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Partial Seizures, Complete Illumination!

Shilpa Sankhe¹, Bhavin Jankharia²

The article “Association between clinical features and magnetic resonance findings in patient with temporal lobe epilepsy” by Ojha et al. is a single-center observational “one point in time” evaluation of patients with temporal lobe epilepsy (TLE). They have attempted to correlate clinical features and magnetic resonance imaging (MRI) findings in patients with TLE.

Temporal lobe epilepsy generally affects the younger age-group, with the mean age of patients in the study being 29 years. More importantly, these are refractory to drug therapy and may benefit from surgery. Their study reaffirms the pre-eminence of mesial temporal sclerosis (MTS) as the etiological factor for TLE.

The study has found that aura and automatism are significantly associated with the incidence of TLE; however, while a significant association was found between the occurrence of aura and specific etiological findings, automatism had no significant association with a specific etiology of TLE. In both, MTS was the most common finding on MRI. The presence of aura was associated with a higher incidence of positive imaging, again most commonly MTS. The other important finding identified was the presence of a positive correlation between drug-refractory seizures and MTS. Drug resistance was also associated significantly with the presence of dual pathology.

No significant association between childhood febrile seizures and development of MTS was identified. However, a higher incidence of drug-resistant epilepsy was found in patients with childhood febrile seizures. There was no significant lateralization of disorders and cerebellar atrophy was found to be almost exclusively in patients with MTS.

Immediately, this study underlines the pre-eminent role of high-field strength MRI in detecting a specific etiology for TLE. Our experience with 3-TESLA MRI has proven to be the same. We have found that using a dedicated protocol in addition to routine brain sequences outlined in Appendix, increases the imaging sensitivity in detecting subtle lesions. The input from electroencephalography (EEG) studies has been of great assistance in guiding us where to look; more often than not, an EEG-guided second look at an area of interest with reconstructions in multiple planes has aided in unmasking a subtle focus of dysplasia or other migrational abnormalities.

In our experience also, MTS has been found to be the most common cause of TLE. Automated hippocampal volumetry offers incremental benefits in the diagnosis of hippocampal atrophy. However, in our experience, we have found a significantly greater incidence of focal cortical dysplasia, partly due to high-field strengths and thinner (0.9 mm thin) volumetric images we routinely obtain.

Finally, the authors accept the inherent limitations of their study. To critique this study further, the use of 3-TESLA with the dedicated protocol outlined in Appendix may further help. In addition, epilepsy is a longitudinal disease with disease onset in childhood, manifestation in adulthood, and ongoing neurodegeneration, with or without treatment. This study is a snapshot in time and longer longitudinal studies in epilepsy cohorts may help further elucidate the etiology and progression of epilepsy.

Appendix

3D FLAIR
3D FLAIR volumetric sequence with isotropic voxels and 512 x 512 matrix and submillimeter or at least 1 mm thickness with 0 interstice gap, so as not to miss the tiniest of seizure focus. FLAIR scores over T2 as the CSF intensity is nulled hence the lesion stands out.

3DT1WI
High-resolution 3D T1WI using the magnetization-prepared rapid gradient-echo (MPRAGE) sequence providing isotropic millimetric voxel resolution (i.e., 1 x 1 x 1 mm without interslice gap) is particularly helpful in evaluating developmental malformations and granulomas.

2D T2 CORONAL
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Association between Clinical Features and Magnetic Resonance Imaging Findings in Patients with Temporal Lobe Epilepsy

Vineeta Ojha1*, Avinash Mani2, Debasis Basu3, Ashok Bhadra5
Received: 22 January 2021; Accepted: 10 March 2022

Abstract
Background: Temporal lobe epilepsy (TLE) is the most common cause of partial seizures. However, there is a paucity of data on the correlation of clinical and semiological features of TLE with specific imaging findings on magnetic resonance imaging (MRI).
Objective: In this study, we sought to evaluate the association between the semiology of TLE with specific etiological findings as identified on MRI.
Materials and methods: This was a single-center, observational study in which consecutive patients presenting with clinical features diagnostic of TLE underwent a brain MRI on a 1.5 T scanner. The data collected from the various MR parameters were then correlated with history.
Results: A total of 90 patients were included in the study. The mean age of the study population was 29.1 years. Females comprised 45% of the study population. Mesial temporal sclerosis (MTS) was the most common imaging finding in about 60% of patients. Four out of five patients had aura whereas 70% had automatism. The presence of aura in TLE patients was significantly associated with MTS on MRI (p = 0.042). The presence of automatism and history of childhood febrile seizure did not have a significant association with any specific etiological findings on MRI (p = 0.254 and 0.731, respectively). Drug-refractory epilepsy was commonly associated with the presence of MTS on MRI (p = 0.004). The presence of dual pathology on MRI was associated with drug-refractory epilepsy (p = 0.031).
Conclusions: The presence of aura and drug-refractory epilepsy point towards the presence of MTS. Dual pathology on MRI, in TLE patients may be a risk factor for drug-refractory epilepsy.

Journal of the Association of Physicians of India (2022): 10.5005/japi-11001-0125

Key Message
The presence of aura and drug-refractory epilepsy predicts the presence of MTS as the cause of TLE and TLE patients with dual pathology on MRI are prone to drug-refractory epilepsy.

Introduction
Temporal lobe epilepsy is the most common cause of partial seizures in adults. It is clinically associated with cardinal semiologies like prodrome, aura, automatism, and altered consciousness. Patients usually have a family history of epilepsy and may also have a history of childhood-onset febrile seizures. Commonly, these seizures are refractory to drug therapy and may require surgery. MTS is the most common cause of TLE accounting for more than 80% of the cases.1 TLE can also be associated with numerous other causes like infections, malignancy, paranepoleptic syndromes, vascular malformations, or perinatal injury. Recognition of etiology is important for guided management strategy. MRI has revolutionized the detection and management of TLE and has an important role in guiding therapy.2 MRI features in TLE usually include a small hippocampus with hippocampal sclerosis (HS), a small temporal lobe, and an enlarged temporal horn.1 MRI can also be used to localize and characterize the lesions, help in predicting the etiology, and guide therapy.3 Studies on MRI findings on TLE have well described the various MRI features noted in this condition—the most common is HS.5-11 However, none of the studies have shown any correlation between imaging abnormalities and semiological features of TLE. In this study, our aim was to assess the correlation between specific clinical and semiological features of TLE with the etiology of TLE identified on MRI and other imaging findings.

Materials and Methods
Our study was a single-center hospital-based observational study. Patients presenting with clinical features diagnostic of TLE were included in the study. Patients who had another neurological disease, who were not able to undergo imaging (claustrophobia, contrast allergy, and pacemaker implantation), and those who were not willing to take part in the study were excluded. The study period extended from January 2016 to January 2017. All patients were clinically evaluated for semiology and clinical characteristics of TLE including prodrome, aura, automatism, history of febrile seizures, drug history, and prior treatment history.1 Febrile seizure was defined in accordance with the International League Against Epilepsy as “a seizure occurring in childhood after one month of age associated with a febrile illness not caused by a central nervous system infection, without previous seizures, and not meeting the criteria for any other acute seizures.” All clinical data were recorded using a structured questionnaire. All study participants subsequently underwent brain MRI in a 1.5 T MR scanner (GE SIGNA). The routine protocol consisted of T1 weighted axial (slice thickness 5 mm) and sagittal, T2-weighted axial and sagittal, FLAIR axial and coronal, susceptibility-weighted imaging and diffusion-weighted imaging sequences, and postcontrast studies were performed in all patients following a standard epilepsy protocol. The data collected from the various imaging parameters were then analyzed to identify the underlying pathologies/etiologies. Increased hippocampal signal intensity and reduced size of the hippocampus were considered diagnostic of MTS. These imaging findings were then correlated with the history and clinical features of the patients in order to derive a clinical association.

Statistical Analysis
All the data were recorded in tabular format in Microsoft Excel. All statistical analysis was done using SPSS software v20. Data were divided into categorical and continuous variables. Student’s t-test and analysis

1 Resident, Department of Radiodiagnosis; 2 Resident, Department of Internal Medicine; 3 Professor, Department of Neurology; 4 Professor, Department of Radiodiagnosis, Medical College Kolkata, Kolkata, West Bengal, India; *Corresponding Author

of variance were used to study statistical significance between groups of continuous variables. Chi-square test was used to evaluate the relationship between categorical variables. p-value <0.05 was considered to be significant.

**Results**

A total of 90 patients with clinical features of TLE were included in the study. The mean age of the study population was 29.1 years (range 3–62 years). Females comprised 45% of the study population. Most of the TLE cases occurred in the 20–39 years age group (young adult) (43.3%). Specific etiological findings on MRI were detected in 80% of the study population. MTS was the most common etiology of TLE (62.5%) followed by tumors (12.5%) (Table 1 and Figs 1A and B). Out of the nine cases of tumors, there were two cases of ganglioglioma, two cases of low-grade glioma, two cases of metastases (Figs 2A to D), one case each of high-grade glioma, pleomorphic xanthoastrocytoma, and dysembryoplastic neuroepithelial tumor. Infectious etiology was noted in around 10% (n = 7) of the study group. Tuberculoma was detected in three cases whereas herpes encephalitis (n = 2) (Figs 3A and B) and neurocysticercosis (n = 2) (Figs 4A and B) were noted in others. Chronic infarct was the most common ischemic cause among adults and periventricular leukomalacia (PVL) was the most common ischemic cause among children in our study. About 4% (n = 3) of the study patients were detected to have developmental abnormalities. Focal cortical dysplasia (FCD) was noted in two patients whereas gray matter heterotopia was found in one patient.

Table 1 shows the prevalence of various clinical parameters in the study population. Out of 90 cases, maximum cases had automatism (83.33%) and 71.11% of cases had aura. Fifty cases had both aura and automatism (55.56%) during seizures. About 15.56% of patients had a history of febrile seizures in childhood. About 46.66% of patients had refractory epilepsy.

Aura was noted in about 70% (n = 51) of TLE patients who had specific etiological findings on MRI. MTS was the most common etiology (72.5%) noted in this group of patients (Table 3). A significant association was noted between the presence of aura and specific etiological findings on MRI (p = 0.042). History of automatism was noted in about 85% of the study group with MTS being the most common associated etiology on MRI (Table 3). History of automatism had no significant association with the specific etiology of TLE (p = 0.254).

Fourteen patients had a history of childhood febrile seizures and eight of them had abnormality on MRI. Six patients had a positive history of childhood-onset febrile seizures, however, no abnormality was found on MRI. There was no significant relationship between the history of childhood-onset febrile seizures with various etiologies of TLE (p = 0.731) (Table 4). It was seen that the history of childhood-onset febrile seizures did not have any significant association with the specific etiological findings of TLE.
not predict the occurrence of MTS in later life ($p = 0.561$). Out of the 90 patients in the study population, 42 had drug-resistant epilepsy. There were only three patients in whom there was a positive history of refractory epilepsy, however, no abnormality was found on MRI, 39 patients had an MRI abnormality (Table 4). Drug-refractory seizures were most commonly associated with mesial temporal lobe sclerosis on MRI ($p = 0.004$).

Dual pathology on MRI was noted in about 8% ($n = 7$) of the study population. MTS was found in all seven patients associated with FCD in four patients (Figs 5A and B). Heterotopia, PVL, and cavernous malformation were noted in the other three patients. The presence of dual pathology on MRI was significantly associated with drug-resistant epilepsy ($p = 0.031$).

Among the broad etiological groups causing TLE, the lateralization of temporal lobe abnormalities was studied and the result was not statistically significant, that is, the lesions had no preferred lateralization—left or right. Among the MTS group, 25 (55.56%) patients had lesion on the left side, 14 patients on the right side, and six patients had lesions bilaterally. No significant difference was noted among the groups ($p = 0.644$).

Six MRI features of MTS were specifically evaluated: (1) increased signal intensity of the hippocampus, (2) reduced size of the hippocampus, (3) atrophy of the white matter of the ipsilateral hippocampus, (4) enlarged temporal horn of the ipsilateral side, (5) reduced gray-white matter demarcation in the temporal lobe, and (6) decreased size of the temporal lobe. In our study, we used the increased signal intensity of the hippocampus and reduced size of the hippocampus as prerequisites for defining cases of “hippocampal/mesial temporal sclerosis.” There were 45 cases which fulfilled these criteria. Table 5 shows the prevalence of various imaging features of MTS. Out of 90 patients, six had cerebellar atrophy on imaging and all six cases of cerebellar atrophy were found in those patients who had an imaging diagnosis of MTS. Cerebellar atrophy was significantly associated with the presence of MTS in our study ($p = 0.048$).

**Discussion**

Our study showed that MRI has a sensitivity of 80% in the detection of the etiology of TLE. The study conducted by Lehéricy et al. also showed that in TLE, no specific abnormality was found on MRI in 20% of the cases. Another study also mentioned the sensitivity of MRI in the detection of structural temporal lobe lesions like tumors, vascular malformations, etc. to be 90%.

**Figs 2A to D:** Brain MRI in a patient with epileptic seizures: T2 coronal image (A) shows a heterogeneous hyperintense mass (white asterisk) involving the right frontal lobe, basal ganglia, and periventricular white matter causing midline shift to the left. A small hyperintense nodule is also noted in the right medial temporal lobe (white arrow). Postcontrast T1 coronal (B) and axial (C) images show the heterogeneous enhancement in the mass (with central areas of necrosis) (white asterisk) and enhancing nodule in the temporal lobe (white arrow). There were multiple other enhancing lesions (black arrow) in the brain parenchyma too. (D) MR spectroscopy (MRS) shows increased choline:creatinine ratio in the mass (black arrow). Image features were suggestive of high-grade glioma with metastatic deposits in the temporal lobe.

**Figs 3A and B:** MRI brain in a follow-up patient with herpes encephalitis on treatment: T2 (A) and FLAIR (B) axial images showing hyperintensity in both medial temporal lobes (white arrows). Features are suggestive of residual changes of herpes encephalitis.
Association between Clinical Features and MRI Findings

In the present study, MTS was the most common etiology of TLE comprising 62.5%, followed by tumors (12.5%), similar to previously published studies. Lehéricy et al. showed that HS was the most common cause in patients with TLE (50–70%), followed by tumors (10–15%), developmental abnormalities (5–7%), vascular malformations (mostly cavernous malformations, 1–5%), and traumatic scars (5–10%).

The prevalence of aura and automatism in our study population was 71 and 83%, respectively. In a previous study, a large number of patients with TLE demonstrated or described an aura, which was typically of short duration. About 40–80% of the patients in this study had automatisms during a seizure. MTS emerged to be the most common etiology in patients describing aura or automatism in our study group.

In the present study, there was no significant relationship between the history of childhood febrile seizures with various etiologies of TLE or with the occurrence of MTS in later life. Our findings correlate well with the study by Tarkka et al. which showed that the relationship of MTS with febrile seizures is controversial. Up to one-third of patients with refractory TLE have a history of febrile seizures. Follow-up of the children with a history of febrile seizures did not demonstrate a statistically significant increase in the incidence of TLE in this study. Another study by Labate et al., however, showed that febrile seizures were more frequent in patients with MTS detected on MRI (36%) as compared with those with normal MRI (22.7%), but again, this difference was not significant.

In our study, out of 90 subjects, 42 had drug-refractory epilepsy. Previous studies have described the prevalence of drug-refractory epilepsy.

### Table 4: Number of cases with a history of febrile seizures and refractory epilepsy among the etiological groups

<table>
<thead>
<tr>
<th>Etiologies detected on MRI</th>
<th>Number of cases with a history of febrile seizures in childhood (percentage)</th>
<th>Number of cases with refractory epilepsy (percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTS</td>
<td>6 (75%)</td>
<td>27 (69.2%)</td>
</tr>
<tr>
<td>Tumors</td>
<td>1 (12.5%) (high-grade glioma)</td>
<td>7 (17.9%)</td>
</tr>
<tr>
<td>Developmental</td>
<td>1 (12.5%) (heterotopia)</td>
<td>3 (7.7%) (FCD = 2 and heterotopia = 1)</td>
</tr>
<tr>
<td>Ischemic</td>
<td>0</td>
<td>1 (2.6%) (chronic infarct)</td>
</tr>
<tr>
<td>Vascular malformation</td>
<td>0</td>
<td>1 (2.6%) (cavernoma)</td>
</tr>
<tr>
<td>Total</td>
<td>8 (100%)</td>
<td>39 (100%)</td>
</tr>
</tbody>
</table>

### Table 5: The prevalence of various imaging features of MTS

<table>
<thead>
<tr>
<th>Serial number</th>
<th>Imaging finding</th>
<th>Number of patients (n = 45)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Increased hippocampal signal intensity (essential criteria)</td>
<td>45</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>Reduced hippocampal size (essential criteria)</td>
<td>45</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>Atrophy of the ipsilateral hippocampal collateral white matter</td>
<td>35</td>
<td>77.77</td>
</tr>
<tr>
<td>4</td>
<td>Enlarged ipsilateral temporal horn</td>
<td>44</td>
<td>97.77</td>
</tr>
<tr>
<td>5</td>
<td>Reduced gray-white matter demarcation in the temporal lobe</td>
<td>27</td>
<td>60.00</td>
</tr>
<tr>
<td>6</td>
<td>Decreased temporal lobe size</td>
<td>20</td>
<td>44.44</td>
</tr>
</tbody>
</table>
epilepsy to be 40% among patients with TLE.\(^2\) We observed that those patients who have refractory epilepsy are more likely to have an abnormality on MRI than those who do not. This finding is in agreement with the study by Lehéricy et al. which showed that only 8.5% of cases of refractory epilepsy did not demonstrate any specific abnormality on MRI.\(^5\)

Cendes et al. showed that MTS is associated with other extrahippocampal anomalies which could be epileptogenic in 15% of cases. The presence of such dual pathologies was associated with a poor postoperative prognosis and refractory epilepsy in their study.\(^1\)\(^5\) Indeed in our population also, similar findings were noted.

The term mesial temporal sclerosis was coined by Falconer et al. to describe a lesion with gliosis and neuronal loss involving mainly the amygdala and the hippocampus, or both, but sometimes involving other temporal lobe components or even the whole temporal lobe, leading to generalized atrophy and gliosis.\(^1\)\(^6\) T2/FLAIR hyperintensity of the hippocampus and hippocampal atrophy were the most prevalent findings in our population. Enlarged ipsilateral temporal horn was found in 97.77%. Various studies propose that the FLAIR sequence is ideal to identify hippocampal signal abnormalities since water content increases with gliosis which appears as an increased signal on T2-weighted MRI. The FLAIR sequence nulls the bright signal because of the cerebrospinal fluid, hence, the increased signal of the hippocampus is more apparent.\(^1,\)\(^1\)\(^7\)

In our study, there was a significant association between the occurrence of cerebellar atrophy and the presence of MTS. However, this is in contrast to a study published by Hagemann et al. in which the results did not support the concept that cerebellar atrophy predisposes to epilepsy rather, the authors were of the view that cerebellar atrophy is the result of epileptic seizures or antiseizure drugs.\(^1\)\(^8\)

The current study has inherent limitations. As the present study was conducted in a tertiary level center, the study population may not be representative of the general population with TLE. So, to further support our results and observations, studies with more sample size are warranted. Many patients were lost to follow-up. Many newer technologies could not be utilized in our study like spectroscopy and volumetry. Histopathological confirmation also could not be obtained for most of the cases.

**Conclusion**

The presence of aura and drug-refractory epilepsy predicts the presence of MTS as the cause of TLE. The presence of automatism and history of childhood-onset febrile seizures did not predict the etiology of TLE in our study. TLE patients with dual pathology on MRI are prone to drug-refractory epilepsy.

**References**

Unsuspected Subclinical Left Ventricular Dysfunction in Post-COVID Patients: A Real-world Observation

Parthasarathi Bhattacharyya1, Sayoni Sengupta2, Aniruddha De3, Sikta Mukherjee4, Mintu Paul5, Debkanya Dey6

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Abstract

Background: Subclinical myocardial dysfunction may exist in post-COVID-19 patients and may carry significance in long term.

Methodology: Subjects of long-COVID-19 with historically and radiologically significant pulmonary involvement (without documented cardiac involvement) were evaluated on outpatient follow-up echocardiographically when they had disproportionate shortness of breath (SOB), fatigue, or high pulse rate as perceived by the physicians. The common acute-phase symptoms were noted and scored retrospectively. The assessment included spirometry and measurement of chronic obstructive pulmonary disease (COPD) assessment test (CAT) score with measurement of the left ventricular (LV) and right ventricular (RV) free wall global longitudinal strain as an adjunct to routine two-dimensional and Doppler echocardiography and spirometry. The results were evaluated statistically with respect to the history of hospitalization.

Results: The hospitalized (n = 15) and nonhospitalized (n = 10) patients were demographically similar. However, the nonhospitalized patients had higher total symptom score (p = 0.03), anemia (p = 0.017), and ageusia (p = 0.0019). At follow-up (>3 months of acute illness), the nonhospitalized patients had a better CAT score (p = 0.04), higher change in max pulse rate (p = 0.03), and higher forced expiratory volume in 1 second (FEV1) (p = 0.002), tricuspid annular plane systolic excursion (TAPSE) (p = 0.02), and left ventricular global longitudinal strain (LVGLS) (−17.15 ± 1.19 vs −13.11 ± 1.91) (p = 0.0001). Overall, the two groups formed distinct clusters. The LVGLS and the maximum pulse rate difference in the two chair test (2CT) seem to contribute maximally to the variance between the two groups in multivariate analysis.

Conclusion: The subclinical myocardial dysfunction persisting in post-COVID patients (without suspected cardiac affection and lower neuroinflammatory symptoms in the acute phase) with significant pulmonary affection needs further evaluation. They demonstrate a higher max pulse rate difference in the 2CT. This real-world observation demands further investigations.

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Introduction

COVID-19 is a multisystemic viral affection posing a widespread impact on different organs of the body. It has been the cause of acute severe respiratory illness observed in the first and second wave of the pandemic along with a variety of cardiovascular morbidities and myocardial dysfunction.2–4 Different methods (both invasive and noninvasive) exist to diagnose myocardial dysfunction, of which echocardiography holds prominence for its simplicity and quick ability to identify the condition.5,6 Offsite echocardiography-derived global longitudinal strain (GLS) has been innovated as a sensitive marker of myocardial dysfunction with prognostic potential.2–9 The reduction of GLS can be obvious even in the absence of regional wall motion abnormality in conventional echocardiography.10,11

We decided to apply this knowledge to a cohort of survivors of acute severe COVID-19 with overt pulmonary involvement with or without hospitalization at their follow-up in the outpatient department. Alongside assessment of both RV and LVGLS, we also intended to look for the association of the measured post-COVID LVGLS with retrospectively assessed parameters of the severity of symptoms at the acute phase of the illness.

Methodology

The study was conducted at the Institute of Pulmocare & Research, Kolkata, after proper regulatory approval by the Institutional Ethics Committee. The post-COVID patients were randomly selected from our outpatient department with a history of pulmonary involvement and documentation of more than 20% of lung parenchymal affection at any stage of the disease. The symptoms at the acute stage were enquired both in duration and severity; the latter has been noted on a Likert scale of “0” to “5” (suggesting a range from none to the extreme). A symptom score was made out of the multiplication of the duration and the severity. The symptoms included for such measurement were cough, SOB, fever, weakness, anemia, and loss of taste. The patients having relatively or disproportionately higher SOB or pulse rate at the visit as perceived by two independent consultant pulmonologists separately (compared to the expected radiological status) were subjected to 2CT, spirometry, and Doppler echocardiography observing a protocol by a single dedicated cardiologist who records the echocardiographic details (on Vivid S6 ON (GC 314438-01)) including the GLS of both the ventricles. The patients having symptoms of orthostatic hypotension or postural orthostatic tachycardia syndrome (POTS) were excluded along with those having conditions to explain resting tachycardia as fever, postexercise state, intake of caffeine within at least preceding 6 hours, features of hyperthyroidism, or history of any medication that can cause a high pulse rate. The duration of hospitalizations was also noted.

Statistical Methodology

The data of the patients were compiled on the basis of the history of hospitalization and the two groups of patients (hospitalized and nonhospitalized) were compared statistically (by the Student’s t-test) based on the available variables such as symptom score, spirometric, and echocardiographic data. A subsequent corelationship between the RV and LVGLS was looked for and a receiver operating characteristic curve was drawn with values of LVGLS to determine a cutoff value for group-specific discrimination using the GraphPad Prism (version 8) software. Finally, a multivariate analysis was also conducted between both the groups using the software MetaboAnalyst, to understand the relative role of demographic, clinical, spirometric, and...
Unsuspected Subclinical Left Ventricular Dysfunction in Post-COVID Patients

**Results**

Twenty-five patients were subjected to Doppler echocardiography out of a total of 118 post-COVID patients seen at the outpatient department in the month of July 2021. None of them had any features of POTS or clinically any obvious secondary reason for testing tachycardia. The two groups of patients showed differences based on their history of hospitalization. There was no demographic difference between the groups; but, patients without hospitalization had higher total symptom scores (33.83 ± 50.58 vs 25.17 ± 63.05, p-value = 0.008) and significantly higher anosmia (19.54 ± 20.10 vs 5.92 ± 16.61, p-value = 0.002). Lower TAPSE (p = 0.41), higher tricuspid regurgitation (TR) jet (p = 0.90), and left atrial (LA) volume index (p = 0.31). Interestingly, the hospitalized patients had highly significantly lower (−17.15 ± 1.19% vs −13.11 ± 1.91%; p = 0.0001) LVGLS in echocardiography.

A moderate correlation was observed between LVGLS and RVGLS parameters (r = 0.33) (Fig. 1). According to the VIP score obtained on the basis of multivariate analysis, it was observed that LVGLS and loss of taste and the peak pulse rate are the three most important variables expressing the highest contribution in the variance between the two groups (Fig. 2).

The VIP plot done with the data of the two groups of patients reveals that the most important factors contributing to the variance between the two groups were the LVGLS, maximum pulse rate change, fever, loss of taste, CAT score, and anosmia (Fig. 2). A score plot with orthogonal partial least squares discriminant analysis (o-PLSDA) reveals clearly two distinct clusters (Fig. 3).

**Discussion**

The most important revelation of the observation is that significant LV dysfunction persists even after about 12 weeks of recovery from acute COVID-19. This dysfunction could have been missed without assessment of the LVGLS as the left ventricular ejection fraction (LVEF) of the patients was normal at the follow-up visits. It is obvious that the patients with a history of hospitalization bear a relatively worse LVGLS in their follow-ups even after about 4 months.

COVID-19 is known to inflict myocardial damage. None of the subjects attending our clinic in post-COVID-19 status had any mention of cardiac affection in their discharge certificate or the prescriptions given at the acute phase. They were enquired about the symptoms and hospitalization without any perception of possible cardiac involvements. The advice for echocardiography was made when the clinicians felt that there was likely more exercise limitation or fatigability or dyspnea and a higher pulse rate than expected in the clinical examination. However, they were not recorded on an objective scale or questionnaire.

Global longitudinal strain represents the global longitudinal shortening as a percentage of change in length compared to the baseline length of the myocardium. The normal reference range of GLS ranges from 15.9 to 22.1% (mean 19.7%; 95% confidence interval [CI] 20.4–18.9) as derived from a meta-analysis of 24 studies. A borderline low or overtly low LVGLS has been found universally in those who underwent the echocardiographic evaluation in our series. It was found significantly lower (p = 0.0001) (a mean value of −13.11 ± 1.91%) in those hospitalized with COVID-19 compared to those who were home treated (−17.15 ± 1.19%). The RVGLS was also lower (though not statistically significant) in hospitalized patients compared to those treated at home (Table 1). However, both groups had normal...
Unsuspected Subclinical Left Ventricular Dysfunction in Post-COVID Patients

Table 1: Elucidating the demographic, spirometric, and echocardiographic parameters, and health status of post-COVID patients with or without hospitalization

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Nonhospitalized patients</th>
<th>CI</th>
<th>Hospitalized patients</th>
<th>CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>10</td>
<td></td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demography details</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>58.1 ± 8.93</td>
<td>54 ± 12.36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M:F</td>
<td>8:2</td>
<td>11:4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td>24.31 ± 2.56</td>
<td>24.79 ± 3.85</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAT score</td>
<td>7 ± 4.56</td>
<td>11.25 ± 3.93</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration between acute illness and follow-up</td>
<td>165.75 ± 98.49</td>
<td>83.41–248.1</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Duration of hospitalization</td>
<td>NA</td>
<td>18.16 ± 14.95</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Severity score (active symptoms)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cough</td>
<td>25.64 ± 45.58</td>
<td>–6.97 to 58.25</td>
<td></td>
<td></td>
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<tr>
<td>SOB</td>
<td>18.9 ± 46.77</td>
<td>–14.56 to 53.26</td>
<td></td>
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<tr>
<td>Fever</td>
<td>18.37 ± 30.48</td>
<td>–7.11 to 43.86</td>
<td></td>
<td></td>
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<tr>
<td>Weakness</td>
<td>95.82 ± 89.68</td>
<td>32.08–160.4</td>
<td></td>
<td></td>
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<tr>
<td>Anosmia</td>
<td>19.54 ± 20.10</td>
<td>5.15–33.92</td>
<td></td>
<td></td>
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<tr>
<td>Loss of taste</td>
<td>30.34 ± 28.39</td>
<td>10.03–50.65</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total symptom score</td>
<td>33.83 ± 50.58</td>
<td>19.75–48.03</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Changes in 2CT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desat-max</td>
<td>–2.9 ± 3.28</td>
<td>–5.24 to (–0.55)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative SpO2 change</td>
<td>–17.1 ± 23.61</td>
<td>–34.00 to (–2.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline PR</td>
<td>77.5 ± 12.61</td>
<td>68.47–86.53</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max pulse rate difference</td>
<td>30.7 ± 7.51</td>
<td>25.33–36.07</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative pulse rate change</td>
<td>137.7 ± 78.76</td>
<td>116.4–269.4</td>
<td></td>
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<tr>
<td>Spirometry</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>FVC</td>
<td>71.25 ± 24.39</td>
<td>32.44–110.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1</td>
<td>89 ± 11.16</td>
<td>71.23–106.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC/FEV1</td>
<td>0.85 ± 0.03</td>
<td>0.80–0.91</td>
<td></td>
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<tr>
<td>FEF25–75</td>
<td>77.25 ± 16.68</td>
<td>50.71–103.8</td>
<td></td>
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<tr>
<td>Echocardiography</td>
<td></td>
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<tr>
<td>PAP (systolic)</td>
<td>44 ± 6.58</td>
<td>39.29–48.71</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>EF</td>
<td>61.5 ± 2.41</td>
<td>59.77–63.23</td>
<td></td>
<td></td>
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<tr>
<td>TAPSE</td>
<td>23.66 ± 3.50</td>
<td>19.99–27.34</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>RVGLS</td>
<td>–21.72 ± 8.05</td>
<td>–27.92 to (–15.53)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TR-jet velocity</td>
<td>3.01 ± 0.17</td>
<td>2.02–3.41</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LA-volume index</td>
<td>26.10 ± 8.16</td>
<td>11.48–30.29</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVGLS</td>
<td>–17.15 ± 1.19</td>
<td>–18.01 to (–16.29)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bold values are statistically significant according to p-value. Hence they are marked bold in the text and Table 1; CAT, COPD assessment test; LA, left atrium; LV, left ventricle; GLS, global longitudinal strain; TAPSE, tricuspid annular plane systolic excursion; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second, FEF25-75, forced expiratory flow at 25–75% of the FVC

Acute myocardial injury in COVID-19 is found to be in 16.1–23.8% with a higher predilection for older age, males, and presence of comorbidities. Incidentally, we have no clue about myocardial damage in any of the patients from the discharge note or from the available record of transthoracic echocardiography. It is possible that in our patients the myocardial damage in the acute phase was overlooked. The plausible reasons being either the index of suspicion for myocardial injury was possibly low in these cases at the given point of time when the attention could have been diverted to respiratory failure or other complications or a sensitive test to look for myocardial dysfunction as a measurement of quantitative hs troponin-I or LVGLS was not available or possible to be performed. The possibility of having no myocardial injury at the acute phase and such myocardial dysfunction evolving from some other reason but COVID-19 during convalescence is unlikely as there had been a historically progressive improvement in hemodynamic status in terms of blood pressure and LVEF. The reason for looking for the RV free wall and LVGLS was merely incidental as the echocardiographer was himself engaged in looking at the GLS in some other subset of patients and he found this change in some post-COVID-19 subjects already.
Unsuspected Subclinical Left Ventricular Dysfunction in Post-COVID Patients

clinical status in all the included subjects following the suffering from the acute stage. The very presence of myocardial dysfunction as revealed by LVGLS may suggest most likely a myocardial insult at the acute state with slow recovery. We could have missed the diagnosis had the echocardiographer did not include LVGLS measurement in his protocol. LVGLS has been found to be a better and superior sensitive marker of detecting even subclinical myocardial dysfunction compared to M-mode, 2D, and Doppler echocardiography.17,18

Several studies have looked for the subclinical myocardial dysfunction in acute COVID-19 illness and a few in COVID-19 survivors. Even the nonhospitalized and mildly symptomatic COVID-19 patients had subclinical myocardial dysfunction found on assessment of the LVGLS.19 It was found that LVGLS can detect subclinical LV systolic dysfunction reasonably well while the standard echo and Doppler parameters failed to identify that.190 Kujur et al. analyzed the severity of myocardial dysfunction in post-COVID survivors. The study observed that 30% of patients in recovery had reduced ejection fraction (EF) and 22% showed normal EF with reduced LVGLS, after 1 month of acute illness.20 A single-center prospective observation for the presence of LV function in post-COVID (after 30–45 days) cases with variable COVID severity has reported subclinical LV dysfunction in one-third of the population under evaluation.21 In our series, we selectively looked for LV dysfunction in subjects with a history of predominant lung affection in the acute phase. The majority (60%) of our patients had demonstrated the presence of LV dysfunction even after more than 120 days of so-called recovery from acute illness. The observation also reveals the overall status of the hospitalized subjects being poor than the home-treated patients as regards the major symptoms (such as cough, SOB, and weakness), the spirometric lung function (especially the FEV1), the 2CT, and the overall echocardiographic-hemodynamic parameters (see Table 1).

We have used the CAT score to denote the health status of the patients. Although the CAT score is meant originally for COPD,22,23 the instrument has been used for diffuse parenchymal lung disease as well.24 The idea of incorporating the CAT score is because the domains in the questionnaire indicate the health status of post-COVID patients too. Paradoxically, the propensity of higher cardiac dysfunction in the hospitalized group has been found to be more with apparently innocuous neurological symptoms such as loss of taste and loss of smell.25,26 This evokes a question of a possible relationship between neuronal inflammation and myocardial affection. Incidentally, cough and/or SOB may ensue from both pulmonary and/or cardiac involvement. Since all the patients had significant pulmonary involvement in their acute phase, it is possible that the event of hospitalization was related to the compounding effects of cardiac dysfunction that could have been missed for lack of awareness and/or sensitive investigative parameters. In fact, the LVGLS appears more sensitive than LVEF to identify LV systolic dysfunction19,27 and the performance does not demand much training on the part of the performer. The parameter has been tried in COVID-19 with success to identify myocardial dysfunction.3 In fact, there has been a global myocardial dysfunction in the patients recruited with the LV dysfunction being statistically highly significant.14 It is noteworthy that LVGLS and the maximum change in pulse rate in 2CT are the two most powerful discriminating factors involved in the process. RV myocardial dysfunction is also obvious with lower TAPSE and RVGLS values in hospitalized patients on follow-up. The result mandates to look for the clinical parameters more vigorously and objectively as an indicator of reduced GLS in post-COVID-19 patients. Although the third wave of COVID-19 was largely mild with minimal lung parenchymal disease, we did not have the opportunity to look for similar changes as the subjects rarely have severe lung involvement or clues for cardiac involvement in the COVID-19-related follow-up visits to us. However, the knowledge may be important to prepare for more objective future research on the surge of COVID-19 or a different viral infection.

