabetes as a control group attending Medical Outdoor and those Admitted in Hospital IPD Wards. All participants were subjected to detailed clinical examination and relevant investigations. Only after the inclusion and exclusion criteria’s are met, the subjects were included in the study.

**Inclusion Criteria**

Patients above 18 years of age who have or recently diagnosed to have type 2 diabetes (according to ADA 2017 guidelines), Patients who are known or recently diagnosed to have either tuberculous or non tuberculous (bacterial) pneumonia (according to RNTCP and WHO guidelines) and patients willing to participate in study.

**Exclusion Criteria**

Patients who are seriously ill and systemic illness like chronic liver disease, chronic kidney disease, HIV, malignancy and connective tissue disorders, Patients having history of use or on immunosuppressive drugs, corticosteroids or on radiotherapy. For each patient the following data was collected: Age, Sex, biochemical parameters (complete blood count including hemoglobin, total and differential leukocyte count, total platelet count, HbA1c and fasting plasma glucose). Complete physical examination of each participant was done. Flow cytometry was used for CD4 and CD8 count.

**Results**

Mean age of type-2 diabetic patients having tuberculous pneumonia included in the study was 59.66±10.57, mean age of 50 type-2 diabetic patients having non tuberculosis pneumonia was 57.52±12.49 years and mean age of controls was 59.20±8.11 years. There were 85 males (56.66%) and 65 females (43.33%) in the study population.

Table 1 shows, the mean CD4 and CD8 count of male diabetics and female diabetics of tuberculosis pneumonia and non tuberculosis pneumonia. In tuberculosis pneumonia, the mean CD4 and CD8 male diabetics were 971.26 and 658.95 respectively, and 1006.06 and 650.29 was of female diabetics. Whereas, in non tuberculosis pneumonia, the mean CD4 and CD8 of male diabetics were 972.43 and 451.29 respectively, and 740.22, 448.81 was of female diabetics. On statistical comparison the difference was found to be significant (p value-0.001) when all the three groups diabetics of tuberculosis pneumonia, diabetics of non tuberculosis pneumonia and diabetic controls were compared with each other. But when we compare male to female within group we did not found any significant difference in CD4 and CD8.
Figure 1 shows age wise distribution of diabetic cases and Non Diabetic Controls. In age group 21-40 years, there are 5 cases (5%) all of them are type 2 diabetics and there are 0 Controls in this Age Group of 21-40 years. In age group 41-60 years, there are 53 cases (53%) all of them are type 2 diabetics and 24 (48%) patients were of tuberculous pneumonia and 29 (58%) Patients were of non tuberculous pneumonia. There are 32 Controls in this Age Group of 21-40 years. In age group 61-80 years there are 42 cases all of them are type 2 (4%) diabetics and 23 (46%) Patients were of tuberculous pneumonia and 19 (38%) patients were of non tuberculous pneumonia. There are 18 (36%) controls in this age group of 61-80 Years.

Table 2 shows in tuberculous pneumonia, the mean CD4 and CD8 of 21–40 years of age group diabetics were 1026±120.38 and 668.9±97.7 respectively. In the diabetic subgroup 6–10 years the mean CD4 and CD8 were 1037.8±74.2 and 661.5±100.3 respectively. In the diabetic subgroup 11–15 years the mean CD4 and CD8 were 949.0±210.7 and 639.5±178.9 respectively. In the diabetic subgroup <5 years were 950.3±89.1 and 653.4±107.5 respectively. In the diabetic subgroup >15 years the mean CD4 and CD8 were 779.0 and 522.0 respectively. On statistical comparison the difference was found to be significant (p-value <0.05) when all the three groups diabetics of tuberculous pneumonia, diabetics of non tuberculous pneumonia and diabetic controls were compared with each other. But when we calculate p-value between age group within group we did not found any significant difference in CD4 and CD8 count.

Figure 2 shows, distribution of cases according to duration of diabetes of tuberculous pneumonia group and non tuberculous pneumonia group. All patients in these two groups were divided in four subgroups as duration of diabetes <5 years, 6 to 10 years, 11 to 15 years, and >15 years. There are respectively 19(19%), 28(28%), 2(2%), and 1(1%) cases in tuberculosis pneumonia group and respectively 19(19%), 28(28%), 3(3%) and 0(0%) in non tuberculosis pneumonia group.

Table 3 shows in tuberculous pneumonia, the mean CD4 and CD8 of diabetic subgroup <5 years were 950.3±89.1 and 653.4±107.5 respectively. In the diabetic subgroup 6–10 years the mean CD4 and CD8 were 1037.8±74.2 and 661.5±100.3 respectively. In the diabetic subgroup 11–15 years the mean CD4 and CD8 were 949.0±210.7 and 639.5±178.9 respectively. In the diabetic subgroup <5 years were 950.3±89.1 and 653.4±107.5 respectively. In the diabetic subgroup >15 years the mean CD4 and CD8 were 779.0 and 522.0 respectively. On statistical comparison the difference was found to be significant (p-value <0.05) when all the three groups diabetics of tuberculous pneumonia, diabetics of non tuberculous pneumonia and diabetic controls were compared with each other. But when we calculate p-value between age group within group we did not found any significant difference in CD4 and CD8 count.

**Discussion**

An effective immune response to *S. pneumoniae* involves both T-cell dependent and independent responses. Type 2 diabetes and its associated inflammation results in alteration of immune system and increased susceptibility to infections by pathogens such as *Streptococcus pneumoniae*. The study therefore investigated the CD4+ and CD8+ cells in those with and without diabetes. Patients with diabetes demonstrated a lower frequency of total CD+ T-cells, which showed significant inverse association with elevated fasting blood glucose. This study demonstrated that those with type 2 diabetes have a diminished pathogen-specific memory CD4+ and Th17 response, and low percentages of CD+ T-cells in response to *S. pneumoniae* stimulation.

Type 2 diabetes is a major risk factor for active pulmonary TB as well as a predictor of poor treatment outcomes and reduced survival among those with TB disease. Susceptibility to active TB is influenced by many host factors, including DM. Tuberculosis infection and disease are known to induce alterations in innate and adaptive immune responses, modulations that determine the status of infection (latent versus active) as well as the degree of pathology. Establishment of a pro-inflammatory environment both locally and systemically is a hallmark of chronic TB disease. Similarly, DM is also characterized by a chronic state of low-grade inflammation due to activation of pro-inflammatory mediators and increased formation of advanced glycation end products. In addition DM can also profoundly modulate cells of the innate and adaptive immune system, most notably monocytes/macrophages and neutrophils. Finally, T-cell responses are also known to be altered in DM.
with hyperactivation of T cells being a major feature. However, the role of innate and adaptive immune cells in diabetes with coincident TB has not been explored in detail.

A detailed meta-analysis of 13 observational studies on the risk for TB disease in diabetes determined that diabetic patients were 3.1 times more likely to develop TB than non-diabetic individuals. In a study done by Kumar et al. shows that those with tuberculosis coincident with DM have elevated frequencies of CD4+ Th1 cells, as well as increased frequencies of Th17 subsets following mycobacterial antigen stimulation in comparison to individuals with tuberculosis and without DM. The immunological basis for this susceptibility to TB among those with DM is poorly understood. The initial explanation for the increased susceptibility to TB related to the suggestion that an impaired immune response in diabetic patients could potentially facilitate either primary infection with TB or reactivation of latent TB. Indeed, a few studies examining the innate and adaptive immune response to microbial antigens in diabetic patients had suggested that these responses are compromised, particularly in patients with chronic hyperglycaemia. More recent data from animal models suggest that diabetic mice infected with TB actually manifest an exuberant Th1 response that leads to immune mediated pathology. In a study done, mice with chronic hyperglycaemia exhibit deficient priming of the adaptive immune response, resulting in a higher bacterial burden in the lung that is associated with an exuberant (not impaired) Th1 response, leading to immune mediated pathology. Interestingly, these data mirror the finding that human TB patients with DM over-express cytokines that are normally protective in TB. In addition, in a previous study, it was demonstrated that TB-DM is associated with the presence of expanded frequencies of antigen-specific CD4+ Th1 and Th17 cells as well as a pro-inflammatory cytokine milieu. Both CD4+ and CD8+ T cells are essential for immunity to TB; these cells are known to play a protective role in the immune response to murine TB and M. tuberculosis-specific CD8+ T cells have also been found in humans.

**Conclusion**

TB-DM co-morbidity is characterized by major alterations in the homeostatic levels of CD4+ and CD8+ T-cell subsets. T cells in TB-DM are known to be hyper activated, although the exact memory phenotype of these cells is not known. Our study highlights the contribution of poorly controlled type2 DM to the pathogenesis of TB disease by alternation in the absolute numbers of CD4 and CD8 cells. Our study also provides an impetus to perform longitudinal studies examining the role of immunological biomarkers in the development of tuberculosis in diabetic patients.

**References**

Artificial Intelligence in Medicine

Rahul Deshmukh1*, Pravin Rathi2

Abstract
Artificial intelligence as the name suggests is intelligence given to machines by man. AI learns and performs like humans without human instructions. We encounter AI in daily activities, like music and video suggestions in video applications, and personalize what we see on Facebook, Twitter, Instagram. AI makes our day-to-day life easier, efficient and it increases the speed and accuracy of our efforts. In this article, we reviewed previous articles and internet sites to understand the general principles of artificial intelligence. We included general articles and few articles related to medicine to understand the basics of AI and its application in the medical field. A literature search was done using the following search terms: ‘AI’ and ‘AI in medicine’.

Introduction

The term Artificial intelligence was coined by John McCarthy in 1956. It includes a set of concepts, technologies, and methods that aim at making machines or robots think and learn like humans so they can perform tasks without any human instructions and intervention. Artificial intelligence (AI), in general, is the capability of a machine to imitate intelligent human behavior.1 It means any work performed by a machine or robot will be carried out in the same way in which a human being would have done it. Parts of human intelligence like learning, planning, reasoning, creativity are linked to some of the behaviors of AI. It learns from experience, understanding language, recognizing objects, human faces, puzzle solving etc. AI is now part of our daily life. It has the ability to become smarter than the best human brain in practically every field.

Artificial intelligence

AI is a branch of computer science that attempts to both understand and build intelligent entities, often represented as software programs.2 It is made up of 3 core processes
1. Machine learning
2. Deep learning
3. Artificial neural network

Machine learning

It is a branch of AI that learns from data and in-process improve their accuracy over time. It gives machines/robots the capability to learn without being explicitly programmed. Digital assistants that respond to voice commands browse the web and play music are examples of machine learning.3 Machine learning in AI is similar to the “learning” and “problem solving” skills of humans. A machine cannot learn on its own, so it aims to give machines the ability to learn without pre-existing code. A large amount of trial examples for a task is given to a machine. As it goes through these examples, machines learn and make a strategy to achieve those goals. It automatically develops mathematical algorithms from given data (input data) and predicts or makes decisions (output) in certain conditions without human instructions.

For example, face-recognition machines used in smartphones. It may be given millions of pictures to analyze. After going through endless permutations, the machine acquires the ability to recognize patterns, faces, shapes, and more. Machine learning help to understand, predict and support decision making of computer.4 Machine learning gives computers the ability to develop their own rules using advanced software algorithms.

Big data is an important part of machine learning. It is the large amount of data, both structured and unstructured that has to be analyzed to get valuable information. Big data in form of images, texts, scanned documents, patient’s record etc. can be stored in the cloud rather than on-premises, and that can be analyzed faster and cheaper and makes it possible to “train” machines to do a job without being explicitly programmed to do so.4

Supervised machine learning

It is part of machine learning which trains itself on a labeled data set. It requires less training data and makes training easier as compared to other machine learning methods because the results can be compared to actual labeled results.3 It takes a known set of input data and known responses to the data (output), correctly labeled by a human expert and trains the machine to find patterns and make predictions for the response to new data.5 Using supervised machine learning an algorithm can learn the correct relationship between the input label and the output label and then use this data to classify unlabeled images the computer has not seen before. Supervised learning may be more accurate but it is resource-intensive and human experts are needed to make training data set.6

In supervised machine learning actual output vector is compared with the desired output vector. An error signal is generated during this comparison if the actual output and desired output vector are not matched. Based on this error signal, an adjustment in the weights is done until the actual output is matched with the desired output, as shown in Figure 1.

For example, in colonoscopy, an image of polyp is given as an input vector, then desired output vector will be a polyp. In the process, if

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five, as shown in Figure 2.

desired output and if it is correct or environment as to what should be the clusters. There is no feedback from the kinds of tissues.

Reinforcement learning

Reinforcement learning is a training method based on positive and negative reinforcement i.e., rewarding desired behaviors and/or punishing undesired ones respectively. It’s all about taking suitable action to maximize reward in a particular situation. It enables a computer/machine to learn and correct outcomes through rewards and penalties using the trial-and-error method. In the absence of a training dataset, it is bound to learn from its experience. Reinforcement learning can be used in robotics for industrial automation.

While supervised learning models predict whether a person is suffering from a disease or not, RL predicts treatment options for patients suffering from a particular disease.

**How does Machine Learning Work?**

Humans learn from experience. Learning of machines is in a similar fashion to human beings. Humans can predict better if we have more knowledge of the situation. When we face an unknown situation, the likelihood of success is lower than the known situation. Training to machines is done similarly. To make an accurate prediction, the machine is provided with an example, it can figure out the outcome. However, like a human, if a previously unseen example is given, the machine has difficulty in predicting. Medicine fields that deal with large image datasets for diagnosis, such as gastroenterology, cardiology, radiology are strong candidates who benefit from machine learning. Machine learning can be trained to process and analyze images and identify abnormalities, thus improving accuracy.

Deep learning

It is a subset of machine learning technique that composed of multiple-layered neural network algorithms. Deep learning is a part of machine learning which functions similar to human brain processing, taking into account multiple data sets at the same time. It is called deep learning as there is use of multiple layers in the network. It is a computer-based method that analyzes data and provides predictive models. Deep learning is part of artificial intelligence that contains many specialized artificial intelligences that acts together in a coordinated way. It works on the principle of gaining knowledge from analyzing data and use that knowledge to analyze different data sets. Deep learning helps to formulate general-purpose learning algorithms that help machines learn more than just one task. In the same way that the human brain processes information through neurons and synapses, deep learning gets information from multiple data sources and process it through multiple layers. With each layer of neural network in deep learning, it performs calculations and makes predictions, learns progressively, and gradually improves the accuracy of the outcome over time. To make the outcome accurate, deep learning programme need access to a large amount of data or big data and processing power. A deep learning programme is capable to create accurate predictive models from large quantities of unlabeled, unstructured data. Deep neural networks consist of multiple layers of interconnected nodes, each of which uses a progressively more complex deep learning algorithm to extract and identify features and patterns in the data. With deep learning algorithms AI able to achieve significant success at image recognition, speech recognition, and language understanding. Voice recognition applications (such as Apple’s Siri, Amazon Alexa and Google Assistant), are instances of deep learning because they can recognize anyone’s voice commands without a specific training session.

**How it differs from machine learning?**

While machine learning can work with structured, labeled data, deep learning can also process and analyze unstructured, unlabeled data. Deep-learning uses a multi-layered neural network to get output from the data and get better and better at identifying and classifying data on its own. While machine-learning algorithms are linear, deep learning algorithms are arranged...
in a network of increasing complexity. The number of processing layers through which data must pass is what inspired the label ‘deep’.12 While machine learning uses simpler concepts, deep learning works with artificial neural networks, which are designed to imitate how humans think and learn.

**Artificial neural network (ANN)**

ANN is machine intelligence that has cognitive functions similar to those of humans such as “learning” and “problem-solving.” ANN is the most popular AI technique in medicine.13 ANN is inspired by the biological nervous system (biological neural network). Neural networks contain three layers, an input layer, a hidden layer, and an output layer. The input layer is the first layer where the deep learning model is given the data for processing, and the output layer is where the final identification is done. Inputs are given a certain weight (value/importance). In between layers contain thousands, sometimes millions, of nodes (processing units). Interconnected nodes multiply the weight of the connection as they travel through layers. layers between input and output are called hidden layers, where the calculations of each previous layer are weighted and refined by progressively more complex algorithms. This movement of calculations through the network is called forward propagation. A final output layer puts together all the pieces of information generated to identify the output. If the output is incorrect, the neural network notes the error and adjusts its neurons’ weights. The network examines another input, repeats this step thousands of times, adjusting weights each time, narrowing the error rate until the network correctly identifies the output. Another process called back propagation identifies errors in calculations and pushes them back to previous layers to refine the model.14 Forward propagation and back propagation in combination allow the network to make predictions of the outcome and at the same time learn from inconsistencies in the outcomes. It helps to make a system that learns and gets more accurate over time when processing big data. When compared to a biological neural network, nodes correspond to the somatic body of a neuron, input and output of ANN corresponds to the dendrites and axons of neurons, and synapses are connections between two nodes where memory is stored. Though the processing of information in a neural network is faster it is inferior to the human brain. While the human brain can tolerate some amount of ambiguity, learning in a neural network is very precise and structured. It can learn from previous data, handle imprecise information, analyze non-linear data, and can apply this to another independent set of data thus make them a helpful tool in the field of medicine.15

**Feed forward Network**

A feed-forward network is a non-recurrent type of network. It has nodes arranged in layers and all the nodes are connected with the nodes of the previous layers. The connection has different weights upon them. It is of two types: Single layer feed-forward network and multilayer feed-forward network.

1. **Single layer feed forward network**

   Type of feed-forward ANN having only one weighted layer. In other words, the input layer is fully connected to the output layer, as shown in Figure 3.

2. **Multilayer feed forward network:**

   Type of Feed forward ANN having more than one weighted layer. There are one or more layers between the input and output layers, called hidden layers, as shown in Figure 4. Connection in the hidden layer has strength (known as weight) that is used for the learning process of the network. Through an appropriate learning process, the network can adjust the value of the connection weight to optimize the best result.

**Adjustments of Weights**

Synaptic weight refers to the strength of a connection between two nodes. When compared to a human neural network, it is the influence of the firing of one neuron on another neuron. It helps to reinforce or strengthen the network over some important information.

**Learning**

Learning is a method of modifying the weights of connections between the neurons of the neural network. Learning helps to adapt to the change when there is a change in the environment.

**Application in medicine**

There are certain challenges faced by modern medicine in acquiring, processing, and applying a large amount of knowledge that help to solve complex clinical conditions. The development of artificial intelligence in the medical field is intended to help the clinician in making a diagnosis, therapeutic decisions, and also predicting outcomes. They help healthcare staff in their duties and task that depend on the processing of large data.15 Neural network algorithms can detect polyps and mucosal changes and during colonoscopy, thus minimise the chance of missing such potentially malignant lesions.16
Increasingly, machine learning devices are replacing several time-consuming, labour-intensive and repetitive tasks of clinicians.\textsuperscript{17} ANN can classify and recognise patterns accurately and this can be applied in clinical problem-solving. In many clinical situations, treatment and outcome prediction depend on a complex interaction of clinical, biological, and pathological factors; there is a growing need for tools like ANN which can exploit such interaction. Electronic medical records of patients can be used to develop an algorithm that can identify subjects with a family history of a hereditary disease. Such record-keeping which is accessible to all will be helpful in individual patient management and also in epidemiological research and planning.\textsuperscript{19} New research and clinical findings should be shared through open-source, and combined data must be displayed for open-access by physicians and scientists. The application of AI in medicine includes medical devices and sophisticated robots taking part in patient management. Robots can be used as assistant-surgeons or even as primary surgeons.\textsuperscript{19} AI can make a big impact in the field of gastroenterology as a diagnosis of most of the conditions depends on image-based investigations. AI is becoming highly useful in procedures such as esophagogastroduodenoscopy (EGD), colonoscopy and capsule endoscopy (CE). In EGD, an ANN-based program will be useful to recognize the anatomical location, to detect mucosal changes. For colonoscopy, ANN was applied to detect and classify colorectal polyps and to minimise the chance of missing them.\textsuperscript{10} With capsule endoscopy, AI can be used to detect celiac disease, small intestinal bleeding. Because of poorer image quality due to hardware and light limitation, AI based diagnostic program using CE is difficult to develop. Free motion of the capsule and other factors such as bile, food, and faecal material further limit the image quality of capsule endoscopy.\textsuperscript{21}

**Conclusion**

There is enough evidence that suggests, medical AI can play a vital role in assisting the clinician to deliver health care efficiently. Medical AI technology has not been incorporated with enthusiasm. AI helps to analyze and process a large amount of data and helps to develop an algorithm for patient management, treatment and outcome predictions. It generates information that helps to improve healthcare design. It helps to reduce the time for processing and also increases decision-making accuracy. Researchers should continue to work on new AI technology to familiarise and improve diagnostic and prognostic accuracy. Though it helps us in many ways, there is concern regarding AI is that it may surpass human brain capabilities and eventually will take control over our lives.

**References**


Management of Lupus Nephritis: An Update

Krishan Lal Gupta1*, Joyita Bharati2

Abstract
Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease, and lupus nephritis (LN) is associated with increased morbidity and mortality. Renal biopsy is essential and the gold standard to diagnose LN. Extra-glomerular involvement is seen in up to 60% of patients with LN and is associated with poor outcomes. The revised International Society of Nephrology/Renal Pathology Society classification for LN has changed the parameters for activity index scoring, redefined crescent and highlighted the significance of extra-glomerular involvement. Repeat renal biopsy is done for resistant disease or during a flare, usually when atypical features are present or when the baseline biopsy showed non-proliferative histology. Protocol repeat biopsy may prove to be valuable as a monitoring tool in patients with LN. Newer modalities of therapy like multitargeted therapy and biological agents may pave a way for better outcomes with minimal adverse effects to the patients.

Introduction
Systemic lupus nephritis (SLE) is an autoimmune disease with multisystem involvement with a female preponderance. At the onset, clinical renal involvement is seen in 25-50% of the patients and about 60% of the patients are affected during the disease course, which varies with race and ethnicity.1-3 Use of aggressive immunosuppressive therapy (induction phase) to achieve rapid control of inflammation in the kidneys followed by continued lower doses of immunosuppression to maintain remission has resulted in improved survival amongst patients with lupus nephritis (LN). The probability of a new renal flare is 20-30% per patient-year of follow up.4 Patients with LN, particularly those with proliferative histology, are at 2.28 times higher risk of mortality as compared to those without LN and up to one-third of them progress to ESRD within 15 years.5,6

Epidemiology
SLE is more prevalent in women than men across all age groups and populations; the female-to-male ratio is highest at reproductive age, ranging between 8:1 and 15:1, and is lowest in prepubertal children at about 4:3. The prevalence of SLE and the chances of developing LN vary considerably between different regions of the world and different races and ethnicities, with higher rates in Africans and Hispanics.7 Studies conducted at our center showed similar age at onset and female to male ratio as reported worldwide.8-10 Children and adolescents comprise one-fourth of affected patients with SLE and 40-80% of them have renal involvement.10 Diffuse proliferative glomerulonephritis was the predominant histological presentation in children and more common in boys than girls.10

Pathogenesis
SLE results from the loss of immune tolerance to self-antigens. Defects in tightly regulated mechanisms like apoptosis and clearance of dead cells by macrophages contribute to the exposure of self-antigens. In genetically susceptible individuals, triggers from the environment and a favorable hormonal milieu can lead to the development of auto-reactive lymphocytes producing polyclonal antibodies. These antibodies react with various autoantigens to form immune complexes, which deposit in various organs and cause damage.

Genetic factors like deficiency of early complement components like C1q, C2, C4;11 mutation of TREX1 gene (encodes 3’Endonuclease that degrades DNA), presence of genetic loci like HLA DR2 and HLA DR3, HLA DRB1 loci (especially HLA DRB*0301 and HLA DRB1*1501) carry higher risk for developing SLE. GWAS (Genome-wide association studies) done in patients with SLE revealed presence of >50 gene polymorphisms affecting various components of inflammatory pathway like lymphocyte activation, innate immune signaling, apoptotic & immune complex clearing mechanisms. Immune complexes containing self-antigens interact with Toll-like receptors (TLR7 for RNA and TLR9 for DNA). This activates the innate immune system leading to release of cytokines like type 1 interferons and TNF-alpha from the antigen-presenting cells (dendritic cells) and macrophages. Further, the antigen-presenting cells stimulate the T lymphocytes to secrete cytokines such as IFN-gamma, IL-6, IL-10, IL-17 and IL-21. These cytokines result in sustained inflammatory response by stimulating back the B lymphocytes and macrophages/neutrophils. B-lymphocytes are critical in the development of SLE and LN. They mature into antibody-producing plasma cells and also act as antigen-presenting cells to the T lymphocytes. T lymphocytes, in turn, express stimulatory tumor necrosis factor superfamily (TNFSF) ligands such as BAFF (B-cell activating factor) and APRIL (a proliferation inducing ligand) that bind to TNNFSF receptors present exclusively on the B lymphocytes. The TNFSF ligands BAFF and APRIL can be released from the membrane by proteolytic cleavage to form soluble

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molecules. The binding between these TNFSF ligands on T lymphocytes with the TNFSF ligand receptors on the B lymphocytes promotes differentiation and proliferation of B cells. Sex hormones like estradiol, testosterone, progesterone, dehydroepiandrosterone (DHEA) may influence the disease process by modulating immune responsiveness. Estrogen stimulates T cells, B cells, macrophages and expression of both HLA and cell adhesion molecules (VCAM, ICAM). Estradiol selectively reduces apoptosis of self-reactive B cells; thus promoting the production of autoantibodies. Environmental factors like exposure to infectious agents like viruses or mycobacteria may induce anti-DNA antibodies through molecular mimicry. Exposure to Ultraviolet (UV) light stimulate secretion of cytokines like IL-1, IL-3, IL-6, GM-CSF and TNF-alpha, activation of B cells, interference with clearance of apoptotic material by macrophages and thus promotes autoantibody production. Exposure to environmental toxins like silica dust, cement, cigarette smoke, allergens and drugs are associated increased risk of developing SLE.

**Pathology of Lupus Nephritis**

LN is initiated by deposition of circulating immune complexes or by binding of autoantibodies to antigens in the glomerulus and vessel walls. This interaction activates complement mediated cytotoxicity, macrophage and NK cell induced cell cytotoxicity along with Fc receptor based T-cell mediated cell damage. Anti-phospholipid antibodies can result in thrombotic lesions in the glomerulus and in the vessels. In 20-30% of patients with LN, anti-neutrophil cytoplasmic antibody can be positive and may contribute to the development of vasculitic lesions.

**Value of Renal Biopsy**

Treatment of LN is guided by the histological patterns described in the classification system International society of Nephrology/Renal Pathology Society (ISN/RPS) classification. Clinical severity does not correlate well with histological severity. Therefore, renal biopsy remains indispensable and the “gold standard” to correctly classify LN. The KDIGO, ACR and EULAR/ERA– EDTA guidelines recommend that a renal biopsy is performed to confirm the diagnosis of LN, assess disease activity and/or chronicity and guide treatment.

**Classification of lupus nephritis:** The classification of LN based on histology has been in place for over five decades with the latest change being done in 2018. 1964: Pirani and Pollak classified LN into focal segmental, diffuse proliferative and membranous glomerulopathy groups.15 1974: WHO classification: Included 5 classes : class I-normal glomeruli; class II- pure mesangial; class III-focal proliferative glomerulonephritis; class IV- diffuse proliferative glomerulonephritis; class V-membranous glomerulonephritis.13 1982: Modifications by the International Study of Kidney Disease in Children14 1995: Modification by WHO, included sub classification of class III, IV, V and class IV-advanced sclerosing glomerulonephritis was added.15 2003: ISN/RPS (International Society of Nephrology/ Renal Pathology Society) proposed a new classification system that would provide better clinical correlation, uniformity in reporting and reproducibility. The classification schema is based on glomerular pathology which includes assessment by light microscopy (LM) and immunofluorescence (IF) (Table 1). Updates included a new definition for class I LN, an emphasis on the diagnosis of combinations of membranous and proliferative glomerulonephritis (class III and V, or class IV and V), the separation of class IV LN into segmental (IVS) and global (IVG) variants, and clearer definitions for all classes.16 Class IV LN is the commonest pattern seen worldwide. In a study from our center, of total 232 patients, Class II was seen in 21, Class III in 36, Class IV in 130 and Class V in 30 patients.17 ISN/RPS revision 2018: Concerns of the ISN/RPS 2003 classification were: extraglomerular lesions such as tubulointerstitial and vascular lesions were not given significance, the degree of subendothelial deposits that would differentiate between class II and III/IV was not clearly described, and other entities commonly seen in SLE such as collapsing glomerulopathy and lupus podocytopathy were not included. These are addressed to a great extent in the latest modification of the classification system, ISN/RPS revision 2018 (Table 2). **Extraglomerular Involvement**

Extraglomerular disease in LN involving tubulo-interstitial and vessels are seen in 2/3rd of renal biopsies. Tubulointerstitial lesions is seen predominantly in class IV LN. The severity of tubulointerstitial inflammation correlates broadly with glomerular proliferative lesions.

### Table 1: International Society of Nephrology/ Renal Pathology Society 2003 Classification of Lupus Nephritis (LN)

<table>
<thead>
<tr>
<th>Class</th>
<th>Light Microscopy</th>
<th>IF / EM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I - Minimal mesangial LN</td>
<td>Normal glomeruli</td>
<td>Immune deposits in mesangium</td>
</tr>
<tr>
<td>Class II – Mesangial proliferative LN</td>
<td>Pure mesangial hypercellularity of any degree or mesangial matrix expansion</td>
<td>Immune deposits in mesangium along with a few subendothelial or subepithelial deposits</td>
</tr>
<tr>
<td>Class III - Focal proliferative LN</td>
<td>Segmental or global proliferative lesions in &lt;50% of glomeruli</td>
<td>Sub-endothelial immune deposits with or without mesangial involvement</td>
</tr>
<tr>
<td>III (A)</td>
<td>Focal proliferative Lupus nephritis</td>
<td></td>
</tr>
<tr>
<td>III (A/C)</td>
<td>Focal proliferative and sclerosing lupus nephritis</td>
<td></td>
</tr>
<tr>
<td>III (C)</td>
<td>Focal sclerosing lupus nephritis</td>
<td></td>
</tr>
<tr>
<td>Class IV - Diffuse proliferative LN</td>
<td>Segmental or global proliferative lesions in &gt;50% of glomeruli</td>
<td>Subepithelial immune deposits with or without mesangial involvement</td>
</tr>
<tr>
<td>IV-S (A)</td>
<td>Diffuse segmental proliferative lupus nephritis</td>
<td></td>
</tr>
<tr>
<td>IV-G (A)</td>
<td>Diffuse global proliferative lupus nephritis</td>
<td></td>
</tr>
<tr>
<td>IV-S (A/C)</td>
<td>Diffuse segmental proliferative &amp; sclerosing lupus nephritis</td>
<td></td>
</tr>
<tr>
<td>IV-G (A/C)</td>
<td>Diffuse global proliferative &amp; sclerosing lupus nephritis</td>
<td></td>
</tr>
<tr>
<td>IV-S (C)</td>
<td>Diffuse segmental sclerosing lupus nephritis</td>
<td></td>
</tr>
<tr>
<td>IV-G (C)</td>
<td>Diffuse global sclerosing lupus nephritis</td>
<td></td>
</tr>
<tr>
<td>Class V – Membranous LN</td>
<td>Global or segmental thickening of glomerular basement membrane in &gt;50% of glomeruli</td>
<td>Subepithelial immune deposits with or without mesangial involvement</td>
</tr>
<tr>
<td>Class VI – Advanced sclerotic LN</td>
<td>≥ 90% of glomeruli are globally sclerosed without residual activity</td>
<td></td>
</tr>
</tbody>
</table>

### WHO classification: Included 5 classes : class I-normal glomeruli; class II- pure mesangial; class III-focal proliferative glomerulonephritis; class IV- diffuse proliferative glomerulonephritis; class V-membranous glomerulonephritis.
Table 2: Salient Differences in International Society of Nephrology/ Renal Pathology Society (ISN-RPS) 2003 and ISN-RPS Revision 2018

<table>
<thead>
<tr>
<th>ISN-RPS 2003</th>
<th>ISN-RPS 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesangial cellularity: &lt; 3 cells in one mesangial area</td>
<td>Mesangial cellularity: ≥ 4 cells in one mesangial area</td>
</tr>
<tr>
<td>Endocapillary “proliferation”</td>
<td>Endocapillary “hypercullarity”</td>
</tr>
<tr>
<td>Class IV-G and IV-S subdivision</td>
<td>No subdivision of IV-G and IV-S</td>
</tr>
<tr>
<td>Crescents: &gt;25% of circumference of Bowman capsule</td>
<td>Crescents: &gt;10% of circumference of Bowman’s capsule</td>
</tr>
<tr>
<td>Fibrinoid necrosis not defined</td>
<td>Fibrinoid necrosis defined as fibrin associated with glomerular basement membrane disruption and/or lysis of the mesangial matrix, does not require the presence of karyorrhexis</td>
</tr>
<tr>
<td>National Institute of Health (NIH)-activity index (AI): endocapillary proliferation, fibrinoid necrosis OR karyorrhexis, leucocyte infiltration, hyaline deposits, interstitial inflammation, cellular crescents</td>
<td>NIH-AI endocapillary proliferation, fibrinoid necrosis AND karyorrhexis, hyaline deposits, interstitial inflammation, cellular crescents</td>
</tr>
<tr>
<td>NIH activity and chronicity scores are to be used instead of A, C or A/C parameters</td>
<td>Activity and/or chronicity were reflected through nonspecific A,C or A/C parameters</td>
</tr>
</tbody>
</table>

Presence of IFTA >30% and thrombotic microangiopathy on the second biopsy correlated with worse long-term outcome.

Management of Lupus Nephritis

Treatment of LN involves use of aggressive immunosuppressive therapy in the induction phase to achieve rapid control of inflammation in the kidneys followed by lesser amount of immunosuppression to maintain the remission. The initial phase for induction is for a duration of 3-6 months followed by a maintenance phase of 3-5 years usually.