There are several weaknesses of the observation. The number is small and there is no echocardiography report available from the acute stage to compare with that of the present findings. The persisting myocardial dysfunction (even after a period of over 120 days of acute illness) makes one to conjecture the possible presence of a far more serious myocardial dysfunction in the acute phase that contributed to the suffering to mandate hospitalization. Incidentally, the second phase of COVID-19 to which these patients belonged to was very severe and there was a problem of getting admission too. The dearth of clinical data in the acute phase, therefore, is the biggest weakness. It would have been better to ask and get echocardiography universally in all the patients on follow-up; however, it was not possible with the real-world logistics. The higher prevalence of neuroinflammatory symptoms in patients having silent/unsuspected cardiac affection is an important observation and needs further investigations to explore any association from the pathophysiological point of view. An assessment of the intra and interobserver variability could have strengthened our findings; however, they were not feasible under real-world circumstances. Finally, the suggestion of myocardial dysfunction was not verified in our observation by relevant investigations such as cardiac magnetic resonance imaging. Further, a concomitant measurement of the myocardial damage biomarker as (high-sensitive) hs-troponin, N-terminal pro-brain natriuretic peptide (NT-proBNP), and inflammatory markers as high sensitive C-reactive protein (hsCRP) or interleukin-6 (IL-6) could have enriched the study.

Conclusion

A good number of subjects recovering from acute COVID-19 continue to have LV dysfunction in terms of GLS even after 3 months of recovery. They show more dyspnea, fatigue, and pulse rate than the other patients and of them, the hospitalized patients had significantly worse LVGLS. The significance of such LV dysfunction in long term needs to be looked for.

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Obituary

Prof Dr Ashok A. Mahashur
14 December 1948—29 August 2022

Clinician par excellence, Teacher of teachers, Astute researcher, and Stem administrator

Dr Mahashur left us for heavenly abode on 29 August 2022.

After completing his MBBS from Nagpur University, he did his MD in Pulmonary Medicine from Bombay University in 1976.

He joined Seth G S Medical College and KEM Hospital as a lecturer in Respiratory Medicine in 1977 and gradually shouldered the responsibility of Professor and Head, Department for Chest and TB at GS Medical College and KEM Hospital from 1990. He was also the Chief of Intensive Respiratory Care Unit and In-charge of Environmental Pollution Research Centre at KEM Hospital. He was a visiting physician to Sewri TB Group of Hospitals for over 20 years as well.

After bestowing 25 years of his life to medical college, he joined P D Hinduja Hospital as a Senior Chest Physician and DNB teacher in Respiratory Medicine.

Teaching was his passion and he was involved in undergraduate and postgraduate teaching. He was an examiner for both undergraduate and postgraduate courses in Respiratory Medicine as well as an examiner of CPS course in Respiratory and Industrial Medicine. He was also a PhD examiner at Osmania and Indore universities.

He made his academic mark outside the medical colleges and teaching institutes by serving various professional organizations and associations in various decision-making capacities. He was on the editorial board of various journals of national and international repute such as JAMA, BIOMED journals, Tuberculosis Update Current Trends, JAPI, Indian Journal of Chest Diseases, Lung India, and Thorax (India).

In appreciation of his immense contribution to science and services to the community, he was rightfully awarded by various fellowships and honors of national and international decency. Fellowship of American College of Physicians, Royal College of Physicians, National College of Physicians, and Indian College of Physicians are a few of the notable recognitions of his herculean services. He was also awarded many national orations at medical conferences and his lectures have always been best crowd-pullers and most attended.

He also contributed his expertise by writing multiple chapters in various medical textbooks. He was also widely published for his humongous research work he had to his credit.

On a personal note, I had the chance to work under his leadership for about 25 years. He was a perfect guide, teacher, clinician, researcher, and at times a true friend. His capacity to give time and importance to juniors and students was astonishing. His humble attitude and down-to-earth behavior added extra flavor to his magnanimous personality. He was always available and just a phone call away for his students and patients.

Dr Mahashur’s contribution to Pulmonary Medicine, Tuberculosis, and Environmental illnesses is unparalleled and unequivocal. Teachers like Dr Mahashur Sir never leave us, they are immortal with their gracious presence in our lives. He will always live in the hearts of his thousands of students and millions of patients.

Dr. Agam Vora
Consultant Chest Physician and Pulmonologist
Vora Clinic, Mumbai
Hon. Gen. Sec. National API
We Protect The Hands That Protect Millions Of Lives.

In an era where global public health is a worldwide concern, the world’s healthcare facilities trust the most reliable medical gloves to protect healthcare workers from infectious diseases. Today, more than half of the world’s medical gloves are Made in Malaysia. It’s trust built on the consistent quality of the products, and on Malaysian manufacturers’ established reputations. Malaysian manufacturers are committed to social responsibility and sustainability initiatives to not only ensure human health is preserved, but to have an equally positive impact on communities and the environment. When it comes to rubber, No One Knows Rubber Like Malaysia Does.

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Cutaneous Features, Autoantibody Profile, and Nailfold Capillaroscopy of Systemic Sclerosis: A Study of 60 Cases

Jayati Dave1*, Sunanda Mahajan2, Prasad Khadilkar3, Vandana Pradhan4

Received: 02 May 2022; Revised: 15 July 2022; Accepted: 20 July 2022

ORIGINAL ARTICLE

Abstract

Background: Systemic sclerosis (SSc) is an autoimmune chronic multisystem disorder with a plethora of cutaneous manifestations. These manifestations often may be the only presenting complaint. Early identification of these helps in diagnosing grievous systemic manifestations and their prompt and appropriate treatment.

Aims: To study the clinical profile of SSc, modified Rodnan's skin scoring (mRSS), nailfold capillaroscopy (NFC) patterns, antibody profile in the western India population, and their association with cutaneous manifestations.

Methods: Patients of SSc fulfilling the European League Against Rheumatism (EULAR) 2013 classification of SSc criteria, who attended dermatology outpatient department (OPD) between January 2017 and September 2018 were included in the study. The demographic data, cutaneous features, autoantibody profile, mRSS, and NFC pattern were noted.

Results: A total of 60 patients (57 females and 3 males; mean age years) of SSc were evaluated. Clinical subtypes were 40 diffuse cutaneous SSc and 20 limited cutaneous SSc. The most common presenting symptoms were Raynaud's phenomenon (RP) (95%) and skin tightening (90%). The common cutaneous findings were sclerodactyly (86.7%), stellate scars (78.3%), parrot-beaked nose (76.7%), mask-like facies (75%), microstomia (56.7%), salt and pepper pigmentation (55%), puffy finger (46.7%), telangiectasia (46.7%), digital ulcer (38.3%), fixed flexion deformity (33.3%), and calcinosis cutis (8.3%). Limited cutaneous systemic sclerosis (lcSSc) had mRSS score of 8.3 ± 4.1 and diffuse cutaneous systemic sclerosis (dcSSc) subset had a score of 28 ± 10.4. Antinuclear antibody (ANA), Anti-topoisomerase antibody (ATA), and anti-centromere antibody (ACA) were positive in 59, 49, and 7 patients, respectively. The NFC patterns were early (23.3%), active (45%), and late (18.3%).

Limitation: The sample size of the study was small. We were not able to determine the significance of other less common autoantibodies with scleroderma.

Conclusion: The study highlights the importance of identifying early cutaneous findings and the role of a useful diagnostic and prognostic reproducible scoring system (mRSS) and NFC.

Journal of the Association of Physicians of India (2022): 10.5005/japi-11001-0136

Introduction

Systemic sclerosis is an autoimmune chronic multisystem disorder of uncertain etiology. Vascular injury (microangiopathy), fibroblast proliferation, and autoimmunity are the main pathogenic events responsible for the disease.1 It is classified into two subtypes based on the extent of skin involvement, autoantibody, and associated organ damage.

Limited cutaneous systemic sclerosis, the thickening is distal to clavicles (face and neck), distal to elbows (forearms and hands), and distal to knees whereas dcSSc subset presents with skin thickening on the trunk, thighs, and arms. dcSSc has a rapid onset of disease progression with the concomitant onset of RP and visceral organ involvement. ATA/anti-Scl-70 antibody is a marker of dcSSc, whereas ACA is a marker of lcSSc. Limited SSc has a relatively slow onset of disease progression and organ involvement.

Cutaneous findings of scleroderma are plenty but sometimes subtle. Early recognition of these features is of utmost importance to diagnose early visceral involvement.

Nailfold capillaroscopy is a simple, noninvasive reproducible tool to study microvascular changes. It helps in diagnosing and prognosticating SSc.2

We conducted this study to evaluate the clinical profile of scleroderma, mRSS, NFC patterns, and antibody profile in the western India population and their association with cutaneous manifestations.

Methods

This was a cross-sectional, single-center clinical observational study conducted in the OPD of a tertiary hospital in western India. Approval by the ethics committee was obtained from the hospital for the same. All the patients in the age group of 18 years and above who came to the dermatology OPD between January 2017 and September 2018 and who fulfilled the American College of Rheumatology/EULAR 2013 classification of SSc criteria were enrolled in the study.3

Informed consent was obtained from all the participants. Patients with clinically overlapping connective tissue disease were not recruited for the study. Detailed history regarding the demographic profile, symptoms, duration, and evolution of the cutaneous lesions, family history, and occupation was obtained. These patients were thoroughly examined clinically keeping a focus on the cutaneous manifestations. These patients were classified into two subtypes based on the extent of skin involvement as defined by LeRoy et al., lcSSc and dcSSc.4 Skin thickness assessment was done by two independent authors using the mRSS at 17 different sites based on 0–3 severity scale.5

Apart from routine laboratory investigations such as hemogram, liver and renal function test, chest X-ray, and thyroid profile, investigations such as ANA by indirect immunofluorescence test, ANA line blot by enzyme immunoassay to detect other antibodies were done for all patients, and scleroderma blot in few patients was done as per the availability.

Patients with systemic complaints were evaluated after rheumatology consultation and appropriate tests such as high-resolution computed tomography chest, barium swallow, pulmonary function test, and 2D echo were done. Skin biopsy was performed in all consenting patients. NFC was done on eight fingers excluding thumbs using Oitez eScope dermoscope with 20× and 200× magnification. The dermoscope was attached to the monitor of the computer screen and...

1Bonded Assistant Professor; 2Additional Professor, Department of Dermatology, Seth Gordhandas Sunderdas Medical College (GSMC) and King Edward Memorial (KEM) Hospital; 3PhD Student; 4Scientist, National Institute of Immunohaematology, Seth Gordhandas Sunderdas Medical College (GSMC) and King Edward Memorial (KEM) Hospital, Mumbai, Maharashtra, India; *Corresponding Author


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Cutaneous Features, Autoantibody Profile, and NFC of SSc

On cutaneous examination, common findings were sclerodactyly (Fig. 2), stellate scars (Fig. 3), sausage-shaped digits (Fig. 4), dry digital gangrene (Fig. 5), digital ulcers (Fig. 6), calcinosis cutis (Fig. 7), pigmentation disturbances, etc. as illustrated in Table 1.

Nail unit changes such as inverse pterygium and ragged cuticle were seen in five patients (8.33%). Other findings were clubbing seen in four (6.7%), anonychia in three (5%), and distal onycholysis in two patients (3.3%). Dystrophy of nails, onychomadesis, leuconychia, subungual hematoma, and longitudinal melanonychia were seen in one (1.67%) patient each.

Pigmentary changes such as hyperpigmentation were seen in 17 patients (28.33%), salt and pepper-like pigmentation (Fig. 8) in 33 patients (55%), and vitiligo-like depigmented macules in 22 patients (36.67%). Hyperpigmentation was generalized in seven patients and rippled-like macular amyloidosis (Fig. 9) in the remaining. Salt and pepper-like pigmentation was particularly

Clinical Profile

Out of 60 patients, dcSSc was noted in 40 (66.7%) patients while lcSSc in 20 (33.3%) patients. The most common presenting manifestation to OPD was RP seen in 57 patients (95%), skin tightening in 54 patients (90%), and facial changes (Fig. 1) in 47 patients (78.3%). The most common presenting systemic symptoms were dyspnea in 36 (60%) patients, difficulty in swallowing in 25 patients (41.7%), and postprandial abdominal pain with reflux and joint pains in 22 patients each (36.7%).

Statistics

All data were entered in an MS Excel spreadsheet and analyzed with the help of OpenEpi and SPSS v 20. Qualitative data were explained with frequency and percentage. Quantitative data were explained with mean and standard deviation (SD). Unpaired t-test was applied to see the statistically significant difference of mean and SD between independent groups. Chi-square test was applied to see the association between two variables. Analysis of variance test was applied when more than two groups were present. p-value less than 0.05 was considered as significant in the study.

Results

Demographic Data

A total of 60 patients of scleroderma having a mean age of 36.5 ± 11.3 years and a mean disease duration of 6 years were included in the study. There were 57 females (95%) and 3 males (5%) in the study. The sex ratio of female-to-male was 19:1. The maximum number of patients (63.3%) had disease duration between 2 months and 5 years. It was observed that 70% of our study patients were treatment naïve. Systemic illnesses like tuberculosis (18.3%) followed by thyroid-related disorders (15%) were noted in our patients. Lesser common manifestations include anemia, hypertension, migraine, trigeminal neuralgia, primary infertility, osteoporosis, and leprosy. The most common non-scleroderma-related cutaneous manifestation was melanoma (15%) followed by keloid, ichthyosis vulgaris, xerosis, tinea corporis, and lichen planus.

On cutaneous examination, common findings were sclerodactyly (Fig. 2), stellate scars (Fig. 3), sausage-shaped digits (Fig. 4), dry digital gangrene (Fig. 5), digital ulcers (Fig. 6), calcinosis cutis (Fig. 7), pigmentary disturbances, etc. as illustrated in Table 1.

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Fig. 1: Typical mask-like facies, perioral furrowing, and parrot beaking of nose with mat-like telangiectasias on the malar region

Fig. 2: Sclerodactyly with fixed flexion deformity on bilateral interphalangeal joints and vitiligo-like macules
Cutaneous Features, Autoantibody Profile, and NFC of SSc

was lower than the mean of mRSS of dcSSc (28 ± 10.4). On comparing the mean and SD of mRSS with the duration of disease, there was no significant statistical correlation, but there was a drop in the mean value of mRSS with increasing duration of disease.

NFC Findings
The NFC findings were better visible and consistent in the ring finger. NFC findings were dilated capillaries in 51 patients (85%), dropouts in 43 patients (71.6%), giant capillaries in 41 patients (68.3%), microhemorrhages in 31 patients (51.6%), bushy capillaries in 23 patients (38.3%), and avascular areas in 18 patients (30%). NFC patterns such as early (Fig. 10) were seen in 14 (23.3%), active (Fig. 11) in 27 (45%), late (Fig. 12) in 11 (18.3%), and nonspecific in eight (13.4%) patients.

Autoantibody Profile
Antinuclear antibody was positive in 59 (98.3%) patients. The most common pattern of immunofluorescence was homogenous + nucleolar (27.1%) followed by speckled pattern (20.3%). Other patterns seen were unrecognized (23.8%), homogenous (17%), nucleolar (5.3%), centromere pattern (5.3%), and speckled + nucleolar (1.6%).

Anti-topoisomerase antibody also known as anti-Scl-70 antibody was positive in 49 patients (81.7%), ACA was positive in seven patients (11.7%), and anti-RNA polymerase III antibody was seen in three patients (5%).

Chi-square was used to find an association between the type of scleroderma and positivity of various antibodies. The \( p \)-value was significant (<0.05) for the association of dcSSc with Scl-70. Association of type of scleroderma with other antibodies such as ACA and anti-RNA-Pol III was insignificant.

On comparing the mean and SD of mRSS of patients with positive autoantibodies, we found a statistical correlation of ATA with the mean and SD of mRSS being higher compared to negative ATA (\( p \)-value 0.03). Similarly, the mean and SD of mRSS were significantly lower values in ACA-positive as compared to non-ACA-positive patients (\( p \)-value 0.01).

Nailfold capillaroscopy pattern had no statistical correlation with the duration of disease, type of scleroderma, mean and SD of mRSS, and antibody profile.

higher on areas such as retroauricular area (25%) and face (23.33%). Vitiligo-like macules were common in acral areas of the upper extremities. Periangual telangiectasia was seen in 10 patients (16.67%), telangiectasia in malar region in nine (15 %), and facial region in eight (13.3%) patients. mRSS was highest in 11–20 (28.3%) range followed by 0–10 (23.3%) and 21–30 (23.3%) range, and least in 31–40 (16.8%) and 41–50 (8.3%) range.

Differences between various features of lcSSc and dcSSc are mentioned in Table 2. On comparing the mean and SD of mRSS with a type of scleroderma, there was a statistical significance (\( p \)-value < 0.05). The mean of mRSS of lcSSc (8.3 ± 4.1) as expected

Fig. 3: Multiple pitted/stellate scars on the tips of fingers

Fig. 4: Sausage-shaped digits with Mizutani’s sign. The image also demonstrates resorption of digits with amputation of the left index finger

Fig. 5: Dry digital gangrene on the middle finger
Cutaneous Features, Autoantibody Profile, and NFC of SSc

**Table 1:** Distribution according to cutaneous manifestation

<table>
<thead>
<tr>
<th>Cutaneous manifestation</th>
<th>n (%)</th>
</tr>
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<tbody>
<tr>
<td>RP</td>
<td>57 (95)</td>
</tr>
<tr>
<td>Skin tightening</td>
<td>54 (90)</td>
</tr>
<tr>
<td>Sclerodactyly</td>
<td>52 (86.7)</td>
</tr>
<tr>
<td>Stellate scars</td>
<td>47 (78.3)</td>
</tr>
<tr>
<td>Ingram sign (inability to retract lower eyelid)</td>
<td>47 (78.3)</td>
</tr>
<tr>
<td>Parrot-beaked nose</td>
<td>46 (76.7)</td>
</tr>
<tr>
<td>Mask-like facies</td>
<td>45 (75%)</td>
</tr>
<tr>
<td>Microstomia</td>
<td>34 (56.7)</td>
</tr>
<tr>
<td>Salt and pepper pigmentation</td>
<td>33 (55)</td>
</tr>
<tr>
<td>Sausage-shaped</td>
<td>33 (55)</td>
</tr>
<tr>
<td>Perioral furrowing</td>
<td>32 (53.3)</td>
</tr>
<tr>
<td>Mizutani’s sign (round finger pad sign)</td>
<td>28 (46.7)</td>
</tr>
<tr>
<td>Puffy fingers</td>
<td>28 (46.7)</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>28 (46.7)</td>
</tr>
<tr>
<td>Digital ulcer</td>
<td>23 (38.3)</td>
</tr>
<tr>
<td>Fixed flexion deformity</td>
<td>20 (33.3)</td>
</tr>
<tr>
<td>Nail changes</td>
<td>18 (30)</td>
</tr>
<tr>
<td>Resorption of digits</td>
<td>11 (18.3)</td>
</tr>
<tr>
<td>Barnett’s neck sign (ridging and tightening of skin)</td>
<td>08 (13.3)</td>
</tr>
<tr>
<td>Calcinosis cutis</td>
<td>05 (8.33)</td>
</tr>
<tr>
<td>Dry gangrene</td>
<td>04 (6.7%)</td>
</tr>
<tr>
<td>Amputation of digit</td>
<td>02 (3.3%)</td>
</tr>
</tbody>
</table>

6.01 ± 6.1 years. The mean disease duration of lcSSc (7.4 ± 6.6) years was less than dcSSc (5.3 ± 5.8) years. The mean duration of disease was similar to a study by Sharma et al. (6.75 ± 4.53 years)\(^8\) while the duration was much less compared to the cohort of White (21 ± 18 months), Hispanics (30 ± 20 months), and African American (24 ± 21 months).\(^{13}\) This difference may be due to the early presentation of the patient with systemic manifestations of the disease to a physician compared to dermatologists for cutaneous manifestations.

The most common presenting complaints in our study were cutaneous manifestations such as tightening of skin, facial changes, and vascular complaints such as RP. Few patients had come to OPD for cutaneous symptoms and on investigations were found to have systemic involvement. RP was the most common manifestation like other studies irrespective of the type of scleroderma (Table 4). Some studies had reported less incidence of RP which could be due to the inclusion of overlap syndromes which do not necessarily present with RP.\(^7\) Skin tightening was comparable to most studies, except Spanish registry where the thickening may have been underreported as the study was multicentric similar to other Indian studies, that is, the early third decade of life.\(^7,^{10-13}\) while cohorts from Malaysia, Spanish, South Brazil, and different racial cohorts like Hispanics, African American, and Whites showed mean age in the fourth decade.\(^{10-13}\) The sex ratio (female: male) in our study was 19:1 which was much higher compared to other studies.\(^7,^{10,11,13}\) The mean disease duration in the present study was

**Fig. 6:** Digital ulcers on the dorsa of hand

**Fig. 7:** Calcinosis cutis on the elbow

**Fig. 8:** Salt and pepper pigmentation on pinna and retroauricular region extending onto the neck. Dermoscopy showing perifollicular retention of pigment

**Discussion**

Our study described the clinical profile focussing on cutaneous manifestations of scleroderma patients. There have been studies on clinical profiles, however, those studies were done by non-dermatological physicians focussing mainly on systemic manifestations. The mean age of patients in our study was 36.5 ± 11.3 years which was similar to other Indian studies, that is, the early third decade of life,\(^7,^{10-13}\) while cohorts from Malaysia, Spanish, South Brazil, and different racial cohorts like Hispanics, African American, and Whites showed mean age in the fourth decade.\(^{10-13}\) The sex ratio (female: male) in our study was 19:1 which was much higher compared to other studies.\(^7,^{10,11,13}\) The mean disease duration in the present study was

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so there was subject variation and lack of objective tools such as mRSS. Sclerodactyly and microstomia are other important presenting cutaneous findings in the present study which were similar to other studies. Like other Indian studies, we also found an increase in pigmented disturbances. Similarly, according to a study on three ethnic populations by Reveille et al., there was an increase in the incidence of pigmented disturbances in African Americans. Skin of color showed a higher incidence of pigmented disturbances which will help physicians to pick up early cases. Salt and pepper-like pigmentation also known as mottled pigmentation was particularly

![Fig. 9: Rippled pigmentation on the neck](image)

**Table 2: Difference between types of SSc**

<table>
<thead>
<tr>
<th>Type of SSc</th>
<th>lcSSc</th>
<th>dcSSc</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n)</td>
<td>20</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>18</td>
<td>39</td>
<td>0.6</td>
</tr>
<tr>
<td>Mean age of diagnosis (years)</td>
<td>37.5 ± 9</td>
<td>36 ± 12.4</td>
<td></td>
</tr>
<tr>
<td>Mean duration of disease (in years)</td>
<td>7.4 ± 6.6</td>
<td>5.3 ± 5.8</td>
<td>0.2</td>
</tr>
<tr>
<td>mRSS</td>
<td>8.3 ± 4.1</td>
<td>28 ± 10.4</td>
<td>&lt;0.00 (unpaired t-test)</td>
</tr>
<tr>
<td>RP</td>
<td>18</td>
<td>39</td>
<td>0.1</td>
</tr>
<tr>
<td>Sclerodactyly</td>
<td>17</td>
<td>35</td>
<td>0.3</td>
</tr>
<tr>
<td>Ingram sign (inability to retract lower eyelid)</td>
<td>11</td>
<td>36</td>
<td>0.0001</td>
</tr>
<tr>
<td>Stellate scars</td>
<td>15</td>
<td>32</td>
<td>0.7</td>
</tr>
<tr>
<td>Parrot-beaked nose</td>
<td>12</td>
<td>34</td>
<td>0.01</td>
</tr>
<tr>
<td>Mask-like facies</td>
<td>11</td>
<td>34</td>
<td>0.005</td>
</tr>
<tr>
<td>Microstomia</td>
<td>09</td>
<td>25</td>
<td>0.09</td>
</tr>
<tr>
<td>Salt and pepper pigmentation</td>
<td>04</td>
<td>29</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sausage-shaped digit</td>
<td>08</td>
<td>25</td>
<td>0.04</td>
</tr>
<tr>
<td>Perioral furrowing</td>
<td>07</td>
<td>25</td>
<td>0.02</td>
</tr>
<tr>
<td>Mizutani’s sign</td>
<td>08</td>
<td>20</td>
<td>0.1</td>
</tr>
<tr>
<td>Puffy fingers</td>
<td>07</td>
<td>21</td>
<td>0.5</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>09</td>
<td>19</td>
<td>0.4</td>
</tr>
<tr>
<td>Digital ulcer</td>
<td>06</td>
<td>17</td>
<td>0.8</td>
</tr>
<tr>
<td>Fixed flexion deformity</td>
<td>08</td>
<td>14</td>
<td>0.1</td>
</tr>
<tr>
<td>Nail changes</td>
<td>07</td>
<td>11</td>
<td>0.3</td>
</tr>
<tr>
<td>Resorption of digits</td>
<td>02</td>
<td>09</td>
<td>0.1</td>
</tr>
<tr>
<td>Barnett’s neck sign</td>
<td>00</td>
<td>08</td>
<td>0.01</td>
</tr>
<tr>
<td>Calcinosis cutis</td>
<td>00</td>
<td>03</td>
<td>0.1</td>
</tr>
<tr>
<td>Dry gangrene</td>
<td>02</td>
<td>02</td>
<td>0.2</td>
</tr>
<tr>
<td>Amputation of digit</td>
<td>01</td>
<td>05</td>
<td>0.3</td>
</tr>
<tr>
<td>ATA positive</td>
<td>04</td>
<td>03</td>
<td>Chi-square 2, DOF 1, p-value 0.07</td>
</tr>
<tr>
<td>Anti-RNAP III positive</td>
<td>02</td>
<td>01</td>
<td>Chi-square 1.5, DOF 1, p-value 0.1</td>
</tr>
<tr>
<td>Scleroderma capillaroscopy pattern</td>
<td>19</td>
<td>33</td>
<td>82.5</td>
</tr>
</tbody>
</table>

Bold values are significant p-values
Higher in the retroauricular region (25%) and face (23.33%). Depigmented macules like in vitiligo were seen in acral areas (30%), dorsa of hands, and at sites of healed digital ulcers. We also noticed in patients which was diffuse in 11.66% of patients while it was rippled like macular amyloidosis more commonly seen in the upper extremities (16.66) and back (11.66%). We need to do a study with a larger sample size to confirm these findings and its association with scleroderma. Telangiectasias were lesser noticed in the present study compared to white skin as they were not a cosmetic concern and not visible in brown skin easily.11,13 Pitting scars were found in a higher proportion in our study, as compared to others.13,14 These scars are extremely helpful in diagnosing and are also a part of the 2013 EULAR classification criteria for SSC.

Antinuclear antibody was a highly sensitive test in the present study, the sensitivity has been reported to occur variably from 78 to 92% in various studies.7-9,13 There was a significant correlation between ATA and type of SSC. There was a statistical correlation of parrot-beaked nose and inability to retract eyelids with antibodies. Srivastava et al. reported that skin serologies were more relevant in predicting organ involvement whereas skin subsets were a better predictor of certain features such as digital ulcers, pitting scars, calcinosis cutis, and mortality.15 Like in the present study, there was a significant correlation between mRSS and subset of SSC in a study by Peytrignet et al.16 Mean of mRSS in dcSSc subset (28 ± 10.4) was higher as compared to other studies.16,17 Mean of mRSS in lcSSc subset (8.3 ± 4.1) was higher than Peytrignet et al. (3.7 ± 3.7).16 and similar to Walker et al. (8.1 ± 5.3).17 Mean of mRSS of ATA positive cohort was 23.5 ± 12.8 which was higher as compared to Walker et al. (15.1 ± 9.9).17 and Hamaguchi et al. (14.6 ± 10.0).18 Mean of mRSS of ACA positive cohort was 15.5 ± 5.06 which was higher as compared to Walker et al. (8.2 ± 5.9)17 and Hamaguchi et al. (5.8 ± 5.7).18 The mean of mRSS of patients with anti-RNAP III was 17 ± 14.7 which was lower than Hamaguchi et al. (20.7 ± 10.6).18

The pathogenesis of scleroderma involves microcirculation abnormalities which can be easily studied by a simple handy device dermoscope. The early scleroderma capillary pattern of NFC was seen in 23.3% of study patients which was less compared to Cutolo et al. (33%).19 Maximum number of patients were seen to be having active pattern (45%) and least number of patients had late pattern (18.3%) similar to Cutolo et al.19

**Limitations**

There was a limitation in sample size and comparing our study with larger cohorts and registries was difficult. Few studies had not defined overlap syndrome as a different entity and included those cases.
### Table 3: Autoantibody-wise distribution of cutaneous manifestation with their association

<table>
<thead>
<tr>
<th></th>
<th>ATA</th>
<th></th>
<th>ACA</th>
<th></th>
<th>RNA-Pol III</th>
<th></th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>49</td>
<td>81.67%</td>
<td>07</td>
<td>11.67%</td>
<td>03</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>36 ± 11.9</td>
<td>–</td>
<td>39.8 ± 8.7</td>
<td>–</td>
<td>33.6 ± 7.6</td>
<td>–</td>
<td>0.4</td>
</tr>
<tr>
<td>Mean duration of disease (years)</td>
<td>7.6 ± 6.3</td>
<td>–</td>
<td>6.1 ± 4.3</td>
<td>–</td>
<td>10.3 ± 8.5</td>
<td>–</td>
<td>0.6</td>
</tr>
<tr>
<td>dcSSc</td>
<td>36</td>
<td>73.46%</td>
<td>03</td>
<td>42.85%</td>
<td>01</td>
<td>33.33%</td>
<td>0.1</td>
</tr>
<tr>
<td>lcSSc</td>
<td>13</td>
<td>39.47%</td>
<td>04</td>
<td>57.14%</td>
<td>02</td>
<td>66.67%</td>
<td>0.006</td>
</tr>
<tr>
<td>Mean mRSS</td>
<td>23.5 ± 12.8</td>
<td>p-value 0.03</td>
<td>15.5 ± 5.06</td>
<td>p-value 0.01</td>
<td>17 ± 14.7</td>
<td>p-value 0.3</td>
<td></td>
</tr>
<tr>
<td>RP</td>
<td>47</td>
<td>95.91%</td>
<td>06</td>
<td>85.71%</td>
<td>03</td>
<td>100%</td>
<td>0.4</td>
</tr>
<tr>
<td>Sclerodactyly</td>
<td>42</td>
<td>85.71%</td>
<td>06</td>
<td>85.71%</td>
<td>03</td>
<td>100%</td>
<td>0.7</td>
</tr>
<tr>
<td>Inman sign (inability to retract lower eyelid)</td>
<td>42</td>
<td>85.71%</td>
<td>04</td>
<td>57.14%</td>
<td>01</td>
<td>33.33%</td>
<td>0.02</td>
</tr>
<tr>
<td>Stellate scars</td>
<td>41</td>
<td>83.67%</td>
<td>06</td>
<td>85.71%</td>
<td>02</td>
<td>66.67%</td>
<td>0.7</td>
</tr>
<tr>
<td>Parrot-beaked nose</td>
<td>39</td>
<td>79.59%</td>
<td>04</td>
<td>57.14%</td>
<td>02</td>
<td>66.67%</td>
<td>0.006</td>
</tr>
<tr>
<td>Mask-like facies</td>
<td>38</td>
<td>77.55%</td>
<td>04</td>
<td>57.14%</td>
<td>02</td>
<td>66.67%</td>
<td>0.4</td>
</tr>
<tr>
<td>Microstomia</td>
<td>30</td>
<td>61.22%</td>
<td>03</td>
<td>42.85%</td>
<td>03</td>
<td>100%</td>
<td>0.2</td>
</tr>
<tr>
<td>Salt and pepper pigmentation</td>
<td>29</td>
<td>59.18%</td>
<td>03</td>
<td>42.85%</td>
<td>02</td>
<td>66.67%</td>
<td>0.6</td>
</tr>
<tr>
<td>Sausage digit</td>
<td>30</td>
<td>61.22%</td>
<td>04</td>
<td>57.14%</td>
<td>02</td>
<td>66.67%</td>
<td>0.9</td>
</tr>
<tr>
<td>Perioral furrowing</td>
<td>27</td>
<td>55.10%</td>
<td>03</td>
<td>42.85%</td>
<td>02</td>
<td>66.67%</td>
<td>0.7</td>
</tr>
<tr>
<td>Mizutani’s sign</td>
<td>25</td>
<td>51.02%</td>
<td>04</td>
<td>57.14%</td>
<td>02</td>
<td>66.67%</td>
<td>0.8</td>
</tr>
<tr>
<td>Puffy fingers</td>
<td>25</td>
<td>51.02%</td>
<td>02</td>
<td>28.57%</td>
<td>01</td>
<td>33.33%</td>
<td>0.4</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>23</td>
<td>46.93%</td>
<td>02</td>
<td>28.57%</td>
<td>01</td>
<td>33.33%</td>
<td>0.6</td>
</tr>
<tr>
<td>Digital ulcers</td>
<td>20</td>
<td>40.81%</td>
<td>03</td>
<td>42.85%</td>
<td>01</td>
<td>33.33%</td>
<td>0.9</td>
</tr>
<tr>
<td>Fixed flexion deformity</td>
<td>17</td>
<td>34.69%</td>
<td>01</td>
<td>14.28%</td>
<td>01</td>
<td>33.33%</td>
<td>0.5</td>
</tr>
<tr>
<td>Nail changes</td>
<td>15</td>
<td>30.61%</td>
<td>03</td>
<td>42.85%</td>
<td>01</td>
<td>33.33%</td>
<td>0.8</td>
</tr>
<tr>
<td>Resorption of digits</td>
<td>10</td>
<td>20.40%</td>
<td>01</td>
<td>14.28%</td>
<td>01</td>
<td>33.33%</td>
<td>0.7</td>
</tr>
<tr>
<td>Barnett’s neck sign</td>
<td>08</td>
<td>16.32%</td>
<td>00</td>
<td>–</td>
<td>00</td>
<td>–</td>
<td>0.3</td>
</tr>
<tr>
<td>Calcinosis cutis</td>
<td>03</td>
<td>6.12%</td>
<td>00</td>
<td>–</td>
<td>00</td>
<td>–</td>
<td>0.7</td>
</tr>
<tr>
<td>Dry gangrene</td>
<td>03</td>
<td>6.12%</td>
<td>01</td>
<td>14.28%</td>
<td>00</td>
<td>–</td>
<td>0.6</td>
</tr>
<tr>
<td>Amputation of digit</td>
<td>02</td>
<td>4.08%</td>
<td>00</td>
<td>–</td>
<td>00</td>
<td>–</td>
<td>0.8</td>
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</tbody>
</table>

Bold values are significant p-values.