Induction Agents

Cyclophosphamide: Intravenous cyclophosphamide along with corticosteroids became the standard of care for treatment of LN based on the randomized control trials conducted by National institute of health (NIH). The NIH regimen includes monthly intravenous pulses of cyclophosphamide at a dose of 500-1000 mg/m² for 6 months followed by maintenance with quarterly infusions at same dose for the next 2 years. Using this protocol, remission could be achieved in 61% of patients at the end of induction phase and there were no relapses in the 2-year follow-up period. A similar study at our center revealed overall response rate of 70% (Complete + Partial remission) and 30% failure rate (Failure 20% + Death 10%). Major side effects associated with cyclophosphamide such as leukopenia, infections, gonadotoxicity, hemorrhagic cystitis and risk of malignancies in long-term are associated with cumulative dose received. Fixed low-dose intravenous cyclophosphamide i.e., 6 doses of 500 mg every 2 weekly followed by azathioprine (2mg/kg) as maintenance agent was compared with NIH regimen in the Euro-Lupus trial. This trial, which was performed on predominantly white population with mild renal disease, showed that there was no difference in long term outcomes like patient survival, renal survival or doubling of serum creatinine level in the two arms. Another trial done at our center comparing Euro-Lupus protocol with Mycophenolate mofetil (MMF) for induction in patients with mild renal disease has shown similar renal outcomes. Of a total 173 patients, 100 were equally randomized to

and degree of renal insufficiency at biopsy. Tubular atrophy and interstitial fibrosis (IFTA) are one of the strongest predictors of renal failure. Vascular lesions seen in LN are seen in 1/3rd of the cases. The vascular lesions vary from uncomplicated vascular immune deposits, non-inflammatory necrotizing vasculopathy, true inflammatory vasculitis, thrombotic microangiopathy and arteriosclerosis. Studies showed that vascular involvement in LN indicates increased risk for progression to renal failure. In a study from our center, of total 197 patients, TMA was found in 50 patients (25.4%) with 60% of them having concomitant APS. Patients of LN with TMA had significantly higher rates of oliguria (p=0.035), advanced renal injury i.e. serum creatinine >3mg/dl (p=0.002), fibrocellular and fibrous crescents (p=0.01) and tubular atrophy (0.001) compared to non-TMA patients. They also had higher rates of treatment failure (P=0.02) compared to the group without TMA. Another study (unpublished data) from our centre included 241 patients with LN with 60% having tubulointerstitial involvement, 32.3% having vascular involvement. Those with tubulointerstitial and vascular involvement had lower rates of remission.

Role of Repeat Biopsy

There is no clinical trial that has tested the role of repeat biopsy against clinical data alone to decide therapy. Repeat biopsy is done during renal flare, for refractory LN or as a protocol after induction and/or maintenance therapy for LN. Repeat biopsy can be diagnostic, as clinical and histological activity often do not correlate and it can be decisive, as histological transformations are common and may affect treatment decisions. It has also been shown to be predictive of long term outcomes. Protocol re-biopsies can guide on decision to withdraw maintenance immunosuppression in patients having clinical complete response, as patients with clinical complete response are shown to have activity and chronicity on the biopsy. The indications by the various guidelines are as follows:

**EULAR/ERA-EDEA 2012**: Refractory disease/relapse

**EULAR 2019**: Incomplete renal response defined as 24-hour proteinuria >0.8-1 g/day with stable/improved renal function despite at least 1 year of immunosuppressive treatment

**KDIGO 2012**: During relapse if there is suspicion that the histologic class of LN has changed, or there is uncertainty between activity or chronicity

**Dutch Working Party 2012**: In those where it is anticipated that the findings have therapeutic consequences or/& to differentiate active versus chronic disease.

In a study from our centre (unpublished data) which included 62 patients who underwent repeat biopsy for clinical indications, we found histological transformations in 61.3% of the patients. Class switch from proliferative to non-proliferative occurred in 13.7% and 18.2% of patients with non-proliferative histology switched to proliferative classes. On repeat biopsy, endocapillary proliferation and fibrinoid necrosis decreased whereas glomerulosclerosis and IFTA increased (P<0.001).
receive either CYC or MMF. Baseline characteristics were similar, except for higher 24 h proteinuria in the CYC group. At 24 weeks, 37 patients in each group achieved the primary end point. The complete remission rate was 50% in CYC and 54% in MMF group.

**Mycophenolate Mofetil:** MMF was first used in induction phase in a pilot study conducted in Chinese patients with class IV LN. MMF was shown to be non-inferior to oral cyclophosphamide in that study. Subsequently, a multiethnic study comparing MMF with intravenous cyclophosphamide, by Ginzler et al. showed non-inferiority of MMF. One of the largest multi-centric randomized control trials by Appel et al., Aspreva Lupus Management study (ALMS) involving 370 patients comparing intravenous monthly cyclophosphamide with MMF showed similar clinical response rates (53% vs 56%, respectively) at the end of 6 months. MMF had better response rates compared to cyclophosphamide in Blacks and Hispanics (60% vs 39%).

Although guidelines for management of lupus nephritis including American college of rheumatology (ACR), European league against rheumatism/ European Renal Association-European Dialysis and Transplant association (EULAR/ERA-EDTA) recommends Cyclophosphamide or MMF as agents for induction in LN, high dose of cyclophosphamide (NIH regimen) is routinely reserved for severe renal disease (Sr Creatinine > 3 mg/dl), crescentic glomerulonephritis, thrombotic microangiopathy and in extraglomerular lesions like CNS lupus or diffuse alveolar hemorrhage.

**Calcineurin inhibitors:** Act by inhibiting T-cell activation by binding to calcineurin and suppressing the transcription of IL-2. This in turn will decrease B-cell activation and antibody production. Furthermore, it stabilizes the actin cytoskeleton in podocytes, thus contributing to reduction in the degree of proteinuria. However, long term use of CNIs are associated with nephrotoxicity and higher chances of relapses once the drug is withdrawn.

**Cyclosporine:** Cyclosporine in podocytes, and were followed up till 5 years. There was no difference between rates of renal flare between MMF (19%) and Azathioprine (25%) maintenance, respectively.

**Tacrolimus:** Tacrolimus is a structural analogue (trans-isomer) of cyclosporine which is 4 fold more potent than cyclosporine and is associated with lesser off target side effects such as cosmetic effects and nephrotoxicity. In addition, it does not require drug level monitoring owing to stable pharmacokinetics. In a recently completed phase IIb trial on patients with lupus nephritis, voclosporin, added to MMF and low dose steroid achieved complete remission in 49% patients with 23.7 mg dosage regimen as compared to placebo. The phase III AURA-LV trial evaluating the efficacy and safety of voclosporin in patients with active lupus nephritis is ongoing, with interim analysis showing promising results.

**Multitargeted therapy:** Combination of tacrolimus (4 mg per day) with MMF (1 g/day) and steroids (intravenous methylprednisolone 500 mg for 3 days followed by 0.6 mg/kg/day of prednisolone), called multi-targeted therapy (MTT), as induction therapy was compared with I.V monthly cyclophosphamide (0.75 g/m²) in 368 Chinese patients with active LN. MTT was superior to I.V CYC, with complete remission rates being 46% vs 26% at the end of 6 months. However, rates of serious infections were higher in the MTT group.

**Maintenance Therapy**

After the induction phase, maintenance immunosuppressive agent is necessary to reduce the risk of flares and further renal damage. NIH trials showed that maintenance with quarterly pulses of intravenous cyclophosphamide for a period of 2 years had lesser episodes of relapses in comparison to no maintenance. Contreras et al. showed that maintenance with MMF or Azathioprine was better than quarterly pulses of cyclophosphamide in terms of efficacy and side effects.

**Comparison Between MMF and Azathioprine as Maintenance Agent**

**MAINTAIN trial:** It included 105 predominantly white patients induced with IV Cyclophosphamide by Euro-Lupus regimen, and were followed up till 5 years. There was no difference between rates of renal flare between MMF (19%) and Azathioprine (25%) maintenance, respectively.

**ALMS maintenance trial:** It included 227 patients who achieved remission with MMF induction and were randomized to MMF and Azathioprine maintenance. After a median follow up of 2.3 years, composite outcome which included renal flare, ESRD, doubling of serum creatinine, death or use of rescue therapy was significantly lesser in the MMF group than the azathioprine group (16.4% vs 32.4%). The ALMS maintenance trial which included multiethnic patients, larger number of patients and had compared composite outcomes favors use of MMF as maintenance agent over azathioprine.

ACR and EULAR/ERA-EDTA guidelines recommend use of either MMF or azathioprine as maintenance agent unless patient has been induced with MMF, where continuation with MMF is advised. Duration of maintenance immunosuppression is for at least 3 years in patients who achieve complete remission at the end of induction therapy. In those with high risk of deterioration of renal function such as young age, male sex, failure to achieve complete remission after induction therapy, glomerular crescents on histology, frequent renal flares and high disease activity index,
prolonged immunosuppression is given.

**Biological Agents**

Despite using the conventional immunosuppressive agents, response rates to LN are only 60-70% at the end of induction therapy. High rates of relapses after achieving remission and reduction of drug toxicity have been unmet goals in the management of LN. Hence, there is need for newer drugs that are safe and effective. Biological agents with specific targets in the immune system such as B-cells, costimulatory molecules and cytokines, have been used as alternative options for conventional drugs for achieving rapid and higher rates of remission, for managing refractory & frequently relapsing diseases and as steroid sparing agents.

**Rituximab:** This is a chimeric monoclonal antibody against CD20 on the B-cell surface. Several non-randomized studies have shown efficacy of rituximab in managing patients with lupus nephritis. LUNAR (Lupus nephritis assessment with Rituximab) trial\(^1\) is a placebo controlled phase III RCT. Those in rituximab arm received 1000 mg of Rituximab 2 weeks apart at the start and it was repeated after 6 months. All the patients received 3 pulses of IV Methyl prednisolone followed by oral steroids along with MMF at a dose of 2-3 gm/day. Renal response at the end of 52 weeks was not different between both the arms (57% vs 46% in Rituximab vs placebo arms). Rituximab has shown to be effective in refractory lupus nephritis. In a systematic review on rituximab in refractory lupus nephritis, patients with class III/IV lupus nephritis had better response rates of >75% when compared with class V lupus nephritis. RING (Rituximab for lupus nephritis with remission as a goal) trial, a phase III open label, multicentric RCT with 200 patients who failed to achieve complete remission at the end of induction therapy is ongoing and the results are expected soon. Rituximab has also been proven as a steroid sparing agent. In a pilot trial of 50 patients of active lupus nephritis, 2 doses of 1 gm rituximab 2 weeks apart was given along with MMF and single dose of intravenous methyl prednisolone (500 mg). 86% of patients achieved response (52% complete response and 34% partial response) at the end of 52 weeks. Based on the encouraging results, an open label, multicentric RCT (RITUXILUP) is being carried out using Rituximab + MMF as steroid free regimen. Rituximab or any B-cell depleting agent causes BAFF/BLyS (B cell activating factor/ B lymphocyte stimulating agent) to increase in amount. So theoretically, combination of agents to block both would have maximum effect. To test this hypothesis, CALIBRATE trial was conducted. Both Rituximab and Belimumab were being used, however, it showed no improvement in clinical outcome at 24 weeks, although addition of anti-BLyS antibody did help in delaying B-cell reconstitution.

**Belimumab:** This humanized monoclonal antibody binds to BAFF (B cell activating factor) leading to decreased activation of B cells. BLISS-52 and BLISS-76, two RCTs conducted in patients with active SLE (without lupus nephritis) on standard treatment had shown significant improvement in SLE responder index. A post hoc pooled analysis of all SLE patients with Lupus nephritis (16% of patients enrolled in the two BLISS trials) at baseline showed improved renal outcomes (which were not significant statistically) in parameters like proteinuria, renal remission and serology when compared with placebo. Belimumab is the only biological agent approved by FDA for treatment of active SLE. The BLISS-LN (Efficacy and safety of Belimumab in patients with Active Lupus Nephritis) study is ongoing.

**Atacicept:** This is a fully human recombinant fusion protein that blocks the activity of both BAFF and APRIL (a proliferation inducing ligand). Two RCTs conducted using this drug had to be terminated in view of serious infections. No significant difference was observed between this drug vs placebo in disease activity score at the time of termination.

**Abatacept:** This is a recombinant fusion protein which consists of the extracellular domain of CTLA4 and Fc domain of IgG1. This prevents the binding of CD28 to its receptors CD80 and CD86 leading to block of T-cell co-stimulatory pathway. A phase II RCT of abatacept with MMF & steroids failed to show any difference in renal response when compared with placebo. **ACCESS trial**, a phase II placebo controlled RCT combining abatacept with low dose cyclophosphamide (Euro-Lupus regimen) also failed to show any difference in renal response at the end of 24 weeks.

**Other biological agents that were tested or being tested in clinical trials for lupus nephritis are -**

Sirukumab: IL-6 inhibitor (phase III RCT – failed)

Epratuzumab: anti-CD22 antibody (phase III RCT – EMBODY : failed)

Eculizumab: anti C5a antibody (no trials in SLE or lupus nephritis)

Anti-CD40 ligand: BI 655064 (ongoing phase II trial)

Obintuzumab: humanized glycoengineered anti-CD20 antibody: phase 3 clinical trial comparing Obintuzumab plus MMF versus MMF plus placebo is ongoing

Belimumab: anti-BLyS antibody: phase 3 clinical trial

Rituximab + Belimumab: combination: phase 2 clinical trial

IXAZOMIB: Proteasome inhibitor: phase 1b clinical trial

Anifrolumab: anti-IFN alpha-R antibody: phase 2 clinical trial

Voclosporin: Calcineurin inhibitor: phase 3 clinical trial

**Conclusion**

The clinical course of LN is characterized by flares and about 10-30% of patients do not respond to conventional induction therapy. Newer classification system for LN have highlighted the significance of tubulointerstitial and vascular lesions. Protocol repeat biopsy needs to be evaluated further to be used as a monitoring tool in LN. The toxicity associated with conventional immunosuppressive agents can be avoided by targeted therapies in the future.

**References**


5. Mok CC, Kwok RCL, Yip PSF. Effect of renal disease on the standardized mortality ratio and life expectancy of patients
**Abstract**

Nucleotide-binding oligomerization domain like receptors (NLRs) – intracellular proteins, are a recently discovered class of innate immune receptors that play a crucial role in initiating the inflammatory response following pathogen recognition. The dysregulation of NLRP3 inflammasome can cause uncontrolled inflammation and drive the development of a wide variety of human diseases. Mefenamic acid which belongs to fenamate group inhibits the NLRP3 inflammasome by inhibiting efflux of chloride ions and influx of calcium ions through blocking VRAC and TRPM2 respectively. Thus, Mefenamic acid provides a potentially practical pharmacological approach for treating NLRP3-driven diseases.

**Introduction**

Inflammasomes, first identified in 2002, are a class of cytosolic complexes of proteins that mediate the activation of potent inflammatory mediators. They are integral parts of the innate immune response against the invading pathogens and get activated upon infections or stressors that promote release of pro-inflammatory cytokines, triggering a cascade of inflammatory responses.1

The nucleotide-binding oligomerization (NOD) like receptors (NLRs), a type of pattern recognition receptors (PRRs) which detect both the endogenous products or exogenous pathogenic microbes2,3 are important components of inflammasomes and are located within the cytoplasm which recognize pathogen / damage-associated molecular patterns (PAMPs/ DAMPs).4,6

There are 4 known inflammasomes (NLRP1, NLRP3, NLRP4, and AIM2 inflammasomes) and NLRP3 inflammasome has shown to play an important role in the immune response and therefore has been the most studied amongst all these inflammasomes.7,8

NLRP3, a multiprotein complex consists of a scaffold, an adaptor-apoptosis speck-like protein (ASC) and effector procaspase-1, which initiates the formation of the inflammasome by interacting with ASC, which further recruits and activates procaspase-1 to generate active caspase-1 and then converts the cytokine precursor’s pro-IL-1β and pro-IL-18 into mature and biologically active IL-1β and IL-18, respectively. Once activated, these active interleukins trigger a series of inflammatory responses and pyroptotic cell death.9-11

**Source and Activation of NLRP3 Inflammasome**

The NLRP3 inflammasome are mainly formed in the bone marrow derived cells-macrophages to the stimulation of pathogenic factors like bacterial toxins, particulate matter, and lipopolysaccharide (LPS).26,30

Several molecular and cellular events like ionic mobilization, mitochondrial dysfunction, lysosomal disruption and reactive oxygen species (ROS) production have been proposed for its activation.12 It was shown that the NLRP3 inflammasome can spontaneously assemble if potassium levels get lowered below the physiological intracellular concentration of 70 Mm.13

**Ionic Mobilization**

Abnormal influx of Na+ ions along with efflux of K+ ions seems to be responsible for activating the NLRP3 inflammasome, however Na+ ions alone are insufficient to induce the activation.12 Cl– channels too that have been identified to regulate the NLRP3 activation and include both the volume-regulated anion channel (VRAC) and chloride intracellular channels (CLICs).14,15 Due to the mitochondrial damage and production of oxidative stress the CLICs get translocated to the plasma membrane and induce efflux of chloride ions (Figure 1).14,15 Literature has identified NSAIDs belonging to fenamate class like mefenamic acid, flufenamic acid inhibit the membrane Cl– channels (VRAC) and are selective inhibitors of the NLRP3 inflammasome.15 Calcium mobilization from various sources as endoplasmic reticulum (ER), lysosome lumen and extracellular milieu, leads to activation of NLRP3 inflammasome. The extracellular calcium influxes via the plasma membrane cation channel known as transient receptor potential melastatin 2 (TRPM2) (Figure 1)16,17 and activation of TRPM2 channels increases the NLRP3 activity and IL secretions, intensifying inflammation and cytokine storm.18 Fenamate analogues like flufenamic acid, mefenamic acid, niflumic acid are found to inhibit the transient receptor potential melastatin 2 (TRPM2) channels and thereby reduce the calcium influx.19

NLRP3 inflammasome activation is a self-defending mechanism against invading pathogens and their components assemble and oligomerize which leads to cleaving of procaspase-1 and forming active caspase-1 which are responsible for transforming the pro-inflammatory cytokines into their mature forms, leading to inflammatory response.