### Table 4: Comparison of the present study with other published data

<table>
<thead>
<tr>
<th></th>
<th>Present study</th>
<th>Pradhan et al.²</th>
<th>Sharma et al.⁸</th>
<th>Ghosh et al.⁹</th>
<th>Simeón-Aznar et al.¹¹</th>
<th>Skare et al.¹²</th>
<th>White³</th>
<th>Hispanic⁰</th>
<th>African American¹³</th>
<th>Chularatjanamontri et al.¹⁴</th>
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<tbody>
<tr>
<td>n</td>
<td>60</td>
<td>110</td>
<td>100</td>
<td>46</td>
<td>916</td>
<td>66</td>
<td>79</td>
<td>54</td>
<td>28</td>
<td>80</td>
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<tr>
<td>Sex ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>36.5 ± 11.3</td>
<td>34.7 ± 10.7</td>
<td>32.75 ± 11.62</td>
<td>29.3 ± 12.3</td>
<td>51.2 ± 15.2</td>
<td>51.35 ± 13.72</td>
<td>51.4 ± 14.6</td>
<td>49.5 ± 14.1</td>
<td>49.5 ± 14.1</td>
<td>37.8 ± 14.55</td>
</tr>
<tr>
<td>Duration of disease</td>
<td>6.01 ± 6.1 years</td>
<td>43.7 ± 35.4 months</td>
<td>6.75 ± 4.53 years</td>
<td>23 months</td>
<td>6.2 ± 9.1 years</td>
<td>11.8 ± 8.56 months</td>
<td>21 ± 18 months</td>
<td>24 ± 21 months</td>
<td>9 ± 12.8 years</td>
<td>9 ± 12.8 years</td>
</tr>
<tr>
<td>dcSSc (n)</td>
<td>40</td>
<td>45</td>
<td>–</td>
<td>27</td>
<td>516</td>
<td>14</td>
<td>46%</td>
<td>61%</td>
<td>62%</td>
<td>68</td>
</tr>
<tr>
<td>lcSSc (n)</td>
<td>20</td>
<td>32</td>
<td>–</td>
<td>19</td>
<td>242</td>
<td>41</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>RP</td>
<td>95%</td>
<td>76.5%</td>
<td>92.9%</td>
<td>84.8%</td>
<td>93.1%</td>
<td>98.4%</td>
<td>86%</td>
<td>93%</td>
<td>96%</td>
<td>76.3%</td>
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<tr>
<td>Skin tightening</td>
<td>90%</td>
<td>74.1%</td>
<td>98.5%</td>
<td>82%</td>
<td>6.2%</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Sclerodactyly</td>
<td>86.7%</td>
<td>–</td>
<td>82.6%</td>
<td>–</td>
<td>–</td>
<td>80%</td>
<td>87%</td>
<td>89%</td>
<td>95%</td>
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<tr>
<td>Microstomia</td>
<td>56.7%</td>
<td>–</td>
<td>55.5%</td>
<td>82.6%</td>
<td>–</td>
<td>15.87%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>55%</td>
</tr>
<tr>
<td>Pigmentary disturbances</td>
<td>78.33%</td>
<td>–</td>
<td>91%</td>
<td>86.9%</td>
<td>–</td>
<td>51%</td>
<td>59%</td>
<td>82%</td>
<td>–</td>
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<tr>
<td>Salt and pepper pigmentation</td>
<td>55%</td>
<td>–</td>
<td>51.2%</td>
<td>54.3%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>43.8%</td>
</tr>
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</table>

Contd...
in the scleroderma pool. We were not able to determine the significance of other less common autoantibodies with scleroderma.

**Conclusion**

To conclude, our study demonstrated that cutaneous manifestations of SSc are early markers of disease, sometimes preceding the systemic manifestations. Knowledge of these features helps in early diagnosis and treatment. mRSS is an easily reproducible test to measure skin thickness and define scleroderma subsets. NFC is an extremely beneficial tool to diagnose and define scleroderma subsets. Autoantibodies in SSc are early markers of disease, sometimes preceding the systemic manifestations. NFC is an extremely beneficial tool to diagnose early microvascular changes and helps in the monitoring of disease. The disease has a considerable impact on quality of life, thus measures to improve the same should be done by detecting early disease and appropriate treatment.

**References**

Predictors Associated with In-hospital Mortality among COVID-19 Patients during the Second Wave in a Tertiary Care Hospital, Gujarat, India: A Retrospective Observational Study

Kinnari Gupta1, Dipak Solanki2, Tejas Shah3, Tinkal Patel4*, Dharmendra Panchal5

Received: 10 May 2022; Accepted: 21 July 2022

ABSTRACT

Background: Fatalities due to coronavirus disease 2019 (COVID-19) have already crossed to more than 5 million globally so far. Hence, it is crucial for us to identify the risk factors associated with hospital deaths starting from first contact which can help to give timely treatment to the targeted population.

Objectives: This retrospective cohort study was conducted to identify various factors related to in-hospital mortality related to COVID-19 in our region.

Materials and methods: The present study was a single-center, retrospective cohort study of 675 adults patients, admitted with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection between 1st April and 25th May 2021 in our tertiary care hospital. Baseline demographic profile, comorbidities, clinical characteristics, and investigatory findings were analyzed for increased odds of mortality.

Results: A total of 181 (26.8%) patients died and 494 (73.2%) survived. There were 65.4% of males and no difference was found between genders in terms of mortality. Comorbidities associated with in-hospital death in our cohort were age group ≥50 years (p < 0.001), diabetes (p < 0.0007), and renal injury (p < 0.0001). More than half of the patients died during the first week of admission. Breathlessness (83%) was the most common symptom in non-survivors. Neutrophil-to-lymphocyte ratio (NLR), S. creatinine, D-dimer, ferritin, and C-reactive protein (CRP) were increased significantly among the patients who died. Multivariate logistic regression revealed age ≥50 years (adjusted odds ratio (AOR) 2.30, 95% confidence interval (CI) 1.45–3.64) and oxygen (O₂) saturation <94% at the time of admission (AOR 2.62, 95% CI 1.75–3.93) were associated with mortality.

Conclusion: Overall in-hospital mortality was 26.8%. Higher age and low O₂ saturation were the major risk factors associated with in-hospital mortality.

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INTRODUCTION

The emergence of COVID-19 is the most serious threat of the 21st century and it was announced as a pandemic by the World Health Organization (WHO) on 11th March 2020.1 As of 17th January 2022, the WHO officially confirmed 328,826,023 cases with 5,557,754 deaths worldwide. India has reported the second highest number of COVID-19 cases among the top 20 highest-burden countries. After USA till 17th January 2022,2 Interestingly, India observed a case fatality ratio at 1.2%, the lowest among the top 20 highest-burden countries.2 The explanation may be far more complex given the method of data collection and reporting structures, the prevalence of comorbid diseases, testing strategy, gender differences, and attribution of deaths to COVID-19 infections. The first wave of the COVID-19 pandemic commenced in India with increased detection of cases from January to March 2020 with the September 2020 peak, cases declined later.3 Surprisingly, the second wave in India from April to May 2021 placed an unprecedented burden on the Indian health systems, with 47% of single-day case incidence in the world during its peak.3

The clinical features and severity of COVID-19 vary among individuals from asymptomatic to severe acute respiratory syndrome based on multiple comorbidities.4,5 Additionally, there is a dearth of data existing on specific treatment for COVID-19. Therefore, effective treatment for mild to moderate patients is an important means to prevent them from turning into severe patients or even death. It is conducive to reversing the overwhelming situation of hospitals and preventing the spread of the epidemic on a large scale.

Reports globally have indicated that increasing age and comorbidities are all associated with adverse outcomes. In addition, certain demographic characteristics and laboratory parameters have also been associated with the severe form of COVID-19 and increased mortality in western countries.6,7 After all, there is a need to update and increase the limited available evidence on the epidemiological and clinical features of patients who die due to COVID-19, particularly in India, owing to genetic and ethnic differences, skewed age distribution, high prevalence of risk factors among populations, and the rate at which the virus is mutating and evolving. In addition, to the best of our knowledge, the epidemiological and clinical characteristics of a large cohort of hospitalized COVID-19 patients in western India, Gujarat, have not been evaluated in any prior study.

MATERIALS AND METHODS

Study Design and Area

The study was approved by the Institutional Ethics Committee of the institute. All procedures were followed in accordance with good clinical practice and applicable regulatory requirements. As data were collected retrospectively and anonymously (secondary data), consent was waived.

Data Collection

Out of a total of 751 COVID-19 confirmed patients admitted between 1st April and 25th May 2021 in our tertiary care hospital attached to the medical college, 675 patients were included in the study after excluding the incomplete records either in medical record files or electronic medical record system. The inclusion criteria for patients were as follows: (i) age 18 years or above, (ii) SARS-CoV-2-positive real-time reverse transcriptase-polymerase chain reaction

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or rapid antigen test positive. Any pregnant patients and those with a hospital stay of less than 24 hours were excluded from the study.

The decision of admission as per the severity of the disease and treatment modalities were defined as per Ministry of Health and Family Welfare guidelines for COVID-19 at the time of admission by the trained physicians. All moderate and severe category patients and patients with comorbidities were admitted while mild cases initially and then worsening symptoms or depletion of O₂ saturation were also admitted.

Epidemiological information (age, gender, and comorbidities), symptoms (cough, breathlessness, persistent fever, fatigue, myalgia, diarrhea, and abdominal pain), and radiological and laboratory test results were collected. Comorbidities included hypertension, diabetes, renal impairment, history of any cardiovascular diseases (CVDs), pre-existing lung disease, and thyroid disorders. Diabetes was defined as having a glycosylated hemoglobin level of 6.5% or higher in the preceding 3 months or patients already on diabetic medication or random blood glucose level of more than 200 mg/dL on admission without any history of steroid intake. CVD was described as any patient having a history of myocardial infarction, ischemic heart disease, heart failure, and cerebrovascular event. We considered patients with chronic obstructive pulmonary disease, asthma, pulmonary fibrosis, or any interstitial lung disease as pre-existing lung diseases. Kidney function was ascertained from the admission serum creatinine measurement, where available, and was converted into the estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration equation; with reduced kidney function grouped into eGFR <60 mL min⁻¹ per 1.73 m². Patients with multiple laboratory testing during their hospital stay, only test results nearest to the admission were considered for analysis.

Data were also collected for clinical parameters, treatment modalities, and period of hospitalization. Persistent fever is defined as high-grade fever lasting for >5 days as per national guidelines. Saturation at the time of admission was categorized into two groups for multivariate analysis; SpO₂ <94% and SpO₂ ≥94% as it was the cut-off to start O₂ therapy in the study population. Patients with 10 days of symptoms onset, remaining afebrile, and maintaining without O₂ were discharged safely as per guidelines. There were 187 patients with computerized tomography (CT) scan reports available; the severity of pulmonary involvement was assessed using a semi-quantitative scoring system (0–25) and the score was categorized as mild (<8/25), moderate (8–15/25), and severe (>15/25).

The extracted data were reviewed by the team of authors for accuracy and completeness. Finally, we categorized all the patients into two groups: patients who died in the hospital (non-survivors) and who recovered and got discharged (survivors).

### Statistical Analysis

We utilized IBM SPSS version 20.0 statistical package software for the analysis. We conducted descriptive statistics to determine mean, median, frequency, and percentage of various characteristics of the study cohort. When the data were nonparametric, independent group tests were used to compare the medians of continuous variables. The ratio of categorical variables was compared using Chi-square test. Univariate and multivariate logistic regression methods were used to adjust for the effects of the patient’s age, gender, risk factors, and saturation at the time of admission and outcome. We considered our results as AORs with 95% CIs and p-values <0.05 were considered significant.

### Results

The present study included 675 patients who were stratified as survivors (26.8%) and non-survivors (73.2%). The average survival time of the deceased patients was 7.17 ± 5.4 days in the hospital. Moreover, more than half (58%) of them succumbed to the infection during the first week of admission. The median age of the population was 58 years (interquartile range (IQR), 45–68 years) and a significantly higher age (63 years, IQR 53–70) was observed in non-survivors as compared to survivors. A total of 65.4% of the participants were males. Diabetes (31.7%) was the most common risk factor in the study population followed by hypertension (29.2%), renal impairment (21.2%), thyroid disorders (3.6%), history of cardiovascular events (2.07%), and pre-existing lung diseases (1.2%). Comorbidities were evaluated using Chi-square test, and it was established that a significantly high proportion of COVID-19 patients who died had diabetes (p = 0.0007) and renal dysfunction (p < 0.0001). It is important to note that dyspnea (83%) was reported significantly in a higher proportion in hospitalized patients who died while persistent fever (71.1%), cough (67.4%), and body ache (14.6%) were significantly more prevalent in survived patients. Differences among patients’ other clinical symptoms were not identified. Almost half of the patients (46.9%) who were demised were admitted in the intensive care unit (ICU) from the admission point; additionally, one-third of them required bilevel positive airway pressure (BiPAP) support, and 43.6% needed mechanical ventilation (Table 1).

As presented in Table 2, we compared the laboratory findings between the two groups. White blood cells (WBC), neutrophils, NLR, red blood cell distribution width (RDW), and S. creatinine were higher in deceased patients (p < 0.0001). However, lymphopenia was observed in the non-survived group (p < 0.0001).

We categorized the patients for inflammatory markers with higher cut-off values between the two groups as shown in Table 3; significantly higher CRP, S. ferritin, and D-dimer values were observed in the patients who died in the hospital (p < 0.0001). A CT severity index of ≥15/25 was found in over two third of the patients (68.3%) who had in-hospital mortality as compared to the patients who survived (30.8%, p < 0.0001). Likewise, lung involvement of more than 60% on CT scan was also observed in a higher proportion in patients with poor outcomes (63.4%).

In Table 4, we performed univariate and multivariate analyses between the two groups. Univariate logistic regression analysis revealed that patients with more than 50 years, diabetes, presence of both hypertension and diabetes, and O₂ saturation at the time of admission were associated with in-hospital mortality. Whereas multivariate logistic regression analysis showed only higher age (AOR 2.30, 95% CI 1.45–3.64) and low saturation during admission (AOR 2.62, 95% CI 1.75–3.93) are the most important risk factors that led to an increase in mortality in the present study.

### Discussion

The existing study represents the predictors of mortality of 675 patients in a tertiary care hospital. We demonstrated the case fatality rate of 26.8% which is in the range of 13–28%; as reported in studies from northern India.11,12 However, it varies among various countries; high reporting of in-hospital mortality (31.8–48.2%) from African countries while around 21% from USA.13–15 This phenomenon is influenced by multiple factors such as differences in age distribution, genetic profile of the patients, climate, comorbidities of patients, and healthcare infrastructure system.

The median age of the study population was slightly higher than globally published data where the median age ranges from 49 to 56 years.14,15 Moreover, most studies reported old age as a predictor of mortality; similarly, more than 80% of the patients who died were ≥50 years of age in our study.1,16
Although the mortality rate in male patients was higher (68.5%) compared with female patients (31.5%) this difference was not statistically significant which is in agreement with findings in most parts of the developed world. COVID-19 positive male patients were noted to have a significantly worse prognosis than female patients, attributable to both a biological and behavioral predisposition in some studies. It is evident from previous studies that diabetes is associated with a severe form of pneumonia and even fatalities among COVID-19 patients. Similarly, our study demonstrated a high number of diabetics (42%) in the demise group. Moreover, we observed a high prevalence of renal dysfunction (37%) in these patients which suggests an elevated risk of mortality from COVID-19 in chronic kidney disease (CKD).

Data for hypertension are interesting here, despite having been widely mentioned as a risk factor for adverse outcomes in COVID-19 patients. Hypertension was not associated with death in our study which is also reported in findings by Williamson et al. It has been discussed so far that CVD and pre-existing lung diseases increase the risk of severe disease and mortality; both the risk

**Table 1:** Clinical characteristics, admitting place, and initial respiratory support at the time of admission

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total study populations Overall, N = 675 (%)</th>
<th>Patient outcomes</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-survivors, N = 181 (26.8%)</td>
<td>Survivors, N = 494 (73.2%)</td>
<td></td>
</tr>
<tr>
<td>Age ≥50 years</td>
<td>465 (69)</td>
<td>149 (82.3)</td>
<td>316 (64)</td>
</tr>
<tr>
<td>Median (IQR) (year)</td>
<td>58 (45–68)</td>
<td>63 (53–70)</td>
<td>56 (43–67)</td>
</tr>
<tr>
<td>Sex Female</td>
<td>234 (34.6)</td>
<td>57 (31.5)</td>
<td>177 (35.8)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>197 (29.2)</td>
<td>54 (29.8)</td>
<td>143 (28.9)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>214 (31.7)</td>
<td>76 (42)</td>
<td>138 (27.9)</td>
</tr>
<tr>
<td>Previous CVD</td>
<td>14 (2.07)</td>
<td>7 (3.9)</td>
<td>7 (1.4)</td>
</tr>
<tr>
<td>Pre-existing lung disease</td>
<td>8 (1.2)</td>
<td>4 (2.2)</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>Thyroid disorders</td>
<td>24 (3.6)</td>
<td>10 (5.4)</td>
<td>14 (2.8)</td>
</tr>
<tr>
<td>Renal injury (n = 580)</td>
<td>143 (21.2)</td>
<td>67 (37)</td>
<td>76 (15.4)</td>
</tr>
<tr>
<td>Presenting symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>415 (61.5)</td>
<td>82 (45.3)</td>
<td>333 (67.4)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>425 (63)</td>
<td>151 (83.4)</td>
<td>274 (55.5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>325 (48.1)</td>
<td>82 (45.3)</td>
<td>243 (49.2)</td>
</tr>
<tr>
<td>Body ache</td>
<td>86 (18.1)</td>
<td>14 (7.7)</td>
<td>72 (14.6)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19 (2.8)</td>
<td>3 (1.7)</td>
<td>16 (3.2)</td>
</tr>
<tr>
<td>Persistent fever</td>
<td>420 (62.2)</td>
<td>69 (38.1)</td>
<td>351 (71.1)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>8 (1.2)</td>
<td>1 (0.85)</td>
<td>7 (1.4)</td>
</tr>
<tr>
<td>Initial place of admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ward</td>
<td>521 (77.2)</td>
<td>89 (49.2)</td>
<td>432 (87.4)</td>
</tr>
<tr>
<td>HDU</td>
<td>23 (3.4)</td>
<td>7 (3.9)</td>
<td>16 (3.3)</td>
</tr>
<tr>
<td>ICU</td>
<td>131 (19.4)</td>
<td>85 (46.9)</td>
<td>46 (9.3)</td>
</tr>
<tr>
<td>Initial respiratory support</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O₂ therapy through nasal cannula or mask</td>
<td>339 (50.2)</td>
<td>66 (36.5)</td>
<td>273 (55.3)</td>
</tr>
<tr>
<td>Non-rebreather mask</td>
<td>192 (28.4)</td>
<td>74 (41)</td>
<td>118 (23.9)</td>
</tr>
<tr>
<td>BiPAP support</td>
<td>71 (10.5)</td>
<td>61 (33.7)</td>
<td>10 (2.02)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>82 (12.1)</td>
<td>79 (43.6)</td>
<td>3 (0.61)</td>
</tr>
</tbody>
</table>

*<0.05 significant; IQR, interquartile range; HDU, high dependency unit; ICU, intensive care unit; BiPAP, bilevel positive airway pressure

**Table 2:** Laboratory parameters on admission

<table>
<thead>
<tr>
<th>Investigations</th>
<th>N, (normal range)</th>
<th>Total cohort median (IQR)</th>
<th>Non-survivors Median (IQR)</th>
<th>Survivors Median (IQR)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>604, (12–15 gm/L)</td>
<td>12.3 (11.3–13.5)</td>
<td>12.2 (11.3–13.6)</td>
<td>12.3 (11.3–13.4)</td>
<td>0.612</td>
</tr>
<tr>
<td>WBC</td>
<td>604, (4000–11,000 cell/mm³)</td>
<td>6500 (4600–9900)</td>
<td>8200 (5400–12,500)</td>
<td>6100 (4400–8200)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>604, (60–70%)</td>
<td>80 (72–87)</td>
<td>85 (79–90)</td>
<td>79 (70–85)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>604, (20–35%)</td>
<td>15 (10–24)</td>
<td>10 (6–17)</td>
<td>17 (10–26)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NLR</td>
<td>604</td>
<td>5.3 (2.9–8.8)</td>
<td>8.5 (5–15.16)</td>
<td>4.6 (2.69–8.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Platelets</td>
<td>604, (150,000–450,000/mm³)</td>
<td>187,000 (15,000–248,000)</td>
<td>192,500 (149,750–252,000)</td>
<td>185,000 (15,000–245,500)</td>
<td>0.867</td>
</tr>
<tr>
<td>RDW</td>
<td>604, (13–15%)</td>
<td>13.5 (12.8–14.5)</td>
<td>14 (13–15.2)</td>
<td>13.4 (12.7–14.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>S. creatinine</td>
<td>517, (0.6–1.1 mg%)</td>
<td>0.8 (0.7–1.1)</td>
<td>0.9 (0.7–1.3)</td>
<td>0.8 (0.7–1)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>S. SGPT</td>
<td>575, (13–45 U/L)</td>
<td>28 (17–53)</td>
<td>28 (17–51)</td>
<td>29 (17–54)</td>
<td>0.94</td>
</tr>
</tbody>
</table>

<0.05 significant; WBC, white blood cell; NLR, neutrophil to lymphocyte ratio; RDW, red cell distribution width; SGPT, serum glutamic pyruvic transaminase
Predictors Associated with In-hospital Mortality among COVID-19 Patients

Table 3: Radiological and inflammatory markers at the time of admission

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal value</th>
<th>N</th>
<th>Non-survivors</th>
<th>Survivors</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>&lt;6 mg/L</td>
<td>202/602 (33%)</td>
<td>97/156 (62%)</td>
<td>105/446 (23%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>D-dimer</td>
<td>&lt;0.5 ng/mL</td>
<td>58/286 (20.3%)</td>
<td>38/91 (41.6%)</td>
<td>20/195 (10.3%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ferritin</td>
<td>10–250 ng/mL</td>
<td>62/458 (51.5%)</td>
<td>34/117 (29%)</td>
<td>28/341 (8.2%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CT findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT severity index score &gt;15/25</td>
<td></td>
<td>73/187 (39%)</td>
<td>28/41 (68.3%)</td>
<td>45/146 (30.8%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&gt;60% of lung involvement</td>
<td></td>
<td>78/187 (41.7%)</td>
<td>26/41 (63.4%)</td>
<td>52/146 (35.6%)</td>
<td>&lt;0.002</td>
</tr>
</tbody>
</table>

*p<0.05 significant; CRP, C-reactive protein; CT, computerized tomography

Table 4: Factors associated with increased odds of mortality among hospitalized COVID-19 patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI p-value*</td>
<td>OR 95% CI p-value*</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 (Ref)</td>
<td>2.51 1.62–3.81 0.0001</td>
<td>2.306 1.45–3.64 0.0001</td>
</tr>
<tr>
<td>≥50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (Ref)</td>
<td>1.14 0.78–1.66 0.49</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (Ref)</td>
<td>1.01 0.685–1.48 0.96</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (Ref)</td>
<td>1.74 1.21–2.51 0.003</td>
<td>1.65 0.89–3.05 0.113</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension and diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (Ref)</td>
<td>1.49 1.05–2.14 0.02</td>
<td>0.848 0.46–1.55 0.592</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (Ref)</td>
<td>2.07 0.65–6.62 0.22</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-existing lung issues</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (Ref)</td>
<td>1.92 0.32–11.56 0.48</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O₂ saturation at the time of admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SpO₂ ≥94 (Ref)</td>
<td>2.75 1.85–4.1 0.0001</td>
<td>2.621 1.75–3.93 0.0001</td>
</tr>
<tr>
<td>SpO₂ &lt;94</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p<0.05 significant; Ref, Reference

Factors were also found to be relatively high in demise group in the current study but not statistically significant.\textsuperscript{22,23} It could be due to the low prevalence of these risk factors in the study population.

The most frequently reported clinical symptom of hospitalized COVID-19 who died was dyspnea (83%); similar findings were also noted elsewhere.\textsuperscript{3} We also observed that 85 patients who were directly admitted to ICU and 79 (92%) patients required mechanical ventilation, in agreement with other studies in which 90% of patients admitted in ICU needed mechanical ventilation.\textsuperscript{4} Among various modalities of respiratory support, advanced respiratory support (non-breathable mask, BiPAP support, and mechanical ventilation) was needed in a higher proportion in patients with adverse outcomes while basic O₂ support by nasal cannula or facemask was more common in patients who survived. A study from Tanzania also identified similar findings.\textsuperscript{14} The laboratory parameters are predictive of severe COVID-19 infection and the risk of early mortality. In this study, hemoglobin and platelet counts were within the normal range in both groups, in accordance with some findings reported somewhere.\textsuperscript{13,14} In spite of the fact that the WBC count was relatively high in patients who died in the hospital, we did not
observe gross leukocytosis in either group like in other studies. As far as the NLR report is concerned which is higher in the demise group, it is observed in some studies that the absolute value of lymphocytes decreases progressively while WBC count gradually increases over time in non-survivors; the NLR may be correlated with the prognosis of COVID-19.

We also noted neutrophilia and lymphopenia during admission in the non-survivor group. Thus these findings may be utilized to determine the risk of mortality at the initial stage of admission. A notable finding in our study is that RDW which is a part of routine complete blood count was noted to be high in deceased patients. Elevated RDW is associated with an increased risk for all-cause mortality and appears to be a nonspecific marker of illness that has the potential to provide general quantitative risk stratification that may be particularly useful for relatively new diseases like COVID-19. This prompts further detailed evaluation.

A rise in acute phase proteins like ferritin and CRP is also noted in the current study; they are markers of inflammation and play an important role in the progression to cytokine storm and rapid impairment of endothelial dysfunction which ultimately lead to poor outcome including death. Furthermore, high D-imer levels are also associated with high fibrin degradation product levels and low antithrombin activity, as well as the risk of thrombotic and hemorrhagic complications which ultimately leads to unfavorable outcomes. This result mirrors various previous reports.

We also corroborated findings from other studies that a higher CT severity imaging score depicts significant lung involvement and has been linked to a higher risk of death and has been proven to be predictive of death among patients.

Overall, we can surmise that proportion of comorbidities, abnormal laboratory findings, and higher inflammatory markers were high in hospitalized patients who died. Age more than 50 years and O2 saturation <94% during admission have emerged as a significant predictor of mortality.

**Conclusion**

In conclusion, identifying patients with COVID-19 with adverse prognosis is possible with proper clinical vigilance, and this large cohort study provided two important determinants of in-hospital mortality; higher age and low saturation level at admission.

**Study Strengths and Limitations**

The strengths of the study are the large sample size and sample representativeness in our region. Nevertheless, there are some limitations that should be noted in this research. First, this study is a single-center, retrospective, and non-randomized study. Therefore, multicenter and prospective studies are necessary to further explore the risk factors and adverse events in COVID-19 patients. Second, reduced kidney function in the current study solely depends on admission S. creatinine level; renal injury quantification was not assessed as acute kidney injury, CKD, or acute on CKD due to unavailability of the last 3 months’ renal profile and also missing information about albuminuria which defines CKD status. Third, the study lacks the data about complications related to COVID-19 so attribution to mortality could not be assessed.

**References**


INTRODUCTION

Early diagnosis and immediate treatment form the cornerstone of the management of sepsis. The need for early diagnosis has led to studies on a large spectrum of biomarkers like lactate, proinflammatory cytokines, C-reactive protein, and procalcitonin. Some of these are also expected to have prognostic value. Presepsin, a soluble CD14 subtype (sCD14-ST), is a 64 amino acid residue made of the N-terminal 13 kDa fragment of CD14 protein which acts as a receptor for the lipopolysaccharide–lipopolysaccharide-binding protein complexes. Through indirect interaction with B and T cells, it is found to have a regulatory role in cellular and humoral immune response modulation. We aimed to determine the prognostic utility of presepsin in predicting 28-day mortality with bacterial sepsis in comparison with procalcitonin.

METHODOLOGY

Study Design

This was a prospective observational cohort study conducted from November 2018 to June 2020 in a tertiary care center in South India. Institute Ethics Committee approval was obtained and 92 patients with suspected sepsis were enrolled after taking informed consent. The following were excluded: (a) chronic kidney disease stages IV and V (glomerular filtration rate <30 mL/min); (b) those who received antibiotics for ≥24 hours prior to admission; and (c) immunocompromised individuals. In this study, sepsis was defined as an increase in the Sequential Organ Failure Assessment (SOFA) score ≥2 or an admission SOFA score of 2 or more.

Thorough clinical history was taken and an examination was done. Blood samples were taken on the day of admission and day 3 for the estimation of presepsin and procalcitonin. The presepsin levels were measured using human serum presepsin ELISA kits, ELK Biotechnology Company from China. The procalcitonin levels were measured using human procalcitonin ELISA kits, ELK Biotechnology Company from China.

Statistical Analysis

The sample size was calculated to be 92, based on an estimated 40% mortality with a sensitivity of 70%, precision of 15%, and a-epsilon of 5%. Convenient sampling was done. Mortality was expressed as proportions and analyzed using the Chi-square test. Quantitative variables such as days of ICU stay were expressed as means and analyzed using the unpaired t-test. Estimates of sensitivity, specificity, and positive and negative likelihood ratios with 95% confidence interval were calculated. p < 0.05 is taken as significant. The prognostic accuracy of the presepsin was determined by generating ROC curves and comparing the AUCs of procalcitonin and presepsin.

RESULTS

A total of 92 participants with suspected sepsis were recruited in the study who met the inclusion criteria during the period November 2018 to June 2020. Nineteen participants expired before day 3. Of the remaining 73 participants on day 3, 42 (57.5%) survived sepsis and 31 (42.4%) did not survive. These were termed as survivor group and nonsurvivor group, respectively. The baseline characteristics of the study population and that of the two groups are shown in Table 1. The most common presenting symptom was fever in 85 (92.4%) followed by altered sensorium in 41 (44.6%) patients. The distribution of the laboratory parameters is given in Table 2. The most common focus of infection was pneumonia in 53 (57.6%). This was followed by urinary tract infection (UTI) in 23 (25%), soft tissue infections in five (5.4%), and meningitis in four (4.3%) patients. The remaining seven had other foci like endocarditis and scrub typhus. Overall mortality was 53.2%. Acute kidney injury was present in 37, out of which 21 (56.76%) patients expired. Multiple organ dysfunction syndrome (MODS) was seen in 21 of which 15 (71.43%) expired. Patients who had prolonged hypotension, high respiratory rate, and higher mean SOFA values were associated with poor outcomes.

Microbiological Profile of the Study Population

Of the 92 patients in the study population, 48 patients showed growth of organisms in the blood culture, five in exudate culture, and 48 patients showed growth of organisms in 10 in urine culture. Pneumonia was caused by Klebsiella in nine (31.03%) and Pseudomonas in five patients (17.24%). UTI was often caused by Escherichia coli (66.67%) and Klebsiella (9.54%). E. coli had 50% susceptibility to ceftriaxone and 65% to amikacin. Klebsiella species showed 62% sensitivity to meropenem and 100% to colistin. Pseudomonas aeruginosa had 75% sensitivity to meropenem and 100% to colistin.

Patients who had thrombocytopenia, high neutrophil count and urea, and elevated levels of bilirubin, presepsin, and procalcitonin were
associated with poor outcomes. Presepsin and procalcitonin tend to increase significantly from day 0 to day 3 in the nonsurvivor group as compared to the survivor group.

**ROC Curve for Presepsin**

The ROC was graphed using the sensitivity and 1-specificity values of every value of presepsin (Fig. 1). The AUC was 0.856 (0.764–0.947) with a significance of \( p \)-value <0.001. With the coordinates of the sensitivity and 1-specificity, the most appropriate value for sensitivity was taken as 0.774, at a cutoff value of 1.466 ng/dL. Values above it are taken as positive and below as negative.

**ROC Curve for Procalcitonin**

The ROC for procalcitonin was graphed using the sensitivity and 1-specificity values of every value of procalcitonin (Fig. 2). The AUC was 0.740 (0.642–0.857) with a significance of \( p \)-value <0.001. With the coordinates of the sensitivity and 1-specificity, the most appropriate value for sensitivity was taken as 0.774, at a cutoff value of 0.774 pg/dL. Values above it are taken as positive and below as negative.

On comparing the ROC curve of presepsin and procalcitonin, the AUC is more than that of presepsin signifying that it is a better biomarker of mortality due to sepsis when compared to procalcitonin (Table 3).

**Diagnostic Accuracy of the Predictors of Mortality**

The parameters for diagnostic accuracy as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio, and negative likelihood ratio are given in Table 4.

**Presepsin as a Predictor of Mortality**

Mortality among those with a presepsin value of more than 1.466 ng/dL was more than those with a presepsin value of less than 1.466 ng/dL (Table 5).

The cutoff value for presepsin is taken as 1.466 ng/dL from the ROC curve. Pearson’s Chi-square value for the association between mortality and presepsin was found to be 24.683 with a significance of 0.000. The OR was 14.571.

**Discussion**

In this study, presepsin was found to be a good diagnostic and prognostic marker of sepsis and a strong predictor of mortality in patients with bacterial sepsis. It also proved to be a better predictor of mortality in sepsis when compared to an already existing and

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**Table 1:** Comparison of clinical characteristics among the survivors and nonsurvivors

<table>
<thead>
<tr>
<th>Sl. no.</th>
<th>Parameter</th>
<th>Total</th>
<th>Nonsurvivors (n = 31)</th>
<th>Survivors (n = 42)</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Age of the patient (n = 92)</td>
<td>50.07 (13.31)</td>
<td>49.84 (12.54)</td>
<td>50.35 (14.28)</td>
<td>0.256</td>
</tr>
<tr>
<td>2</td>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>51 (55.4)</td>
<td>26</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>41 (44.6)</td>
<td>23</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>46</td>
<td>22</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>9</td>
<td>6</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Respiratory rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0 (n = 92)</td>
<td>32.04 (3.53)</td>
<td>32.82 (3.41)</td>
<td>31.15 (3.50)</td>
<td>0.0288</td>
<td></td>
</tr>
<tr>
<td>Day 3 (n = 73)</td>
<td>33.89 (4.54)</td>
<td>35.11 (5.21)</td>
<td>26.56 (4.77)</td>
<td>0.027</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Systolic blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0 (n = 92)</td>
<td>84.25 (6.35)</td>
<td>84.25 (6.59)</td>
<td>86.87 (5.81)</td>
<td>0.034</td>
<td></td>
</tr>
<tr>
<td>Day 3 (n = 73)</td>
<td>76.87 (13.40)</td>
<td>83.47 (15.24)</td>
<td>89.77 (18.47)</td>
<td>0.022</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>GCS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0 (n = 92)</td>
<td>11.32 (4.6)</td>
<td>11.33 (2.145)</td>
<td>12.57 (2.39)</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Day 3 (n = 73)</td>
<td>12.64 (2.47)</td>
<td>10.74 (1.97)</td>
<td>14.05 (1.78)</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>qSOFA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0 (n = 92)</td>
<td>2.62 (0.53)</td>
<td>2.78 (0.47)</td>
<td>2.44 (0.55)</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Day 3 (n = 73)</td>
<td>384.55 (67.93)</td>
<td>322.61 (61.74)</td>
<td>430.52 (14.63)</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Mean arterial pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0 (n = 92)</td>
<td>67.63 (3.31)</td>
<td>66.85 (3.80)</td>
<td>68.43 (2.52)</td>
<td>0.028</td>
<td></td>
</tr>
<tr>
<td>Day 3 (n = 73)</td>
<td>70.23 (10.61)</td>
<td>61.77 (9.10)</td>
<td>76.48 (6.57)</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>SOFA score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0 (n = 92)</td>
<td>5.93 (3.30)</td>
<td>7.50 (3.30)</td>
<td>4.18 (2.30)</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Day 3 (n = 73)</td>
<td>6.58 (4.90)</td>
<td>11.65 (2.50)</td>
<td>2.83 (1.97)</td>
<td>0.000</td>
<td></td>
</tr>
</tbody>
</table>

The difference in means between the survivor and nonsurvivor groups was computed using unpaired \( t \)-test.

**Table 2:** Distribution of laboratory parameters in the study population on day 3 (n = 73)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total</th>
<th>Nonsurvivors (n = 31)</th>
<th>Survivors (n = 42)</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>9.39 (2.05)</td>
<td>9.02 (2.39)</td>
<td>9.67 (1.73)</td>
<td>0.219</td>
</tr>
<tr>
<td>TLC</td>
<td>14,197.61 (6565.25)</td>
<td>15,295.27 (5867.61)</td>
<td>13,413.57 (6984.10)</td>
<td>0.220</td>
</tr>
<tr>
<td>Neutrophil %</td>
<td>84.28 (6.50)</td>
<td>86.52 (5.53)</td>
<td>82.58 (6.72)</td>
<td>0.011</td>
</tr>
<tr>
<td>Lymphocyte %</td>
<td>10.31 (5.22)</td>
<td>8.77 (3.98)</td>
<td>11.54 (5.75)</td>
<td>0.019</td>
</tr>
<tr>
<td>Platelet count</td>
<td>216,342.5 (109,069.3)</td>
<td>189,870.97 (109,282.43)</td>
<td>235,880.95 (105,977.95)</td>
<td>0.076</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>2.70 (1.20)</td>
<td>4.74 (2.96)</td>
<td>1.19 (0.81)</td>
<td>0.024</td>
</tr>
<tr>
<td>Direct bilirubin</td>
<td>0.56 (0.48)</td>
<td>0.86 (0.49)</td>
<td>0.36 (0.25)</td>
<td>0.100</td>
</tr>
<tr>
<td>Total protein</td>
<td>5.85 (0.51)</td>
<td>5.88 (0.47)</td>
<td>5.83 (0.58)</td>
<td>0.699</td>
</tr>
<tr>
<td>Albumin</td>
<td>2.76 (0.58)</td>
<td>2.75 (0.68)</td>
<td>2.78 (0.50)</td>
<td>0.848</td>
</tr>
<tr>
<td>AST</td>
<td>49.81 (29.06)</td>
<td>46.24 (23.43)</td>
<td>52.10 (32.24)</td>
<td>0.403</td>
</tr>
<tr>
<td>ALT</td>
<td>33.26 (15.17)</td>
<td>28.92 (10.20)</td>
<td>36.37 (17.38)</td>
<td>0.041</td>
</tr>
<tr>
<td>Urea</td>
<td>74.31 (50.62)</td>
<td>84.41 (52.83)</td>
<td>67.33 (48.44)</td>
<td>0.171</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.95 (0.62)</td>
<td>2.17 (0.81)</td>
<td>1.80 (0.494)</td>
<td>0.392</td>
</tr>
<tr>
<td>Day 0 presepsin (n = 92)</td>
<td>1.333 (0.788)</td>
<td>1.206 (0.770)</td>
<td>1.478 (0.793)</td>
<td>0.045</td>
</tr>
<tr>
<td>Day 3 presepsin (n = 73)</td>
<td>1.764 (1.261)</td>
<td>2.679 (1.397)</td>
<td>1.124 (0.632)</td>
<td>0.000</td>
</tr>
<tr>
<td>Day 0 procalcitonin (n = 92)</td>
<td>193.86 (106.39)</td>
<td>172.30 (98.74)</td>
<td>217.99 (110.56)</td>
<td>0.022</td>
</tr>
<tr>
<td>Day 3 procalcitonin (n = 73)</td>
<td>424.51 (19.88)</td>
<td>413.66 (17.07)</td>
<td>424.51 (19.88)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

The difference in means between the survivor and nonsurvivor groups was computed using unpaired \( t \)-test.
established biomarker of sepsis which is procalcitonin.

One of the studies similar to ours was the ALBIOS trial, in which 28-day mortality was studied, the presepsin cutoff was taken as 0.7 ng/dL with AUC 0.740 (0.640–0.850), sensitivity of 74.4%, specificity of 72.7%, 68% PPV, and 78% NPV. This was compared with procalcitonin which had AUC of 0.53 with sensitivity of 59.5%, specificity of 52.7%, 49% PPV, and 63% NPV, arriving at a conclusion that presepsin is a better prognostic marker than procalcitonin. These values being similar to the values from our study, further add to the evidence. This is also supported by evidence from a meta-analysis by Wu et al. which shows a pooled sensitivity and specificity of 0.84 (0.79–0.88) and 0.75 (0.64–0.84) for presepsin and 0.78 (0.72–0.83) and 0.79 (0.73–0.85) for procalcitonin. A study from Croatia reported that presepsin values were higher in deceased and those with septic shock and thus had prognostic value. An Indian study also reported poorer outcomes in those with elevated presepsin. A recent meta-analysis found that presepsin levels measured on the day of admission predicted 30-day mortality, however, they suggested further research in controlled settings. Similar results were reported in a narrative review. Higher presepsin values correlate with the severity of sepsis and MODS. Septic shock patients and those who died of sepsis had a significantly elevated presepsin in an ICU-based study of 114 patients and presepsin was found to have good prognostic value. In another study on 359 patients from emergency who had suspected sepsis, procalcitonin had the highest accuracy followed closely by presepsin. Presepsin has also found use in the diagnosis of postsurgical meningitis, perioperative infections, and cirrhosis with infections acute kidney injury and disseminated intravascular coagulation in septic patients. This study was limited by its small sample size. However, it adds to our understanding of the utility of presepsin as a prognostic marker of sepsis. When compared to procalcitonin, an elevated presepsin (more than 1.47 ng/dL) on day 3 in a patient with suspected sepsis predicts higher mortality. Future research should involve a larger population and use multiple biomarkers to diagnose and prognosticate sepsis. This will improve patient care and deliver better outcomes, in terms of hospital stay and mortality.

### References
A Study on Prevalence of Trigger Factors and Associated Disorders in Tension-type Headache

Deepak Jain¹, Garima Pandey²*

Received: 18 June 2022; Accepted: 02 August 2022

Abstract

Objective: To study the prevalence of trigger factors and associated disorders in tension-type headache (TTH). Trigger factors have been widely studied in the context of migraine, but very few studies have investigated trigger factors in the context of TTH.

Materials and methods: A total of 400 patients above the age of 15 years fulfilling the third edition of the International Classification of Headache Disorders (ICHD 3) criteria of frequent episodic tension-type headache (FETTH) and chronic tension-type headache (CTTH) were enrolled and evaluated using a questionnaire. Details regarding demographics, headache characteristics, triggers, and associated symptoms were obtained. Associated psychiatric disorders were also recorded. Data were analyzed using Microsoft Excel and statistical analysis was done using SPSS 22 trial version. Chi-square test and Fischer’s exact test were used for statistical analysis and subgroup comparison.

Results: Out of 400 patients, 360 (90%) were found to have triggers. The mean headache intensity on visual analog scale (VAS) was 6.7. The most common trigger factor was emotional stress among both males and females. There was a statistically significant difference in the frequency of trigger factors between men and women for emotional stress, sunlight, sleep deprivation/insomnia, noise, weather change, studying, fried food, and hypersonmia. Psychiatric comorbidity was found in 29% of individuals, with sleep disorder being the most common.

Conclusions: TTH has been an underrated diagnosis despite being an extremely common disorder. The trigger factors are less studied and their interactions are lesser known. The diagnostic criteria as per ICHD 3 make TTH a diagnosis of exclusion, rather than a positive diagnosis of inclusion. The trigger factors must be included in the diagnostic criteria in future versions of ICHD and associated psychiatric disorders should be sought for and treated simultaneously for better management and quality of life.

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Introduction

Tension-type headache is the most common primary headache disorder. As per the Global Burden of Disease Study 2010, TTH is the second most common disorder worldwide with an estimated prevalence of 20.8%. However, as per a meta-analysis study by Stovner et al., the global burden of TTH was 42%. TTHs can begin at any age, are generally bilateral, and are often described as a sense of pressure or wearing a tight band around the head. The pain is of mild to moderate intensity, tends to not be aggravated by routine physical activity, and may wax and wane throughout the day or may be present and be steady for days, weeks, or even years at a time. Tension headaches have no associated nausea or vomiting and are much less commonly associated with light and sound sensitivity than migraine. Despite being the most common headache disorder, yet the least studied of all the primary headaches. The pathophysiological mechanisms behind TTH are not clearly elucidated. The role of neurotrophic factors and neuronal plasticity has been highlighted recently in several studies. Trigger factors are temporally associated events or stimuli that precipitate or aggravate the headache. Various trigger factors have been clearly known to cause migraine, but such trigger factors have not been studied widely in the context of TTH. The trigger factors range from various food, environment, and emotional stress to climate and menstruation in women. TTH is also found in the literature to be associated with certain psychiatric conditions/diagnoses. Prakash has described the stigmatization experienced by people with TTH and compared it with “denial” as witnessed in individuals with depression. The current study was taken up to study the prevalence of trigger factors and associated disorders in TTH. The study also highlights the sociodemographic, and geo-climatic factors in such individuals.

Materials and Methods

The study evaluated 400 patients in a cross-sectional manner from October 2019 to October 2021. The study was duly approved by the Institutional Ethics Committee and patients were recruited to the study after informed written consent in the local language. Patients above the age of 15 years with headache who were diagnosed as FETTH and CTTH as per the ICHD 3 criteria were included in the study. The study was conducted in the outpatient department (OPD) of Division of Neurology, S.M.S Medical College, Jaipur, Rajasthan, India. All patients who consented to participate in the study were interviewed by the same team in a semi-structured format using a questionnaire/proforma. Demographic characteristics of all individuals were recorded including education, marital status, and occupation. Medical history included current and previous diseases and medications (particularly, analgesics, antidepressants, and oral contraceptive drugs). Family history of migraine and other diseases, and consumption of caffeine, tea, and smoking habits were elicited. All patients were quizzed for potential trigger factors of headache, headache duration, characteristics, and relieving factors, if any. The trigger factors included in the study were based on previous studies on the subject and from studies on migraine. Patients were also evaluated for any coexisting conditions particularly any psychiatric diagnoses as per the Diagnostic and Statistical Manual of Mental Disorders (DSM) V criteria. Patients with medication overuse headache were excluded from the study. Sinus tenderness and pericranial tenderness were assessed in sternocleidomastoid (both cranial and sterna ends), trapezius muscles along the upper border from shoulder to neck, and temporalis muscle.

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A detailed neurological evaluation was done. All patients underwent fundus examination. Neuroimaging like X-ray cervical spine (to rule out cervicogenic headache), X-ray paranasal sinus (suspected sinusitis), and computed tomography/magnetic resonance imaging brain were ordered in selected individuals only to rule out secondary headache. Psychiatry consultation was taken for the patient showing psychiatric symptoms/signs. Statistical analysis was done using Microsoft Excel 2007 and SPSS trial version 22. Frequency distribution analysis, mean, and range were obtained for demographic variables. The frequency of triggers and the associated psychiatric disorders were compared between the male and female subgroups using Chi-square test/Fischer’s exact test, with a confidence level for statistical significance set to 95%.

**Results**

A total of 400 patients with TTH (FETTH and CTTH) were enrolled in the study after fulfilling the eligibility criteria. Of the entire study group of 400 patients, 360 (90%) reported one or more trigger factors for TTH.

**Demographics**

The majority of the patients were females (70%). The mean age was 33 with an age range of 15–75 years. The mean age at onset of headache was 22 years. About 41.2% of individuals were illiterate, while another 22.2% had only attended primary school. Nearly 20.5% had attended high school, and only 16% reported having attended graduate courses and above. Almost 82.2% of patients were not involved in gainful employment (housewives 46%, students 20.5%, and unemployed 15%).

**Headache Characteristics**

The mean duration of each headache episode was 12.2 hours. The mean headache intensity was 6.7 on VAS. The headache was bilateral in the majority of the patients (86.25%). The headache was described as diffuse in 36% of patients, temporal in 33%, frontal in 18%, and retro-orbital in 10%. Only 2% described the pain as being occipital while only 0.5% described the pain as being parietal.

Patients most commonly reported pain being pressing and-band-like in nature (55%), only 9% reported stabbing character while 6% reported pulsating pain. Up to 30% reported mixed characteristics of headache (Fig. 1).

Only 2% reported mild nausea of all the patients. Photophobia only was reported in 11% while 9% reported phonophobia. Around 37% of patients were found to have pericranial tenderness on examination. Other symptoms were present in only a few patients. Only 22% of patients had neck pain, vertigo in 10%, and gastritis in 1%.

**Diagnosis**

A total of 72 patients (18%) presented with FETTH while 328 (82%) presented with CTTH. Among the FETTH group, 22.2% were males while 77.7% were females. Among the patients with CTTH, 31.7% were males and 68.2% were females.

**Trigger Factors**

The most commonly reported trigger factor was emotional stress in 59% of patients, followed by sunlight in another 44.16%, sleep deprivation/insomnia in 39.16%, and noise in 36.11%. Missed meal/fasting or hunger was reported to be a trigger factor by 35% of individuals. Fatigue, weather change, and screen use were reported as a trigger by 29%, 22.7%, and 20% of individuals, respectively. Smoking and alcohol were reported as a trigger by 20% and 16%, respectively, among those reporting their intake. Other triggers like temperature, traveling, menstruation in women, tea, and coffee were also reported by patients, and are detailed in Table 1. None of the patients reported cheese consumption or head bending in our study.

There was a statistically significant difference in the frequency of trigger factors among men and women as evaluated by Chi-square test considering 95% confidence limits, for emotional stress, sunlight, sleep deprivation/insomnia, noise, weather change, studying, fried food, and hypersomnia. The triggers in men and women are depicted in Figures 2 and 3.

**Associated Disorders**

In the present study, a psychiatric disorder was found associated with TTH in 29% of subjects. The most common associated disorder with TTH in the current study was sleep disorder in 21%, followed by depressive disorder (9%), generalized anxiety disorder (GAD) (8.25%), somatoform disorder (6%), panic disorder (4.25%), social phobia (2.75%), obsessive-compulsive disorder (OCD) (1.5%), suicidality (1.25%), and agoraphobias (0.25%) as detailed in Table 2 and Figure 4. Other psychiatric disorders were present in 2.5%.

**Discussion**

The present study was conducted as a cross-sectional study at a tertiary care center in northwestern India. The worldwide prevalence of TTH in adults is 42%. TTH is a less studied entity. Trigger factors in the context of migraine have been studied quite extensively, while few studies have been published in the context of TTH, none from the region of the current study. Most of the studies have compared trigger factors for migraine and TTH, with a limited number of patients. Prominent studies on the matter and their reported data have been compiled in Table 3.

The current study represents the largest cohort of patients (n = 400) with TTH who have been studied for trigger factors and other parameters, followed by Wang et al. who have reported triggers of TTH in a cohort of 344 patients. Nearly 90% of individuals reported some trigger in the current study, while Wang et al. have reported triggers only in 67.4% of individuals.

**Demographics**

In the current study, the cohort of TTH patients was enrolled in an antegrade manner from a hospital-based neurology OPD of a tertiary care center. The study design was cross-sectional observational. Wang et al. had conducted a similarly designed study. Wöber et al. had conducted a study on patients from a headache clinic, both with migraine and TTH, and a few from a community setting. The study by Gupta and Bhatia compared trigger factors between migraine and TTH (n = 50), and so did Iliopoulos et al. (n = 28 TTH). The study published by Haque et al. was based on a document review of 250 patients each of migraine and TTH from a tertiary care hospital. The females dominated the TTH cohort in all studies, with all 50 patients (100%) in the study by Gupta and Bhatia being females. As detailed in Table 3, the percentage female
Iliopoulos et al., Education and employment status have a profound bearing on the understanding of individuals of their disease process and on how well equipped one is in dealing with them.

Headache Characteristics

In this study, headache was bilateral in the location in the majority of patients (86.25%), pressing and band-like characteristics in most of them (55%), stabbing (9%), pulsatile only in 6% of the patients, and none had aggravation of headache by routine physical activity, while a study done by Kaniecki et al. subset of patient may have pulsatile quality up to 62%, strictly unilateral headache (up to 18%), and headache aggravation by routine physical activity in more than 50% of cases.1

Also in our study, photophobia and phonophobia were reported in 11 and 9%, respectively. A review of the literature suggests that more than 60% of patients with TTH can have phonophobia and photophobia which was associated in around 15–20% of patients.12

### Table 1: Trigger factors in TTH

<table>
<thead>
<tr>
<th>In percentage</th>
<th>Overall percentage (n = 360)</th>
<th>Men % among men (n = 120)</th>
<th>Women % among women (n = 280)</th>
<th>Chi-square/Fisher's exact value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emotional stress</td>
<td>59.00</td>
<td>53 (44.1)</td>
<td>159 (56.7)</td>
<td>5.370</td>
<td>0.020</td>
</tr>
<tr>
<td>Sunlight</td>
<td>44.16</td>
<td>35 (29.16)</td>
<td>124 (44.2)</td>
<td>8.017</td>
<td>0.005</td>
</tr>
<tr>
<td>Sleep deprivation/insomnia</td>
<td>39.16</td>
<td>25 (20.8)</td>
<td>116 (41.4)</td>
<td>15.610</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Noise</td>
<td>36.11</td>
<td>24 (20)</td>
<td>106 (37.85)</td>
<td>12.210</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Missed meal/fasting/hunger</td>
<td>35</td>
<td>44 (36.6)</td>
<td>82 (29.28)</td>
<td>2.121</td>
<td>0.145</td>
</tr>
<tr>
<td>Fatigue</td>
<td>29.5</td>
<td>30 (25)</td>
<td>76 (27.14)</td>
<td>0.198</td>
<td>0.656</td>
</tr>
<tr>
<td>Weather change</td>
<td>22.7</td>
<td>32 (26.6)</td>
<td>50 (17.85)</td>
<td>4.000</td>
<td>0.045</td>
</tr>
<tr>
<td>Mobile/TV/computer</td>
<td>20</td>
<td>23 (19.1)</td>
<td>49 (17.5)</td>
<td>0.158</td>
<td>0.691</td>
</tr>
<tr>
<td>Smoking</td>
<td>20 (among smokers)</td>
<td>6 out of 30 smokers</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Alcohol</td>
<td>33.3% among alcoholics</td>
<td>5 out of 15 alcoholics</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Temperature</td>
<td>10</td>
<td>14 (11.6)</td>
<td>22 (7.8)</td>
<td>1.488</td>
<td>0.222</td>
</tr>
<tr>
<td>Strenuous physical activity/stress/exercise</td>
<td>9.1</td>
<td>9 (7.5)</td>
<td>24 (8.5)</td>
<td>0.127</td>
<td>0.721</td>
</tr>
<tr>
<td>Traveling</td>
<td>9.1</td>
<td>17 (14.16)</td>
<td>16 (5.7)</td>
<td>7.928</td>
<td>0.005</td>
</tr>
<tr>
<td>Menstruation</td>
<td>9.2</td>
<td>26 (9.28)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Studying</td>
<td>5</td>
<td>12 (10)</td>
<td>6 (2.1)</td>
<td>12.067</td>
<td>0.001</td>
</tr>
<tr>
<td>Strong smell</td>
<td>2.7</td>
<td>4 (3.33)</td>
<td>6 (2.1)</td>
<td>0.490</td>
<td>0.495</td>
</tr>
<tr>
<td>Fried food</td>
<td>2.22</td>
<td>5 (4.1)</td>
<td>3 (1.0)</td>
<td>4.203</td>
<td>0.056</td>
</tr>
<tr>
<td>Chocolate</td>
<td>1.6</td>
<td>3 (2.5)</td>
<td>3 (1.0)</td>
<td>1.286</td>
<td>0.370</td>
</tr>
<tr>
<td>Tea</td>
<td>1.1</td>
<td>2 (1.6)</td>
<td>2 (0.7)</td>
<td>0.790</td>
<td>0.587</td>
</tr>
<tr>
<td>Coffee</td>
<td>0.8</td>
<td>2 (1.6)</td>
<td>1 (0.3)</td>
<td>1.960</td>
<td>0.215</td>
</tr>
<tr>
<td>Hypersomnia</td>
<td>0.5</td>
<td>2 (1.6)</td>
<td>0</td>
<td>4.765</td>
<td>0.089</td>
</tr>
<tr>
<td>Thirst</td>
<td>0.5</td>
<td>1 (0.8)</td>
<td>1 (0.3)</td>
<td>0.458</td>
<td>0.511</td>
</tr>
<tr>
<td>Cheese</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Head bending</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Fig. 2: Depicting absolute number of various triggers among men and women

Population ranged from 61.9 to 100% in various studies. In our study, the female population comprised 70% of the entire study group. The composition of patients in our study with regard to education was similar to the study by Wang et al., with the majority being educated only up to high school or less. A vast majority of patients reported being unemployed in the current study (61.7%), in contrast to 52.6% by Wang et al. and 53.6 by Iliopoulos et al. Education and employment status have a profound bearing on the understanding of individuals of their disease process and on how well equipped one is in dealing with them.
recorded sympathetic skin response compared to normal control in TTH. This electrophysiological similarity to migraine without aura supports the hypothesis that some patients with TTH might be at the mild end of the migraine spectrum.

As TTH shares several trigger factors with migraine, the search is on for common pathophysiological mechanisms, including chemical mediators.

Triggers
The most common trigger factor reported in the current study was emotional stress in both men and women, while Wang et al. have reported negative affect as the most common trigger factor in contrast to our study, Wöber et al., Gupta and Bhatia, Haque et al., and Constantinides et al. have all reported stress as the most common trigger factor similar to emotional stress as reported in our study.8,9,11,14 In our study physical stress when combined with emotional stress, added up to a trigger in almost 68% of individuals.

The most common four trigger factors in all studies are tabulated in Table 3, along with details of the study.

Stress
Across studies, as in the present one, stress has been highlighted as an important trigger factor. Gupta and Bhatia reported stress as a trigger factor in 84% of individuals. Several studies have investigated the relationship between stress and migraine, but similar studies are few and far between for TTH. Folchini and Kowachs have highlighted the putative role of neurotrophic factors in TTH pathophysiology.3

Genetic factors have been thought to be of significance in the context of CTTH. Genetic factors have been thought to be of significance in the context of CTTH.

The association of psychiatric disorders as found in the current study and as has been reported by several authors provides validation to the association.9

### Table 2: Associated psychiatric disorders in TTH

<table>
<thead>
<tr>
<th>Associated Psychiatric disorders</th>
<th>Percentage (n = 400)</th>
<th>Male N out of 120</th>
<th>Female N out of 280</th>
<th>Chi-square/Fisher's exact value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep disorders</td>
<td>21%</td>
<td>30</td>
<td>25%</td>
<td>19.28%</td>
<td>0.153</td>
</tr>
<tr>
<td>Depressive disorder</td>
<td>9%</td>
<td>10</td>
<td>8.3%</td>
<td>9.2%</td>
<td>0.093</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>8.25%</td>
<td>9</td>
<td>7.5%</td>
<td>8.5%</td>
<td>0.127</td>
</tr>
<tr>
<td>Somatoform disorder</td>
<td>6</td>
<td>4</td>
<td>3.3%</td>
<td>7.14%</td>
<td>0.199</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>4.25</td>
<td>1</td>
<td>0.83%</td>
<td>4.28%</td>
<td>0.127</td>
</tr>
<tr>
<td>Social phobia</td>
<td>2.75</td>
<td>5</td>
<td>4.1%</td>
<td>2.14%</td>
<td>0.257</td>
</tr>
<tr>
<td>Other psychiatric disorder</td>
<td>2.5</td>
<td>4</td>
<td>3.3%</td>
<td>2.14%</td>
<td>0.490</td>
</tr>
<tr>
<td>OCD</td>
<td>1.5</td>
<td>2</td>
<td>1.6%</td>
<td>2.8%</td>
<td>0.730</td>
</tr>
<tr>
<td>Suicidality</td>
<td>1.25</td>
<td>2</td>
<td>1.6%</td>
<td>1.07%</td>
<td>0.639</td>
</tr>
<tr>
<td>Agoraphobia</td>
<td>0.25</td>
<td>0</td>
<td>0%</td>
<td>0.35%</td>
<td>0.999</td>
</tr>
</tbody>
</table>

Pathophysiology of TTH
The pathophysiological mechanisms of TTH have not been elucidated completely. The current evidence has refuted the previously accepted muscle contraction theory. Heightened sensitivity of peripheral nociceptive pathway in FETTH and central sensitization of pain pathway due to prolonged nociceptive stimuli from pericranial myofascial tissue leading to conversion of FTTH to CTTH has been supported by recent evidence on pathophysiology of TTH.3

Genetic factors have been thought to be of significance in the context of CTTH. Like migraine without aura, there has been found lack of habituation when...
Environmental Factors

Sunlight was the second most common trigger factor (44.6%) reported by patients in the current study. The northwestern part of India where this study was conducted receives ample sunlight during most parts of the year. Sunlight was reported by Haque et al. as well as the second most common trigger factor in TTH.11

Weather change was reported by 22.7% of participants as a trigger in our study, while another 10% reported a change in temperature as a trigger factor, thereby highlighting the importance of environmental influences in triggering TTH. Such influences can often not be fully prevented by patients, as exposure to environmental influences may often be unavoidable. Heat has also been reported by Gupta and Bhatia as a trigger for TTH.

Noise as an environmental influence was the fourth most common trigger factor reported by 36.1% of individuals as a trigger factor for TTH. This has less often been reported by other authors as such a prominent factor.

Sleep

Disturbed sleep/insomnia was reported as the third most common trigger in our patients (36.6%). Changes in sleep patterns have been reported as a trigger by Iliopoulos et al, Gupta and Bhatia, and Wang et al. in their studies.

Table 3: Comparison of recent studies on TTH with current study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Wöber et al., 2006</th>
<th>Gupta and Bhatia, 2011</th>
<th>Haque et al., 2012</th>
<th>Wang et al., 2013</th>
<th>Constantinides et al., 2014</th>
<th>Iliopoulos et al., 2015</th>
<th>Current study</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (TTH)</td>
<td>49</td>
<td>50</td>
<td>250</td>
<td>344</td>
<td>12</td>
<td>28</td>
<td>400</td>
</tr>
<tr>
<td>No. (%) with triggers</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>232 (67.4)</td>
<td>NA</td>
<td>DNA</td>
<td>360 (90)</td>
</tr>
<tr>
<td>Age range (mean)</td>
<td>(27.6)</td>
<td>NA</td>
<td>Majority between 11 and 40 years</td>
<td>(45.32 ± 14.9)</td>
<td>(40.7)</td>
<td>18–69</td>
<td>15–75 (32.8)</td>
</tr>
<tr>
<td>Female population</td>
<td>100%</td>
<td>67%</td>
<td>61.9%</td>
<td>Female to male 6:1 (85.7%)</td>
<td>71.4%</td>
<td>70%</td>
<td></td>
</tr>
<tr>
<td>Education of patients %</td>
<td>DNA</td>
<td>NA</td>
<td>Illiterate</td>
<td>3.6</td>
<td>41.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td></td>
<td></td>
<td>Less than high school</td>
<td>63.3</td>
<td>14.2</td>
<td>22.2</td>
<td></td>
</tr>
<tr>
<td>High school and university</td>
<td>18.5</td>
<td></td>
<td>46.4</td>
<td>20.50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postgrad</td>
<td>18.1</td>
<td>42.8</td>
<td>16.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employment status %</td>
<td>DNA</td>
<td>NA</td>
<td>Employed</td>
<td>49.2</td>
<td>46.5</td>
<td>17.75</td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td></td>
<td></td>
<td>Unemployed</td>
<td>3.6</td>
<td>53.6</td>
<td>61.7%</td>
<td></td>
</tr>
<tr>
<td>Housewife</td>
<td>49</td>
<td>49</td>
<td>46.25%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Students</td>
<td>4.4</td>
<td>4.4</td>
<td>20.5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>10.8%</td>
<td>10.8%</td>
<td>3.75%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>18.9%</td>
<td>18.9%</td>
<td>7.5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most common triggers (top 4)</td>
<td></td>
<td>Stress</td>
<td>Stress</td>
<td>Stress</td>
<td>Stress</td>
<td>Emotional stress</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heat</td>
<td>Sunlight</td>
<td>Negative effect</td>
<td>Weather change</td>
<td>Sunlight</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lack of sleep</td>
<td>Anxiety</td>
<td>Sleep disturbance</td>
<td>Fatigue</td>
<td>Sleep deprivation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hunger</td>
<td>Journey</td>
<td>Sunlight</td>
<td>Temperature</td>
<td>Menstruation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fatigue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Temperature</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparison of triggers in male and female</td>
<td></td>
<td>Female patients with TTH had more wind (p = 0.028), sunlight (p = 0.010), sleep disturbance (p = 0.020), and less alcohol (p &lt; 0.001) triggers than male patients with TTH</td>
<td>NA</td>
<td>Emotional stress, sunlight, sleep deprivation/insomnia, noise, weather change, studying, fried food, and hypersomnia; all these were statistically significantly more in females</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Sleep disorder, depression, and GAD were the most common features</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DNA, data not available; NA, not analyzed
their studies among the top four trigger factors.

**Fatigue**

Fatigue was reported by 29.5% of individuals as a trigger factor in our study. Wang et al. and Constantinides et al. have reported fatigue as a prominent trigger of headaches for TTH in their studies. Iliopoulos et al. published that more than 50% of patients in their study reported fatigue as a trigger for TTH.

**Food**

Missed meal/hunger was reported by 35.5% of individuals as a trigger for TTH in the study. Other authors also have reported similar data regarding hunger and TTH.

A few patients reported fried/oily food as a trigger factor in the study (2.2%); similar to what has been reported in the literature.

None of the patients in our study group reported cheese or chocolate as a trigger which has been reported by several authors. Smoking was reported as an occasional trigger by 20% (6 out of 30 smokers) in our study, while 33% of alcoholics (5 out of 15) reported having a headache after alcohol ingestion. Detailed data regarding these are not available for comparison among studies on TTH.

**Menstruation and TTH**

Among 280 females, 26 (9.2%) reported menstruation as a trigger factor for migraine, this is in contrast to Wöber et al. (56%) and Constantinides et al. (41.6%) who have reported higher incidences. This may be due to sociocultural influences where women of the region are reluctant to admit and report the association of menses with their headache.8,14

**Psychiatric Associations**

The current study has revealed several psychiatric comorbidities, the most common of which was sleep disorder (21%) followed by depressive disorders (9%), GAD (8.25), and somatoform disorder (6%). In their study on psychiatric comorbidity, quality of life and disability in patients of migraine and TTH, Bera et al. have reported a prevalence of any psychiatric disorder to be around 60%, depression around 30%, social phobia around 12.5%, panic disorder around 12.5%, and GAD around 7.5%.15 In a study by Singh et al., generalized anxiety disorder and major depression were common in patients with CTH. Optimal treatment strategies for the treatment of TTH should aim at evaluation and appropriate treatment of these comorbidities.16

**CONCLUSION**

We have found a high prevalence of trigger factors (90%) among the patients with TTH (FETTH/CTTH) in our hospital-based cross-sectional study, where most of the patients were females. The triggers between males and females were statistically significant for emotional stress, sunlight, sleep deprivation/insomnia, noise, weather change, studying, fried food, and hypersomnia. Geo-climatic and sociocultural influences probably account for the difference in trigger factors as observed in comparison with other studies on the topic. Psychiatric comorbidities were noted 56% of individuals in this study. Psychiatric issues in these patients should be treated adequately so as to achieve optimal outcomes and patient satisfaction. Mental disorders in the context of TTH and trigger factors in TTH should be further investigated in multicenter and community-based studies to enhance knowledge and improve treatment strategies.

Prakash in his article has emphasized on the stigma associated with the word “tension” in TTH based on his own firsthand experience of having to suffer both the disease and stigma. He has described a particular denial among the patients on the diagnosis of “tension”-type headache, which stems mostly from the lack of knowledge and understanding on part of all stakeholders.2 Like migraine, triggers for TTH should also be identified and should be included in the diagnostic criteria of TTH. Also, disorders commonly associated with TTH should be sought for and treated simultaneously for effective management.

**Strength and Limitations of the Study**

The current study comprises 400 TTH patients who were quizzed by the same examiner in a semi-structured format. This comprises one of the largest cohorts of TTH in any recent study on the subject in English literature.

The current study is a hospital-based single-center study and is likely to recruit more severe cases of TTH compared to the milder ones from the community, who may not seek medical help.

The ICHD 3 criteria used for diagnosis in the current study make TTH a diagnosis of exclusion, rather than a positive diagnosis based on accurate disease and trigger characteristics. This approach may leave some patients without appropriate diagnosis and hence without adequate treatment. In this study, the author feels the need to include triggers, and criteria for a positive diagnosis of TTH in the future versions of ICHD or other classification and defining criteria for TTH.

Further, because of symptom similarity between TTH and migraine as indicated by current evidence, a few patients of probable migraine may be included in the study. Further research in the field is likely to clarify on this ambiguity.

**References**

1 Out of 3
Deaths in Indian Women occurs due to Heart Disease

Let’s join hands to
Knockout Heart Disease
with Awareness, Diagnosis & Care

Shakti
An initiative to Knockout Heart Disease

Novastat
Rosuvastatin 40 mg / 20 mg / 10 mg / 5 mg

MC Mary Kom
6 Times World Boxing Champion
7th INTERNATIONAL DIABETES SUMMIT 2023
DATE: 10th – 12th MARCH 2023 | JW MARRIOTT, PUNE
CHELLARAM HOSPITAL: DIABETES CARE AND MULTISPECIALITY ● CDI E-LEARNING ACADEMY ● DIABETES HEALTH MAGAZINE ● CHELLARAM DIABETES RESEARCH CENTRE

HIGHLIGHTS – 6th INTERNATIONAL DIABETES SUMMIT – 2022 (VIRTUAL)

- 113 National and 18 Best in class International Speakers from USA, UK and Europe.
- 10,000 virtual delegate registrations from all over India and abroad.
- Oral abstract presentations by 84 young researchers virtually.
- The Chellaram Foundation Diabetes Research Awards were presented. A total prize of Rs. 6,00,000/- was awarded to the winners for outstanding research in basic and clinical sciences.
- The results of the first “Call for proposals-Innovation Grant-2021” were announced. The total grant of approximately Rs. 2.7 crores for six projects together were announced by the Chellaram Diabetes Research Centre (CDRC).
- The 5-day mega event comprised of a number of interesting sessions including Workshop on Classic Diabetology, A Certificate CME on Type 1 Diabetes, Special Seminar on Type 2 Diabetes and Obesity, CME Certificate Course on Innovation in Endocrinology and Diabetes, CME Certificate Course on Type 2 Diabetes Remission, CME on Diabetes and Related Disorders.
- The Maharashtra Medical Council awarded 6 Credit Points to the programs.