**The activation of the NLRP3**
inflammasome occurs in two-stages as sensing and assembling. The first stage which begins with the recognition of PAMPs and DAMPs by TLRs which further activates the NF-κB signalling, resulting in elevated production of precursor proteins, including the NLRP3 protein, pro-IL-1β, and pro-IL-18. The second stage is the assembly and effector stage, which begins with the assembly of the NLRP3 inflammasome. The NLRP3 protein, ASC, and procaspase-1 assemble into the mature complex, which then transforms the immature forms of IL-1β and IL-18 into their mature forms, to participate in the inflammatory effect (Figure 2).

The activation of the NLRP3 inflammasome contributes to the host defense against microbial infections. However, when dysregulated, the NLRP3 inflammasome is implicated in the pathogenesis of several inflammatory disorders. Therefore, it is critical that NLRP3 inflammasome activation is precisely regulated to provide adequate immune protection without causing damage to the host tissues.20

Inflammasome, Inflammation and Associated Diseases

Inflammation represents an immune response of the host to damaging stimulation, realized by pathogens or irritants. Persistent inflammation leads to development of chronic diseases, such as autoinflammatory or autoimmune disorders, neurodegenerative diseases, metabolic conditions, and cancer.21

NLRP3 being non selective gets activated with a wide variety of factors leading to secretion of pro-inflammatory cytokines, driving the chronic inflammation.22

Aberrant NLRP3 inflammasome activation is linked with the development of many diseases and it has been implicated in the pathogenesis of a number of complex acute and chronic diseases, such as coronary heart disease, pericarditis, stroke, pneumonia, acute kidney injury, inflammatory bowel disease, ulcerative colitis, type 2 diabetes, atherosclerosis, dysmenorrhea, periodontal disease, obesity, chronic liver disease, non-alcoholic steatohepatitis (NASH), gout, osteoarthritis, neuroinflammation-related disorders (e.g. multiple sclerosis, encephalomyelitis, brain infection, acute injury, neurodegenerative diseases, Alzheimer’s disease, Parkinson disease). NLRP3 inflammasome is also linked with various cancers, such as colon cancer, breast cancer, melanoma, hepatitis C virus-associated hepatocellular carcinoma, and gastrointestinal cancers.4,23,41 Persistent and abnormal NLRP3 signalling is the basis for all these diseases.24-41,60

NLRP3 Inflammasome and Infections

Inflammasomes play a crucial role in innate immunity by serving as signaling platforms which deal with a plethora of pathogenic products (exogenous) and cellular products (endogenous) associated with stress and damage.24

Inflammasomes are multi-molecular complexes that contain many copies of receptors that recognize the molecular structures of cell-damaging factors and pathogenic agents as already mentioned earlier. Exposure to viruses, bacteria, yeasts or parasites, can induce uncontrolled inflammation.42 Multiple scientific reports have demonstrated that viruses entering the body activate an innate immune response in which inflammasomes play a crucial role in pathogen destruction.43-45

There are two systems of first-line of defense against viruses: the production of Type I interferons and the production of the cytokines IL-1β and IL-18 by inflammasomes. Type I interferons promote an antiviral state in the infected host, whereas cytokines have antiviral effects by inducing inflammatory processes and modulating adaptive immune responses.46

Several studies have demonstrated that infection of cells with the various pathogenic micro-organisms (viruses, bacteria, fungi and protozoa) like influenza A virus (IAV), Human immunodeficiency virus (HIV), Enteroviruses, Epstein Barr virus (EBV), corona viruses, dengue viruses, Zika virus, Helicobacter Pylori, Mycobacterium Tuberculosis, Salmonella Typhomurium, Brucellosis,
Streptococcus pneumoniae, Malassezia, Microsporum canis, albicans, Aspergillus, Paracoccidioides brasilienis, Neospora caninum, Leishmania, Entamoeba histolytica, Schistosoma induces the assembly of inflammasome complexes and IL-1β and IL-18 secretion.30

During host defense against microbial infections, a prominent role is played by the pattern recognition receptors (PRRs) which include membrane bound Toll-like receptors (TLRs) and C-type lectin receptors (CLRs) and non-membrane bound AIM2-like receptor (ALR), RIG-I-like receptor (RLR), nucleotide-binding protein domain and leucine-rich-repeat-containing (NLR) proteins. Activation of these receptors upregulates the inflammasome activity that helps in controlling these microbial pathogens. Further an imbalance in the reactive oxygen species (ROS) and lysosomal rupture due to microorganisms, lead to activation of NLRP3 inflammasome and release of IL-1β.31 Thus, it can be understood that Inflammasomes are activated by a wide range of stimuli such as: pathogenic toxins and components (eg. Lipopoly saccharide (LPS), bacterial flagellin, SARS-CoV E, viroporin proteins, etc.) and endogenous components (eg. DAMPs, PAMPs, K + efflux, cathepsin B release, amyloid-β, etc.).

It is evident from the literature data that the host activates the mechanism of inflammasomes formation as a defense response against the described pathogenic microorganisms, but in turn, some pathogens using their virulence factors may antagonize inflammasome pathways and increase their ability to survive in the host and cause disease. The host organism then expresses excessive amounts of inflammasomes to remove harmful factors, which leads to the overproduction of inflammatory cytokines and can cause excessive inflammation.

Mefenamic acid and NLRP3 Inflammasome

Mefenamic acid belonging to the class of NSAIDs and fenamate family, is a versatile agent with an established antipyretic, analgesic and anti-inflammatory actions. These actions of Mefenamic acid are related to its preferential COX inhibition and EP receptors blockade both centrally and peripherally.32

Given the role of NLRP3 inflammasome in many of acute and chronic diseases, there is a great potential in developing NLRP3 inflammasome inhibitors as therapeutic options. Cytokines like interleukins-1β play a key role in causing inflammation; hence, blocking their effects through NLRP3 inhibition can be effective in the treatment of several conditions like rheumatoid arthritis, psoriasis, dysmenorrhoea, inflammatory bowel disease and other auto inflammatory diseases as discussed in this review.1 Following an infection or injury, the components of inflammasome collect, oligomerize, and assemble to cleave procaspase-1 to its active form. This activation facilitates the conversion of pro-inflammatory cytokines to their active forms (pro-interleukin (IL)-1β and pro-IL-18 to active form IL-1β and IL-18), causing an inflammatory response. It is well understood that the inhibition of aberrantly activated NLRP3 inflammasome can be an important therapeutic target in the array of inflammatory diseases as discussed herein.33

NSAIDs of the fenamate type such as flufenamic acid and mefenamic acid have shown to inhibit NLRP3 inflammasome by reversibly blocking volume-regulated anion channels, which regulate Cl- transport across plasma membrane and also the volume-modulated transient receptor potential (TRP) channels.34

NSAIDs also contribute to limiting the secretion of proinflammatory cytokines through their conventional action on the cyclooxygenase enzyme.34

Evidences from in vitro and preclinical studies have demonstrated, mefenamic acid and flufenamic acid to have the potential neurotoxic inflammatory reducing response through their potent NLRP3 inflammasome inhibition.35

Increased NLRP3 can mediate IL-1β secretion that is responsible for the occurrence of febrile seizures (FS) and FIRES, thus the NLRP3 inflammasome inhibitory action of mefenamic acid may attenuate the pro-inflammatory cytokine (IL-1β) levels.36

Accumulating evidence derived from investigations and clinical observations converges to implicate the auto-inflammatory nature of febrile illness related epilepsy syndrome (FIRES). A closer analysis suggests excessive activation of microglial / NLRP3 inflammasome / IL-1 axis might represent the pivotal event in FIRES, which creates a pro-inflammatory and pro-convulsive milieu.37

In the first-ever study in humans, it has also been shown that mefenamic acid may be used as a neuroprotector. Mefenamic acid in dosage of 500 mg twice daily was safely administered for six months. The anti-inflammatory activity of mefenamic acid, particularly targeting the NLRP3 inflammasome pathway, improved cognitive impairment and reversed memory loss and brain inflammation.38

It is evident from the literature that aberrant activation of NLRP3 inflammasome plays a key role in the pathogenesis of SARS-CoVs diseases progressing to hyper immune response and cytokine storm. The promising results obtained after repurposing of mefenamic acid in covid-19 patients may be related to its synergistic anti-inflammatory action on the COX enzymes and NLRP3 inflammasome, which potentially might have decreased the excessive inflammation, relieved the pain and fever associated with this viral infection.39

Conclusion

Inflammasomes play a crucial role in innate immunity by serving as signalling platforms which deal with a plethora of pathogenic products and cellular products associated with stress and damage.

Aberrant activation of the NLRP3 inflammasome and release of excess interleukin IL-1β is implicated in various acute and chronic inflammatory diseases. Aberrant activation of inflammasome / IL-1β axis in febrile seizures and FIRES is also evident from clinical observations. Thus, inhibition of NLRP3 will help alleviate the excess inflammation associated with these various conditions.

Only fenamates like mefenamic acid and flufenamic acid have shown to inhibit the NLRP3 inflammasome, which may help reduce the excess secretion of pro-inflammatory cytokine IL-1β. Anti-inflammatory action of Mefenamic acid may thus get augmented with the NLRP3 inhibitory action, which has been evident from the literatures and recent clinical evidences. The usual therapeutic dose...
recommended for Mefenamic acid is 500 mg thrice daily for adults and 25 mg/kg/day in three divided dosages for children above 6 months of age. Thus, with this understanding and corroborating evidences, Mefenamic acid seems promising in situations of dysregulated NLRP3 inflammasome conditions and should be explored clinically as relevant.

References

Hemorrhagic PRES: A Rare Neurological Manifestation of COVID-19 Infection

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Abstract
As of August 2021, the COVID-19 pandemic has affected approximately 200 million cases worldwide. Most of the reported medical literature about the COVID-19 infection discusses its respiratory and haematological manifestations, with limited information about its neurological complications. Encephalitis, meningitis, acute disseminated encephalomyelitis, stroke and encephalopathy have been reported in patients with COVID-19 infection. Symptomatology of CNS involvement includes dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and seizures. Encephalopathy is encountered commonly in patients with severe disease, multi-organ dysfunction and elevated inflammatory markers. Acute cerebrovascular disease is another major manifestation of COVID-19 infection and is mainly due to occlusion of large vessels, hypercoagulability and a pro-inflammatory state. In this report, we discuss the diagnosis and outcome of a 30-year-old patient detected with Posterior Reversible Encephalopathy Syndrome (PRES) as a complication of COVID-19 infection. We hope this report will provide physicians with a useful framework for understanding pathophysiology and imaging findings of PRES in COVID-19 infection.

Case report
A 30-year-old patient was admitted to an outside facility with complaints of breathlessness and weakness. He tested positive for COVID-19 infection using reverse transcriptase-polymerase chain reaction (RT-PCR) analysis of his nasopharyngeal swabs. A High-Resolution CT (HRCT) of the chest, performed to evaluate the extent of the lung parenchymal changes, revealed a CT severity score of 18/25. The patient was administered all doses of Remdesivir. However, due to his worsening respiratory and neurological status, he was intubated and shifted to our dedicated COVID-19 tertiary care centre for further management.

On admission, the patient complained of breathlessness and altered sensorium his GCS (Glasgow coma scale) was 3/15. His labs revealed CRP-HS (highly sensitive C reactive protein) of 6.9 mg/l, serum Creatinine level was 0.7mg/dl, BUN and Urea were borderline elevated. Serum Ferritin was also elevated (1440 ng). D-dimer was 1440 ng. D-dimer was borderline elevated. Serum Ferritin was also elevated. Serum Neutrophil count rose to 25000 cells with 92% neutrophils. Two days later the WBC count was 43500, D-dimer was 473 ng/ml, IL-6 levels rose significantly and he needed ionotropic support.

Neurological symptoms were unchanged and repeat CT brain on 4th August 2021 revealed no new areas of involvement or improvement and findings were consistent with the previous MRI scan. Due to the critical condition of the patient an MRI brain could not be performed. While his course in-hospital patient continued to deteriorate clinically and eventually succumbed to the illness on 10th August 2021.

Discussion
PRES is a common clinical condition seen in eclampsia, autoimmune disorders, patients on immunosuppressive therapy and in patients with severe inflammation and sepsis. It presents with headaches, altered mental status, seizures and/or visual disturbances. The pathophysiology of PRES is yet unclear but there are multiple theories to explain this phenomenon. The first suggests that in severe hypertension when the autoregulatory mechanism of the brain fails there is damage to the blood-brain barrier with resultant fluid egress and vasogenic oedema. But contradictory to this theory is the fact that PRES also occurs in patients with mild hypertension or even normal
normotensive patients and also there is no close correlation between the severity of hypertension and the degree of brain oedema.

Another theory describes the development of vasoconstriction as an autoregulatory mechanism of severe hypertension leading to ischemia, reduced perfusion and cytotoxic oedema. This theory is supported by the development of PRES in patients with endothelial injury, sepsis, bone marrow transplantation, systemic chemotherapy and vasculopathy diagnosed on angiography.

A third theory explains systemic activation as a cause, particularly cytokines like Tumor necrosis factor-alpha and interleukins express adhesion molecules that react with the leukocytes to release reactive oxygen species, this, in turn, causes endothelial damage and fluid leakage. These cytokines also produce Vascular endothelial growth factor (VEGF) which increases blood-brain barrier permeability by weakening endothelial tight junctions. Evidence to support this theory is presented by Marra et al. who found increased levels of VEGF in preeclamptic patients.

A fourth theory states the role of increased arginine vasopressin (AVP) secretion as a causative factor. Increased AVP secretion leads to activation of vasopressin V1a resulting in vasoconstriction, endothelial dysfunction, cerebral oedema.

COVID-19 patients suffer from cytokine release syndrome which is due to a massive inflammatory reaction resulting accumulation of T-cells and macrophages, they release multiple cytokines in the blood. There is an increase in interleukin-6 leading to fever and multi-organ failure. This massive release of cytokines and breakdown of blood-brain barrier is one explanation for the pathophysiology of PRES in COVID-19 infection.

Hypoxia also triggers inflammation at systemic and local levels. Also, the COVID-19 virus by means of the S1 spike protein has an affinity for the ACE2 receptors which including numerous cells types are expressed on the capillary endothelium. There is increased permeability of the blood-brain barrier (BBB) due to engagement of the virus with the ACE2 receptor on capillary endothelium and resultant damage, this results in increased blood pressure variation and brain oedema. Liver dysfunction and consumption of clotting factors results in coagulopathy and resultant haemorrhage as a part of the disseminated intravascular coagulation cascade. There may also be damage to the neurons by the S1-ACE2 interaction resulting in severe parenchymal destruction.

Typically PRES involves cortical and subcortical areas in the parieto-occipital region and some variable involvement of deep structures in the posterior

Fig. 1: Initial MRI revealed Axial FLAIR images (A) showing symmetric hyperintense areas in bilateral parietooccipital regions. Axial T2WI(B) reveal symmetric hyperintense areas in bilateral cerebellar hemispheres. Axial DWI(C) reveals symmetric areas of restricted diffusion in bilateral parietooccipital regions. Axial T1WI (D) reveals hyperintense areas in both parieto-occipital regions representing subacute blood products. Susceptibility noted on Axial SWI(E) images. Axial T1 post contrast images (F) reveal symmetric areas of post contrast enhancement.
and cerebral autoregulation and the in the face of severe hypertension.

Two types of haemorrhage have been described

1. Sulcal subarachnoid haemorrhage
2. Petrochial microhemorrhages and
3. Hematoma formation.

Our patient presented with gyriform areas of haemorrhage in the involved areas.

Cases with diffusion restriction have been reported in literature secondary to cytotoxic oedema.\(^6\) Contrast enhancement is also a variable phenomenon in PRES.\(^7\)

In our case, there was diffusion restriction in the above-mentioned areas suggestive of cytotoxic oedema.

Typically, PRES is reversible with removal of the offending condition, however complication by diffusion restriction, haemorrhage is associated with poor clinical outcomes and are possibly fatal.\(^11, 12\) This was also seen in our patient whose imaging findings on repeat scan after an interval from the initial diagnosis showed no reversibility of PRES and findings were consistent with the previous scan. Eventually, the patient manifested with sepsis had worsening of clinical and neurological status requiring ionotropic support and eventually succumbed to the illness.

**Conclusion**

Neurological findings are seen with COVID-19 infection, however, there is relatively less literature published on the same compared to respiratory involvement. Due to its rare occurrence, this condition often presents as a diagnostic dilemma. We hope this case report serves as a tool for the diagnosis of hemorrhagic PRES in COVID-19 infection.

**References**

Adult Onset Still’s Disease

Ankur Dalal

Abstract

Adult onset Still’s disease (AOSD) is a rare systemic inflammatory disorder of unknown aetiology, characterised by daily spiking high fevers accompanied by rash, arthritis, and systemic manifestations. There are no specific diagnostic tests for AOSD. To establish the diagnosis of AOSD one should require the fulfilment of proposed major and minor criteria as well as exclusion of other diseases. This report described a 35-year-old female who was presented with fever, pruritus, arthritis, sore throat, leukocytosis and hyperferritinemia. She was diagnosed to have AOSD based on Yamaguchi et al.'s criteria after the exclusion of other possible conditions.