REGISTRATION FORM

First Name: ___________________________ Surname ___________________________ Gender M/F

MMC/ Other Council No.___________________________ Hospital / Institution ___________________________

Qualification ___________________________ Speciality ___________________________

Address For Communication ___________________________________________________________________________

City ___________________________ Pincode ___________________________ State/Country ___________________________

Mobile No/Contact No (With Area Code) ___________________________ Email ___________________________

Registration Fee ( Fee/Person in INR And USD) + 18% GST

<table>
<thead>
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<th>Category</th>
<th>Upto 1st Jan 2023</th>
<th>Upto 9th March 2023</th>
<th>Spot</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Delegate</td>
<td>INR 10,000</td>
<td>INR 11,300</td>
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*Includes PHFI / CDI course participants

Note: Final decision on registration will be taken by Organizing Committee.

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Asymptomatic Renal Function Abnormalities in Patients having Silicosis

Ramakant Dixit¹, Jitendra Jalutharia², Mukesh Goyal³

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ABSTRACT

Background: A number of occupational exposures are associated with various types of renal dysfunction. Several studies for many years have drawn attention to renal dysfunction and nephrotoxicity among workers exposed to silica. This study was conducted to evaluate renal dysfunction, if any, among Indian patients having silicosis and its correlation with the duration of exposure to silica dust.

Materials and methods: This study includes 52 eligible patients with a history of silica dust exposure and silicosis confirm on radiological examination by the pneumoconiosis board. Investigations like serum creatinine, urinary albumin creatinine ratio, etc. were done. The “modification of diet in renal disease” (MDRD) formula was used to calculate the glomerular filtration rate (GFR).

Results: This study showed 53.84% of patients (n=28) having albuminuria and a mean “urinary albumin to creatinine ratio” (UACR) of 101.88 ± 128.99 mg/gm. Isolated macroalbuminuria was detected in 11.5% of patients (n=6) while 42.3% of patients (n=22) presented with microalbuminuria. The mean GFR was 81.94 ± 22.09 mL/min/1.73 m² among study patients of which four (7.7%) patients had GFR value <60 mL/min/1.73 m². We could also identify a significant association between the duration of exposure to silica dust and UACR and GFR (p < 0.01).

Conclusion: Albuminuria and reduced estimated GFR in patients with silica dust exposure is not uncommon and reflect early underlying renal dysfunctions. Our study suggests a simple and cost-effective screening strategy for early detection of renal dysfunction among silicosis patients that may be considered as a tool to prevent further renal damage in such patients.

INTRODUCTION

Silicosis is one of the oldest occupational lung diseases known that is caused by inhalation, retention, and pulmonary reaction to the crystalline form of silica.¹ Silica is basically silicon dioxide, a naturally occurring mineral that constitutes most of the Earth’s crust. A variety of occupational exposures are associated with the occurrence of silicosis, that is, mining, quarrying, cement, glass construction, ceramic, foundries, shipbuilding, rubber, cosmetic industries, jewelry, arts, crafts, sculpture, dental material, and many others. Silica exposure in India is mostly in the unorganized sector with stone cutting, stone drilling, stone crushing, stone powder workers, slate pencil and agate industries, etc. The occupational disease with silica dust exposure is mainly via inhalation route and almost negligible via skin or digestive tract. Although silica exposure is mainly associated with progressive fibrotic lung disease, there are evidences that it is also linked with a variety of connective tissue disorders, vasculitis, autoimmune process, and renal damage.²

Heavy metals, organic solvents, and silica exposure are known toxic agents for kidneys due to unique renal circulation and metabolic characteristics. Occupational and environmental exposure to such agents is associated with various renal involvements. Identification of occupational exposure is of utmost importance to prevent occupational renal diseases among the exposed individuals. Lead, cadmium, chromium, mercury, arsenic, organic solvents, and silica are the most common agents associated with environmental and occupational renal diseases.³ Among these toxic agents, mercury is associated with glomerular disease while lead, cadmium, and chromium mainly cause renal tubule-interstitial disease. Other toxins can lead to damage at both the tubule-interstitial and glomerular level.³

Chronic kidney disease (CKD) is now emerging as a global health issue and is among the common causes of mortality worldwide.⁴ Increased mortality due to CKD is also evidenced in low-income and middle-income countries.⁵ In the “gold standard” definition of CKD, a person is classified as having CKD if either of the following is present⁶:

- Glomerular filtration rate <60 mL/min/1.73 m² for 3 months.
- Evidence of renal damage such as UACR >30 mg/gm.

Altered renal functions can be detected by measurement of blood urea, serum creatinine levels, GFR, and proteins in the urine sample. The presence of albumin in urine and its measurement specifically indicates a risk of CKD in an individual.

The present study was carried out to evaluate urinary abnormalities and assess renal dysfunction, if any, in persons having occupational exposure to silica dust and having confirmed silicosis on the radiological assessment by the pneumoconiosis board.

MATERIALS AND METHODS

This was a descriptive cross-sectional study among diagnosed patients with silicosis attending our tertiary health center over the last 2 years after approval by the Institutional Ethical Committee. A convenient method of sampling was adopted for this study as the sample size could not be calculated due to the lack of prevalence figure for renal abnormalities among silicosis patients in India.

Inclusion and Exclusion Criteria

Study subjects with a past medical history of hypertension, diabetes mellitus, evidence of chronic renal diseases (gout, urinary tract infections, glomerulonephritis, or renal calculus), and those taking regular medications with nephrotoxic potential, that is, antibiotics, analgesics, and steroids, or those with a past or current exposure to nephrotoxic agents, like heavy metals or solvents, etc. were excluded in this study.

The diagnosis of silicosis was made by the patient’s history of occupational/environmental exposure to silica and chest radiograph, that is, radiological features....

1. Senior Professor and Head, Department of Respiratory Medicine, JLN Medical College, Ajmer; 2. Assistant Professor, Department of Respiratory Medicine, Mahatma Gandhi Medical College, Jaipur; 3. Assistant Professor, Department of Respiratory Medicine, JLN Medical College, Ajmer, Rajasthan, India; *Corresponding Author

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consistent with silicosis like small, round opacities that can be categorized using International Labor Organization classification by size, shape, and profusion category. Based on different degrees and duration of exposure to silica dust during occupational settings, silicosis patients were classified as chronic silicosis, accelerated silicosis, and acute silicosis. The chronic or classic form of silicosis usually follows one or more decades of exposure to respirable dust. Accelerated silicosis occurs with higher exposures and develops over 5–10 years. In the acute form of silicosis, the exposures are at the highest level, usually from a few weeks or months up to 5 years with rapid clinical progression.1

For all study subjects, a general clinical examination was done including measurement of the blood pressure using a mercury sphygmomanometer to exclude hypertensive state. All other routine investigations were also done including blood counts, blood sugar, blood urea, serum creatinine, etc. apart from induced sputum smear microscopy to detect acid-fast bacilli and/or cartridge-based nucleic acid amplification test to exclude active tuberculosis. Diabetes was further excluded by the glycosylated hemoglobin levels in all patients.

The venous blood samples were collected to estimate serum creatinine level. Serum creatinine was measured by Jaffé method using reagents picric acid solution and sodium hydroxide solution along with creatinine standard 2 mg/dL.

A random single void morning urine sample was collected from the eligible participant in an acid-washed plastic container and centrifuged at 4500 rpm for 10 minutes. The top 15 mL of the supernatant was stored frozen at −20°C in aliquots without preservatives. In the laboratory, 2K98-02 MULTIGENT Microalbumin reagent kit was used to detect albumin and 07P99 ALINITY ‘C’ creatinine reagent kit was added to urine samples to measure serum creatinine as described by isotope dilution mass spectrometry traceable modification of MDRD study equation8 as below:

\[
\text{Glu}merular\;\text{filtration\;rate}\;\text{in}\;\text{mL/min/1.73m}^2 = 175 \times \text{serum creatinine}^{1.154 \times \text{age}^{0.203} \times 1.212}\;\text{(if\;patient\;is\;black) } \times 0.742\;\text{(if\;female)}.
\]

The normal GFR value considered was 90–120 mL/min/1.73 m². Quantitative data were collected and entered in MS Excel. Descriptive analysis of the data variable was done using proportion and mean with standard deviation. Data were analyzed and statistically evaluated by the SPSS software, version 20 (Chicago, IL, USA). The p-value below 0.05 was considered to be statistically significant. “Spearman’s correlation coefficient” was utilized to detect the correlation between the two quantitative variables.

**RESULTS**

Fifty-two patients having silicosis fulfilled the eligibility criteria of this study and all of them were subjected to assessment for early renal disease by measuring UACR and GFR. There were 50 (96.2%) male and two (3.8%) female patients. The age range of patients was 32–73 years with a mean age of 46.69 ± 12.95 years. The minimum duration of exposure to silica dust was 4 years while the maximum was 30 years (mean duration 13.58 ± 6.85 years). The most common dust exposure was observed in stone cutters (40.3%), followed by stone grinding (19.2%), stone drilling (13.4%), and others.

The mean GFR of study patients was 81.94 ± 22.09 mL/min/1.73 m² (ranging between 31.21 and 125.18). Only four (7%) patients had GFR values <60 mL/min/1.73 m².

Twenty-eight out of 52 (53.84%) patients had albuminuria. The mean UACR was 101.88 ± 128.99 mg/gm (range 8.4–470 mg/gm) (Table 1). We could identify isolated proteinuria in only six (11.5%) patients while 22 (42.3%) patients presented with microalbuminuria. Four out of 52 patients (7.69%) have microalbuminuria with decreased GFR <60 mL/min/1.73 m². Six patients with isolated proteinuria were observed to have GFR values not below 60 mL/min/1.73 m² but well below 90 mL/min/1.73 m² which is not within the normal range and considered abnormal.

The average length of occupational exposure to silica dust was 13.58 ± 6.85 years. Twenty out of 22 patients with microalbuminuria had chronic silicosis while all six patients with isolated proteinuria had chronic silicosis according to the duration of exposure to silica dust. These findings were statistically significant (p-value < 0.01). Four patients were observed to have a GFR value <60 mL/min/1.73 m² in this study and among them two had chronic silicosis while the other two had accelerated silicosis (p-value < 0.01) (Tables 2 and 3).

We observed direct correlation between working duration and UACR (r value = 0.615).

### Table 1: UACR and GFR values among study subjects having silicosis

<table>
<thead>
<tr>
<th>Duration of exposure</th>
<th>GFR (mL/min/1.73 m²)</th>
<th>UACR (mg/gm)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>60–89</td>
<td>0–30</td>
<td>&gt;300</td>
</tr>
<tr>
<td>Accelerate</td>
<td>30–59</td>
<td>0–30</td>
<td>&gt;300</td>
</tr>
<tr>
<td>Chronic</td>
<td>15–29</td>
<td>0–30</td>
<td>&gt;300</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
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</tbody>
</table>

*p-value < 0.01*

### Table 2: UACR values in silicosis patients having a different duration of exposure

<table>
<thead>
<tr>
<th>Duration of exposure</th>
<th>UACR (mg/gm)</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>Acute</td>
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<td>0</td>
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<tr>
<td>Accelerate</td>
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<td>2</td>
</tr>
<tr>
<td>Chronic</td>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>22</td>
</tr>
</tbody>
</table>

*p-value < 0.01*

### Table 3: GFR values in silicosis patients having a different duration of exposure

<table>
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<tr>
<th>Duration of exposure</th>
<th>GFR (mL/min/1.73 m²)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
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<tr>
<td>Accelerate</td>
<td>60–89</td>
<td>0</td>
</tr>
<tr>
<td>Chronic</td>
<td>30–59</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
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</tbody>
</table>

*p-value < 0.01*
Asymptomatic Renal Function Abnormalities in Patients having Silicosis

for p-value < 0.001) but inverse correlation between duration of exposure and GFR (r value = -0.545 for p-value < 0.001).

**Discussion**

An association of occupational exposure to silica dust with chronic nephropathy has been suspected for many years. Dose-related nephropathy induced by silica has been demonstrated in animal studies that can be primarily tubular and associated with interstitial inflammatory reactions and subsequent fibrosis. Several cases of nephropathy in workers exposed to silica have been reported.

Isolated proteinuria was detected in only six (11.5%) patients while 22 (42.3%) patients presented with microalbuminuria. A study done by Emilia et al., identified 24% of patients with isolated proteinuria and 34% with microalbuminuria in gold mine workers while 12% of patients with isolated proteinuria and 19% of patients with microalbuminuria in coal mine workers. When comparing with this study, we observed a smaller number of patients with isolated proteinuria but a high number of patients with microalbuminuria. This might be due to differences in sample size and nature of dust exposure. Studies done by Ng et al., Boujemaa et al., El-Safty et al., and Ibrahim et al., also observed proteinuria with a significant rise in urinary albumin among the workers exposed to silica dust, and these findings are also supported by our study results.

Renal manifestations determined by silica are represented by both glomerular and tubule interstitial nephropathies. They are achieved by deposits of immune complexes at the glomerular level or by deposits of crystalline matter at the interstitial level. Another renal manifestation of silica-induced toxicity is interstitial nephritis caused by a direct toxic mechanism via deposits of crystalline matter at the interstitial level. The accumulation of silica particles at the level of the kidney determines a fibrotic process similar to the one seen in pulmonary disease. Patients with short-term exposure to silica may present with subclinical symptoms of renal dysfunction. Prolonged exposure to the silica dust is accompanied by CKD which may further complicate into end-stage renal disease. Acute renal failure was also noticed after massive exposure to silica dust. A polyanionic sialoprotein coating covers the glomerular capillary epithelial cells that possibly repel polyanionic proteins and prevent passage of serum proteins into the urine. The deposits of immune complexes at the glomerular level cause damage of this sialoprotein coat and subsequently results into glomerular dysfunctions.

The results of the present study showed a positive correlation between the duration of exposure to silica dust with raised levels of the UACR and this was highly significant statistically. These results were also supported by other studies done by Emilia et al., Ng et al., Rapiti et al., Calvert et al., etc.

We also observed patients with asymptomatic urinary anomalies having GFR higher than 60 mL/min/1.73 m². Thus, 18 out of 22 patients with microalbuminuria had GFR higher than 60 mL/min/1.73 m² but below 90 mL/min/1.73 m². All six patients having isolated proteinuria had GFR levels of more than 60 mL/min/1.73 m² but were still not in the normal range. As we know that GFR in the range of 90–120 mL/min/1.73 m² reflects normal renal functions and reduced GFR with proteinuria supports subclinical renal dysfunction that in the future may progress to life-threatening conditions, that is, CKD. A similar study from Egypt also demonstrated subclinical nephrotoxicity following occupational exposure to silica dust among workers in the pottery industry. They also observed an increased level of "urinary total protein, microalbumin, activities of alkaline phosphatase, γ-glutamyl transferase, lactate dehydrogenase, kidney injury molecule-1, and silicon" with a positive and significant correlation with duration of work among exposed workers.

We observed an inverse correlation between the duration of silica dust exposure and GFR, (r value = -0.545 for p-value = 0.001) in this study. A study done by Emilia et al., also showed an inverted correlation between the working duration and GFR in gold mine workers (r = -0.346 for p = 0.0004) and in coal mine workers (GFR: r = -0.220 for p = 0.02). The presence of a significant relationship between duration of work exposure and GFR has not been extensively assessed in reported literature among stone mine workers. We also observed that GFR significantly reduces with increasing duration of exposure to silica dust.

The present study has a few limitations. According to the definition of CKD, an alteration of the renal function or the presence of markers of renal dysfunction or lesion for a period of 3 months is necessary; this type of time-bound assessment for CKD could not be done. Despite this limitation, the presence of asymptomatic urinary anomalies at one point in time in the present study shows the significance of their identification in patients having silicosis. Early detection and close monitoring of such patients would definitely detect CKD early and this in turn substantially reduces morbidity and mortality. The other limitation of this study was not using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for estimating the GFR which is now the recommended standard. Although UACR and GFR are usually simple and noninvasive methods for assessing renal functions, these biomarkers do not indicate definite renal injury, but rather serve as surrogates for renal injury. Blood biomarkers and renal biopsies could not be done for more accurate assessments of silica-induced nephropathy in this study.

In conclusion, despite a few limitations, this study highlights the potential subclinical nephrotoxic effects induced by inhaled silica dust in occupational settings. The significantly raised levels of UACR and GFR among silica dust-exposed workers suggest the risk of CKD with the possibility of subsequent end-stage renal disease depending upon the duration and intensity of exposure. Further large, multicentric studies in this direction will address this issue more accurately among silicosis patients who already struggle from poor lung functions.

This will definitely reduce additional suffering by early interventions in such patients. In summary, we have attempted a simple, cost-effective screening strategy for early detection of renal dysfunction in a country like India for the very first time where primary health care services are suboptimally resourced and silicosis largely remains underdiagnosed and underreported.

**References**

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Editor-in-Chief, JAPI
Modified Nutrition Risk in Critically Ill Score, A Prognostic Marker of Morbidity and Mortality in Mechanically Ventilated Patients: A Prospective Observational Study

Marius Dsouza1*, Vidya S Nagar2, Rahul Radhakrishnan3, Kalpita Suresh Pai4, Vinay Kumar Ireddy5

Received: 02 May 2022; Revised: 02, July 2022; Accepted: 21 July 2022

ABSTRACT

Background: Critically ill (CI) patients, especially those requiring mechanical ventilation (MV) are at a higher risk of malnutrition, which in turn is associated with increased hospitalization and excess mortality. The modified Nutrition Risk in Critically Ill (mNUTRIC) score is the first nutritional risk assessment tool to identify CI patients at nutritional risk and those that will benefit from aggressive nutritional intervention, as available literature suggests that, relative to patients with low nutritional risk, those with high nutritional risk benefit from early nutritional intervention, leading to enhanced clinical outcomes, including reduced risk of nosocomial infection, morbidity, and mortality.7,8 Introduced in 2011, the Nutrition Risk in Critically Ill (NUTRIC) score is the first nutritional risk assessment tool to identify high nutritional risk patients admitted to ICUs. It comprises six parameters, including age, number of comorbidities, APACHE II score, SOFA score, number of days between hospital and ICU admission, and blood interleukin-6 (IL-6) levels.7 This scoring system helps in classifying the CI patients at either low or high nutritional risk and simultaneously identifying the CI patients that are most likely to respond to aggressive nutritional therapy. Subsequently, in 2015, IL-6 was excluded from the NUTRIC score and a second validated version termed as mNUTRIC score was introduced.9 Additionally, a study demonstrated no significant difference between the two scoring systems in predicting 28-day mortality.10 However, the mNUTRIC score has not been adequately validated with respect to CI Indian patients requiring MV. An initial study from southern India suggested that the mNUTRIC score has 41.5% sensitivity and 73.8% specificity in predicting mortality in CI mechanically ventilated patients.11 Another recent study from central India reported that the mNUTRIC score has a sensitivity and specificity of 97.2 and 74.0%, respectively, in predicting mortality in CI patients.12 Considering the huge burden of CI Indian patients requiring MV, further validation of the mNUTRIC score would help in aggressive management of CI patients at high nutritional risk. Thus, the present study was planned to evaluate the mNUTRIC score as a prognostic marker of morbidity and mortality in CI mechanically ventilated patients.

INTRODUCTION

With the advancement in intensive care, more patients are able to survive critical illnesses. However, this has resulted in a large proportion of patients with extended reliance on MV and other supportive therapies.1 Annually, around 20 million patients require admission in ICUs and MV.2 Majority of these patients require short-term MV, while a minority require long-term MV.1 The prevalence of MV use ranges between 6.6 and 23 per 100,000.2

In CI patients, malnutrition is immensely prevalent, with expeditious muscle loss observed in the initial stages of the disease, and is more usual in those with multiple organ dysfunction.3 Indeed, sarcopenia is exceedingly common in patients requiring MV and is reported in 56% of patients admitted to ICUs.4 Malnutrition has been reported to be associated with increased nosocomial infections, prolonged MV, extended hospitalization, frequent rehospitalization, reduced quality of life, and greater mortality.5,6 Additionally, muscle weakness and reduced functional capacity can affect the survivors for up to 5 years.2 Thus, it is critical to identify MV patients at nutritional risk and those that will benefit from aggressive nutritional intervention, as available literature suggests that, relative to patients with low nutritional risk, those with high nutritional risk benefit from early nutritional intervention, leading to enhanced clinical outcomes, including reduced risk of nosocomial infection, morbidity, and mortality.7,8

Materials and Methods

This prospective, observational study was performed, over a period of 18 months (January 2018 to June 2019), in the ICU of the medicine department of a tertiary care hospital located in western India. All the patients aged above 12 years, admitted in ICU, and requiring MV for >48 hours were included in the study. While, those aged 12 years or less, who died within 48 hours of ICU admission, and required MV for <48 hours were excluded. The study began after the approval of the study protocol by the...
Institutional Ethics Committee and obtaining written informed consent from the relatives.

Of 356 consecutively ICU admitted patients, 250 were enrolled. Following ICU admission, a detailed examination of all the patients was performed and findings were recorded. The collected data included demographics, vital signs (pulse, blood pressure, and respiratory rate), Glasgow Coma Scale (GCS), laboratory investigations (hemoglobin, hematocrit, platelet count, white blood count, serum bilirubin, albumin, creatinine, urea, potassium, sodium, and arterial blood gases), indication for intubation, and diagnosis. Details related to comorbidities, including hypertension, diabetes, chronic renal failure (CRF), coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), liver disorders, and neurological disorders, were obtained from the patient, their medical records, or the accompanying relatives. Data collected were used to calculate APACHE II and SOFA scores. Variables used to calculate the mNUTRIC score (without using IL-6) included age, number of comorbidities, days from hospital to ICU stay, APACHE II score, and SOFA score. The nine-point mNUTRIC score was associated with worse clinical outcomes.

Outcomes including death. In their original study, Heyland et al. reported that an increase in the score leads to a proportional increase in mortality and duration of MV. In the present study, the original mNUTRIC score, a cutoff value of ≥5 revealed that more than a quarter of patients had a high mNUTRIC score (28.4%) and the mortality rate was 35.6% (Table 1). The overall mean APACHE II, SOFA, and mNUTRIC scores were 13.53 ± 7.6, 5.73 ± 3.39, and 2.57 ± 2.04, respectively. Additionally, the mean ICU stay, days on MV, and MV-free days were 12.62 ± 6.24, 6.74 ± 5.01, and 5.88 ± 1.74 days, respectively.

Comparison of comorbidities among survivors and non-survivors revealed that significantly higher proportion of non-survivors had hypertension (56.2 vs 39.8%; p-value = 0.013), diabetes (34.8 vs 18.6%; p-value = 0.004), CAD (21.3 vs 10.6%; value = 0.020), and liver disorders (21.3 vs 10.6%; p-value = 0.020) (Table 2).

Comparison of various characteristics among non-survivors and survivors suggested that mean age (54.52 ± 16.17 vs 48.81 ± 18.15 years; p-value = 0.026), pulse rate (101.73 ± 17.48 vs 94.97 ± 15.89 per min; p-value = 0.002), and respiratory rate (22.48 ± 5.45 vs 20.98 ± 4.22 per min; p-value = 0.039) were significantly higher among the non-survivors than the survivors. The mean GCS score was significantly higher among the survivors than the non-survivors (12.11 ± 3.35 vs 10.34 ± 4.32; p-value = 0.002). A significantly greater proportion of non-survivors had serum albumin <3 gm/dL (38.2 vs 10.6%; p-value < 0.0001) and high mNUTRIC score (57.3 vs 12.4%; p-value < 0.0001). Likewise, the mean APACHE II score (18.88 ± 6.79 vs 10.57 ± 6.31; p-value < 0.0001), SOFA score (7.81 ± 3.14 vs 4.58 ± 2.96; p-value < 0.0001), ARDS (14.1 ± 1.64 vs 1.71 ± 1.7; p-value < 0.0001), and mNUTRIC score (4.11 ± 1.64 vs 1.71 ± 1.7; p-value < 0.0001) were significantly higher among the non-survivors than the survivors (Table 3).

On ROC curve analysis, a cutoff value of >2 predicted mortality (AUC: 0.83; 95% confidence interval: 0.778–0.874) with a sensitivity, specificity, PPV, and NPV of 80.9, 76.4, 65.5, and 87.9%, respectively (Fig. 1).

### DISCUSSION

The CI mechanically ventilated patients remain at high nutritional risk. The poor nutritional status is linked to the nature of the background disease of the patient in the ICU that may affect the outcomes regardless of the nutritional status. In this group of patients, high nutritional risk is associated with adverse outcomes including death. In their original NUTRIC score, Heyland et al. reported that an increase in the score leads to a proportional increase in mortality and duration of MV. In the present study, based on the original mNUTRIC score, a cutoff value of ≥5 revealed that more than a quarter of patients had high nutritional risk. Additionally, more than a third of patients succumbed to the illness. Analysis revealed that a significantly greater proportion of non-survivors had a high mNUTRIC score.

### Table 1: Baseline characteristics

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<th>Characteristics</th>
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<tr>
<td>Pulmonary edema</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>COPD</td>
<td>21</td>
<td>8.4</td>
</tr>
<tr>
<td>CRF</td>
<td>14</td>
<td>5.6</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>12</td>
<td>4.8</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>11</td>
<td>4.4</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>9</td>
<td>3.6</td>
</tr>
<tr>
<td>Others</td>
<td>73</td>
<td>29.2</td>
</tr>
<tr>
<td>Indications of intubation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>116</td>
<td>46.4</td>
</tr>
<tr>
<td>Neurological deterioration</td>
<td>99</td>
<td>39.6</td>
</tr>
<tr>
<td>Shock</td>
<td>35</td>
<td>14</td>
</tr>
<tr>
<td>mNUTRIC score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (0–4)</td>
<td>179</td>
<td>71.6</td>
</tr>
<tr>
<td>High (5–9)</td>
<td>71</td>
<td>28.4</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survivors</td>
<td>161</td>
<td>64.4</td>
</tr>
<tr>
<td>Non-survivors</td>
<td>89</td>
<td>35.6</td>
</tr>
</tbody>
</table>

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; ARDS, acute respiratory distress syndrome; GBs, Guillain–Barré syndrome; TBM, tubercular meningitis; mNUTRIC, Modified Nutrition Risk in Critically Ill
Thus, a high mNUTRIC score suggests higher mortality among CI mechanically ventilated patients.

High nutritional risk is associated with poor prognosis, but patients with low nutritional risk do not always have better outcomes, due to several other illness-related factors. It is known that CI patients are at a risk or may have malnutrition during hospitalization mainly as a result of underlying disease severity. In these patients, malnutrition is mainly due to the stress catabolism that is linked to the degree of inflammation and disease severity. It is further reported that disease severity and nutritional status separately and in combination can predict mortality. Thus, highlighting the impact of disease severity on the outcome. In the present study, non-survivors had significantly greater disease severity, assessed with APACHE II, SOFA, and mNUTRIC scores. It was further observed that a significantly greater proportion of non-survivors had comorbidities including hypertension, diabetes, CAD, and liver disorders. These findings suggest that the severity of background disease and comorbidities adversely influence the nutritional status and the outcome.

The findings of the present study suggest that a high mNUTRIC score was associated with adverse outcomes. A cutoff of ≥2 predicted mortality with a higher sensitivity of 80.9%, and a specificity of 76.4%. Kalaiselvan et al. reported that a cutoff of ≥5 predicted mortality with a sensitivity and specificity of 41.5 and 73.8%, respectively. Wang et al. observed that a cutoff value of >4 had a sensitivity of 61.48% and a specificity of 78.81% in predicting mortality, which is similar to that reported by de Vries et al. The lower cutoff value of >2, in the present study, resulted in higher sensitivity and specificity in predicting mortality. Additionally, the AUC of 0.83 was greater than that reported by the initial validation study performed by Heyland et al. (AUC: 0.783), and a subsequent study by Mukhopadhyay et al. validating the mNUTRIC score (AUC 0.71). The high sensitivity and specificity suggest that the CI mechanically ventilated patients had malnutrition. Additionally, the lower cutoff of >2 observed in the present study could be attributed to the disease severity and the fact that patients were on MV.

The present study had certain limitations. First, we evaluated only the ICU-admitted patients requiring MV. Thus, the findings cannot be extrapolated to other ICU patients. Second, we did not assess the effect of nutritional intervention. Hence, the association between nutritional intervention and mortality could not be ascertained. Third, the absence of IL-6 data in all the patients did not allow us to use the NUTRIC scoring system.

In the present study, we observed that the mNUTRIC score can be easily implemented among CI patients. However, whether clinical outcomes would be improved by its use in the Indian critical care setup remains to be determined. Thus, further prospective studies evaluating the effect of implementing the mNUTRIC score on nutrition and outcomes compared with standard care in CI mechanically ventilated patients are required.

Table 2: Comparison of comorbidities among survivors and non-survivors

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Survivors (N = 161)</th>
<th>Non-survivors (N = 89)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension, N (%)</td>
<td>64 (39.8)</td>
<td>50 (56.2)</td>
<td>0.013</td>
</tr>
<tr>
<td>Diabetes, N (%)</td>
<td>30 (18.6)</td>
<td>31 (34.8)</td>
<td>0.004</td>
</tr>
<tr>
<td>CAD, N (%)</td>
<td>17 (10.6)</td>
<td>19 (21.3)</td>
<td>0.020</td>
</tr>
<tr>
<td>COPD, N (%)</td>
<td>20 (12.4)</td>
<td>8 (8.9)</td>
<td>0.410</td>
</tr>
<tr>
<td>CRF, N (%)</td>
<td>11 (6.8)</td>
<td>10 (11.2)</td>
<td>0.229</td>
</tr>
<tr>
<td>Liver disorders, N (%)</td>
<td>7 (4.3)</td>
<td>11 (12.4)</td>
<td>0.019</td>
</tr>
<tr>
<td>Neurological disorders, N (%)</td>
<td>13 (8.1)</td>
<td>2 (2.2)</td>
<td>0.093</td>
</tr>
</tbody>
</table>

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure

Table 3: Comparison of survivors and non-survivors

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Survivors (N = 161)</th>
<th>Non-survivors (N = 89)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean ± SD</td>
<td>48.81 ± 18.15</td>
<td>54.52 ± 16.17</td>
<td>0.026</td>
</tr>
<tr>
<td>Days to ICU, mean ± SD</td>
<td>0.65 ± 2</td>
<td>1.1 ± 2.84</td>
<td>0.056</td>
</tr>
<tr>
<td>Vital parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse rate, per min, mean ± SD</td>
<td>94.97 ± 15.89</td>
<td>101.73 ± 17.48</td>
<td>0.002</td>
</tr>
<tr>
<td>SBP, mm Hg, mean ± SD</td>
<td>118.94 ± 23.06</td>
<td>119.01 ± 30.3</td>
<td>0.492</td>
</tr>
<tr>
<td>DBP, mm Hg, mean ± SD</td>
<td>72.48 ± 13.98</td>
<td>71.91 ± 17.57</td>
<td>0.613</td>
</tr>
<tr>
<td>MAP, mm Hg, mean ± SD</td>
<td>87.97 ± 16.47</td>
<td>87.61 ± 21.51</td>
<td>0.477</td>
</tr>
<tr>
<td>RR, per min, mean ± SD</td>
<td>20.98 ± 4.22</td>
<td>22.48 ± 5.45</td>
<td>0.039</td>
</tr>
<tr>
<td>GCS score, mean ± SD</td>
<td>12.11 ± 3.35</td>
<td>10.34 ± 4.32</td>
<td>0.002</td>
</tr>
<tr>
<td>Laboratory parameter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum albumin, (&lt;3 gm/dL), N (%)</td>
<td>17 (10.6)</td>
<td>34 (38.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Severity of disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APACHE II score, mean ± SD</td>
<td>10.57 ± 6.31</td>
<td>18.88 ± 6.79</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SOFA score, mean ± SD</td>
<td>4.58 ± 2.96</td>
<td>7.81 ± 3.14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>mNUTRIC score, mean ± SD</td>
<td>1.71 ± 1.7</td>
<td>4.11 ± 1.64</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>High mNUTRIC score, N (%)</td>
<td>20 (12.4)</td>
<td>51 (57.3)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

ICU, intensive care unit; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; RR, respiratory rate; GCS, glasgow Coma; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; mNUTRIC, modified nutrition risk in critically ill
mNUTRIC Score in Mechanically Ventilated Patients

Fig. 1: ROC analysis of mNUTRIC scores in predicting mortality

CONCLUSION

The mNUTRIC score of >2 suggested high mortality among CI patients requiring MV. More than a quarter of patients had high nutritional risk and these patients had a significantly severe illness at admission. Further prospective studies are to validate the mNUTRIC scoring system with respective CI Indian patients requiring MV.

ACKNOWLEDGMENT

The authors would like to thank Dr. Vikas S Sharma (MD), Principal Consultant, Maverick Medicorum* (India) for medical writing assistance in the preparation of this article.

REFERENCES


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Hon. General Secretary
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Prevalence of Antineutrophil Cytoplasmic Antibodies and Antinuclear Antibodies in Patients with Pulmonary Tuberculosis: A Tertiary Care Center Experience from North India

Yogesh Chander1, Nupoor Acharya2, GSRSNK Naidu3, Manish Rathi4, Ranjana Minz5, Sanjay Jain6, Digambar Behera7, Aman Sharma8*

Received: 23 August 2020; Revised: 17 June 2022; Accepted: 21 July 2022

ABSTRACT

Background: Tuberculosis (TB) can have manifestations closely mimicking autoimmune diseases. The prevalence of autoantibodies in TB varies among different populations.

Objectives: To study the prevalence of anti-neutrophilic cytoplasmic antibodies (ANCA) and antinuclear antibodies (ANA) in pulmonary tuberculosis (PTB).

Methods: This was a cross-sectional, observational study. Subjects with microbiologically confirmed PTB, either via smear or culture positivity on sputum or bronchoalveolar lavage (BAL) fluid, or positive rapid diagnostic tests were included. ANCA against proteinase-3 (PR3), myeloperoxidase (MPO), lactoferrin, and elastase were tested using an enzyme-linked immunosorbent assay (ELISA). ANA was detected using indirect immunofluorescence (IIF).

Results: Eighty-nine subjects with a median (interquartile range [IQR]) age of 28 (20–46) years, 67.4% males, were recruited. Eighty-one subjects had microbiological confirmation on sputum examination, and eight required examination of BAL fluid. Sera were drawn from 62 treatment-naïve subjects, the rest (27) were on antitubercular therapy (ATT). Eighty-six (96.6%) subjects tested positive for anti-elastase antibody, seven of which were also positive for anti-PR3. None were positive for anti-MPO and anti-lactoferrin. Six (6.7%) subjects tested positive for ANA. None of the subjects had features of underlying connective tissue disease or vasculitis.

Conclusion: PTB patients showed a high prevalence of anti-elastase and a low prevalence of ANA and anti-PR3 antibodies. ANCA positivity should be interpreted with caution in TB endemic areas. The role of anti-elastase antibodies in differentiating TB from ANCA-associated vasculitides (AAV) needs further research.

Journal of the Association of Physicians of India (2022); 70(11):62–64.

KEY MESSAGES

- It is important for clinicians to remember that anti-PR3 antibody positivity can be seen in up to 7.8% of the patients with microbiologically proven PTB and this can have a very important clinical implication.
- In PTB, anti-elastase positivity is very high (96.6%), ANA positivity is low, and anti-MPO and anti-lactoferrin antibodies are not detected.

INTRODUCTION

Pulmonary tuberculosis accounts for the majority of tubercular manifestations. In India, the annual incidence of TB is around 28 lakh cases/year, and the disease burden remains very high. PTB has many features that closely mimic AAV and sometimes systemic lupus erythematosus. ANCA are used to make a diagnosis of AAV in most cases. The antigens important in AAV are MPO and PR3, seen in granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis. Some studies have shown that ANCA is positive in a significant number of TB patients, although a few studies have refuted the fact. Caution needs to be exercised while interpreting ANCA results, especially in TB endemic areas. Mycobacteria are also known to induce ANA. The prevalence of ANA in PTB varies from 6.1 to 46.7%. In a previous Indian study of 70 patients with PTB, the prevalence of ANCA positivity by IIF was reported to be 30%. ELISA for PR3 and MPO was carried out in only those patients who had ANCA positivity by IIF. In 2017, the revised international consensus on ANCA testing for GPA and MPA proposed that high-quality immunoassays can be used as the primary screening method for patients suspected of having the ANCA-associated vasculitides GPA and MPA without the categorical need for IIF since these assays had higher sensitivity than IIF. Thus we planned to study the prevalence of ANCA (PR3 and MPO) by ELISA as per the latest international consensus along with lactoferrin, and elastase (by ELISA) and ANA (IIF) in microbiologically confirmed PTB cases in the North Indian population.

METHODS

This was a cross-sectional observational study carried out between July 2017 and December 2018. Subjects visiting the outpatient department, revised national tuberculosis program clinic, or admitted under internal medicine were screened for PTB. The subjects meeting the following inclusion criteria were enrolled—age >12 years, diagnosed with PTB, and willing to give consent. The diagnosis of PTB was made by either positive sputum smear examination and/or culture, BAL fluid cytology, or WHO-approved rapid diagnostic (WRD) tests on sputum or BAL fluid. The WRD tests included GeneXpert, cartridge-based nucleic acid amplification test, and other rapid molecular assays. Subjects with coinfection with human immunodeficiency virus (HIV), hepatitis B or C, or suffering from any other chronic inflammatory diseases were excluded from the study. The study was approved by the institutional ethics committee and informed consent was obtained from all participants.
Detection of Autoantibodies
Blood samples were collected from the patients in plain tubes. Sera were separated and stored at −20°C. Auto-antibodies were tested against MPO, PR-3, lactoferrin, and elastase using ELISA. Anti-MPO and anti-PR3 were tested using commercially available ELISA kits (DiaMetrA S.r.l., Italy) and the cut-offs used were 20 AU/mL for both. For anti-elastase and anti-lactoferrin antibodies, ELISA kits (Orgentec Diagnostika, Germany) were used with cut-offs of 10 U/mL for both. The tests were performed as per the manufacturer’s instructions. ANA was tested by IIF using Hep-2 cell lines (Immco Diagnostics, USA) at 1:40 dilutions (as per departmental protocol). Sera that tested positive for ANA were further tested using line immunoassay.

Outcomes
The primary outcomes of the study were to assess the prevalence of ANCA and ANA in subjects with PTB. The secondary outcomes were to study the clinical characteristics of the subjects who tested positive for ANCA and ANA.

Statistical Analysis
Data were analyzed using SPSS version 22.0 software. Descriptive statistics were used for continuous variables. The normality of continuous data was checked using Kolmogorov–Smirnov z test. Data are presented as mean ± standard deviation or median (IQR) as per the distribution.

Results
Ninety-three subjects were screened for PTB, 89 subjects met the inclusion criteria and were enrolled in the study. The median (IQR) age of the study group was 28 (20–46) years, and 67.4% were males. The diagnosis of PTB was established by sputum examination and BAL in 81 and 8 subjects, respectively. Seventy-nine subjects had sputum smear positive for acid-fast bacilli (AFB), and two had sputum GeneXpert positive. Five and three subjects, respectively, had AFB and GeneXpert/WRDs positive in BAL fluid. The most common symptoms were cough with expectoration, seen in all but one subject (98.9%), followed by fever in 70 (78.7%) subjects. The common radiological features were consolidation (60.6%), reticulonodular opacities (49.4%), and cavities (43.8%). Diabetes mellitus was the most common comorbidity seen in 22 (24.7%) subjects. Samples were withdrawn from 69 subjects before the initiation of ATT, while the rest were on ATT for variable periods ranging from <2 weeks to >6 months. Eight subjects also had a prior history of TB. The demographic, clinical, and radiological characteristics of the study group are described in Table 1.

Prevalence of ANCA and ANA
Anti-PR3 antibodies were found positive in seven (7.8%) patients. Anti-elastase antibodies were found to be positive in 86 (96.62%) patients including all seven subjects who were also positive for anti-PR3. No samples were found to be positive for anti-MPO and anti-lactoferrin antibodies. Sera from six subjects tested positive for ANA by IIF. Two of them tested positive for anti-SS-A and anti-U1-RNP antibodies on line blot assay, rest four did not have any specific ANA. All of these six subjects also tested positive for anti-elastase antibodies. None of the subjects tested positive for both ANA and anti-PR3 antibody. The clinical and serological characteristics of the subjects who tested positive for anti-PR3 and ANA, respectively, are described in Table 2.

Among the subjects who tested positive for anti-PR3, one developed transient subnephrotic range proteinuria, while another one had pulmonary embolism. None of the subjects who tested positive for anti-PR3 or ANA had any clinical features suggestive of systemic vasculitis or connective tissue disease.

Discussion
Anti-neutrophilic cytoplasmic antibodies are important serological markers used as a screeningtest for AAV.3,4 The preferred screening method is high-quality antigen-specific assays for anti-MPO and anti-PR3 antibodies.5 Apart from MPO and PR3, the other neutrophilic antigens targeted by ANCs are lactoferrin, elastase, cathepsin-G, bacterial-permeability increasing protein, lysozyme, defensins, and catalase.12,13 ANCs have also been reported in patients with infective endocarditis, TB, malaria, chronic hepatitis, and other chronic infections.8,14–16 Similarly, ANA has also been reported positive in chronic infections, and mycobacterial infections.11,15,16 The prevalence of ANCA and ANA in the healthy Indian population has been reported as 3.2 and 2.1%, respectively.

The majority of our subjects (96%) tested positive for anti-elastase, 7.8% of them had dual positivity for anti-elastase and anti-PR3. ANA positivity was seen in 6.7% of subjects. In a previous study involving Indian subjects with PTB, ANCA positivity (by IIF method) was seen in 30%, while ANA positivity was seen in 24.3%. Anti-MPO antibodies were detected in 47.6%, anti-PR3 antibodies in 28.6%, and anti-lactoferrin antibodies in 19.1% by ELISA in subjects having ANCA positivity by IIF.7 There have been some racial differences of ANCA positivity in different populations. In a Mexican study, 20 (44.4%) subjects with TB tested positive for ANCA.8 Fifteen and three of

Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Age in years, median (IQR)</th>
<th>Males/females</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 (20–46)</td>
<td>60 (67.4)/29 (32.6)</td>
</tr>
</tbody>
</table>

Clinical features

<table>
<thead>
<tr>
<th>Fever</th>
<th>Cough</th>
<th>Expectoration</th>
<th>Chest pain</th>
<th>Shortness of breath</th>
<th>Loss of weight</th>
<th>Hemoptyasis</th>
<th>Loss of appetite</th>
<th>Diabetes mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 (78.7)</td>
<td>88 (98.9)</td>
<td>88 (98.9)</td>
<td>12 (13.5)</td>
<td>22 (24.7)</td>
<td>12 (13.5)</td>
<td>22 (24.7)</td>
<td>39 (43.8)</td>
<td>22 (24.7)</td>
</tr>
</tbody>
</table>

Method of PTB diagnosis

<table>
<thead>
<tr>
<th>Sputum examination</th>
<th>81</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZN stain</td>
<td>79 (88.7)</td>
</tr>
<tr>
<td>GeneXpert</td>
<td>2 (2.24)</td>
</tr>
<tr>
<td>BAL fluid examination</td>
<td>8</td>
</tr>
<tr>
<td>ZN stain</td>
<td>5 (5.61)</td>
</tr>
<tr>
<td>GeneXpert</td>
<td>3 (3.37)</td>
</tr>
</tbody>
</table>

Duration of ATT

| ATT naive | 62 (69.6) |
| 1–15 days | 5 (5.6)  |
| 15–30 days| 4 (4.4)  |
| 1–2 months| 9 (10.1) |
| >2–4 months| 3 (3.4) |
| >4–6 months| 5 (5.6) |
| >6 months | 1 (1.1)  |
| Prior history of TB | 8 (8.9) |

Radiological features

| Cavity | 39 (43.8) |
| Consolidation | 54 (60.6) |
| Reticulonodular opacities | 44 (49.4) |
| Collapse | 3 (3.3) |
| Bronchiectasis | 7 (5.6) |
| Pleural effusion | 7 (7.9) |
| Hydropneumothorax | 1 (1.1) |
| Pneumothorax | 1 (1.1) |
| Mediastinal lymphadenopathy | 2 (2.2) |

Antibodies tested

| Anti-MPO | 0 |
| Anti-PR3 | 7 (7.8) |
| Anti-elastase | 86 (96.6) |
| Anti-lactoferrin | 0 |
| ANA | 6 (6.7) |

ANA, antinuclear antibody; ATT, antitubercular therapy; MPO, myeloperoxidase; PR3, proteinase-3; PTB, pulmonary tuberculosis; ZN, Ziehl–Neelsen
these patients had anti-PR3 and anti-MPO antibodies, respectively. In an Iranian study, ANCA positivity was compared between confirmed PTB cases and healthy controls. A significant difference was observed in the ANCA status between the case and controls with 28% of cases being ANCA positive.17 However, in both the Indian and the Iranian study, some of the healthy controls also tested positive for ANCA.21 In a study by Teixeira et al., 10% of subjects with TB tested positive for ANCA on IIF; only one was positive for anti-PR3 antibody, none for anti-MPO, on ELISA.18 Most of these patients also had coinfection with HIV or chronic hepatitis. These conditions were excluded from our study.

In our study, we did not find any subjects positive for anti-MPO or anti-lactoferrin as opposed to the above-mentioned studies. All but one of our subjects tested positive for anti-elastase antibodies. We could find only two published literature where anti-elastase antibodies were studied in TB. In one study, none of the sera tested positive for anti-elastase. In the other study, anti-elastase positivity was seen in TB cases and healthy controls (28 and 29, respectively). Our study did not have a healthy control group. Further research will be needed to study the prevalence of anti-elastase in the healthy Indian population as well. The difference in the results between our study and previous studies could be due to differences in ethnicity as none of the previous studies have assessed anti-elastase positivity in Indian TB patients.

One study also suggested the effect of ATT on de novo anti-MPO/PR3 formation in treated patients.19 Majority of the subjects in our study were treatment-naive, but six of the seven subjects who tested positive for anti-PR3 had received at least one dose of ATT. Since we did not have their baseline sera, it would be difficult to ascertain the effect of the drugs. But the overwhelming presence of anti-elastase positivity was seen in treatment-naive subjects as well. We could not find any literature describing the mechanism of anti-elastase antibody formation in TB.

Tuberculosis is known to induce ANA.11 The prevalence of positive ANA in a healthy Indian population was reported as 2.1% at 1:40 dilution. The prevalence of ANA in our study is less than what is reported in most of the previous studies.10,11 ATT, especially isoniazid, is also implicated in the induction of ANA in treated subjects.20 Half of our subjects who tested positive for ANA, were treatment-naive. None of them tested positive for anti-dsDNA antibody too. It would be fair to say that ANA positivity in our subjects is due to chronic infection and inflammatory state, and not ATT. None of the subjects who were autoantibody positive showed any special features to suggest an overlap with an autoimmune disease, except one subject, who had transient subnephrotic range proteinuria.

Our study had a few limitations. The study did not include healthy controls, so a comparison between cases and controls cannot be made. We did not test ANCA against other minor antigens.

### CONCLUSION

Our study highlights the fact that autoantibody positivity could be seen in confirmed PTB subjects without any coexisting autoimmune disease. It is therefore prudent to interpret the results of ANA and ANCA in such subjects with caution, especially in anti-PR3 positivity, since PTB may mimic GPA and vice versa. Other factors supporting the diagnosis of vasculitis or CTD must be taken into consideration before reaching any conclusion. Also, antigen-based assays might be more useful in distinguishing the type of ANCA positivity. Further research is needed to study the role of autoantibodies in the pathogenesis of TB and its effect on prognosis.

### REFERENCES

Validation of Spleen Shear Wave Elastography for the Screening of High-risk Varices in Patients with Compensated Advanced Chronic Liver Disease

Rathan Cyriac Joseph¹, Krishnadas Devadas², Jijo Varghese³, Tharun Tom Oommen⁴, Atul Hareendran⁵, Nibin Nahaz⁶, Vijay Narayanan⁷, Bony George⁸

Received: 17 November 2021; Accepted: 02 June 2022

ABSTRACT

Objectives: Total number of avoided endoscopies using Baveno VI criteria is relatively low. Spleen elastography is an attractive tool and when compared with liver stiffness, it better represents the dynamic changes occurring in portal hypertension. The aim of the study was to evaluate spleen shear wave elastography (SWE) in compensated advanced chronic liver disease (cACLD) patients for ruling out the presence of esophageal high-risk varices (HRV).

Methods: A total of 401 patients with cACLD were included in this cross-sectional study. The total sample was split into training set (200 patients) and validation set (201 patients). Spleen stiffness was measured with two-dimensional shear wave elastography (2D SWE). Esophageal HRV were defined as large varices (diameter >5 mm) or small varices with red color signs. In the training set, the receiver operating characteristic (ROC) curve was drawn and the area under the curve (AUC) of spleen SWE was assessed. A cutoff value was chosen (highest sensitivity and negative predictive value). In the validation set, the spleen SWE cutoff score and Baveno VI criteria were validated.

Results: The prevalence of HRV was 12% in the training set and 13% in the validation set. Spleen SWE had an AUC of 0.89 in ruling out the presence of high-risk esophageal varices (cutoff value of 48.7 kPa, sensitivity of 100%, and specificity of 53%). Validating spleen SWE ≤48.7 kPa in a different cohort of 201 cACLD patients, 55% of screening endoscopies could be avoided without missing any HRV, whereas using Baveno VI criteria only 30% of screening endoscopies could be spared.

Conclusion: Spleen SWE ≤48.7 kPa was able to identify cACLD patients who could safely avoid screening endoscopy with good accuracy. Spleen SWE could avoid an additional 25% of screening endoscopies compared to the Baveno VI criteria and no HRV were missed.

INTRODUCTION

The advent of liver elastography in the detection of fibrosis has enabled us to identify asymptomatic patients with severe fibrosis/early cirrhosis. These patients were defined in Baveno VI consensus as cACLD.¹ cACLD patients are at risk of developing clinically significant portal hypertension and gastroesophageal varices, which are important events in the evolution of cirrhosis.²,³ However, the probability of finding HRV, defined as medium-large varices or small varices with red color signs as per Baveno VI guidelines, is low (<10%) in cACLD. As a result, only a minority among these patients benefit from the strategy of universal screening endoscopy for esophageal varices.

Endoscopy is associated with complications related to the procedure and sedation, in addition to increased resource utilization.⁴ The Baveno VI consensus recommended that screening endoscopy could be safely avoided in patients with cACLD who have a liver stiffness measurement (LSM) of <20 kPa and a platelet count greater than 150 × 10⁹ cells/L since they have a very low risk of HRV.¹ Several studies have subsequently validated these criteria, which allow avoiding 10–30% of screening endoscopies with a very low risk of missing HRV.⁵–⁸ However, due to the low prevalence of HRV in these patients (<10%), up to 40% of endoscopies might still be performed unnecessarily.⁶ When compared with the gold standard for diagnosing HRV (i.e., endoscopy), the Baveno VI criteria are not 100% accurate and have some limitations. Thus there arises the need for more accurate noninvasive tests to identify patients with a low risk of having varices requiring treatment so that unnecessary screening endoscopies can be avoided.

In recent years, spleen stiffness measurement, using various elastographic techniques, has been proposed by several authors as an accurate diagnostic tool to predict the presence or absence of esophageal varices.⁹ Spleen stiffness may be a better measurement of the dynamic changes occurring in portal hypertension in comparison to liver stiffness. The aim of the study was to find new criteria using spleen SWE for screening of HRV in cACLD patients, maximizing the number of spared endoscopies, and externally validate spleen SWE criteria and the existing “Baveno VI criteria” in a different set of cACLD patients.

METHODS

This was a cross-sectional study, carried out in the Department of Medical Gastroenterology, Government Medical College, Thiruvananthapuram after obtaining approval from the Institutional Ethics Committee (HEC No. 05/22/2019/MCT).

A total of 401 consecutive patients with cACLD, of different etiologies, defined by LSM ≥10 kPa according to the Baveno VI recommendations were included in the study. Liver stiffness was determined with a FibroScan device (Echosens, Paris, France) after a fasting period of 2 hours. Patients with a history of decompensated liver disease (including variceal bleeding, ascites, hepatic encephalopathy, and Child B or C) were excluded. We also excluded patients with a previous history of varices, past/current treatment with propranolol, portal vein thrombosis, and hepatocellular carcinoma.

The total number of patients was divided into two: training set consisting of 200 patients and validation set of 201 patients.

Enrollment of patients was done after getting written informed consent. Baseline clinical and laboratory results were obtained at the time of enrollment. Spleen SWE was accomplished with real-time 2D SWE (Aixplorer®, Supersonic Imagine, France), using a convex transducer with a frequency

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range of 1–6 MHz. Spleen SWE examinations were performed through the intercostal space with the patient lying supine with the arms behind his head. In order to minimize breathing motion, the patient was instructed to inhale and hold his breath. The mean value of the three valid measurements expressed in kilopascals (kPa) was taken as the representative measurement.

Endoscopy was considered the gold standard for the diagnosis of esophageal varices. All patients underwent upper gastrointestinal endoscopy on the same day to document the grade and other characteristics of the varices. HRV were defined by size as follows: large varices (diameter >5 mm) or small varices with the presence of high-risk stigmata (red color signs).1

In the training set, ROC was drawn for spleen SWE. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were assessed. The cutoff value with the highest sensitivity and negative predictive value was determined. This spleen SWE cutoff value and the Baveno VI criteria were further validated in the validation set. We further determined the total number of endoscopies that could have been avoided and the number of HRV that would be missed, using the spleen SWE criteria and compared it with the Baveno VI criteria.

**RESULTS**

Baseline Clinical Characteristics of Patients

Table 1 illustrates the baseline characteristics of 200 patients in the training set. The mean age was 49.8 ± 10.6 years and 68% were males. The main etiology of cACLD was hepatitis B (29%), followed by hepatitis C (27%), alcoholic liver disease (25%), nonalcoholic steatohepatitis (NASH) (17.5%), and autoimmune hepatitis (1.5%). Fifty-six (28%) patients had esophageal varices, out of which 24 (12%) had HRV.

The baseline characteristics of 201 patients in the validation set are given in Table 2. The mean age was 48.4 years ± 10 and 59% were males. Hepatitis B (34%) was the most common etiology of cACLD in the validation set. This was followed by NASH (23%), alcoholic liver disease (22%), hepatitis C (16.4 %), and autoimmune hepatitis (3.9%). Sixty (30%) patients had esophageal varices and 26 (13%) had HRV.

Performance of Spleen SWE in Screening of HRV

Spleen SWE had an AUC of 0.89 in ruling out the presence of high-risk esophageal varices (Fig. 1). Spleen SWE cutoff value of 48.7 kPa yielded sensitivity of 100%, specificity of 53%, positive predictive value of 22%, and negative predictive value of 100%.

Validating Spleen SWE <48.7 kPa and the Baveno VI criteria

- Validating spleen SWE <48.7 kPa in a different cohort of 201 cACLD patients, 55% of screening endoscopies could have been avoided without missing any HRV, whereas using Baveno criteria, only 30% of screening endoscopies could be avoided.

**DISCUSSION**

The present study throws light on the commendable accuracy of spleen SWE in ruling out the presence of HRV in cACLD patients, with an AUC of 0.89. Spleen SWE with a cutoff score <48.7 kPa, identified 100% of cACLD patients who could safely avoid screening endoscopy. Furthermore, external validation showed that an additional 25% of screening endoscopies could be avoided compared to the existing Baveno VI criteria (55 vs 30%) without missing any HRV.

Splenomegaly, a key finding in portal hypertension, is due to vascular congestion, increased portal pressure, increased resistance to splenic vein outflow, and increased angiogenesis and fibrogenesis.10 In earlier phases, portal hypertension is proportional to liver fibrosis, however, in the later phases, hyperdynamic circulation and splanchnic vasodilatation become more important.2 Spleen stiffness represents the dynamic changes occurring in the portal circulation and directly reflects portal pressure.11 Considering the pivotal role of the spleen in splanchnic circulation and the course of portal hypertension, the measurement of spleen stiffness seems to be a more reasonable alternative to liver stiffness.

Spleen elastography can be assessed with transient elastography (TE), acoustic radiation force impulse (ARFI), 2D SWE, and magnetic resonance elastography. As TE is available in many clinical centers, it is the most widely used method for organ stiffness assessment. However, in patients with cirrhosis and portal hypertension, spleen stiffness measurements very often reach a level of 75 kPa or more, which is the maximum value reported by routine TE.12 Therefore, dedicated software.

![Fig. 1: AUROC of SWE and HRV](image)
and various calculation algorithms are needed in order to identify the correct range of SSM values. Point SWE using ARFI measures the shear wave velocity within a small fixed region of interest (ROI), monitored by real-time B-mode ultrasound. Real-time 2D SWE provides a color-coded elastogram and measures shear wave velocities in a user-adjustable ROI rather than in a single small point.

Real-time 2D SWE has some potential advantages over other elastographic techniques. Unlike traditional TE, 2D SWE can be implemented on a regular ultrasound machine and avoid masses and large vessels precisely. Furthermore, it has better applicability than TE, especially in patients with ascites and obesity. When compared with point SWE, 2D SWE has a larger detection field and can show the elastographic measures in a real-time color display. Even though the whole liver can be examined by magnetic resonance elastography, it is too expensive and time-consuming for routine clinical practice. One potential limitation in using 2D SWE for spleen elastography is the increased number of technical failures, especially when the spleen size is small.

The studies comparing liver elastography and spleen elastography have shown that spleen stiffness had a closer correlation with hepatic venous pressure gradient (HVPG), clinically significant portal hypertension, and presence and size of esophageal varices as compared to LSM. Previously, Colechia et al. in their study particularly observed a better diagnostic accuracy of SSM in diagnosing the presence of esophageal varices and clinically significant portal hypertension as compared to liver stiffness—spleen size-to-platelet ratio risk score and platelet-spleen ratio. Using an SSM cutoff value of 41.3 kPa, the negative likelihood ratio was 0.029, showing that the test accurately ruled out the presence of esophageal varices. In a study carried out by Fraquelli et al., spleen stiffness when used as a single test or in combination with liver stiffness, accurately ruled out the presence of esophageal varices (NPV of 100%) using a cutoff value <48 kPa. Singh et al. carried out a meta-analysis that evaluated the diagnostic accuracy of spleen stiffness in predicting esophageal varices and included a total of 12 studies including 1,497 patients with chronic liver disease. The analysis found a moderate accuracy of spleen stiffness in detecting the presence of clinically significant esophageal varices [area under the receiver operating characteristic (AUROC) of 0.80] with a sensitivity of 81% [95% confidence interval (CI), 76–86%] and specificity of 66% (95% CI, 61–69%), respectively. However, all these studies used either TE or ARFI for spleen stiffness measurement. Yet another meta-analysis of 16 studies published in 2016, which included two studies using 2D SWE, has shown that spleen stiffness was significantly superior to liver stiffness in predicting the presence of esophageal varices with an AUC of 0.88.

Only a limited number of studies have evaluated real-time 2D SWE of the spleen in the screening of varices in patients with chronic liver disease. Elkrief et al. reported the technical success rate of 2D SWE to be significantly higher than that of TE for spleen stiffness (97 vs 42%). However, by using 2D SWE, neither liver stiffness nor spleen stiffness differed between patients without and those with HVPG and for diagnosis of HVPG, spleen stiffness by SWE had only an AUC of 0.58 (0.44–0.71) with a cutoff of 32.3 kPa. This study had a sample size of only 79 patients, of which more than half were decompensated patients and hence underpowered to detect a difference. Similarly, in another study by Grgurević et al., spleen SWE at a cutoff of 30.3 kPa, had only 86.6% negative predictive value to exclude varices in a limited sample of 44 patients with compensated cirrhosis with a 35% prevalence of varices. In our study, patients with early cirrhosis with a lower expected prevalence of varices, who would actually be the target population for a noninvasive screening, were taken into consideration. The heterogeneity shown by different studies can be attributed to either differences in the techniques, patient selection, or geographical differences in patient population (e.g., Asian and European populations).

It is to be pointed out that this is one among the few studies that validated real-time 2D SWE of the spleen for screening of varices in cACLD patients. Moreover, this study has included more patients with nonviral etiologies for cACLD; whereas the majority of the previous studies have included fewer such patients.

Nevertheless, the limitation of this study needs to be highlighted. HVPG was not measured, which is considered the gold standard to measure portal hypertension in patients with cirrhosis. Hence, spleen SWE could not be compared with HVPG in this study.

**Conclusion**

Spleen SWE measured by real-time 2D SWE is a useful screening test for ruling out the presence of HRV in cACLD patients; a cutoff score of 48.7 kPa was able to identify those who could safely avoid screening endoscopy. Spleen SWE could avoid an additional 25% of screening endoscopies when compared to Baveno VI criteria and no HRV were missed. Our study showed that spleen SWE should also be included in further recommendations of doing screening endoscopies.

**Disclosure**

This study was presented as a Poster in “AASLD The Liver Meeting® 2019” and the Poster abstract is published in Hepatology 2019;70:188–1382. DOI: https://doi.org/10.1002/hep.30941

**References**

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1. J. Am Coll Cardiol 2021 Mar; 77 (10) 1300-1301
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Blood Stream Infection Caused by Carbapenem-resistant *Chryseobacterium indologenes* Harboring *bla*<sub>NDM-1</sub> Gene Isolated from a Tertiary Care Hospital in Tripura: An Emerging Threat

Ankan Chakrabarti<sup>1</sup>, Sibabrata Bhattacharya<sup>2</sup>, Rana Pratap Dutta<sup>3</sup>, Tapan Majumdar<sup>4</sup>

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**ABSTRACT**

**Objectives:** *Chryseobacterium indologenes* has recently been identified as an inherently drug-resistant organism, responsible for a wide spectrum of infections, mainly device-associated infections in hospital settings. The presence of carbapenem resistance due to *bla*<sub>NDM-1</sub>, metallo-β-lactamase (MBL) gene further complicates the matter, leading to widespread dissemination of carbapenem resistance. This study aims to find out the presence of *bla*<sub>NDM-1</sub>-gene among *C. indologenes* strains causing bloodstream infections in a tertiary care hospital.

**Materials and methods:** During 1 year of the study period, blood culture samples were collected from patients with features of bacteremia, and *C. indologenes* strains were isolated and identified as per protocol. Antibiotic sensitivity test was performed by using VITEK 2 Compact Automated AST machine (Biomerieux, France). Carbapenem-resistant strains were subjected to a combined disk diffusion test for detecting the presence of MBL enzyme. Strains positive for MBL production were subjected to a polymerase chain reaction (PCR) for detection of *bla*<sub>NDM-1</sub> gene.

**Results:** Out of 21 strains isolated during the study period, 12 strains (57.1%) were carbapenem-resistant. Among them, seven strains (58.3%) were MBL producers. After PCR, 3 strains (42.9%) were found to be harboring *bla*<sub>NDM-1</sub> gene.

**Discussion:** As per our knowledge, this is the first report of *bla*<sub>NDM-1</sub>-gene harboring *C. indologenes* strain from Northeast India. This shows the emerging therapeutic dilemma due to the narrowing of treatment options against bloodstream infections due to *C. indologenes* strains. Strict antimicrobial stewardship has to be implemented to prevent the further compounding of the problem.

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**INTRODUCTION**

*Chryseobacterium* spp., an environmental saprophyte, is now being identified as an emerging opportunistic pathogen, particularly in the settings of hospital-acquired infection. 1, 2 These are aerobic, non-fermenter, oxidase-positive, gram-negative bacilli, capable of producing indole in tryptophan broth. 3 *C. indologenes* is the species mostly isolated from clinical specimens, particularly in blood, sputum, and cerebrospinal fluid. 2, 3 Most of the cases are associated with the hospital environment, mainly involving indwelling devices retaining contaminated fluids, like respirators, endotracheal tubes, humidifiers, etc. 4 The alarming situation is that most of these infections are fatal and are inherently resistant to a wide variety of antimicrobials. 4

The first case of *C. indologenes* bacteremia was diagnosed in 1993, following which several cases of bacteremia, pneumonia, meningitis, polymyositis, etc. have been reported worldwide. 5 Between 1997 and 2001, the SENTRY Surveillance Program reported 0.03% cases of all bloodstream infections due to *Chryseobacterium* spp. 5 As of 2018, 6 out of 13 cases (46.2%) reported in India were bacteremia cases and most of them were associated with underlying comorbid conditions. 6

Being resistant to chlorination, the organism can easily survive in municipal water reservoirs. 7 Production of β-lactamase enzymes has been reported in *C. indologenes*, among which, the most important ones are the class B MBL enzymes, which make the organisms resistant to carbapenems. 8, 9 Majority of the strains harbor *bla*<sub>NDM</sub> as the predominant MBL gene in *C. indologenes*. However, in India, cases with *bla*<sub>NDM-1</sub>-harboring strains of *C. indologenes* are reported. 8 This is a matter of grave concern as it limits the therapeutic options available for the patients, who are usually already suffering from underlying comorbid conditions.

This study was performed to find out the proportion of *C. indologenes* isolates causing bacteremia along with the presence of *bla*<sub>NDM-1</sub>-gene among the carbapenem-resistant strains, isolated from a tertiary care hospital in Tripura, Northeast India.

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**MATERIALS AND METHODS**

The study was a cross-sectional study conducted at the Department of Microbiology in a tertiary care hospital in Northeast India. The study period was 1 year from May 2021 to April 2022. Blood samples collected from the patients with features of bacteremia and sepsis 9 were included in the study. Ethical approval was obtained from the Institutional Ethics Committee (Letter No. F.A(5–244)/AGMC/Academic/IEC Certificate/2021/7185).

**Sample Collection**

Blood collection was performed by peripheral venepuncture under strict aseptic precautions as per WHO protocol. 10 Two different sets were collected from two different sites for each patient, with each set comprising two blood culture bottles (Bact/Alert FA Plus and Bact/Alert PF bottles, bioMérieux), each being inoculated with 8–10 mL of blood in adults and as per recommendation in pediatric patients. 11 First set was collected before the initiation of antibiotic therapy and the second set was collected just before administration of the second dose of antibiotic therapy. After collection, the bottles were incubated in Bact/Alert 3D 60 automated blood culture system (bioMérieux) as per the manufacturer’s protocol. 11

**Culture and Identification of Organism**

On positive signaling from the automated blood culture system, subculture was performed in blood agar and MacConkey agar plates, and Gram’s stain report from

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Blood Stream Infection culture. Out of them, 21 samples (7.7%) yielded *C. indologenes* strains of which, 12 strains (57.1%) were isolated from the ICU setup, showing majority of infection occurring in the ICU setup.

The mean age of the patients was 46.3 years. The majority of the patients belonged to the age group between 41 and 60 years. The age group distribution is shown in Figure 3.

Antimicrobial sensitivity test shows the highest sensitivity to ciprofloxacin (100%) followed by cotrimoxazole (81%) and the lowest sensitivity to ceftriaxone and cefepime (both 0%) followed by piperacillin tazobactum (23.8%). The antimicrobial sensitivity pattern of the *C. indologenes* strains is shown in Figure 4.

Out of 21 *C. indologenes* strains, 12 strains (57.1%) were carbapenem-resistant. Among them, all the strains were meropenem resistant. Combined imipenem and meropenem resistance were detected in 11 strains (91.7%).

Antimicrobial Susceptibility Test

Antimicrobial susceptibility was determined using VITEK 2 Compact Automated AST method by determination of minimum inhibitory concentration (MIC) value as per CLSI protocol version M100-Ed 30, 2021. MIC values of ≥16 for imipenem and meropenem were considered as resistant.

Phenotypic Detection of MBL by Combined Disk Diffusion Test

Carbapenem-resistant strains were tested for production of MBL enzyme by combined disk diffusion test. Briefly, a bacterial suspension of test strain in peptone water was inoculated at 37°C for 2 hours. After that, turbidity was matched with 0.5 McFarland turbidity standard and was then inoculated in Mueller–Hinton agar. Imipenem (10 µg) and imipenem-ethylenediaminetetraacetic acid (10 µg + 750 µg) disks were placed at 15 mm distance from center to center to detect MBL production by a difference of ≥7 mm between zones of inhibition.

DNA Extraction for PCR

Metallo-β-lactamase positive strains detected by combined disk diffusion test were then subjected to DNA extraction by boiling lysis method. Briefly, the bacterial colony was suspended in 1 mL of nuclease-free water (NFW) and centrifuged twice at 15,000 × g for 10 minutes. After eliminating supernatant, pellets were resuspended in 40 µL NFW and boiled at 100°C for 10 minutes, and then cooled on ice. They were then centrifuged at 15,000 × g for 30 seconds and then stored at −20°C until the template was used for PCR.

Detection of *bla*NDM-1 by PCR

Polymerase chain reaction for detection of *bla*NDM-1 was performed according to the protocol as described below. Briefly, 2 µL template bacterial DNA was added to a total reaction volume of 25 µL consisting of 10× standard Taq reaction buffer 2.5 µL (final concentration 1×), 2.5 mM dNTP 2 µL (final concentration 200 µM), 1 µL of forward and reverse primers (final concentration of 1 µM each), Taq DNA polymerase 0.25 µL (1.25 units/25 µL PCR) and 16.25 µL of NFW. Reactions were performed in Applied Biosystems™ Veriti™ 96-Well Thermal Cycler (Thermofisher Scientific). For PCR, the forward primer was 5’-CATATGATGGAATTGGCAATATTAG-3’ and the reverse primer used was 5’-CTCGAGTCCGGCGCTTGGG-3’. The PCR protocol followed was:

- Initial denaturation at 94°C for 5 minutes
- Denaturation at 94°C for 30 seconds—30 cycles
- Annealing at 55°C for 30 seconds—30 cycles
- Initial extension at 72°C for 45 seconds—30 cycles
- Final extension at 72°C for 7 minutes
- Hold at 4°C for ∞

The PCR products were then subjected to gel electrophoresis in 1.5% agarose gel in presence of ethidium bromide and observed under UV light for interpretation (Fig. 2).

Results

A total of 2,916 blood culture samples were received during the study period, out of which 272 samples (9.3%) yielded organisms on the blood culture bottle media was reported to the clinician immediately. The organism was identified by conventional methods (yellow pigmented colonies, no growth on MacConkey agar plate, positive catalase, oxidase, bile esculin, and indole tests) (Fig. 1) as well as using Vitek 2 Compact Automated identification and AST system (bioMérieux) as per manufacturer’s protocol.

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Out of the carbapenem-resistant strains, seven strains (58.3%) were detected to be
MBL producers by combined disk diffusion test. All seven strains were subjected to PCR for detection of the presence of \( bla_{NDM-1} \) gene. Of them, three strains (42.9%) were found to be harboring \( bla_{NDM-1} \) gene. All three strains harboring \( bla_{NDM-1} \) gene were having MIC value \( \geq 32 \) for meropenem and MIC value \( \geq 16 \) for imipenem.