Introduction

Adult onset Still’s disease (AOSD) is a rare systemic inflammatory disorder of unknown aetiology. It may be responsible for a significant proportion of cases of fever of unknown origin (FUO) and can also have serious musculoskeletal sequelae. It occurs worldwide and characteristically affects younger people with slight female predominance. The name was derived from Sir George Frederick Still who in 1897 described 22 children with so called Still’s disease (currently known as systemic onset juvenile idiopathic arthritis), however, AOSD was established as a disease entity by Eric Bywater in 1971, when he described 14 adults who had symptoms similar to those seen in paediatric Still’s disease and did not meet the criteria for rheumatoid arthritis (RA).

Case Report

A 35-year-old female patient was presented with H/O high grade fever with chills for 15 days mostly in afternoon and associated with mild pruritus over limbs, soreness of throat for 15 days, low back pain associated with bilateral thigh and leg pain for 7 days, bilateral knee joints pain with swelling and difficulty in walking for 7 days, loose stools 2-3 per day and vomiting after food for 5 days while abdominal pain for 3 days. Patient had P/H/O fever on and off associated with arthralgia especially of lower limbs in last 5-6 months. On general examination skin colour of patient was dark with bilateral mild pedal oedema. Systemic examination was normal. Musculoskeletal examination showed muscle tenderness around hip girdle and evidence of synovitis at both knee joints.

Patient was investigated in view of recurrent FUO (old reports in last 5-6 month were inconclusive regarding aetiology) with significant musculoskeletal system involvement. Investigation results showed: Her urine examination showed albumin +1 and 10-12 pus cells/ h.p.f. Her random blood sugar was 124 mg/dl. Her haemogram showed haemoglobin-10 gm%, total count- (TC)-72400/c.mm (Neutrophils-96%) on admission and 26400/c.mm (Neutrophils-90%) after five days while platelets count- 3.15 lacs/c.mm. Her peripheral blood smear showed normochromic normocytic picture without abnormal cells. Her renal function test showed blood urea- 23 mg/dl, serum creatinine- 1.4 mg/dl, serum sodium- 129 mEq/L and serum potassium- 3.5 mEq/L. Her liver function test showed serum bilirubin-1.7 mg/dl (D-1.0, I- 0.7), SGPT- 38 IU/L, SGOT- 30 IU/L, S.Alk. P.- 154 U/L, and serum protein- 5.8 g/dl (albumin- 2.7 g/ dl). Her ESR and CRP were 40 mm/hour and164 Mg/L. Her HIV/ HBsAg/ HCV were negative. Her S. Procalcitonin was 16.33 ng/ml on admission and was 4.07 ng/ml after five days. Her urine and blood culture were negative. Her serum ferritin was advised, which was turn back to very high at 58375 ng/mL. Her Chest x-ray was normal, x-ray both knee was normal. Her USG abdomen showed small right kidney, USG thorax showed mild bilateral pleural effusion, and MSK USG both knee showed mild effusion in infrapatellar region. Her 2D echo was normal. Her MRI L-S spine with pelvis showed diffuse soft tissue and muscle hyperintensity/ oedema with minimal bilateral hip joint effusion.

According to the fact that S. Procalcitonin is less than a perfect marker, which may sometimes be increased in non-infectious conditions or may even remain low in infection and therefore, the diagnosis of bacterial infections is still requiring a critical clinical awareness, careful patient history, dedicated physical examination, and appropriate cultures. Even though S. Procalcitonin was high on first day in this patient, it was significantly reduced after five days without change in patient’s clinical condition and TC. Patient’s urine and blood culture were also came negative and no obvious focus of infection was found. So after careful analysis of history and investigation results, the bacterial infection was excluded in this patient. Possibility of malignancy and connective tissue diseases (CTD) was also excluded after careful analysis of history and investigations. Patient was suspected as having Adult onset Still’s disease due to presence of recurrent fever with mild pruritic rash, oligoarthropathy, myopathy, sore throat, mild bilateral pleural effusion, low albumin with raised ESR and CRP, leukocytosis with predominant neutrophils, normochromic normocytic anemia, mild raised bilirubin, very high serum ferritin level, negative RF and negative ANA test. Typical rash of AOSD seen in approximately 73% of patients was not obvious in this patient may be due to dark coloured
At present there is no consensus on its incidence and prevalence in different populations.¹ Just like most rheumatic diseases, the aetiology of AOSD is currently unknown. A genetic component has been suggested in different studies; linking it with a number of HLA antigens. A variety of infectious triggers have also been suggested.¹

Clinical manifestations of AOSD include daily high spiking fever typically peak once daily, in the late afternoon or early evening, generally exceeding 39°C and lasting under 4 hours, returning to normal in 80% of patients even without antipyretic treatment. Evanescent salmon-pink macular rash predominantly involving proximal limbs and trunk, which usually emerges with the fever, especially in the evening, may be confused with drug allergy. Arthritis initially may be mild, oligoarticular and transient, evolving over a period of several months into a more severe, destructive, symmetrical and polyarticular form. Generalised myalgias, often coinciding with fever spikes are also found in the majority of patients. Myalgia may be severe and debilitating. Inflammatory myopathy is rarely found in AOSD. Pharyngitis, lymphadenopathy, hepatosplenomegaly, pleuritis/plural effusion, pericarditis, transient pulmonary infiltrates and hematologic manifestations are other clinical manifestations seen in AOSD.¹,³,⁶

The diagnosis of AOSD remains a clinical one. In fact, the laboratory profile of the disease is a reflection of the systemic inflammation and no finding which is specific for AOSD. The ESR and CRP may be found to be raised. Common haematological abnormalities include leukocytosis, which is the result of a striking neutrophilia that is probably secondary to bone marrow granulocyte hyperplasia.¹,³,⁶ Unlike other systemic rheumatic diseases, it is not associated with RF or ANA positivity, and this fact has been used in various sets of criteria used to define the disease.¹ Recently, serum ferritin and glycosylated ferritin have received a lot of attention as diagnostic and disease activity markers. Ferritin, an acute phase reactant, is intimately involved in inflammatory processes and is associated with increased production by the histioctye-macrophage system and/or increased release from damaged hepatocytes.¹ In most studies, a threshold for serum ferritin levels of 1000 ng/ml, five times the upper limits of normal (40–200 ng/ml), has been used to suggest AOSD, however very high levels ranging from 4000 ng/ml to 30 000 ng/ml or more are not uncommon.¹ The usefulness of serum ferritin is limited by the fact that very high levels can also be seen in other diseases such as liver disease, infections, malignancies and especially the haemophagocytic syndrome.¹ A more specific diagnostic marker than ferritin may be its glycosylated fraction; in AOSD, where the glycosylation of ferritin is often <20%,¹ but it is not readily available.

Several different sets of classification criteria have been proposed. In comparison, the classification criteria proposed by Yamaguchi et al. (Table 1) provided the highest sensitivity (93.5%).⁶ A new set of classification criteria proposed by Fautrel et al.⁶ (Table 1) does not contain exclusion criteria, and includes the glycosylated fraction of serum ferritin. This set of classification criteria provided 80.6% sensitivity and 98.5% specificity in a retrospective study.¹,⁶

The clinical course of AOSD can be divided into three main patterns with different prognoses; self-limiting or monophasic pattern, intermittent or polyphasic systemic pattern, and a chronic articular pattern with poor prognosis.¹,⁴,⁵

There are no randomised, controlled, clinical trials assessing efficacy of treatment in AOSD.

### Table 1: Proposed Diagnostic Criteria for Adult-Onset Still’s Disease

<table>
<thead>
<tr>
<th>Yamaguchi et al.³</th>
<th>Fautrel et al.⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major Criteria</strong></td>
<td><strong>Minor Criteria</strong></td>
</tr>
<tr>
<td>Fever of at least 39°C, intermittent, lasting one week or longer</td>
<td>Maculopapular rash</td>
</tr>
<tr>
<td>Arthralgias or arthritis, lasting two weeks or longer</td>
<td>Leukocytosis (10,000/µL or greater)</td>
</tr>
<tr>
<td>Typical rash</td>
<td>(10,000/c.mm or greater) with 80% polymorphonuclear cells</td>
</tr>
<tr>
<td>Leukocytosis (10,000/µL or greater), with 80% granulocytes</td>
<td>Sore throat/Pharyngitis</td>
</tr>
<tr>
<td></td>
<td>Polymorphonuclear cells (80% or more)</td>
</tr>
<tr>
<td></td>
<td>Glycosylated ferritin (20% or less)</td>
</tr>
</tbody>
</table>

**Exclusion criteria**

- Malignancies
- Infections
- Malignancies
- Other rheumatic diseases

The diagnosis AOSD is established with the presence of five criteria or more, with at least two major criteria present.³
Treatment may include NSAIDs and aspirin, glucocorticoids, and immunomodulating drugs. NSAIDs, including aspirin, are generally used as first-line therapy for musculoskeletal symptoms and fever however; most patients require steroids at some point in the course of their diseases. The use of immunomodulating drugs should be reserved for cases that are refractory to NSAIDs and steroids, or when a reduction in the dose of steroids is required. Biological therapy can be added in the form of Anti-IL1 or Anti-TNF (Infliximab > Etanercept) in refractory patients not responding to immunomodulating drugs (such as Methotrexate) and low dose steroids ± NSAIDS. Biological therapy can

References

Spontaneous Pneumomediastinum in a Patient with Covid-19

Bhanupreet Kaur1, Nimish Singh1, Harmeet Kaur2, Navneh Samagh3

Abstract
Spontaneous pneumomediastinum is a rare diagnosis. A thirty-five-year-old female who was admitted to our hospital with fever, cough and breathlessness and positive RT-PCR for COVID-19 was diagnosed with spontaneous pneumomediastinum and pneumothorax. She was managed with symptomatic approach and oxygen therapy. Small pneumomediastinum usually requires close monitoring and follows an uneventful course.

Introduction
Spontaneous pneumomediastinum (SPM) is uncommon in viral pneumonias. It can go undetected because of its rare occurrence and non-specific complaints like diffuse chest pain and dyspnea which are similar to those of patients with other cardiopulmonary diseases. The occurrence of SPM and its detection has been on the rise with Coronavirus disease 2019 (COVID-19) mainly because of the diffuse alveolar injury seen in severe COVID-19 and increased number of serial radiologic imaging in these patients.

Case Report
A 35-year-old female presented to our hospital with history of fever since 7 days followed by cough, dyspnea at rest since 4 days and a positive COVID RT PCR report. There was no associated chest pain, nausea, vomiting or headache. Her vitals on presentation in hospital were pulse rate 82 beats per minute, blood pressure 128/72 mmHg; respiratory rate 24/min with no use of accessory muscle of respiration and oxygen saturation 86% on room air. She was categorized as severe Covid-19 and admitted to level 3 facility in our hospital. The laboratory investigation revealed Hemoglobin 12.9g/dl, TLC 14.83*10 3/µL, CRP, LDH, D dimer and ferritin were 15.8mg/L; 482.6 u/L, 354.35 mg/ml and 888.94 respectively. Renal function and electrolytes were normal. SGOT and SGPT were 84 U/l and 300 U/l respectively.

Chest radiograph (chest x-ray) was done which showed ill-defined opacities in bilateral lung fields suggestive of pneumonic patches. Patient was started on antibiotics, enoxaparin 0.4ml subcutaneously twice a day, methylprednisolone 40 mg iv twice a day, vitamin B, C, D and oxygen therapy via simple face mask at 10 liters per minute. On day 2 of admission there was worsening of dyspnea and increase in oxygen requirement. The patient was shifted to non-rebreather mask at 15 liters per minute. Computerised Tomography (CT) scan showed diffuse ground glass opacities with superimposed interlobular septal thickening in bilateral lung.

Discussion
There are very few case reports on spontaneous pneumomediastinum and pneumothorax in COVID 19 patients worldwide. COVID-19 is an illness caused by severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) and has multisystem involvement. It is characterized by initial cytokine storm that can result in acute respiratory distress syndrome and macrophage.

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Pneumomediastinum, also known as mediastinal emphysema is presence of air in mediastinum. It can be spontaneous (where no causative factor is found) in otherwise healthy subjects or it is called as or may be secondary to various factors.\(^2\)\(^,\)\(^6\)\(^,\)\(^8\) (Figure 2). Pathophysiology is based in the Macklin effect that increase in alveolar pressure causes alveoli to rupture. The released air then migrates through peribronchial and perivascular sheaths to the mediastinum.\(^4\) This air can also enter pleura leading to pneumothorax; or dissect to neck, upper abdomen or skin via loose alveolar fat issue leading to subcutaneous emphysema.\(^5\) It is more common in young patients in age group of 5-34 years.\(^8\)

In our case, the presence of severe COVID pneumonia, cough and young age were the predisposing factors of spontaneous pneumomediastinum. However no precipitating factors were present and the patient was never given positive pressure ventilation.

The presenting symptoms of pneumomediastinum are chest pain (usually retrosternal); radiating to neck or back, dyspnea, coughing spells, neck pain, vomiting. Hamman’s sign is present clinically i.e. mediastinal crunch/ click over cardiac apex and left sternal border during auscultation. Clinically the patient can have tachycardia, tachypnea or anxiety.\(^9\)\(^,\)\(^10\)

Chest Xray (posteroanterior and lateral view) is usually the primary diagnostic tool. If chest radiograph is inconclusive then CT scan of the chest can also be done to diagnose and assess the extent of pneumomediastinum. Ultrasound chest is only done for urgent diagnosis in emergency department and trauma. Bronchoscopy and esophagoscopy may be used if any underlying pathology is suspected.

Management includes symptomatic approach.\(^1\)\(^1\) Any exertional activity should be avoided. Patient is usually advised complete bed rest. Anti tussive must be administrated for cough. Analgesics for pain, O2 administration should be considered for treatment as it increases gas absorption.

Our patient was managed by antitussive medication, analgesics, oxygen therapy and restriction of incentive spirometry, complete bed rest. The patient was discharged on 8th day after complete resolution of symptoms. Follow up was done telephonically at periodic intervals. The patient did not have any symptoms and was maintaining SpO2 > 98% on room air at the time of writing of this manuscript.

**Conclusion**

Asymptomatic and small pneumomediastinums are rare and may go unnoticed. In COVID-19 patients, we should have a high index of suspicion of their occurrence. In most of the cases small pneumomediastinums resolve on their own as the tissues in mediastinum slowly reabsorb the air. They usually follow an uneventful course but may end up in disastrous complications and hence should be kept under a close watch.

**References**

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*English, Hindi, Bengali, Gujarati, Marathi, Punjabi, Tamil, Assamese, Kannada, Malayalam, Oriya and Telugu.
François Magendie (1783-1855) lived during a tumultuous period in French history. He worked in a period when medicine began to discard the traditions of the 18th century and depend more on critical and exact observation and experiment. He was one of the first men to perform experiments on living animals with live dissections. He performed them at public lectures in physiology. Magendie thus gained an unpleasant reputation as a vivisector and provoked an antivivisectionist campaign.

However, he established experimental physiology and his most famous student Claude Bernard (1813-1878) carried the work forward. Magendie greatly influenced the analytical mind of Claude Bernard.

Magendie was elected to the French Academy of Sciences in 1821 and served as its president. He was appointed professor of medicine at the Collège de France, Paris in 1831. He also founded the first periodical of experimental physiology, Journal de Physiologie Expérimentale (1821).

Magendie was one of the first to observe anaphylaxis; an exaggerated reaction by an animal to the injection of foreign protein into its blood; he found that rabbits able to tolerate a single injection of egg albumin, often died following a second injection (1839).

He made pioneering efforts in experimental physiology, pharmacology, pathology, and nutrition. In 1822 he confirmed and elaborated the observation by the Scottish anatomist Sir Charles Bell (1811) that the anterior roots of the spinal nerves are motor in function, while the posterior roots were sensory. (Bell–Magendie Law). He also realized that the exposed meninges were susceptible to painful stimuli. Among his other contributions were his early description of cerebrospinal fluid and a delineation of a foramen in the ventricle that is named after him.

His pioneering studies of the effects of recently discovered compounds on various parts of the body led to the scientific introduction of drugs into medical practice of such compounds as strychnine, morphine, quinine, brucine, and veratrine. He also popularized the therapeutic use of iodine and bromine salts. Although Magendie was interested primarily in experimental physiology, he did not neglect medical practice.

He was appointed chairman of a commission investigating whether nourishing food can be obtained out of gelatinous meat extract. He found that no nutrient food can be made in this manner and showed that life sustaining food needed enough nitrogen containing compounds (proteins). In 1816 he published Précis élémentaire de Physiologie which described an experiment first illustrating the concept of empty calories. Magendie thus laid the foundation for the modern science of nutrition.
Experts’ Consensus on Use of Long-Acting Nitroglycerine in the Management of Angina and Chronic Coronary Syndrome in India

Mohan JC1, Arun Chopra2, Hiremath JS3, Ajay Mahajan4, Tiny Nair5, Saumitra Ray6, Muralitharan TR7, Ajay Pandey8, Sameer Srivastava9, Y Shiva Kumar10, Girish Navasundi11, Deepak Rajan Das12, Mahesh V Abhyankar13, Santosh Revankar14, Pradip Mate14

Abstract

Aim: To address the existing gaps in knowledge about long-acting nitroglycerine (LA-NTG) and provide recommendations to address these issues.