**DISCUSSION**

*C. indologenes* is intrinsically resistant to aminoglycosides, first-generation cephalosporins, aminopenicillins, and aztreonam. So, the therapeutic options are already very narrow for the treatment of *C. indologenes* infection. Emergence of carbapenem-resistant *C. indologenes* strains thus further complicates the situation, putting forth a severe therapeutic challenge.

According to the report of SENTRY Antimicrobial Surveillance program, the quinolone group of drugs has the highest activity against the *C. indologenes* (85–100%). Among the \( \beta \)-lactams, piperacillin-tazobactam had the highest sensitivity (90%), while carbapenems had a poor sensitivity profile (10–15%). In this study, the highest sensitivity was to the quinolone group (100%) which was concordant with the SENTRY Surveillance findings. However, among \( \beta \)-lactams, carbapenem sensitivity was much higher (42.9% for meropenem and 47.6% for imipenem) in this study.

A 3 years prospective study by Yadav et al. shows 33% sensitivity of carbapenems in *C. indologenes* strains, which is lower than the findings of this study. No report of quinolone susceptibility pattern was available from the study.

Among the carbapenem-resistant strains, the major threat is from the strains producing MBL enzymes. Various studies have shown that seven variants of \( bla_{NDM} \) genes (IND-1 to IND-6 and 2a) are the major MBL genes harbored by *C. indologenes*. Recent studies have also revealed newer IND genes (IND-8 to IND-16) responsible for MBL production in *C. indologenes*. Studies from Asian countries show predominance of IND-2 gene among the MBL-producing strains of *C. indologenes*. No Indian reports characterizing the strains harboring IND genes are available in the literature.

The first case of \( bla_{NDM-1} \) harboring *C. indologenes* strain was reported by Khajuria et al. from India. \( bla_{NDM-1} \) is the predominant MBL gene found in the carbapenem-resistant strains of Gram-negative bacilli. So, isolation of *C. indologenes* strains harboring \( bla_{NDM-1} \) genes is a matter of grave concern, as it can lead to widespread carbapenem resistance through horizontal gene transfer.

In the present study, the MIC values of the strains harboring \( bla_{NDM-1} \) gene was \( \geq 32 \) and \( \geq 16 \) against meropenem and imipenem, respectively. This finding is similar to the study by Khajuria et al. who reported a MIC value of 32 for meropenem. However, the MIC value for imipenem in our study was lower than that reported in the above study (MIC of 32). In case of strains harboring \( bla_{IND} \) genes, a higher MIC value (\( \geq 64 \)) for imipenem and meropenem was observed compared to the present study.

In this study, the highest sensitivity was reported against ciprofloxacin (100%) followed by cotrimoxazole (81%). The strain as reported by Khajuria et al. showed resistance to all quinolones, with only sensitivity against colistin (MIC \( \leq 0.5 \)). So, this shows that in the present study settings, *C. indologenes* strains are more susceptible to quinolones and cotrimoxazole therapy, thus minimizing the use of costly drugs like colistin or tigecycline.

**CONCLUSION**

To our knowledge, this is the first study showing the presence of *C. indologenes* strains harboring \( bla_{NDM-1} \) gene, causing bloodstream infection from Northeastern India. The present study shows that carbapenem-resistant *C. indologenes* strains are becoming a threat, mainly in hospital settings. The presence of MBL-producing *C. indologenes* strains has seriously compounded this problem as it severely limits the therapeutic options in the patients. The emergence of strains harboring \( bla_{NDM-1} \) strains has become a matter of grave concern, as it increases the chance of dissemination of carbapenem resistance by horizontal gene transfer. Strict antimicrobial stewardship programs are necessary to combat this situation and to prevent further enhancement of this problem.

**REFERENCES**

Invasive Fungal Sinusitis in Post-COVID-19 Patients with Diabetes Mellitus

Chetan Ingle¹, Aman Goyal²*, Swarup Hange³

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Abstract

Objective: Invasive fungal sinusitis is an invasive disease associated with high mortality of up to 60%. There is a well-documented increase in rhino-orbital-cerebral fungal co-infection in COVID-19 patients. Our study aimed to determine the factors that lead to the development, the natural history of progression and the therapeutic interventions done for this grave complication.

Methods: Patients admitted in general medicine ward in King Edward Memorial (KEM) Hospital, Mumbai were included. Patient’s history and examination findings were noted. Advised investigations—imaging studies like CT scan, MRI done were noted down. Operative procedures like functional endoscopic sinus surgery (FESS), abscess drainage, dental extraction, were performed at the hospital and details were taken. Fungal cultures, sugar monitoring, liver function test, renal function test, complete blood counts, ECGs, chest X-rays, and amphotericin charting were also done.

Results: On retrospective analysis of the presenting patient’s records, we found that all patients had received steroids for COVID-19 treatment and had co-morbidities, especially diabetes mellitus. Prolonged hospitalization further exposes the patient to various multi-resistant bacteria making them prone to various secondary infections.

Conclusions: It is of paramount importance that physicians know the associated risk factors, mentioned in our study, that may lead to invasive fungal co-infection in COVID-19 patients, and to regularly examine the patient for any developing signs so appropriate diagnosis and treatment can be initiated as early as possible. It is an unrelenting disease process that requires the utmost care, and our case series provides an in depth look of four such cases for future reference.

Introduction

Invasive fungal sinusitis like mucormycosis, aspergillosis, etc. is manifested particularly in immunocompromised patients and those with diabetes mellitus.¹ Devastating rhino-orbital-cerebral and pulmonary infections are the most common sequelae of these fungi.

Mucormycosis is highly invasive and relentlessly progressive, resulting in higher rates of morbidity and mortality than many other infections. Hematological malignancy (48.6%), chemotherapy (42.9%), corticosteroids (52.7%), diabetes mellitus (27%), and trauma (22.9%) are the most common comorbidities or risk factors.²

The initial symptoms of rhino-orbital-cerebral mucormycosis are nonspecific and include eye or facial pain and facial numbness followed by the onset of conjunctival suffusion and blurry vision. Fever is also a common sign.³ Infection usually spreads from the ethmoid sinus to the orbit, resulting in the compromise of extraocular muscle function and proptosis.⁴ Biopsy with histopathologic examination remains the most sensitive and specific modality for definitive diagnosis. Biopsy reveals characteristic wide (≥6–30 μm), thick-walled, ribbon-like, aspetae hyphal elements that branch at right angles.³

Aspergillus fumigatus is responsible for most cases of invasive aspergillosis, nearly all cases of chronic aspergillosis, and most allergic syndromes.⁵ The sinuses are involved in 5–10% of cases of invasive aspergillosis, especially affecting patients with leukemia and recipients of hematopoietic stem cell transplants.⁵

COVID-19 patients, particularly those with a history of diabetes, who are immunocompromised or severely ill, have a higher probability of suffering from invasive fungal infections.⁶

Thus, it is paramount for physicians to understand that there is a possibility, especially in diabetics, to develop unrelenting fungal co-infections in those diagnosed with COVID-19 during their hospital stay. We have recorded four such cases for reference, so adequate diagnosis, treatment, and prophylaxis can be made for future cases.

Methodology

Patients admitted in the general medicine ward in King Edward Memorial (KEM) Hospital, Mumbai—a tertiary healthcare center—were included in the case series. The patient’s history and examination findings were noted. Advised investigations—imaging studies like computed tomography (CT) scan and magnetic resonance imaging (MRI) were noted down. Operative procedures like functional endoscopic sinus surgery (FESS), abscess drainage, and dental extraction, were performed at KEM Hospital. Fungal cultures, sugar monitoring, liver function test, renal function test, complete blood counts, electrocardiograms, chest X-rays, and amphotericin charting (to calculate cumulative doses of amphotericin and serum potassium monitoring) were also done.

References

¹Assistant Professor, Department of Medicine; ²Third Year MBBS Student, Department of Medicine; ³Final Year Junior Resident, Department of Medicine, Seth Gordhandas Sunderdas Medical College (GSMC) and King Edward Memorial (KEM) Hospital, Mumbai, Maharashtra, India; *Corresponding Author

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<table>
<thead>
<tr>
<th>Sl. no.</th>
<th>Age/Sex</th>
<th>Diabetes mellitus and drug prescription history</th>
<th>History of COVID-19, severity, and associated treatment</th>
<th>Presenting signs of fungal infection in the sinuses and nose</th>
<th>Presenting signs of fungal infection in the eyes</th>
<th>Presenting signs of fungal infection in the oral cavity</th>
<th>Cranial nerves involvement</th>
<th>Other features</th>
<th>Complete blood count (Hb (gm/dL)/WBC (cumm)/platelets (mCl))</th>
<th>Creatinine (mg/dL)/Potassium (mEq/L)</th>
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<tr>
<td>1</td>
<td>64/Male</td>
<td>Diagnosed 10 years ago On tablet metformin 500 mg twice daily Injection human insulin (R) 10-12-10 as per HGT (N) 14-0-0-14</td>
<td>In December 2020 Patient was admitted for COVID pneumonitis (stage IIB), CORADS 6, CTSS 18/25 Received injection methylprednisolone 40 mg twice daily for 5 days; followed by tablet prednisolone 30 mg for 5 days followed by tapering 5 mg per week</td>
<td>Right—maxillary sinusitis Bilateral sphenoidal and ethmoid sinuses Right nose had presence of nasal crusts</td>
<td>Right eye Complete ptosis along with complete ophthalmoplegia Perception of light absent Orbital cellulitis Bilateral vitreous degeneration</td>
<td>Palatal necrosis and perforation Grade III mobile 7, 5, 6 right upper teeth</td>
<td>Right optic nerve involvement Right third, fourth, sixth nerve involvement</td>
<td>Complaints of right-sided headache and right eye swelling</td>
<td>12.4/18,400/410,000</td>
<td>1.8/4.4</td>
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<tr>
<td>2</td>
<td>57/Male</td>
<td>For the past 3 months on tablet teneligliptin 20 mg once daily Injection human insulin (R) 6-6-6 as per HGT (N) 8-0-0-8</td>
<td>In November 2020 Patient was admitted for COVID pneumonitis (stage IIB), CORADS 6, CTSS 15/25 Received injection methylprednisolone 40 mg twice daily given for 5 days</td>
<td>Left—maxillary sinusitis</td>
<td>Left eye Orbital cellulitis Complete ptosis and ophthalmoplegia Left eye perception of light absent Bilateral vitreous degeneration</td>
<td>Poor oral hygiene Congestion of hard palate with tiny ulcers Grade III mobile right lower 8, 7 teeth with gingival recession</td>
<td></td>
<td>Complaints of swelling over the left cheek</td>
<td>11.1/13,300/103,000</td>
<td>1.7/2.7</td>
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<tr>
<td>3</td>
<td>47/Male</td>
<td>For the last 5 years on tablet metformin 500 mg thrice daily Injection Mixtard insulin 14-0-0-10</td>
<td>In November 2020 Patient was admitted for COVID pneumonitis (stage IIB), CORADS 6, CTSS -17/25 Received injection methylprednisolone 40 mg twice daily for 5 days</td>
<td>Right—maxillary sinusitis Bilateral mastoiditis, bilateral nasal cavity congested and deviated nasal septum</td>
<td>Right eye Complete ptosis along with complete ophthalmoplegia Perception of light absent Orbital cellulitis Right vitreous detachment Left vitreous degeneration</td>
<td></td>
<td></td>
<td>Right-sided palatal slough with necrotic patches Dental caries</td>
<td>8/12,300/297,000</td>
<td>1.8/3.1</td>
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<td>4</td>
<td>54/Female</td>
<td>For the last 5 years on tablet metformin 1 gm once daily, tablet glibemuride 1 mg once daily Injection human insulin (R) 8-10-8 as per HGT, (N) 12-0-0-12</td>
<td>In December 2020 Patient was admitted for COVID pneumonitis (stage IIB), CORADS 6, CTSS 14/25 Received injection methylprednisolone 40 mg twice daily for 3 days</td>
<td>Right—nasal cavity filled with mucormycosis debris; lateral nasal wall completely eroded Left—minimal necrotic mucosa on both lateral wall and septum</td>
<td>Right eye Orbital cellulitis Bilateral vitreous degeneration</td>
<td></td>
<td></td>
<td>Cheek swelling on the right side</td>
<td>8.5/6300/303,000</td>
<td>1.6/3.6</td>
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Contd...
Invasive Fungal Sinusitis in Post-COVID-19 Patients with Diabetes Mellitus

A complex interplay of factors, including pre-existing diseases, such as diabetes mellitus, previous respiratory pathology, use of immunosuppressive therapy, the risk of hospital-acquired infections, and systemic immune alterations due to COVID-19 infection itself may lead to secondary infections, which are increasingly being recognized in view of their impact on morbidity and mortality. In a recent review, 62/806 (8%) patients had secondary bacterial or fungal infections during hospital admission. There was widespread use of broad-spectrum antibiotics, with as many 1450/2010 (72%) of patients receiving these drugs, often with no underlying evidence of infection.

White et al. included a total of 135 adults (median age: 57, M/F: 2.2:1) in the study. They reported the incidence of invasive fungal disease to be 26.7% (14.1% were aspergillosis, 12.6% were yeast infections like Candida). The overall mortality rate was 38%; 53 and 31% in patients with and without fungal disease, respectively (p = 0.0387). The mortality rate was reduced using antifungal therapy (mortality: 38.5% in patients receiving therapy vs 90% in patients not receiving therapy (p = 0.008)). The use of corticosteroids (p = 0.007) and history of chronic respiratory disease (p = 0.05) increased the likelihood of aspergillosis.

**Table:**

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<td>Fasting blood sugar (mg/dL)</td>
<td>286</td>
<td>274</td>
<td>254</td>
<td>268</td>
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<tr>
<td>Previous control of DM—HbA1C (%)</td>
<td>10.50</td>
<td>11.2</td>
<td>10.4</td>
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</tr>
</tbody>
</table>

**Imaging:**
- CT brain, orbit and paranasal sinuses
- MRI 2020, 26th December 2020, 8th January 2021
- Nasal cavity was cleared, along with debridement and tissue was sent for fungal cultures
- Dental extraction of the 7,6,5 right upper molar teeth was done
- Injection amphotericin (conventional) 40 mg/day for 8 weeks given (cumulative dose of 2.24 gm) followed by T. posaconazole 300 mg BD on D1, then 300 mg OD for 3 months. Blood sugar level was brought under control using human insulin. Azithromycin eye drop was administered

**Fungal culture results:**
- Few fungal elements visible on culture
- Aspergillus flavus grown on culture
- Rhizopus species grown on culture

**Therapeutic interventions:**
- FESS was performed thrice on 19th December 2020, 26th December 2020, and 8th January 2021
- Left-sided crusts seen on the inferior aspect of inferior turbinate were removed along with local debridement
- Injection amphotericin (conventional) 40mg/day for 8 weeks given followed by T. voriconazole 300 mg on D1, then 200 mg BD for 3 months; and injection piptaz 4.5 gm every 8 hours for 1 week were given
- Blood sugar level was brought under control using human insulin and azithromycin eye drop was administered

**Fig. 1:** Patient three complains of right maxillary swelling demonstrating palatal perforation

**Fig. 2:** Patient three presenting with a right temporal lobe abscess, MRI of the brain
In our study, all the patients admitted with us had some form of cranial nerve involvement in the form of ptosis, impaired vision, ophthalmoplegia, facial nerve palsy, etc. Angio invasive nature of mucormycosis could be evident in the form of necrosis of the soft palate. Everyone had poor oral hygiene, three of which developed palatal perforation and necrosis. Fungal culture in patients three and four had grown *Rhizopus* spp. while patient two’s culture plate had grown *Aspergillus*; patient one’s culture plate demonstrated visible fungal elements. Patients had 1–3 settings of FESS with crust removal and local debridement. Patient one further had dental extraction and patient three needed craniotomy and drainage of right temporal abscess. Each patient received around 2.2–3.36 gm of injectable conventional amphotericin B followed by T. voriconazole or T. posaconazole.

The patients we described above with COVID-19 infection were long-standing diabetics. The signs of orbital infection and sinusitis were noticed only after the patients were admitted into the hospital for COVID-19 infection, during which they were treated with both broad-spectrum antibiotics and steroids, or after they were discharged from the COVID-19 wards. All of the above patients had uncontrolled sugar levels with HbA1c levels >9.0% and had stage IIB COVID infection requiring oxygen support and injectable steroids during their COVID ward stay. All these factors tend to facilitate fungal coinfection, along with any possible COVID-19 pathophysiological mechanisms. In the above cases, either a previously undiagnosed mucor or fungal infection may have been aggravated or it may have subsequently developed.

**Conclusions**

Physicians must be aware of the possibility of invasive secondary fungal infections in patients with COVID-19 infection, especially in those patients with pre-existing risk factors like diabetes mellitus, and should enable early diagnosis and treatment which would subsequently reduce both mortality and morbidity. The use of therapeutic agents should be monitored to achieve a therapeutic effect at the lowest dose possible and for the shortest duration necessary. Early surgical interventions like FESS, drainage of the abscess, and debridement of the necrosed part should be instituted early to prevent morbidity and mortality.

**References**

Analyzing the Impermeable Structure and Myriad of Antiviral Therapies for SARS-CoV-2

Anna Mary Jose1*, Pramita Muntode2

Received: 14 May 2022; Accepted: 08 August 2022

ABSTRACT

A total number of 1,524,161 active cases, 92,941 deaths, and 213 countries have been affected worldwide by COVID-19 as of 11th April 2020. Much can be attributed to the virus’ structural protein, S protein, which determines its host range and tissue tropism and aids its rapid spread. This review aims to summarize numerous researches carried out with respect to the complex and resistant structure of SARS-CoV-2 in addition to the research performed on various antivirals on the basis of drug repurposing, to aid in better understanding for future researches, clinical trials, and treatment protocols.

INTRODUCTION

Background

A total of 1,524,161 active cases, 92,941 deaths, and 213 countries have been affected worldwide by COVID-19 as of 11th April 2020.2

World Health Organization’s (WHO) first situation report states that there were 282 confirmed cases of nCoV in China, Thailand, Japan, and the Republic of Korea as of 31st December 2019, when the WHO China Country Office was notified of instances of pneumonia of unclear etiology (unknown cause) discovered in Wuhan City, Hubei Province, China.3

It is worth noting that on 30th December 2019, Dr. Li Wenliang, an ophthalmologist at Wuhan Central Hospital, sent a message to a group of colleagues warning them about a possible outbreak of an illness mimicking severe acute respiratory syndrome (SARS) in Wuhan, Hubei Province, China.4 After seeing seven people with SARS-like symptoms, he raised the alarm. He died soon after becoming infected with SARS-CoV-2 in Wuhan, China, on 7th February 2020, at the age of 33.4

Management

Researchers have been exemplary in determining the organizational structure and clinical presentation of SARS-CoV-2 infected patients, but we are far behind when it comes to establishing treatment for the same, despite immense efforts.

Even though we developed treatment modalities for human coronaviruses in the past, we are unable to reinforce the same for SARS-CoV-2 due to their extensive sequence diversity.

Various therapeutic agents have been tested for previous human coronavirus threats such as SARS and MERS-CoV5-10 all of which provide a basis for the discovery of effective treatment strategies to fight the novel coronavirus.

A demotivating factor for pharmaceutical companies that has resulted in the lack of commercial production of vaccines and antiviral drugs can be that, the demand for such vaccines/drugs lasts only up and until the outbreak persists.11,12

Potential therapeutic options include remdesivir, lopinavir/ritonavir alone or in combination with interferon beta, convalescent plasma, and mABs.13

The purpose of this review is to put in a nutshell the numerous researches carried out with respect to the complex and resistant structure of SARS-CoV-2 in addition to the various antivirals presently being employed to reduce the morbidity and mortality caused by the same to not only form a foundation for new researches and health care workers but also to aid future researches, clinical trials, and treatment protocols.

CORONAVIRUSES

Family

Coronaviruses are members of the Nidovirales order and is organized into two subfamilies: coronaviinae and torovirinae,14-16 with four genera: alpha coronavirus, beta coronavirus, gamma coronavirus, and delta coronavirus. Camels, cattle, cats, and bats are all known to have them.

SARS-CoV-2 Structure and Viral Replication

5’-replicase (ORF1/ab), structural proteins: (i) spike (S), (ii) envelope (E); viral particle release from host particles,17 (iii) membrane (M); crucial for virion structure, provides the virus its shape, and works with E protein to orchestrate the virus’ assembly and formation of mature viral envelopes,17 (iv) nucleocapsid (N); binds viral RNA and is necessary for viral RNA packaging into viral particles all through viral assembly,17 3’ and lacks the hemagglutinin-esterase gene seen in lineages A–CoVs.18

It features the normal beta coronavirus S’ and 3’ terminal sequences.19

The genome of the SARS-CoV-2 virus has six primary open-reading frames (ORFs) that are shared by coronaviruses and some additional accessory genes.20

Despite the fact that some of the six major ORFs of SARS-CoV-2 genes have less than 80% nucleotide acid identity to SARS-CoV, the amino acid sequences of the seven conserved replicase domains in ORF1ab that were used for CoV species classification were 94.4% identical between 2019-nCoV and SARS-CoV, implying that the two viruses are related.20

Severe acute respiratory syndrome coronavirus 2 (COVID-19) uses (a) spike glycoprotein to bind to (b) the angiotensin-converting enzyme (ACE2) and allows COVID-19 to enter and infect cells. In order for the virus to complete entry into the cell following this initial process, the spike protein has to be primed by an enzyme called a (c) protease. Similar to SARS-CoV, SARS-CoV-2 (COVID-19) uses a protease called TMPRSS2 to complete this process.21,22

Spike Protein

It is of paramount importance in determining the host range and tissue tropism.23

Spike protein of different genera has little sequence similarity as compared to those from the same genera having significant sequence similarity.23

Spike protein is a trimeric S2 stalk with three S1 heads and a clove-shaped trimer.24
The ectodomain comprises two domains: S1, which attaches to the receptor on the host cell, and S2, which causes the virus to fuse with the host cell membrane, allowing viral genomes to enter.23 Receptor binding and membrane fusion can serve as targets for therapeutic agents. S1 has N terminal and C terminal, one or both of which act as a receptor binding domain.23 S1 N terminal domain is responsible for binding sugar whereas S1 C terminal domain is responsible for binding protein receptors, that is, ACE2. The C terminal domain is divided into the core structure and the receptor binding motif.23 The receptor binding motif region is located in the receptor-binding domain’s carboxy-terminal half that comprises all of the residues that interact with the host receptor, which is the ACE2-binding site.24 It has been reported that antisera raised against human ACE2 blocked SARS-CoV and COVID-19 entry.21

**ACE2 Receptors**

Spike proteins bind to the human ACE2 receptors.20,25 ACE2 has an ectodomain, which has on its membrane distally, a peptidase and proximally domain, a collectrin domain, with the binding sites on the peptidase domain.23 Ou et al. found that endocytosis was the main entry pathway on 293/hACE2 cell.25 Six receptor-binding domain (RBD) amino acids have been found to be essential for SARS-CoV-like viral binding to ACE2 receptors and defining the host range.26 CD147 was found as a new receptor of SARS-CoV-2 in a dose-dependent manner, a potential drug target.23

**Splice Protein Priming Proteases**

During infection, the trimeric S protein is broken by host cell proteases after contacting the host receptor, exposing the fusion peptide of the S2 domain, which triggers the fusing of viral and cellular membranes.29–31 The virus contains a polybasic cleavage site (RRAR) in the intersection of S1 and S2.22 This enables efficient breakdown by furin and some other proteases and has a role in viral infectivity and host range.33 Furthermore, a leading proline is inserted at this location, resulting in PRRA as the inserted sequence. The proline turn should result in the addition of O-linked glycans to S673, T678, and S686, which flank the cleavage site and are unique to SARS-CoV-2. Polybasic cleavage sites have not been found in related “lineage B” beta coronaviruses.34 Experiments reveal inserting a furin cleavage site at the S1–S2 junction improves cell–cell fusion while having no effect on viral entry.35 O-linked glycans are thought to form mucin-like domains that protect epitopes or critical residues on the SARS-CoV-2 spike protein.36

Severe acute respiratory syndrome coronavirus is not broken by furin-like proteases at the S2’ location during viral egress. Furin-like protease is a putative antiviral site of action that requires more investigation. Now, whether coronaviruses enter cells via the plasma membrane or endocytosis is primarily determined by the presence of these proteases on target cells.25 The incompatibility of the host protease and the viral spike prevents the virus from entering.24 Cellular serine proteases TMPRSS2 primes SARS-CoV-2 for entry.21 Camostat mesylate inhibitor of TMPRSS2 blocks COVID-19 infection of lung cells.21 Virus-encoded proteases—papain-like cysteine protease and picorna 3C-like cysteine protease—cleave polyproteins into individual polypeptides needed for replication and transcription.37 The presence of a cathepsin L cleavage site in the SARS-CoV-2 protein implies that cathepsin L inhibitors might be useful in preventing SARS-CoV-2 infection.38 Phosphatidylinositol-3,5-bisphosphonate modulates endosome dynamics, and phosphatidyl 3-phosphate 5-kinase is the primary enzyme responsible for PI(3,5)2 synthesis.39 APILIMOD, a strong inhibitor of PIKfyve, was used to treat HEK293/hACE2 cells in the study. In a dose-dependent manner, APILIMOD prevented the entrance of SARS-CoV-2 pseudovirions. This PIKfyve is a potential drug target.39 Similar effects were seen when 293/Hace2 cells were treated with YM 201,636 in a dose-dependent manner.25

The newly formed enveloped glycoproteins are fed into the endoplasmic reticulum or Golgi, giving rise to the nucleocapsid, a blend of genomic RNA and the nucleocapsid proteins.24 Following membrane fusion, the coronavirus’ viral genome RNA is released into the cytoplasm, where it translates into two polyproteins and forms the replication transcription complex (RTC). RTC repeats and synthesizes a nested series of subgenomic RNAs that encode auxiliary proteins and structural proteins on a continuous basis. Nucleocapsid proteins and envelope glycoproteins assemble and form viral particle buds by mediating newly produced genomic RNA in the endoplasmic reticulum and Golgi. Finally, the virion-containing vesicles merge with the plasma membrane, allowing the virus to be released.24 Mutations in NSP2 and NSP3 contribute to SARS-CoV-2’s infectious potential and differentiation process.30 Tang et al. conducted a population genetic study of 103 SARS-CoV-2 genomes and identified two predominant evolution types: S type and L type, which evolved from S and are more aggressive and infectious, with the L type being more widespread.31

It is hypothesized that 12 functional ORFs are formed from a collection of nine subgenomic mRNAs with a conserved leader sequence in the genome, nine transcription-regulatory sequences, and two terminal untranslated regions. The nucleotide identities of 2019-nCoV s’- and 3’-untranslated region sequences are 83.6% comparable to those of other CoVs.18 After entering the cell, the viral genome is released into the cytoplasm, and the partially overlapping 5’-terminal ORF (1a/b) within the 5’ two-thirds of the genome, which is translated into replicase polyproteins pp1a and pp1ab, is cleaved by host cell proteases into 16 nonstructural proteins, which include two viral cysteine proteases, namely nsp3 (papa). The main difference between SARS-CoV-2 and SARS-CoV is seen in ORF3b, spike, and ORF8.18 Once enough structure proteins and genomic viral RNA have been produced, viral RNA is assembled into virions together with viral structural proteins. In the rough endoplasmic reticulum-Golgi intermediary compartment produced by 16 nsp, viral assembly and budding happens in smooth-walled vesicles.17,19

Severe acute respiratory syndrome coronavirus 2 is more closely related to SARS-like bat CoVs than SARS-CoV and MERS-CoV.24
Examine the whole genome, SARS-CoV-2 maintains ~80% nucleotide identity to original SARS epidemic viruses.42

Severe acute respiratory syndrome coronavirus 2 shares a highly conserved domain in ns1p with SARS-CoV.

Severe acute respiratory syndrome coronavirus 2 is similar to SARS-CoV, in which it carries a predicted ORF 8 gene located between M and N ORF genes.

The receptor-binding domain of S of SARS-CoV-2 was only one amino acid longer than the receptor binding domain of the spike protein of SARS-CoV.19

A recent investigation found a bat COV sequence, RaTG3, which has 92% sequence similarity with the new coronavirus, arguing for bat sources for SARS-CoV-2.43

Severe acute respiratory syndrome coronavirus 2 RBD is 73% conserved relative for bat sources for SARS-CoV-2. The receptor-binding domain of S of SARS-CoV-2 is 73% conserved relative to SARS-CoV RBD. This conservation level places SARS-CoV-2 RBD involving HKU 3-4, a bat virus which does not use human ACE2, and rShC014, the most extreme bat COV spike known to use human ACE2.42

Three viral species whose proteins shared the highest similarity: SARS-CoV, Bat CoV, and Bat beta coronaviruses.43

COVID-19 is the most closely linked to bat COV and shares 100% amino acid identity with bat SL COV2C45.19

Antivirals

Antiviral therapy is based off drug repurposing, such as drugs used for previous SARS epidemics, that is, SARS-CoV and MERS-CoV.

• Wang et al. discovered that remdesivir and chloroquine inhibited SARS-CoV-2 in vitro at low micromolar concentrations and had a high selectivity index. It worked after the virus had entered the system.44 Remdesivir, an adenosine analog, combines into newly developing viral RNA strands, causing them to terminate prematurely. Remdesivir’s EC90 value for SARS-CoV-2 in Vero E6 cells was determined to be 1.76 M.45 Remdesivir also effectively prevented viral infection in a human cell line (Huh-7 cells from human liver cancer), which is known to be susceptible to SARS-CoV-2.46 Chloroquine, an antimalarial medication that prevents viral infection by raising endosomal pH, which is required for virus-cell fusion, and by interfering with the glycosylation of SARS-CoV cellular receptors.47 Chloroquine was shown to act at both the entry and postentry phases of SARS-CoV-2 infection. In Vero E6 cells, the EC90 value of chloroquine for 2019-nCoV was 6.90 M.47 Hoelshue et al. discovered that remdesivir had encouraging outcomes in the management of a COVID-19 patient in the United States.48

Another drug, nafamostat was found to prevent membrane fusion against SARS-CoV-2. Nafamostat requires more research and clinical trials in order to draw the conclusion of the drug being fit for the treatment of COVID-19. Similarly, nitazoxanide, which is an antiprotozoal agent, restricts the SARS-CoV-2 at a low-micromolar concentration.49

• Arbidol, an antiviral medication for influenza, has been recommended as a possible COVID-19 therapy.50 Favipiravir, an antiviral medication that targets the influenza virus RNA-dependent RNA polymerase (RdRP),51 might be used to treat COVID-19. Favipiravir had a clinical cure rate of day 7 (71.43%) and arbidol (55.86%) in moderately ill patients, and the duration of cough recovery and fever decline of favipiravir was noticeably shorter than of arbidol, indicating that favipiravir could be used in the intervention of tolerably ill COVID-19 patients to halt the disease progression into acute respiratory distress syndrome, shock, and multiple organ failure.52

• The AP2-associated protein kinase 1 is a recognized endocytosis regulator (AAK1). The interruption of AAK1 delays both the virus’ entry into cells and the intracellular assembly of viral particles. A janus kinase inhibitor, baricitinib, targets both AAK1 and cyclin G-associated kinase, an additional endocytosis regulator. Because the plasma levels of baricitinib at therapeutic doses (2 mg/4 mg/daily) are sufficient to inhibit AAK1, it can be explored as a therapy option.52

Baricitinib, on contrary, has been linked to lymphocytopenia, neutropenia, and viral reactivation. Epidemiological research has revealed that COVID-19 patients had a lower absolute lymphocyte count around the threshold value, making them susceptible to coinfection. Furthermore, coinfection is one of the primary reasons for death in COVID-19 patients.53

Lithium has been shown to suppress glycogen synthase kinase 3-beta (GSK-3), the enzyme responsible for antiviral action and decreased apoptosis. Chloroquine (hydroxychloroquine), which is expected to be efficacious in COVID-19,54 inhibits GSK-3 and potentiates lithium-induced GSK-3 inhibition. This suggests that mechanistic research might look into not just 0.5–1.2 mM lithium, but also lithium with chloroquine.55

However, data suggest that lithium successfully prevents coronaviral infections when provided at hazardous levels to people.

• Research discovered that atazanavir has a possible binding affinity for RNA-dependent RNA polymerase, helicase, 3′-to-5′ exonuclease, 2′-O-ribose methyltransferase, and endoRNAse, indicating that atazanavir may block all components of the SARS-CoV-2 replication complex concurrently. Ganciclovir is expected to bind to three components of the SARS-CoV-2 replication complex: RNA-dependent RNA polymerase, 3′-to-5′ exonuclease, and RNA helicase.56

• It is widely known that cathepsin L is important in the entrance and fusing of SARS-CoV-2. Teicoplanin was discovered to directly work as a SARS-CoV-2 entrance blocker in a dose-dependent manner. Its inhibiting action on SARS-CoV-2 S pseudoviruses was proven by an IC50 of 1.66 μM. It blocks the activation of the spike protein by directly reducing enzyme reactions of cathepsin L. Teicoplanin is a glycopeptide antibiotic mostly used to treat gram-positive infections such as Staphylococcus aureus and Streptococcus.57–59 Teicoplanin is a dual inhibitor that can be used to treat both the SARS-CoV-2 infection and coinfections with gram-positive bacteria.50

• In human cells, the protease TMPRSS2 generated by host cells plays an essential role in the proteolytic preparation of spike protein, enabling the attachment of the protein to the receptor ACE2. Camostat mesylate is a TMPRSS2 inhibitor, showed inhibition SARS-CoV-2 entrance into human cells, indicating its potential as a COVID-19 treatment.51

• IDV-184, sofosbuvir, and ribavirin may bind to the SARS-CoV-2 RdRpoly and inhibit its activity, resulting in viral eradication.53

• Ribavirin is a guanosine analog with antiviral action that extends beyond the inhibition of polymerases to the inhibition of RNA capping, which relies on natural guanosine to inhibit RNA degradation.52 Ribavirin suppresses natural guanosine production by decreasing inosine monophosphate dehydrogenase directly.53 In the presence of ribavirin, nucleic acid replication proceeds with lower fidelity, resulting in the insertion of random mutations that might diminish the virus’ survival.64

• Thalidomide: it was shown that combining thalidomide with a low-dose glucocorticoid decreased pulmonary effusion symptoms while increasing inflammatory cytokines with no negative effects. The quantity of lymphocytes retrieved was also increased. These findings suggest that thalidomide, in combination with low-dose steroids, might be utilized to treat SARS-CoV-2 pneumonia. The favorable impact of thalidomide on
COVID-19 can be ascribed to its sedative and antiemetic activity, which helps an anxious patient calm down, resulting in a decrease in oxygen consumption and relief of digestive problems.65  
- Nelfinavir was reported in bronchoalveolar lavage fluid in 100% of patients treated for 4 weeks, but lopinavir-ritonavir was detected in only 16.7% of patients.66 The proportion of nelfinavir in lung epithelial lining fluid was reported to be identical to that seen in plasma.67 demonstrating nelfinavir’s excellent penetration capabilities into the alveolar compartment.68  

Nelfinavir was shown to block inflammatory cytokines and lower inflammatory cytokine levels in a group of 31 pediatric HIV-1 patients treated for 2 years.69 This nelfinavir property can be utilized to combat the cytokine storm that drives COVID-19 patients into severe respiratory distress. Another research backs up the previous findings, revealing that nelfinavir is extremely effective in suppressing virus’ ability to replicate. It functions as a lysosomotropic agent, influencing the functional environment of cathepsin L.83  
- By inhibiting CD147, meplazumab, a humanized anti-CD147 antibody, can effectively prevent SARS-CoV-2 from penetrating host cells.70 It was discovered that in patients with COVID-19 who had undergone approved therapy, adding meplazumab 20–30 mg enhanced the recovery of chest radiography and lymphocytopenia, lowered the inflammation index (CRI), and accelerated disease improvement without major side events.84  
- Severe acute respiratory syndrome coronavirus 2 belongs to a virus family with a lipid envelope that connects with the host cell via endocytosis.85 Lipid rafts are crucial plasma membrane regions for the process of endocytosis.85,86 In vitro tests suggest that cholesterol supplementation increases the virus’ susceptibility to fusion with the host cell membrane. To reduce coronavirus attachment to host cells, molecular blockers of virus lipid-dependent attachment macromolecules such as methyl cyclodextrin (MCD) have been utilized.87 The lipophilic core permits these compounds to interact with lipid rafts. These nontoxic macromolecules, which have been studied for their antiviral effect, imitate assault locations for the enveloped virus, contending with host cell attack sites.88,89 Some investigations found that MCD treatment lowered the expression of ACE2 in the cell membrane minimally and dose-dependently, as well as the infectivity of coronaviruses like SARS-CoV.90  
- Lopinavir-ritonavir therapy did not substantially speed up the therapeutic benefit, reduce mortality, or reduce throat viral RNA detection rate in patients with severe COVID-19.91  

CONCLUSION  
Albeit, the SARS-CoV-2 pandemic has caught the world off guard, unforgivably causing damage to mankind, researchers have moved at breakneck speed to figure out the genomic sequence and pathogenicity, and to conduct drug trials. In the face of a new pandemic, although vaccines seem like a desirable option, more drug trials need to be conducted quickly and efficiently using existing drugs to figure out the possible side effects and then weigh the pros and cons and ultimately include/exclude the drug from the treatment protocol, as time is of the essence. Areas that need more research and clinical trials are immunotherapeutic and convalesce plasma or immunoglobulins, collected from recovered patients as a resort.  