Methodology: Approved LA-NTG questionnaire that included 17 questions related to the role of LA-NTG in the management of angina and chronic coronary syndrome (CCS) was shared with 150 expert cardiologists from different regions from India. Results of these survey questionnaires were further discussed in 12 regional level meetings. The opinions and suggestions from all the meetings were compiled and analyzed. Further, recommendations were made with the help of attending national cardiology experts and a consensus statement was derived.

Results: This is the first consensus on LA-NTG, summarizing the clinical evidence from India and suggesting recommendations based on these data. The experts recommended early use of LA-NTG as a first-line antianginal therapy in combination with beta-blocker since it improves exercise tolerance in patients with CCS. A strong consensus was observed for using LA-NTG in patients with co-morbid hypertension, diabetes, chronic kidney disease and post-percutaneous coronary intervention angina. As a part of cardiac rehabilitation, LA-NTG allows patients with angina to exercise to a greater functional capacity.

Conclusions: A national consensus was observed for several aspects of LA-NTG in the management of angina and CCS. The clinical experience of the experts confirmed an extremely satisfied patient perception about the efficacy of LA-NTG.

Introduction

Coronary artery disease occurs as a result of a pathological process comprising plaque accumulation in epicardial arteries. This is categorized as acute coronary syndromes (ACS) or chronic coronary syndromes (CCS) depending upon the clinical presentation. Chronic coronary syndromes are progressive to cardiovascular diseases (CVDs) which is the leading cause of mortality, taking a toll of 17.9 million lives every year and India ranks at the top to register the highest number of cases. World Health Organization states that four out of five deaths are due to CVDs that belong to heart attacks and strokes, and one-third of these deaths occur in individuals <70 years of age.1,2 Thus, premature deaths can be curtailed by prompt and appropriate treatment in those at the highest risk of CVDs.

There is a scarcity of data in terms of prognosis and management of CCS as compared to the patients with ACS. A recent, large, international registry showed the changing and positive trend among the patients with CCS in terms of prevention and treatment strategies.3 The pharmacotherapy for managing CCS includes drugs such as beta-blockers (BB), calcium channel blockers (CCB), ivabradine, nicorandil and trimetazidine and nitrates. Of these, nitrates are used for symptomatic treatment of chronic stable angina (CCA) and CCS for several decades.

Nitroglycerin was the first organic nitrate discovered in 1847 and further, in 1879, its antianginal effect was explored. Later in 1977, Murad and colleagues demonstrated that nitrates exert their action by releasing nitric oxide.4 Nitrates are classified as short-acting and long-acting nitrates (LAN) depending upon the onset and duration of action. These are remarkably potent, effective and safe drugs in the management of angina and CCS. They are potent vasodilators that exert their action by activating endogenous nitric oxide-cyclic guanosine-3’5’-monophosphate (NO-cGMP) which in turn decreases systemic blood pressure and vascular resistance.3 They are one of the important pharmacotherapies for prophylaxis and treating acute angina and prevention of frequent anginal pains.5 They have beneficial effects on coronary circulation and used as an unloading therapy in heart failure (HF). They help control disease, provide symptomatic relief, build exercise capacity and enhance the quality of life. Nevertheless, headache, hypotension and tendency to develop tolerance
has converted pure NTG into long-release/sustained release technology of angina, the inclusion of time-usage in the long-term management a very short half-life that limits its accompanying side effects. Intermittent and cross-tolerance are some of the limitations of symptomatic relief and exercise tolerance. They are specifically indicated in HF and low heart rate (<50). Previous meta-analyses showed consistency between nitrates and other antianginal agents in terms of symptomatic relief and exercise tolerance.

Despite the long history of therapeutic usage and guidelines, the clinical benefits of LA-NTG remain underutilized. In the perspective of ESC-CCS, 2019 guidelines, there are some reestablishments in the positioning of LA-NTG. There is a paucity of data with regards to the recommendation for clinical use of overall LAN and particularly for LA-NTG. We have identified the demand for consensus on the usage of LA-NTG in actual clinical practice. A need to place LA-NTG in the appropriate perspective with correct scientific data was realized which is credible only with the clinician’s experience and existing literature. A consensus report was developed, based on the data collected and analyzed from the answered questionnaires and in-depth discussion on the same by a group of expert cardiologists. This consensus report addresses difficulties and existing gaps in knowledge about LAN and provides evidence to address these issues.

**Methodology**

The questionnaire was drafted, discussed and finalized in a national advisory board meeting of national-level expert cardiologists. The approved LA-NTG questionnaire was shared with 150 expert cardiologists to seek their opinion. Results of region-specific survey questionnaire was further discussed in 12 regional level meetings held from August 2020 to December 2020, attended by one national expert and approximately 20 regional expert cardiologists in each meeting. The opinions and suggestions from all the meetings were compiled and analyzed. Recommendations were made with the help of attending national cardiology specialists.
were made to provide opinion-based recommendations for use of LAN in the management of angina and CCS.

**Preference for the usage of LA-NTG in angina and CCS**

Current guidelines on CCS management recommend that antianginal treatment should be initiated in a stepwise manner starting with a BB; while CCBs, nitrates, and ranolazine are used as adjunctive or second-line therapy when BBs are ineffective, poorly tolerated or contraindicated. As per the consensus from this survey, the majority of experts prefer to start LA-NTG on day 1 (Consensus level B; 116/185, 62.70%) and few suggested initiating LA-NTG within a week (14.59%). The experts strongly agreed that LA-NTG can be combined with BB to reduce the symptoms; since, this combination showed synergistic effects (Consensus level A strong; 177/186, 95.16%).

According to the participating experts, follow-up of the patients in India is an issue with stepwise approach, as recommended by guidelines. Experts also believe that sometimes high expectation of immediate symptom relief by patients makes it difficult to follow the stepwise approach in actual practice.

**Time of initiation of LA-NTG in CCS with Angina**

There was a strong consensus that early initiation of LA-NTG along with BB helps better exercise tolerance in angina patients. Experts strongly agreed (Consensus level A; 172/186; 92.47%) with the early initiation of LA-NTG with BB; since they act synergistically to improve exercise tolerance and compliance. Literature supports the benefits of adding either a LA-NTG or CCB to BB therapy by decreasing incidence of angina, enhancing exercise tolerance and reducing myocardial infarction (Figure 3).

The primary goals of optimal medical therapy in patients with angina are angina pain relief or symptomatic relief, to reduce the risk of mortality from CVDs, prevent future CVDs and enhance the quality of life. Nitrates are an integral part of this therapy supporting other antianginal drugs. The prophylactic use of nitrates has been reported to efficaciously ameliorate exercise tolerance in patients with CVDs. Clinical studies have demonstrated that LAN alone or in combination with CCBs effectively reduce the frequency of angina in patients with vital signs absent and enhance their therapeutic efficacy. A meta-analysis of 29 studies investigated the effects of nitrate supplementation on exercise tolerance revealing its significant effect on exercise tolerance (95% CI: 0.08-0.47; P = 0.006) compared to placebo, but showed no significant effect on exercise performance (ES = -0.05 95% CI: -0.28 –0.17; P = 0.64).17

The experts prescribe LA-NTG for angina with mild (17.74%) and moderate exertion (17.20%) and for angina at rest (16.67%). Several studies have examined that nitrates have antiplatelet activity and they can be added to any classes of angina. The experts confirmed that patients with severe angina and angina at rest can be

### Table 2: Levels of Evidence and Consensus

<table>
<thead>
<tr>
<th>Grade</th>
<th>Level of consensus</th>
<th>Voting description</th>
<th>Responses (%)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Very strong</td>
<td>Strongly agree + Agree voting</td>
<td>280</td>
<td>Accepted completely</td>
</tr>
<tr>
<td>B</td>
<td>Strong</td>
<td>&lt;25% responses then experts accepted with major reservation</td>
<td>≥50 - 79</td>
<td>Accepted with minor reservation</td>
</tr>
<tr>
<td>C</td>
<td>Moderate</td>
<td>Strongly agree + Agree voting</td>
<td>25-49</td>
<td>Accepted with major reservation</td>
</tr>
<tr>
<td>D</td>
<td>Neutral/no consensus</td>
<td>Disagree + Strongly disagree voting</td>
<td>&lt;25</td>
<td>Rejected</td>
</tr>
</tbody>
</table>

### Table 3: Nitrate Formulations Available in India

<table>
<thead>
<tr>
<th>Agents</th>
<th>Formulations/ Dose</th>
<th>Long- vs. short-acting</th>
<th>Onset of action (minutes)</th>
<th>Duration of action</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroglycerin (Glyceryl trinitrate)³⁰</td>
<td>Oral tablets/ 2.5-6.5 mg 3 to 4 times a day</td>
<td>Long</td>
<td>20-45</td>
<td>2-6 h</td>
<td>Contraindicated in patients with early myocardial infarction, severe anemia, increased intracranial pressure, and those with a known hypersensitivity to nitroglycerin; contraindicated in patients who are using a phosphodiesterase-5 (PDE-5) inhibitor (e.g., sildenafil citrate, tadalafil, vardenafil hydrochloride)</td>
</tr>
<tr>
<td></td>
<td>Sublingual tablets/0.3 to 0.6 mg, can be repeated every 5 min up to a maximum of three tablets or up to 1.5 mg as needed.⁴¹</td>
<td>Short</td>
<td>At least 25 min</td>
<td>At least 25 min</td>
<td></td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>Oral tablets/10-60 mg 3 or 4 times daily</td>
<td>Long</td>
<td>15-45</td>
<td>2-6 h</td>
<td>Contraindicated in patients who are allergic to isosorbide dinitrate or any of its ingredients and in patients who are taking certain drugs for erectile dysfunction (phosphodiesterase inhibitors), such as sildenafil, tadalafil, or vardenafil and those taking soluble guanylate cyclase stimulator.</td>
</tr>
<tr>
<td></td>
<td>Sublingual tablets/ 2.5-10 mg</td>
<td>Short</td>
<td>5-20</td>
<td>1-2 h</td>
<td></td>
</tr>
<tr>
<td>Isosorbide mononitrate</td>
<td>Oral tablets/60-240 mg OD</td>
<td>Long</td>
<td>30-45</td>
<td>6-24 h</td>
<td>Contraindicated in patients hypersensitive or have shown idiosyncratic reactions to other nitrates or nitrates.⁴²</td>
</tr>
</tbody>
</table>
managed with LA-NTG.

**Key Recommendations**
- Early use of LA-NTG as a first-line antianginal therapy in combination with BB provides synergetic effect in CCS patients with angina (Consensus level A).
- Early initiation of LA-NTG with BB helps better exercise tolerance in patients with angina (Consensus level A) (Figure 2).

**Duration and dosing of LA-NTG in CCS**

The experts discussed the duration of LAN in non-revascularized patients with CCS. The survey showed that the majority of the cardiologists opted for life-long LAN (Consensus level B;117/186, 62.90%) and some preferred to prescribe it for 6-12 months (Consensus level D; 26/186, 13.98%). If patients are angina-free then nitrates can be withdrawn and the response recorded. If symptoms reappear then LAN should be reconsidered. As per experts, after discontinuation of LAN, observe for a minimum of 6 months-1 year to check whether angina rebound occurs. In case of incomplete revascularization, some angina is expected. Hence, LA-NTG should be given for up to 1-3 months, then reassess the symptoms and proceed accordingly. In case of complete revascularization, if the patient is having angina then a very short duration of nitrate should be given. However, if the angina is persistent then there is a possibility of some post-procedural complications. Coronary revascularization is not an assurance for complete angina relief and recurrent anginal pain is very common. Studies report the occurrence of angina (92% patients) within few weeks, despite the use of anti-anginal therapy and revascularization (Figure 3).

**LA-NTG in Cardiac Rehabilitation**

Cardiac rehabilitation is an essential part of the comprehensive care of patients with cardiovascular disorders. It improves the quality of life by increasing cardiac ejection fraction, exercise tolerance, and physical status of patients with acute myocardial infarction. Implementing cardiac rehabilitation in young patients experiencing myocardial infarction will help attain better clinical outcomes across several risk factors, particularly smoking. Cohort of 1287 patients showed a significant improvement in 1-year outcomes in young patients with myocardial infarction. Kimchi et al. reported that using NTG spray enhanced the duration of time to onset of angina symptoms during the treadmill test by 31% (P<0.001). Thus, indicating that prophylactic sublingual nitrates in combination with cardiac rehabilitation permit patients with angina to exercise with improved functional capacity than in absence of nitrates.

Experts from this survey suggested that LA-NTG as a part of cardiac rehabilitation may allow patients with angina to exercise to a greater functional capacity (Consensus level A:178/185, 96.22%) (Figure 4). The experts suggested nitrates in case of myocardial infarction and coronary artery bypass grafting (CABG) rehabilitation. If asymptomatic angina or silent ischemia is present, LA-NTG addition is important; since LA-NTG acts on both microvasculature and macro vasculature.

**Key Recommendations**
- Longer duration of LA-NTG is required in non-revascularized and incompletely revascularized patients.
- LA-NTG can be considered for management of angina at rest as well as angina with mild to moderate exertion.
- LA-NTG as a part of cardiac rehabilitation, allows patients with angina to exercise to a greater functional capacity (Consensus level A).
- Decision of withdrawal of LA-NTG could be considered after assessing angina free period of patients and could be reintroduced in case symptoms re-appear.

![Fig. 2: Use of LAN in clinical practice for management of stable angina/chronic coronary syndrome](image-url)
Table 4: Recommendation to Use LA-NTG in Different CKD Stage N=183 n (%)  

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>N=183</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>7</td>
<td>(3.83)</td>
</tr>
<tr>
<td>Stage 1 and 2</td>
<td>9</td>
<td>(4.92)</td>
</tr>
<tr>
<td>Stage 1, 2 and 3</td>
<td>18</td>
<td>(9.84)</td>
</tr>
<tr>
<td>Stage 1, 2, 3, and 4</td>
<td>17</td>
<td>(9.29)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>10</td>
<td>(5.46)</td>
</tr>
<tr>
<td>Stage 2 and 3</td>
<td>1</td>
<td>(0.55)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>14</td>
<td>(7.65)</td>
</tr>
<tr>
<td>Stage 3 and 4</td>
<td>5</td>
<td>(2.73)</td>
</tr>
<tr>
<td>Stage 4</td>
<td>10</td>
<td>(5.46)</td>
</tr>
<tr>
<td>Stage 5</td>
<td>5</td>
<td>(2.73)</td>
</tr>
</tbody>
</table>

LA-NTG in Co-Morbidities and Concomitant Medication

Hypertension

At lower dose LAN act as vasodilators and at higher doses they are arteriolarilators. In combination with BB, nitrates can block tachycardia, resulting in a synergetic anti-ischemic effect. There was a strong consensus that besides BB, LA-NTG is the first choice of drug in patients with angina and hypertension (Consensus level A; 156/185, 84.32%). In contrast, some experts agreed that amlodipine is a potentially safe drug for the treatment of angina and hypertension.

The experts agreed that whatever be the estimated glomerular filtration rate (eGFR) there is no contraindication for nitrates in any level of renal disease function.

The nitric oxide released by nitrates leads to vasodilation, improved endothelial function and redistribution of coronary blood flow that is beneficial to patients with diabetes. Furthermore, the survey showed that the majority of experts prefer LA-NTG for the optimal treatment of chronic angina in patients with diabetes (Consensus level A; 161/185, 87.03%). Moreover, patients on LAN, particularly elderly, in volume-depleted or those who have used sildenafil within 24 h should be monitored for hypotension.

Chronic Kidney Disease (CKD)

Experts suggested that whatever be the estimated glomerular filtration rate (eGFR) there is no contraindication for nitrates in any level of renal disease function.

The experts agreed that use LA-NTG safely in all five stages of CKD (Consensus level C; 87/185, 47.54%); however, the remaining 52.46% agreed to use in different stages of CKD (Table 4). It was confirmed that LA-NTG does not produce any serious side effects including methemoglobinemia. Long-acting nitrates undergo extensive hepatic metabolism and renal failure does not impact the absorption or metabolism of nitrates; hence, can be safely used in patients with CKD and angina (Figure 4).

Hydralazine and LAN Combination

Hydralazine and ISDN combination is recommended by American Heart Failure guidelines and European guidelines in African American NYHA class II-IV having HFREF. The two active drugs are available as a fixed drug combination or can also be used separately. This combination is not suitable for patients with HF with preserved ejection fraction (HFpEF). Nitrates are reported to be safe and effective in patients with acute HF in terms of symptoms and mortality. Nitrates in combination with diuretics are the mainstay of acute HF therapy. However, they are not universally adopted and underutilized due to a lack of randomized controlled trials.

Hyperkalemia is reported in about 9% of patients with acute HF and associated with poor clinical outcomes. Patients with HF have demonstrated recurrent hyperkalemia, increased hospitalization rate and death. Cardiovascular diseases occur frequently in patients with CKD; similarly, patients with HF may also have deteriorated renal function or both can co-occur. Increased pathophysiological complexity, severe symptoms, economic burden and high mortality risk are the challenges in patients with CKD.
and HF. The experts recommended LA-NTG with hydralazine in all types of HF (Consensus level D; 37/179, 20.67%) including those with CKD, hyperkalemia or a combination of all these co-morbidities. Many supported the use of this combination in HF with reduced ejection fraction (Consensus level D; 54/179, 30.17%). Potential mechanisms proposed for the beneficial effects of nitrates include an upsurge in patent capillaries, hemodynamic benefits due to vasodilatory action in patent capillaries, hemodynamic effects of nitrates include an upsurge and improvement in myocardial stress and smokers. Most agree that LAN therapy (74/185, 40.00%); while some 5-10% of patients undergoing LA-NTG therapy (74/185, 40.00%) agreed that LA-NTG such as Angispan-TR has less headache risk than ISDN/ISMN preparation because uniform timed release of the drug offers nitrate-free intervals and reduced risk of headache and nitrate tolerance. The experts were of opinion that the combination of more than one revascularization, or atherosclerotic disease or functional factors such as microvascular dysfunction, epicardial coronary spasm, or vasoconstriction. The experts discussed the safety and efficacy of LA-NTG therapy for symptomatic relief in patients with post-PCI angina (Consensus level A; 171/185, 92.43%) confirming that LA-NTG is safe and efficacious in these patients. Experts suggested that if untreated lesions are present or if the patient is symptomatic then LA-NTG is preferred while in asymptomatic patients it should be withdrawn. Some experts suggested LA-NTG for 3-6 months in post- PCI angina patient (Consensus level C; 49/160, 30.63%) while some opined of more than 12 months duration of LA-NTG (Consensus level D; 38/160, 23.75%). In patients with microvascular angina, the clinician may have to continue LA-NTG for an indefinite period depending upon the need and necessity of the individual. Experts discussed that silent ischemia by a halter is an issue that has a tremendous effect on clinical outcomes. Further, it was discussed that LA-NTG has a hemodynamic effect that decreases the pre-load and increases the coronary blood flow to a large extent. Thus, if the patient is hemodynamically stable then LA-NTG is preferable and is routinely given (at least for 6 months-1 year) in post- ACS/ PCI/CABG to prevent rebound angina (Figure 4).

Key Recommendations

- LA-NTG is safe and efficacious in patients (Consensus level A).
- In post-PCI angina, LA-NTG can be given for >12 months depending on angina symptoms (Consensus level C). Withdrawal can be considered depending on the symptom-free interval after temporary therapy pause.

Safety and Tolerability

A meta-analysis of trials comparing BB, CCBs, and nitrates for stable angina showed that nitrates are as effective as BB and CCBs, but the prime reasons to downgrade LAN to second-line therapy in guidelines are their side-effects and the occurrence of tachyphylaxis.

Likewise, the majority of experts from this survey observed headache as the major side effect influencing the therapeutic response of the patient and limiting the use of LA-NTG. The experts reported headache in 5-10% of patients undergoing LA-NTG therapy (74/185, 40.00%); while some others observed in less than 5% (42/185, 22.70%) and 10-20% (41/185, 22.16%). According to the experts, this percentage also depends on sex and age; since females and younger patients get more headaches because of the higher vascular reactivity. Also, headache develops more frequently in patients with normal blood pressure and smokers. Most agree that LAN has lesser headaches than short-acting nitrates. Patient education, counseling and a wait and watch approach may help in the management of this side effect; since generally after 7 days headache subsides (Figure 4).

However, the majority of experts (Consensus level A; 160/186, 86.02%) agreed that LA-NTG such as Angispan-TR has less headache risk than ISDN/ISMN preparation because uniform timed release of the drug offers nitrate-free intervals and reduced risk of headache and nitrate tolerance. The experts were of opinion that the combination of more than one vasodilator along with NTG increases the incidence of headache.

The other issue with the use of this drug is the occurrence of nitrate rebound or withdrawal when discontinued abruptly and classically presented as worsened anginal pain. Hence, gradual dose tapering and adjusting the timing of administration are essential steps.
The considerable variation was identified and recorded in several aspects of the present survey including safety, dosing and initiation of LAN alone and concomitantly with hydralazine in different angina classes and post PCI patients. Variation in strategies employed in clinical practice to overcome the side effects associated with LAN was also noted. Collaborative research needs to be undertaken to assess the impact of these variations and establish concrete evidence in order to adopt the ideal treatment decisions.

Conclusions

This is the first consensus on LA-NTG, summarizing the clinical evidence from India and suggesting recommendations based on these data. A national consensus was observed for several aspects of LA-NTG in the management of angina and CCS and further identified the optimal strategies to deal with its major side effects. A strong consensus exists with respect to the use of LA-NTG as a first-line option apart from BB in patients with angina independent of the presence of co-morbidities. Long-acting nitroglycerine was strongly agreed to be safe and efficacious in patients with co-morbid hypertension, diabetes, CKD and post-PCI angina. The clinical experience of the experts confirmed an extremely satisfied patient perception about the efficacy of LA-NTG. This consensus document is perceived under the guidance of experts to refurbish the therapeutic management of CSA and CCS using LA-NTG.

Future Perspectives

The experts discussed various strategies to overcome the side effects of LAN. Drug-free interval (Consensus level D; 23.78%), patient education (Consensus level D; 16.22%), and some preferred both (Consensus level D; 11.89%) are frequently used strategies to overcome LA-NTG side effects. Few others use intermittent dosing or a combination of all three approaches to deal with the side effects of LA-NTG. Furthermore, experts suggested a combination of LA-NTG with BB such as carvedilol, endothelial receptor blockers, statins, ACE inhibitors in order to overcome the side effect of LA-NTG. Some experts suggest benefits of post-meal administration of nitrates while some prescribe the drug at 8 am and 4 pm to obtain 10 hours of nitrate-free interval.

Based on efficacy including relief of angina pain and frequency of angina and improved exercise tolerance, the majority of the experts have rated satisfactory (Consensus level B; 117/184, 63.59%) and very satisfactory (Consensus level C; 64/184, 34.78%). Experts stated that there is no compliance issue with LA-NTG usage. Only those having significant headaches are unsatisfied with LA-NTG.

Key Recommendations

- Patient education, counseling and wait and watch approach is helpful in the management of headache.
- Drugs belonging to the class of phosphodiesterase-5 inhibitor such as sildenafil should be used cautiously with LA-NTG.
- Drug free-interval, patient education, intermittent dosing or a combination of all three approaches is beneficial to deal with the side effects of LA-NTG (Consensus level D).

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Impact of Covid-19 on Mental Health of Surgical Residents who Suffered from the Disease

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The COVID-19 crisis has placed an enormous pressure on the already overburdened healthcare. While surgeons across the globe are trying to comprehend the evolving pandemic and improvise surgical practice, the psychological impact of the stress on their mental health has been underestimated. The loss of exposure to surgical work, in addition to working in a different environment and the fear factor due to the novelty of the disease lead to physical, mental, and emotional exhaustion of the health care workers and was associated with multiple psychiatric problems.1

A study spanning 5 weeks was conducted on 34 residents who acquired COVID-19, from all surgical departments while working at a COVID only tertiary care hospital in Mumbai, India. Data was collected using a self-devised 20-point questionnaire which included factors which would determine the severity of the disease, presence of coexisting medical conditions, professional & personal hurdles faced and its impact on behaviour.

None of the residents were suffering from any pre-existing systemic or psychiatric illness or were under any pharmacological or psychiatric therapy before being infected with SARS CoV-2.47.1% of the residents reported being afraid of contracting the disease, before being positive. Post discharge 29.4% of were still fearful of a reinfection. 64.7% of the resident doctors after recovering from COVID infection experienced early fatigueability while operating, 23.4% reported a lack of confidence while operating owing to lost hands-on experience. As per the Hamilton Anxiety Rating Scale,17.64% had moderately severe anxiety with scores ranging between 18 - 24. All of these residents had been admitted with breathlessness and had oxygen requirement. Anxiety scores and severity of the disease went hand in hand. A study published by Mazza MG et al. report a higher-than-average incidence of anxiety in COVID-19 survivors.

Fearful anticipation causing anxious mood and insomnia were the most common difficulties which the residents faced. The fears are sufficient enough to affect the overall ability of the resident to manage patients competently. Clinical skills are interfered due to the thoughts of reinfection which can increase the risk of delayed diagnoses and mismanagement.

All the residents felt to have lost out on their specialty training due to the pandemic. It is therefore, the need of the hour to create a framework for residency programs to keep going on uninterrupted without compromising learning. The Cleveland clinic’s urology residency program has set-up a framework which works in a crunch situation like today without compromising the clinical exposure and other academics.3

Mental health of budding surgeons should be adequately monitored and addressed whenever necessary, especially in setting of a global health crisis. The stigma associated with mental health may result in residents not opening up freely which can have disastrous effects on the patients. A support system should be in place for addressing such concerns. Providing post discharge counselling, especially to those suffering from a severe form of the disease. We also suggest restructuring of residency programs in coherence with the new protocols to attenuate the loss of curriculum in quantity as well as quality.

References

Robots and Artificial Intelligence be Helpful in future Covid Research

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Sir,

The world for over almost one and half year has faced the pandemic of Corona, a disease by the Flu virus.

The most important issue which is a hindrance of treatment types and vaccine discovery is mutation. During replication, a virus often undergoes genetic mutations that may create variants.

Artificial intelligence (AI) has helped robots to identify the types of mutations and hence in demographic and geographical distinctions.1

The main concept emphasised here is that there is scope of instilling AI in robots in future to identify mutation in the Corona virus before it can mutate, either to be more virulent, or rarely lose its virulence due to mutation ultimately producing targeted vaccines against the mutant virus, which AI instilled robot can identify.

Broadly mutation different concerns of varying degrees. These relate to their:
- Transmissibility, or propensity to spread
- The severity of illness
- Neutralization capacity, or the likelihood they will infect people who have recovered from a previous Covid-19
Potential impact on vaccination through their ability To evade the protection that immunizations are designed to generate.
- That another surge could occur even as states are flinging open vaccine eligibility criteria, trying to get shots as quickly as possible.

The concept of AI-powered early warning systems can help detect epidemiological patterns by mainstream news, online content and other information channels in multiple languages to provide early warnings, which can complement syndromic surveillance and other healthcare
networks and data flows.

AI tools can help identify virus transmission chains and monitor broader economic impacts. In several cases, AI technologies have demonstrated their potential to infer epidemiological data more rapidly than traditional reporting of health data. Institutions such as Johns Hopkins University have also made available interactive dashboards that track the virus’ spread through live news and real-time data on confirmed cases, recoveries, and deaths.

Semi-autonomous robots and drones are being deployed to respond to immediate needs in hospitals such as delivering food and medications, to immediate needs in hospitals such as delivering food and medications, and performing deliveries of equipment, identifying, finding and contacting vulnerable, high-risk, individuals. AI may eventually play a role in accelerating training and education of healthcare personnel.

Finally, AI tools can help monitor the economic crisis and the recovery – for example, via satellite, and other social networking.

The ability for viruses to mutate and evade the human immune system, a term called viral escape, is an obstacle vaccine development. Hence understanding the complex rules of this escape, using machine models, could design therapeutic design.

Such designs preserve viral infectivity but cause the virus to look different to the immune system.

This approach language models of Influenza hemaglutinin, HIV-Envelope protein and presently, SAARS CoV2 spike proteins can accurately predict structural escape patterns which indicate a promising conceptual bridge between natural language and viral evolution.

Using these tools accelerates the process of detecting virus behaviour - and time is of essence in this ongoing battle against COVID19.

Thus if AI can be of help in such rapid detection of Covid in demography, there can be a scope to research on it, in instilling in Robots and in future help them to identify the DNA coding change in virus, before it occurs, the main idea behind anticipating a new mutant of Corona virus before its outbreak instead of investing hugely in one vaccine after another and trialling them.²

References


Adopting the New Normal in Postgraduate Course Summative Assessment for evaluating Clinical Skills: An Experience from India During COVID-19 Pandemic Nation-Wide Lockdown

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Medical Institutes globally have taken a paradigm shift in teaching learning and assessment due to the circumstances created by Corona virus disease (COVID-19) pandemic. A challenging task during this period for Institutes was to ensure timely conduct of summative assessment for an uninterrupted course. Timely or early certification would ensure additional workforce as recommended by WHO.¹ Summative assessment is outcome-dependent while formative assessment relates to in-process evaluation of students’ performance. Hence, former should comprise of valid, reliable, acceptable and feasible assessment tools.

During the nationwide lockdown in India, pertinent challenges faced by the clinical department of Medical Institutes/Universities were to conduct assessment for the postgraduate courses, without patients. There were no guidelines or protocols available on alternative method for clinical skill evaluation that can be adopted for summative assessment.² Our Institute proactively worked towards conducting summative postgraduate certificate examination by using simulators/task trainers for various clinical subjects.

Advanced Center of Medical Simulation & Skill development of our Institute is well equipped with high fidelity simulators, low fidelity simulators and task trainers. In the traditional format of summative assessment, patient and standardized subjects are used, which was replaced in this assessment by an evaluation largely based on medical simulation. Part task trainer/simulator comprised of <25%, 50% and >76% by various clinical disciplines in summative assessment. Objective Structured Long Examination Record (OSLER) and Mini-CEX (Clinical examination), Objective Structured Clinical examination (OSCE) stations and Spotters were created using simulators and task trainers. A blended type of assessment was conducted with two external examiners stationed in the remote site and two internal examiners, examinee and technical experts positioned in Medical Simulation lab of Institute. Performance of examinee simultaneously evaluated face to face by internal examiners and real-time online through videoconferencing by external examiners.

Clinical discipline that adopted simulator and task trainers to conduct their summative assessment included Anaesthesiology General Medicine General Surgery Obstetrics & Gynaecology, Orthopaedics and Transfusion Medicine. Response to feedback questionnaires was obtained from 70 participants comprising of 28 examiners / technical experts and 42 examinee postgraduates. All 42 examinee were successful in summative assessment held in April 2020. Mean percentage score of examinee who attended simulation based examination was found to be 69.10. ± 5.14% (range 59.5% to 78%). The mean summative assessment scores obtained by the examinees of previous batch (December 2019 taken as historical control) in same 6 subjects held through traditional method was 67.63 ± 4.58% (range 57.9% to 77.5%) The scores obtained by simulation based and traditional methods were comparable and not statistically different from each other.

During the COVID -19 pandemic nationwide lockdown, it was difficult to get clinical cases or standardized patients. Hence, it was most sensible to adopt the best possible and feasible option available keeping
in mind the safety of examinee and examiners. Summative assessment for postgraduates in clinical specialties was successfully and reasonably well-conducted using simulators & task trainers along with other modes at our Institute. Simulators and task trainers assist in the learning process and directs learner on his/her skill acquisition as simultaneous assessment can be done while learning. Hence, these are widely used for formative assessments as instantaneous feedback can be conveyed to the trainee regarding competence achieved and overall improvement. However, perception and experience of stakeholders as noted in our study suggests that it can be used in the summative assessment as also noted by Bould et al in their study.\(^3\) Simulation which was introduced as an educational tool is now increasingly being adopted as an assessment strategy. There is an increasing inclination towards use of simulation as an assessment tool in health professional education. However, further research may be required to evaluate its effectiveness for its implementation as an isolated assessment tool. Use of Simulators and part-task trainers were the best option available for replacing clinical patient in COVID -19 pandemic lockdown was agreeable to 93 % and 85.7% of examiners and examinee respectively in our study.

Assessment of psychomotor domain in clinical subjects encompasses various skills such as history taking, clinical examination and discussion of management protocol and procedural skills which can be assessed using simulators and part-task trainers. Besides, simulation can be used to evaluate other attributes diagnostic and therapeutic management skills and assess clinical judgment, communication and team dynamics in a real like virtual setting. Our study revealed that competence in the psychomotor domain was assessed adequately through simulator/ task trainer station which was agreeable to 85.7% examinee and 92.8% of examiners. Majority of participants expressed that competence in affective & communication domain was also assessed with the assistance of simulator/ task trainer station. Bould et al highlighted in their study this mode of assessment as a fair and dependable tool to evaluate the student on clinical competencies in absence of real clinical cases.\(^3\)

Standardized assessments create a trustworthy, unbiased and more consistent outcome leading to greater integrity and reliability. In our study, examinee was mainly assessed based on a validated checklist to ensure objectivity and uniformity. Our study revealed that the method and process followed in technology-based summative assessment complied with goals of assessment as expressed by the majority of the participants in our study. The Accreditation Council for Graduate Medical Education (ACGME) advocates simulation in the assessment of competence in four of six domains in the patient. Assessment through simulation could achieve high validity and reliability through application of specific criteria in controlled conditions. Hence, formative and summative evaluation can be done through simulation.

In simulation, scenarios need to be created and data has to be fed, programmed accordingly along with the creation of external appearance by methods like a mouldage and hence needs good preparation. In our study, about 50% of examiners expressed that preparations required for skill stations were much more than in traditional examination. One of the facilitatory factor mentioned by examinee was being well versed with skill/simulation based evaluation during formative assessment.

To conclude, COVID-19 pandemic has reiterated the fact that it is essential to integrate technology-based aids in medical training today and in future. Simulation has emerged as functional tool for summative assessment in patient less circumstances and can be utilized in circumstances challenging the use of real patients or even standardized patients.

References


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**Stenotrophomonas Maltophilia Meningitis Following Neuro-Surgical Intervention**

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**Sir,**

Stenotrophomonas maltophilia is an aerobic, non-fermentative, gram-negative bacillus and there have been sporadic reports of nosocomial infection due to this micro-organism. The infections include pneumonia, urinary tract infections, endocarditis, endophthalmitis, skin infection, osteomyelitis, etc. Immunocompromised adults and premature children are more susceptible to this infection. Rare cases of acute meningitis have been described in the literature, particularly occurring after neuro-surgical procedures.\(^1\)

A 62-year old right-handed diabetic, hypertensive man presented with acute onset vertigo, repeated vomiting and unsteadiness of gait. Within a few hours of admission, he developed right hemiparesis. Cerebral MRI scan revealed acute infarction affecting bilateral cerebellum, dentate nuclei and cerebellar vermis (Figures 1A & 1B). Owing to progressive impairment of sensorium, posterior fossa decompressive craniectomy was undertaken. Intra-operatively, cerebellar hemispheres were found to be swollen. After adequate bony decompression, brain pulsation improved. Dura was repaired with fascia lata graft and sealed with fibrin glue. Post-operatively, the patient was electively ventilated. Mild fever developed. Tracheal aspiration and urine culture showed no growth. Intermittent mild fever (\(T_{\text{max}}\) 99°F) continued in spite intra-venous piperacillin-tazobactam administered for 10 days. Two days after discontinuation of antibiotics temperature rose further with \(T_{\text{max}}\) 104°F with worsening of sensorium. There was no evidence of wound infection. Blood revealed leukocytosis (total leucocyte count 13100/mm\(^3\); 89% neutrophils). Chest X-ray, urine culture and blood culture were non-revealing. It was observed that most
of the incisions healed well except a small pseudo-meningocele at the top end of incision with evidence of CSF leakage. Therapeutic CSF drainage for 3 consecutive days were undertaken. CSF analysis revealed 2863 cells/mm³ (94% neutrophils, 6% lymphocytes), protein 227 mg/dl, glucose 31 mg/dl (against concomitant blood glucose 132 mg/dl). In view of the diagnosis of pyogenic meningitis with neutrophilic pleocytosis, the parenteral combination of ceftriaxone, vancomycin and meropenem were initiated empirically pending culture report. But fever continued unabated. Subsequently, the CSF culture report revealed growth of “Stenotrophomonas maltophilia.”

Antibiogram showed the organism sensitive to trimethoprim-sulfamethoxazole (TMP-SMX) with MIC value ≤ 20 mcg/ml. TMP 160 mg-SMX 800 mg dissolved in 250ml 5% dextrose was infused intravenously q8hrly for 10 days followed by a course of oral TMP-SMX for a further 10 days. Fever normalized in a week and the patient discharged in stable condition in due course of time.

Following a neuro-surgical intervention if the patient develops meningitis not responding to standard antibiotics, the possibility of Stenotrophomonas maltophilia meningitis should be strongly suspected. Once the organism is isolated from CSF culture, parenteral TMP-SMX should be administered promptly. Nearly all cases respond to TMP-SMX with favourable outcome. If appropriate treatment is not initiated on time, mortality is almost 100%. However, antibiogram from the CSF culture is necessary since occasional cases are found resistant to TMP-SMX and alternate antibiotic as per the antibiogram is then required.

Comparative Study of Perceived Stress and Quality of Life between Doctors Working During the COVID-19 Pandemic at a Jumbo COVID Center Versus a Tertiary Care Hospital in India Metropolitan City

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Sir,

Unprecedented challenges in the management of coronavirus 2019 (COVID-19) have resulted in revealing major deficiencies in the world’s epidemic preparedness. To reduce the burden, of COVID-19 patients, on tertiary care hospitals, the municipal corporation has erected makeshift jumbo COVID-19 centres. A strong link is observed between COVID-19 pandemic and emotional distress such as depressive symptoms, anxiety and psychosomatic symptoms among doctors. We thus carried out an online questionnaire survey to determine the perceived stress and quality of life among doctors working in jumbo COVID-19 centres in Indian metropolitan city.

Doctors who had worked in wards of jumbo COVID-19 centres were recruited for this cross-sectional survey. Ethical clearance was sought for the study from the Ethics Committee for Academic Projects, BYL Nair Hospital (Reference no. ECARP/2020/172). The survey questionnaire included 3 parts: general and demographic information, perceived stress level (PSS scale) and quality of life assessment (WHOQOL-BREF scale). To follow the norms of physical distancing, these questions were sent to the participants as online Google Forms. Distribution of responses were examined using frequencies and percentages, and comparison was done using student’s t-test.

The average age of the 100 doctors who participated in the study was 27.68 years ± 4.39 years. 21 doctors worked on an average 8 hours for 5 days in a week; whereas, 79 doctors worked on an average 6 hours for 5 days in a week. Among the participants recruited, 75 doctors engaged in physical activities and exercises for less than 7 hours in a week; while only 5 doctors exercised for more than 14 hours every week. 30 doctors complained of a decreased appetite while working in COVID-19 wards, while 14 doctors reported of an increased appetite. The perceived stress level of the doctors was 19.33 ± 4.75, wherein, 71% of the doctors showed a moderate to high level of stress. The quality of life assessment, averaged at 3.61 ± 0.72 for all the participants. Statistically significant (p = 0.0001) negative correlation existed between PSS and all four domains of WHOQOL-BREF scale.

The global COVID-19 outbreak has been declared to be a public health emergency of international concern by the World Health Organization. During acute health crises, doctors are placed under extreme pressure, making working life even more stressful than normal. Given the unknown and unexpected nature of the disease, coupled with
being away from home, the doctors and healthcare workers working in COVID-19 wards usually have a certain psychological pressure.3

The results of this survey showed that doctors working in jumbo COVID-19 centers showed moderate levels of burnout, disengagement and exhaustion. They had neither poor nor good quality of life and showed a little job satisfaction. Regular screening to evaluate stress, anxiety, and depression among medical personnel working in COVID-19 wards should be undertaken, and psychiatric counselling provided when necessary.

References

Myth or Fact: Diet in Diabetes
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Sirs/Madam,

This correspondence is meant to discuss a few issues which are commonly faced by physicians in daily clinical practice. The authors will only try to formulate evidence-based answers for some of these ubiquitous questions.

Doctor, I eat a lot of sweets. Can I get diabetes?

This is a common question faced by doctors all over India. For an average Indian, intake of sweet dishes forms an almost regular part of daily life.

But “sweets” does not mean one homogeneous dish like cakes or candies. In different parts of India, sweets can mean widely different items. For example, in Bengal, sweets are made of cottage cheese (Chana) with molasses or syrup of sugar. In Rajasthan, sweets are made of pulses, dry fruits or nuts. In addition, various sweet dishes of India have various additives like chocolate syrup or cream. So, the metabolic effect of sweetmeats depends on what type of sweet a person consumes.

A prospective study in the USA found that people on diet high in refined carbohydrates and low in fibres had a higher incidence of type 2 diabetes.1 Sweetmeats in India contain refined carbohydrates like Maida or sugar. Another study in Japan found that obese individuals on high carb diet were more likely to develop diabetes compared to non-obese persons with the same diet.2 So, those who are already obese should restrict their sweet intake.

Doctor, I have “borderline” blood sugar. I don’t want to start drugs. Can you advice a diet chart?

This is another common situation faced by physicians in India. People often try to delay initiation of treatment for conditions like diabetes or hypertension. The fact must be emphasized to the patient that once blood sugar has crossed the threshold, treatment is the best option. Delaying treatment will only aggravate other complications like nephropathy.

In general, people with dysglycemia should reduce intake of refined carbohydrate and increase intake of fibres. Fibres are present in fruits, lentils, oats and leafy vegetables like Amaranth. The total intake will depend on gender, level of activity and previous food habits of the patient.

One food item which needs to be totally banned for dysglycemic patients is sweetened beverages. A study from the Harvard School of Public Health found that an average 12 ounce (around 350 ml by Indian denomination) of popular soft drinks contain 10-12 teaspoonsfuls (around 40 g) of sugar.3 Thus, consuming one can of “soft drink” is equal to taking the total daily allowance of sugar at one go. The same holds true for most packaged fruit juices and sports drinks. However, recently many of these manufacturers have come up with “diet” or no-sugar versions of the drinks, which contain sucralose or aspartame. These are comparatively safer.

Doctor, I have diabetes. But I love sweets very much. Can I take one sweet per day?

Sweets are not completely banned for diabetics. The ADA has clearly mentioned in their guideline that sucrose-containing food can be taken by diabetic patients. But it should be in the context of an overall healthy diet.4 Rather than consumption of sweets, the more important issue is glycemic index (G.I.) of food. High G.I. will increase not only the post-prandial sugar but also the fasting sugar and HbA1C, and this is a risk factor for micro- and macro-vascular diseases. Sweets which are mixed with fruits (except pineapple which has high glycemic index) are safer for diabetics. Similarly, another safe way to consume sweets is to take them with breads.

Also, the sweets made with sucralose or such artificial sweeteners are safe, provided the daily intake limit for each sweetener is adhered to.

And finally, doctor, I have diabetes. Can I eat eggs?

The issue of egg in the diet plan of a diabetic subject is a matter of controversy. While some researchers have found a small increased risk in diabetics consuming egg daily, others have not found any such association. In fact, some authors have found that regular egg intake had beneficial metabolic effects for diabetics.5 If blood cholesterol is very high, probably the egg yolk is to be avoided. But the egg white has no problem on daily consumption. Also, it must be remembered that the egg yolk has a lot of beneficial nutrients and occasional consumption is allowed.

References
Revisting National Physicians Day and Inaugural Address by Dr. Jivraj N Mehta

Shambo S Samajdar1, Santanu K Tripathi2, Jyotirmoy Pal3
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Sir,

The 23rd December marks the establishment of the Association of Physicians of India (API), and is celebrated as National Physicians’ Day. It is the day of self-reflection of all specialist physicians of India. The API was officially established on this day in the year 1944. Interestingly, the first conference of API was held in Madras (currently Chennai) in November in the same year. Dr Jivraj N Mehta, the founder president of API, delivered the inaugural address on the 15th November, 1944 wherein he deliberated on issues critical to the growth and development of the organization. The oration was duly published in the Journal of Indian Medical Association (Vol XIV, No 2, 1944). Let us take time to reflect on different aspects of this masterpiece, an epitome of Dr Mehta’s great vision.

He emphasized the indispensability of medical research and government’s obligation to support and foster the same. In a call to philanthropy, he even appealed to the wealthier physicians to extend financial support to advancement of medical research. He urged that all specialist physicians must engage in research in parallel to providing medical care. And they must also publish their research observations and experiences in medical journals.

This piece of advice by him remains ever pertinent, perhaps assuming even more relevance in today’s time. He commented on the need to frame rules for joint authorship based on the relative contribution of each stakeholder in a piece of research – a matter that seems inadequately addressed even today.

Dr Mehta had foreseen the gross imbalance between the need and provision of medical care in the country, and argued for revisiting the undergraduate medical curriculum and making it shorter, simpler, integrative and more relevant. He also urged for employing full-time teachers. It took us five decades to respond to his advice when in 1997 the Medical Council of India amended the MBBS curriculum to make it more goal-oriented and contextual. Then only a couple of years ago – in 2019, the newer competency-based medical education (CBME) curriculum was introduced in the country, in a bid to harmonize with the global trend. The CBME curriculum incorporates early clinical exposure of the learners, the essential elements of attitude, ethics and communication (AETCOM), mandates for greater, more focused and holistic involvement of clinician-teachers and reiterates the importance of alignment and integration of all basic and clinical subjects and their contents.

Dr Mehta spoke about laying emphasis on affordable healthy diet and nutrition, and their importance in care and promotion of heath. He advised for preservation and practice of traditional indigenous knowledge in this area. With the advent of fast foods and inappropriate lifestyles, Dr Mehta’s advices are even more relevant today. The API may consider contribute in this area, guiding the policy makers to take appropriate actions.

He expressed subtle concern about the conduct of the drug industry in general and high price and ill-affordability of medicines. Dr Mehta longed for engagement of more medical professionals there which he believed would perhaps strike a balance between the profiteering motives of the industry and its obligation to health of the nation – a dream that is unfulfilled yet. The existing pharmaceutical pricing policy seems insufficient. Should the API not strive to make drug treatments affordable for all in the country?

Dr Mehta called for the development of Indian Pharmacopoeia and API’s involvement in the same. While the first edition of Indian Pharmacopoeia was published in 1955 under the able guidance and leadership of Col Dr R N Chopra, the eminent physician, and the Indian Pharmacopoeia Commission (IPC) was founded the next year in 1956, the API is however not represented in the present-day activities of the IPC.

Dr Mehta was in favor of integration of principles of Ayurveda and ancient indigenous knowledge with the modern medical science – a theme that most recently the present dispensation in country has been seriously considering.

In fine, we pay our homage to this great thinker and visionary, and most gratefully appreciate the observations he expressed in his presidential oration. We urge our beloved API to take stock of the situation in reference to Dr Mehta’s advices and to work on his unfulfilled expectations.

Long Live API

Dr. Shambo S Samajdar, Prof. Santanu K Tripathi, Prof. Jyotirmoy Pal
ELECTIONS OF API, ICP AND PRF

(Full details circular No. 1 & 2/2022)

Election for Governing Body of API, Faculty Council of ICP and Board of PRF are announced for following posts:

Governing Body of API:
President-Elect – One; Vice President – One; Hon. Treasurer - One; Elected Members – Six and Zonal members – Nine.

Faculty Council of ICP:
Dean-Elect – One; Vice Dean – One and Elected Members – 4 posts.

Board of PRF
Board members – Two

Separate nominations must be submitted for each post.

Requirements for eligibility contest of election to the Governing Body of API
1. **President Elect:** To contest for the post of President Elect the candidate should be a life member of API for at least 10 years and have completed at least two full terms of 3 years each in any elected position in the Governing Body.
2. **Vice President:** To contest for the post of Vice President the candidate should be a life member of API for at least 5 years and should have completed at least one continuous full term of 3 years in any elected position in the Governing Body.
3. **Hon. Treasurer, Governing Body Member and Zonal Member:** To contest for the post of Hon. Treasurer; Member of the Governing Body and Zonal Member, continuous membership of the Association of at least 3 years is mandatory.

Requirements for eligibility contest of election to Board of PRF
**Board Member:** A member of API for at least 10 years with research experience and having 5 research publications in peer reviewed indexed journals.

The members contesting for the PRF election must attach copies of the Research Papers as mentioned above is mandatory.

Nominations shall be made on prescribed forms stating the office for which nominations are filled. The nominations for API/PRF posts shall be proposed by one valid member and seconded by another valid member of API and duly signed by them and shall also be signed by the candidate signing his/her willingness to stand for election and serve on the Governing Body if elected.

Requirements for eligibility for the contests of election to ICP

**Dean Elect:**
1. A member of API for at least 15 years and
   i. A Founder Fellow or a Fellow of the College of 7 year standing and
   ii. Any person who has held the position of President/Secretary of API or served as Vice Dean for one full term or elected member of the Faculty Council for one term.

**Vice – Dean:**
1. A member of API for at least 12 years and
   i. A Founder Fellow or a Fellow of the College of 5 year standing and
   ii. Any person who has held the position of Secretary of API or has been a Jt Secretary from HQ for one full term or a member of the Faculty Council.

**Elected Members:** A member of API for at least 10 years and a Founder Fellow or a Fellow of the college of 3 year standing.

Nominations shall be made on prescribed forms stating the office for which nominations are filled. The nominations for ICP posts shall be proposed by one valid Founder Fellow / Fellow and seconded by another valid Founder Fellow / Fellow of ICP and duly signed by them and shall also be signed by the candidate signing his/her willingness to stand for election and serve on the Faculty Council of ICP if elected.

A member shall not contest simultaneously for more than one post (i.e President-Elect, Vice-President, Hon. Treasurer, Member of the Governing Body and Zonal Member) (Dean-Elect; Vice Dean and Elected Members of Faculty Council) and also (Board members of PRF) Post means not only an office-bearer but also member of the Governing Body of API or Faculty Council of ICP of Board of PRF.

Every member is supplied with a nomination form. The nomination form completed in all respects should reach the API Office not later than 31st May 2022. For every post on the Governing Body / Faculty Council / Board of PRF, the nomination must be accompanied by a sum of Rs. 2950/- (Rupees two thousand five hundred only) nonrefundable in the form of Demand Draft payable at Mumbai. The nomination paper NOT accompanied by the Bank Draft of Rs. 2,950/- will be deemed invalid.

**Important**

Canvassing in any form should not be done by the candidate for the election. Instead, they are requested to send a short bio-data NOT MORE THAN 200 words along with the nomination paper which will be printed and circulated along with the ballot papers. Excess of bio-data beyond the first two hundred words shall be deleted. Canvassing in any form or in favour of the candidate shall not be permitted.

THE CANDIDATE WILL HAVE TO CERTIFY AND SIGN THAT THE INFORMATION PROVIDED IN HIS/HER BIODATA IS CORRECT.

The results will be declared at the end of counting of votes and announced in the subsequent issue of JAPI. The report will be placed before the Governing Body for intimation.

**DEAD LINES OF ELECTION PROCEDURE**
- Last date to receive the nomination at API Office: 31st May 2022
- Last date for withdrawal: 20th June 2022
- Last date to receive ballot papers at API Office: 31st August 2022

Dr. Mangesh Tiwaskar
Hon. General Secretary
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References:
3. Aitkenhead AR: Therapeutic Equivalency Evaluations with Reference to the Department of Health and Human Services Food and Drug Administration (FDAC): A222.e21.5

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