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Analyzing the Impermeable Structure and Myriad of Antiviral Therapies


Gastric Outlet Obstruction: Don’t Miss Duodenal Tuberculosis

Brij Sharma¹, Neetu Sharma², Rashmi Kaul Raina³, Rajesh Sharma⁴, Sujeet Raina⁵*

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Abstract
We report a case of isolated duodenal tuberculosis (TB) in a patient who presented with features of gastric outlet obstruction. The diagnosis was made on repeat endoscopic duodenal biopsy after initial histopathology failed to reveal the diagnosis. The patient recovered with antitubercular therapy. The index of suspicion has to be high in TB endemic countries as clinical, radiological, and endoscopic features are nonspecific.

Introduction
Isolated duodenal TB is a rare entity. It is generally seen in cases with massive involvement of the rest of the intestinal tract.¹ Characteristic clinical and radiological features have not been described so far and there is no specific picture on endoscopy. Further, endoscopic biopsy has been found to have a low diagnostic yield. We report a case of isolated duodenal TB in a patient who presented with features of gastric outlet obstruction. The diagnosis was made on a subsequent biopsy after the initial one failed to reveal the diagnosis. The patient recovered after receiving antitubercular therapy. We report this case for the following reasons: isolated duodenal TB is a rare entity. Second, to highlight that gastric outlet obstruction was an initial presentation of duodenal TB. Third, multiple biopsy samplings (8–10) are required, if initially negative and a high index of suspicion for the diagnosis are present. Fourth, we could identify acid-fast bacilli in biopsy tissue specimens which is an exception rather than the rule.

Case Description
A 32-year-old male presented himself with recurrent vomiting for 6 months. Vomiting happened mostly after eating. Vomitus was non-bilious and contained ingested food residue. He gave a history of weight loss which was undocumented. There was no history of anorexia, fever, abdominal pain, jaundice, gastrointestinal bleeding, cough, or hemoptysis. A review of other systems was normal. There was no significant past history. No family history of TB was present. His body mass index was 18 kg/m². General physical examination and systemic examination were normal. On investigations, hematology and biochemistry parameters were within normal limits. Chest X-ray was normal. He was seronegative for human immunodeficiency virus. Contrast-enhanced computed tomography of the abdomen showed thickened duodenum at D1 and D2 segments junction (Fig. 1). No lymphadenopathy was observed. Upper gastrointestinal endoscopy now revealed features of chronic inflammation, necrosis, giant cells, and granulomas. On Ziehl–Neelsen stain, the tissue specimen was positive for acid-fast bacillus (Figs 3A to C). The patient was initiated on antitubercular therapy; the intensive phase (rifampicin, isoniazid, pyrazinamide, and ethambutol) was given for 2 months followed by a continuation phase (rifampicin and isoniazid) for 8 months. The symptoms of the patient improved. At the end of the treatment, there were no features of gastric outlet obstruction and he had gained weight. Follow-up endoscopy at the end of treatment was grossly normal and revealed mild deformity at the junction of D1 and D2 without any obstruction (Fig. 2B). On follow-up histopathology, no giant cell granuloma was observed and was negative for acid-fast bacillus (Fig. 3D).

Discussion
Tuberculosis is a major global health problem. In 2014, there were an estimated 9.6 million new TB cases globally. India reported 2.2 million cases, out of which 0.2 million were extrapulmonary tuberculosis (EPTB).² The term EPTB has been used to describe the isolated occurrence of TB at body sites other than the lung. The gastrointestinal tract is the sixth most frequent site of extrapulmonary involvement. Duodenal TB constitutes less than 2% of abdominal TB.³ This uncommon

1 Associate Professor; ²Postgraduate Student, Indira Gandhi Medical College, Shimla; ³,⁴Associate Professor, Dr. Rajendra Prasad Govt. Medical College, Kangra; ⁵Assistant Professor, Indira Gandhi Medical College, Shimla, Himachal Pradesh, India; *Corresponding Author

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Figs 1A and B: Computed tomography of abdomen showing thickened D1 and D2 junction in (A) coronal section and (B) sagittal section

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Gastric Outlet Obstruction: Don’t Miss Duodenal Tuberculosis

Duodenal involvement is supposedly related to the inhibitory influence of gastric acid on the mycobacteria, rapid transit time through the duodenum allowing for a reduced contact time, and the relative paucity of the lymphoid tissue in the duodenal segment as compared to the rest of the gastrointestinal tract. Duodenal TB is virtually a disease of young age. Clinical presentation may be in the form of gastric outlet obstruction or nonspecific dyspepsia not responding to medical therapy. Rarely hematemesis, perforation, fistulae (pyeloduodenal, duodenocutaneous, and blind), excavating ulcers extending into the pancreas, and obstructive jaundice by compression of the common bile duct may be the presentation. Constitutional symptoms like fever and weight loss may be present. The gastric outlet obstruction is either due to extrinsic compression or luminal block. Extrinsic obstruction may be caused by lymph nodes or adhesions. Luminal obstruction is due to ulcerations or cicatrization. The contribution of either in the causation of obstruction is debatable. Frequently, the obstruction is the result of both processes acting together. Endoscopic biopsy has been found to have a low diagnostic yield. Multiple biopsies sampling like a combination of endoscopic biopsy with endoscopic mucosal resection is more sensitive to give the histological diagnosis. In the majority of case series or individual case reports, the presence of epithelioid granulomatous inflammation with or without necrosis has been taken as sine qua non of duodenal TB. Demonstration

Figs 2A and B: Endoscopic view of the duodenum (A) before treatment shows edematous infiltrated mucosa at the junction of D1 and D2 segment; (B) After treatment showing no obstruction

Figs 3A to D: Duodenal biopsy showing (A) chronic inflammation and necrosis [hematoxylin and eosin (H and E), ×100]; (B) Granulomas and giant cells (H and E, ×200) with (inset) higher magnification (H and E, ×400); (C) Acid-fast bacilli on Ziehl–Neelsen stain (arrow); (D) Follow-up biopsy did not show any giant cell granulomas (H and E, ×200) with (inset) higher magnification (H and E, ×400)
Gastric Outlet Obstruction: Don’t Miss Duodenal Tuberculosis

Management of duodenal TB is primarily with antitubercular therapy. Endoscopic balloon dilatation may be required for tubercular strictures. Rarely, surgery is required for delayed diagnosis as well as treatment of non-resolving obstruction, perforation, abscess, and fistula formation.

Gastric outlet obstruction is commonly associated with malignancies and peptic ulcer disease. The first diagnosis is always other than duodenal TB in most of the cases. Since the features of duodenal TB can be nonspecific, a high index of suspicion is necessary for the diagnosis based on clinical, radiological, and endoscopic features in TB endemic countries of South East Asia. Multiple biopsy sampling (8–10) or for obtaining deeper specimen a biopsy upon biopsy (well technique) has established histological diagnosis.

References

Book Review

Rheumatoid Arthritis

Editors: Aman Sharma, Rohini Handa • Publisher: Evangel • Price not specified.

This is a welcome issue of Rheumatology Clinics on RA, the most commonly treated inflammatory arthritis by the rheumatologists. The clinic takes us through the Hippocrates times to the modern times, the present understanding of RA, from almost no treatment to today’s effective therapy, and if nothing succeeds, recourse to surgery. No wonder it is almost a 500-page issue. Its important features are exclusively 61 Indian contributors, inclusion of aspects like sleep, sexual health, and juvenile arthritis patients transitioning into adulthood.

The clinic opens with a chapter on history of RA, citing milestones and anecdotes, followed by epidemiology of RA in India (mainly COPCORD studies), and growth of RA in India chapters. Penned by senior rheumatologists, the three chapters set the standard which is maintained in most of the subsequent chapters.

There are excellent chapters on novel biomarkers in RA and novel treatments on the horizon for RA. These provide a glimpse of the future. Some other chapters to be singled out are genetic basis, environmental and non-environmental risk factors chapter (complements the pathogenesis chapter), animal models in RA, and chapters on US, MRI, PET/CT scans. The illustrations of US and MRI are of high quality.

Understanding the pathogenesis of RA and conventional radiography (still the most commonly employed imaging modality) chapters leave an inadequate feeling.

The chapters dealing with classification criteria, preclinical, clinical and extra-articular manifestations are good. These are supplemented by informative chapters on lung, bone health, atherosclerosis, eye, and sleep in RA. Specifically, the chapter on lung involvement is excellent.

Prior to the specific therapy chapters, are important chapters on disease activity and disability, remission in RA (notable for the clarity of concepts, treatment principles and guidelines). These chapters set the stage for the chapters on therapy of RA.

Whether we like it or not, NSAIDs and glucocorticoids continue to be part of the therapeutic armamentarium. These should have been discussed in greater details. The chapter on methotrexate (MTX) is outstandingly informative, has two functional parts, one on anything and everything about MTX and the other on its therapeautic applications. This chapter is followed by informative chapters on conventional DMARDs other than MTX (lefunomide and pregnancy not discussed), TNF inhibitors (should have included Indian experience), non-TNF biologic agents (covers a large ground but does not mention biosimilars). Guidelines for perioperative use of DMARDs would have been useful, and JAK inhibitors (does not include safety or otherwise during pregnancy and lactation).

Next are the chapters on specific problems and aspects in relation to RA, namely infections including COVID-19 (remarkable for clarity), vaccination (very informative but verbose), children with juvenile arthritis transitioning into adulthood, significance of counselling and adherence, diet, sexual health and lastly contraception, pregnancy, breast feeding, and fatherhood. All the chapters provide good information.

In the end are chapters on physical therapies (has many practical tips, but does not explain terms like concentric, eccentric), reconstruction in rheumatoid hand (uses too many abbreviations of muscles, tends to be technical) and orthopaedic aspects of RA (more general than specific). There is an index at the end.

Apart from the omissions mentioned, there are a few grammatical slips and printing errors, e.g. tall in place of toll, tenants in place of tenets. These, however, do not affect the overall quality of the clinic. The clinic will be most useful to in-training students, though there is something for all.

Dr. VR Joshi
Toxic Megacolon: A Rare but Lethal Complication of Ulcerative Colitis

Sanjay Fotedar¹, Manish Kumar²*, V K Katyal³, Sandeep Goyal⁴

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Toxic megacolon is a rare and potentially lethal complication of severe colitis, defined as dilation of the colon more than 6 cm in the absence of distal obstruction. Etiological factors of toxic megacolon include inflammatory (like ulcerative colitis) or infectious conditions (like clostridium difficile), ischemic colitis, collagenous colitis, and malignancy (obstructive colorectal carcinoma).¹ Most commonly associated with ulcerative colitis or ileocolonic Crohn’s disease. The lifetime risk of toxic megacolon in ulcerative colitis is estimated to be 1–2.5%.

The mechanisms involved in the pathogenesis are not clear, although chemical mediators such as nitric oxide and interleukins are thought to play a pivotal role in its pathogenesis. The colon (mainly transverse colon) becomes dilated to at least 6 cm. In addition to dilation of the colon, other suggestive findings include loss of haustral markings, with pseudopolyps often extending into the lumen. In the case of ulcerative colitis, immunosuppressive should be started with corticosteroids and potentially with a calcineurin inhibitor.² The surgical procedure of choice is colectomy and ileostomy.³

Figures 1A to C show a case of a 20-year-old female, a known case of ulcerative colitis presented with complaints of pain in the abdomen and constipation and obstipation. Per abdomen examination showing a tense tender and distended abdomen. X-ray of the abdomen showing dilated transverse and descending colon. Serial X-ray showing increasing dilation of colon. Infectious and other causes were ruled out. Flatus tube and Ryle’s tube were inserted for decompression but did not get relief. After this, the patient was sent for surgical intervention for toxic megacolon.

References

¹²³Associate Professor; ²Junior Resident; ³Senior Professor and Head of Department, Department of General Medicine, Pt. B.D. Sharma, PGIMS, Rohtak, Haryana, India; ⁴Corresponding Author

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Diffuse-calcified Spleen: Post-tubercular Squeal of Isolated Splenic Tuberculosis in Immune-competent Host

Sanjay Fotedar¹, Banoth Sridhar²*, Komal Dahiya³, Vinay Kumar Malik⁴

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A 55-year-old male presented to the outpatient department of our institution for evaluation of dyspnea. History revealed the patient was a chronic smoker, normotensive, non-diabetic, non-reactive for HIV, hepatitis B, A, and C by ELISA, and without any comorbid association. The patient was diagnosed as a case of chronic obstructive pulmonary disease (COPD) and managed accordingly. Chest X-ray revealed COPD changes and multiple calcified lesions in the left upper quadrant of the abdomen (Fig. 1) and the X-ray abdomen showed isolated calcification of the spleen (Fig. 2). Detailed clinical examination and investigations did not reveal any active infection. History was revisited which revealed that the patient had taken antitubercular treatment for abdominal tuberculosis (splenic), records are not available. Contrast-enhanced computed tomography (CECT) abdomen revealed isolated multiple calcified lesions of the spleen (Fig. 3), axial section, and coronal section of CECT abdomen showing the diffuse-calcified spleen (Fig. 4).

Diffuse-calcified spleen is associated with various granulomatous diseases including infections. Isolated splenic tuberculosis, as such being rare, is pathomorphologically described in five subtypes, miliary tuberculosis, nodular, abscess, calcified, and mixed. Various diagnostic modalities include ultrasonography, computed tomography scan, needle biopsy, laparoscopic biopsy, and searching for primary disease in other organs of the body.

**Fig. 1:** X-ray chest—posteroanterior view. Diffuse calcified lesions in the left upper quadrant of the abdomen

**Fig. 2:** X-ray abdomen—anteroposterior view

**Fig. 3:** CECT abdomen—axial section

**Fig. 4:** CECT abdomen—coronal section

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Adolf Windaus (1876–1959) studied medicine in Berlin, and then switched over to chemistry and obtained his PhD at the University of Freiburg, and taught at Gottingen, Germany. He synthesized histamine, a compound with important physiological properties in 1907. Windaus devoted his career spanning some 30 years, exclusively to the elucidation of the structure of cholesterol. This study was a part of his study of complex alcohols known as sterols. Windaus discovered 7-dehydrocholesterol in cod liver oil which is the chemical precursor of vitamin D and showed that it is a steroid. He discovered that it is converted into vitamin D by a specific spectrum of sunlight which breaks one of its chemical bonds within the molecule in 1–3 days. This explained why exposure to sunlight can prevent vitamin D deficiency in humans. Even today with all vitamin D fortified foods, 80% or more of our vitamin D is still produced from sunlight exposure. Windaus also established the relation of cholesterol to bile acids; hitherto unsuspected link between two biological substances. His research also helped establish the chemistry of sex hormones and advanced the development of some cardiac drugs. He was also the first to locate sulfur atom in the molecule of vitamin B1 (thiamine) in 1932.

The final determination of the accepted structure of cholesterol was accomplished by X-ray crystallography by Carlisle and Crawford in 1945. Windaus’ contribution to steroid and sterol chemistry was immense of which vitamin D is only a part. Windaus received the 1928 Nobel Prize in chemistry “For the services rendered through his research into the constitution of steroids and their connection with vitamins.”

Among scientists of Germany, Windaus openly opposed National Socialism. A sense of justice and love of truth brought Windaus dangerously close to the Nazi regime. He stopped all scientific research in 1938 and died in 1959 aged 83 years.

Being fat soluble, the potential for toxic accumulation of vitamin D and toxicity became an issue of exaggerated concern during most of the 20th century. However, in the mid-1990s, a silent revolution questioned the vitamin D levels for human health and showed that vitamin D deficiency was rampant and toxicity rare, occurring with extremely high intake, never from sunlight.
Sudden Rise of Uric Acid Levels in a Patient with Chronic Kidney Disease: Is a Common Food to Blame?

Rudrajit Paul1, Rathindranath Sarkar2
1Consultant Physician, Department of Medicine, Ruby General Hospital; 2Ex-HOD, Department of Medicine, Medical College Kolkata, Kolkata, West Bengal, India

Sir/Madam,

Chronic kidney disease (CKD) is often associated with slightly raised serum uric acid levels.1 Earlier, this urate level was thought to be an innocent biochemical marker of kidney dysfunction. But now, urate levels have been found to be a direct contributor to kidney damage via its role in glomerular injury, tubular fibrosis, and glomerular hypertension.1 Hence, serum urate levels in CKD must be tightly regulated and anything that leads to a rise in urate levels must be curbed. There are a lot of extraneous factors, dietary or otherwise, leading to a surreptitious rise in serum urate levels. We here describe one such dietary factor.

An 80-year-old man, a known case of CKD, presented with sudden onset of right ankle pain and swelling. The kidney disease had been caused by obstructive uropathy secondary to prolonged urethral stricture. His serum creatinine had remained stable at around 2.5–3 mg/dL over the last 6 months along with normal blood biochemistry and he was only on oral medications with no history of hemodialysis. During this acute presentation, his urine output was stable at 1–1.2 L/day. Blood biochemistry revealed serum creatinine of 5.07 mg/dL and serum uric acid of 11.8 mg/dL. The patient had not started any new drugs recently. His complete hemogram was not suggestive of any hematological malignancy. The patient was nonalcoholic and did not take any animal meat or seafood. The clinicians were at first baffled by this sudden enigmatic rise of urate levels. On further probing, it was revealed that during the ongoing heat wave, the patient was feeling very thirsty. Since his daily water intake was tightly regulated, he had started taking a popular brand of soft drinks occasionally instead of water to quench his thirst. This change in diet had occurred from the beginning of summer over the last 1 month.

The ankle pain subsided. His serum creatinine also came down to previous levels.

Soft drinks are very popular nonalcoholic beverages across all age groups in India. Market studies have shown exponential growth in the soft drink market all over the country over the last 5 years.2 A societal taboo on alcohol makes these sweetened carbonated beverages the first choice for public banquets or feasts in this country. However, in contrast to other developed countries where food consumers often make informed choices, the Indian consumer is quite gullible and misled by the prevalent trends.

These soft drinks contain a lot of harmful ingredients including, but not limited to, fructose.3 Fructose is the only carbohydrate which increases blood uric acid levels, in addition to increasing blood sugar levels.3 This occurs due to accelerated degradation of purine nucleotides.4 The intake of fructose leads to rapid production of fructose-1-phosphate via a step that causes intracellular depletion of adenosine triphosphate.4 Accumulation of this intracellular phosphate activates adenosine monophosphate deaminase and leads to rapid purine degradation.4

Since fructose has greater sweetening power compared to glucose, it is the preferred sweetening agent in cold drinks.3 Thus, excess intake of cold drinks is associated with a quick rise in urate levels. Usually, this rise is asymptomatic and the levels come down with cessation of fructose intake. But in cases like ours, this sudden rise may precipitate an acute arthritis attack. Thus, in CKD cases, it is advisable to avoid all these soft drinks completely.

In addition to increasing urate levels, fructose also increases the risk of fatty liver. We present this case to sensitize clinicians to this lesser-known deleterious health effect of soft drinks. In our country, there are a lot of misconceptions about the dietary restrictions in gout. While people tend to focus on red herrings like tomato, lentil, or other vegetables like spinach, which have hardly any effect on serum urate levels, they often tend to gloss over potentially harmful food like soft drinks. Thus, public awareness about the health effect of soft drinks must be raised. Cases like ours are more likely to occur during the summer months in India.

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drink-market/#—text=1%20total%2C%201.2%20billion%20people,and%20one%20third%20of%20
Malaysia.

Post-COVID-19 Isolated Renal Mucormycosis Coincidence vs Association

Minal Shastri1, Vaishnavi M Rathod2, Darshankumar Manubhai Raval3
1Professor and Head of Unit; 2,3Senior Resident Doctor, Department of Medicine, Medical College Baroda, Vadodara, Gujarat, India

Sir,

Mucormycosis (previously called zygomycosis) is a rare but serious angioinvasive infection caused by a group of fungi called mucormycetes. Isolated renal mucormycosis (IRM) is a rare presentation, encountered mainly in developing countries like India and China. Rarer to find this entity in immunocompetent patients without any risk factors.1,2 Specific guidelines for the treatment are not yet known but combined medical and surgical therapy is considered the best modality for its management. After the second wave of COVID-19 infection in India, the country faced an epidemic of mucormycosis in previously COVID-positive patients. Here, we present a rare case of IRM in a previously COVID-positive middle-aged female.

A middle-aged married female, previously COVID positive, known case of hypertension and freshly diagnosed case of diabetes mellitus, presented with complaints of fever, burning micturition, and flank pain for 10–15 days. There was no complaint of cough, headache, decreased urine output, facial swelling, orbital swelling, nasal discharge, loosening of tooth, weight loss, anorexia, vaginal discharge, or breathlessness.

She was treated as moderate COVID-19 disease one month back with antiviral, antibiotic, steroid, anticoagulant, and supportive treatment, without oxygen support, and discharged subsequently. After a month, she developed complaints of fever, burning micturition, and flank pain for which she consulted a private hospital. She was investigated there with routine investigation, urine culture, and abdominal ultrasound.
The investigations were suggestive of acute kidney injury with increased urea and creatinine, raised inflammatory markers [ferritin, total count, C-reactive protein (CRP), and procalcitonin], urine culture was showing growth of *Klebsiella* and *Mucor* spp., and ultrasound abdomen with pelvis showing bilateral pyelonephritis with heterogeneous echogenicity and preserved corticomedullary differentiation (Tables 1 and 2). The patient was operated for pyelonephritis with insertion of DJ stents in both ureters, but due to the non-availability of injection amphotericin-B in the hospital, the patient was referred to the present hospital.

On admission in the present institute, the patient was vitally stable, the systemic examination did not reveal any abnormality, and serial routine investigations were done (Table 1). The patient started treatment with injection liposomal amphotericin-B (total of 21 doses), and higher antibiotics (cefo sulbactam, metronidazole, meropenem, and linezolid). The patient was also treated for acute kidney injury, electrolyte abnormality due to amphotericin-B, and comorbidities, that is, hypertension and diabetes simultaneously. During the course of her hospital stay, the patient was consulted with urosurgeon and nephrologist. As per their advice, CT kidney, ureter, and bladder (KUB) (plain) was done after 1st, 7th, 14th, and 21st day of injection amphotericin-B, suggesting a gradual reduction in the size of left-sided pyelonephritis with normal right kidney. Investigations done to rule out other organ involvement for mucormycosis did not reveal any abnormality, and she was also screened negative for pulmonary and urinary tuberculosis (Table 2).

The patient was treated primarily as IRM with urinary tract infection (UTI) for a month with intensive antifungal and antibiotic therapy with minimal surgical interventions. As her symptoms and renal function improved, along with the reduction in the size of pyelonephritis, she was discharged with oral antibiotics for UTI with advice to follow-up regularly.

As per literature, involvement of the kidneys usually occurs as a result of disseminated mucormycosis. The present pandemic of COVID-19 has increased the incidence of mucormycosis. Apart from the increased number of cases, several rare occurrences of mucormycosis in unusual locations are being reported during this pandemic in India. The predisposing factors for mucormycosis were present in our patient such as past history of COVID-19 infection, use of steroids, freshly developing diabetes, and raised inflammatory markers (total leukocytes, CRP, ferritin, procalcitonin). However, to establish an association between COVID-19 and IRM, further intensified research is needed to be done.

To conclude, although a rhino-orbital form of mucormycosis is most commonly seen in COVID patients, here we have reported a rare case of IRM in a previously COVID-positive middle-aged female who presented with bilateral pyelonephritis and acute kidney injury. The mortality of bilateral mucormycosis along with acute kidney injury is reported to be very high in literature, however we have successfully treated our patient with extensive antifungal (amphotericin-B) and antibiotic treatment, and minimal surgical intervention (bilateral DJ stenting), making it one of the rare case of renal mucormycosis. Here, we are not

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<td>Cl⁻ (mmol/L)</td>
<td>87</td>
<td>111</td>
<td>105</td>
<td>104</td>
</tr>
<tr>
<td>Bicarbonate (mEq/L)</td>
<td>26</td>
<td>25</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>RBS (mg/dL)</td>
<td>192</td>
<td>129</td>
<td>145</td>
<td>132</td>
</tr>
<tr>
<td>Bilirubin—T, D, ID (mg/dL)</td>
<td>0.8, 0.3, 0.5</td>
<td>0.7, 0.3, 0.4</td>
<td>1.0, 0.4, 0.6</td>
<td>0.8, 0.3, 0.5</td>
</tr>
<tr>
<td>Protein (gm/dL)</td>
<td>7.1</td>
<td>7.6</td>
<td>7.8</td>
<td>7.5</td>
</tr>
<tr>
<td>Albumin (gm/dL)</td>
<td>3.6</td>
<td>3.4</td>
<td>3.2</td>
<td>3.3</td>
</tr>
<tr>
<td>SGPT (IU/L)</td>
<td>12</td>
<td>20</td>
<td>19</td>
<td>24</td>
</tr>
<tr>
<td>SGOT (IU/L)</td>
<td>51</td>
<td>47</td>
<td>38</td>
<td>41</td>
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<tr>
<td>ALP (U/L)</td>
<td>383</td>
<td>278</td>
<td>310</td>
<td>265</td>
</tr>
<tr>
<td>EGFR (mL/min/1.72 m²)</td>
<td>20</td>
<td>44</td>
<td>36</td>
<td>40</td>
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</table>
able to find any strong association between COVID-19 and IRM due to very small sample size, therefore, whether the occurrence of renal mucormycosis in post-COVID patients is a coincidence or association, is an area of further research.

References


Urine Drug Screens in Routine Clinical Care: Underutilized?

Raka Jain1, Raman Deep2, Rakesh K Chadda3

1Professor, National Drug Dependence Treatment Centre; 2Additional Professor, 3Professor and Head, Department of Psychiatry; Chief, National Drug Dependence Treatment Centre, All India Institute of Medical Sciences, New Delhi, Delhi, India

Sir,

Urine drug tests are useful clinical tools for assessing and screening for substance use in a variety of clinical settings. However, they have been underutilized in routine clinical care outside of settings such as deadication centers, casualty, or sports medicine. In the Indian context, limited studies are available on urine-based screenings from patients visiting general hospital settings.1–3 Given the high rate of comorbidities between mental disorders and substance use, there is a need for documentation of service utilization of urinalysis within mental healthcare settings. However, it must be added that the same index of suspicion is required in several other medical specialties, where patients often land up with complications due to underlying substance use.

The study aimed to examine the 5-year service utilization of urine drug screens in the context of a mental healthcare setting in a tertiary care general hospital. The urinalysis data from the addiction treatment center of the institute was intentionally not included. After an institutional ethics clearance, the study was undertaken as a retrospective analysis for consecutive urine samples received from the psychiatry department between January 2015 and December 2019. The study was restricted to the pre-pandemic period due to a long break in clinical services during the pandemic. Urine drug testing was carried out using a modified hydrolysis method followed by thin layer chromatography for buprenorphine, morphine, benzodiazepines, pentazocine, and tramadol; gas chromatography to confirm benzodiazepines, pentazocine, and tramadol; and qualitative immunoassay cassette test (Alfa Scientific Designs, Inc., Poway, CA, USA) for cannabis and tramadol.

A total of 475 urinalysis requests were received over the study period, from outpatients (60%) and inpatients (40%). Given the large number of annual patient visits in the psychiatric outpatient setting (about 80,000 patient visits), those sent for urinalysis constituted a rather small fraction. The mean age was 27.54 ± 9.54 years. A total of 133 (28%) had a primary diagnosis of severe mental illness, 161 (33.9%) had previously known substance use disorder, and 176 (37.1%) had no mention of diagnosis.

The overall urinalysis-positivity rate in samples was 44.6% (212/475). Nearly one in two samples came out to be positive, which is a fair detection rate. Opioids were detected in 17.4% of tested samples, largely as morphine which is indicative of heroin (3-acetyl morphine) use. Cannabis was detected in one in four (27.9%). Among those with severe mental illness, 19.5% (n = 26/133) of requisitions had mentioned co-occurring substance use, but urinalysis picked up about 38.6% more samples (36/133). Further, it is to be noted that the window of detection by means of urinalysis is only 48 hours for most drugs and 3–4 weeks for cannabis.
Only 5.7% of samples were from female patients. Those samples had a comparable pattern of positivity for all substances of use except for a higher pentazocine positivity (5/12 vs 2/50; p < 0.001). Literature indicates that women substance users often have higher rates of psychiatric issues (e.g., depression) and medical issues (e.g., chronic pain syndromes) leading to misuse of prescription opioid medication. Continued substance use is associated with poor physical health as well as mental health.

Overall, there is a scope for optimal utilization and availability of urine drug screens in general hospital settings. Effective utilization of urinalysis in clinical practice can help in optimal screening and timely interventions, potentially improving patient outcomes.

**References**


**COVID-19 Patients in the ICU with and without Diabetes: Mortality and Its Predictors**

Swaraj Waddankeri, Kshiti J Arora, Swati S Hiremath, Sharan Shrvan Harsoor, Bharat Konin, Basavaraj Harsoor, Basavaraj Patil Raikod

Sir,

The extremely high prevalence of type 2 diabetes (T2D) in India 8.9% viz., 70 million of the total adult population is truly concerning considering the pandemic situation. The systematic review and meta-analysis of seven studies including 1,576 infected patients demonstrated diabetes (8%) to be the second most common comorbidity after hypertension (17%) in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) patients. The dataset from Mount Sinai Health System showed that the overall mortality in patients (n = 3,841) with SARS-CoV-2 was 8.14%, while in the diabetic subgroup (n = 608) it was 29%. The Chinese Center for Disease Control dataset of 72,314 cases also found that the patients with T2D had twice the risk of ICU admission. These data suggest that diabetes increases the probability of more severe infection, leading to increased morbidity and mortality.

We undertook this single-center prospective, observational study in patients with reverse transcription-polymerase chain reaction (RT-PCR) confirmed SARS-CoV-2 infection admitted to the ICU to determine if there is a difference in clinical, biochemical, radiological parameters, and risk of mortality among critically ill patients with and without T2D and identify the prognostic markers. From a total of 395 patients who presented to the hospital between August and September 2020, 100 clinically symptomatic COVID-19-positive patients necessitated admission to the ICU. RT-PCR negative severe acute respiratory infection (n = 165) or noncritical cases (n = 130) were excluded. The age (59.06 ± 47.04 years; p < 0.0001), respiratory rate (86 vs 44; p < 0.0001), and body mass index (BMI) (24.57 ± 4.5 vs 23.02 ± 2.77; p = 0.04) were significantly higher and SpO2 was (88.62 ± 6.32 vs 92.46 ± 5.73; p = 0.002) lower in the T2D group compared to the non-T2D group. Nonetheless, the two groups showed no differences in gender distribution (p = 0.6413), history of COVID-19 in the family (p = 0.1635), duration of hospitalization (p = 0.96), or systolic and diastolic blood pressure (p = 0.39). There was no difference in the signs and symptoms except for dry cough which was higher in the T2D group (84 vs 64%; p = 0.023). The mortality rate was significantly higher in the T2D group compared to the non-T2D group [20% (n = 10) vs 6% (n = 3); p = 0.0384]. Consolidation occurred in a significantly greater number of patients with than without T2D (38 vs 20%; p = 0.0484). The CT severity score was significantly higher in the patients with than without T2D (14.44 ± 4.91 vs 11.54 ± 5.71; p = 0.007).

The laboratory blood analysis data showed that neutrophil-to-lymphocyte ratio (NLR) (7.02 ± 4.87 vs 4.95 ± 2.69; p = 0.01) and serum glutamic oxaloacetic transaminase (58.66 ± 37.02 vs 41.24 ± 20.37; p = 0.004) were significantly higher in patients in the T2D group compared to the non-T2D group while lymphocyte count (15.15 ± 8.55 vs 20.38 ± 10.46; p = 0.007) was lower. Hemoglobin A1C (HbA1c) (%) was evidently higher in the T2D vs non-T2D group (7.20 ± 3.08 vs 5.418 ± 0.35; p = 0.000). There was no significant difference in the number of drugs administered, oxygen therapy (86 vs 54%; p = 0.0005) and noninvasive ventilation (30 vs 14%; p = 0.05) were required for significantly more patients in the group with T2D than without.

Among those with T2D, the mortality was 20% (10/50). Subgroup analysis of survivors and nonsurvivors in the diabetic group showed that the patients in the nonsurvivor group had significantly lower hemoglobin (12.48 ± 1.28 vs 10.25 ± 1.84; p < 0.0001) and lymphocyte levels (16.33 ± 6.25 vs 11.8 ± 5.92; p = 0.043), and higher total cell count (9500.00 ± 2936.41 vs 13570 ± 4455.47; p < 0.0001), NLR (6.33 ± 5.07 vs 11.21 ± 7.92; p = 0.019), alkaline phosphatase (67.00 ± 25.50 vs 134.7 ± 116.67; p = 0.0), C-reactive protein (CRP) (13.12 ± 9.92 vs 105.13 ± 33.58; p < 0.0001), and D-dimer (504.23 ± 395.50 vs 5831.2 ± 3989.55; p < 0.0001) compared to survivors. Comparison of random blood sugar (400.1 ± 78.33 vs 206.28 ± 72.50; p < 0.0001) and HbA1c (11.568 ± 2.76 vs 6.10 ± 2.04; p < 0.0001) values nonsurvivors and survivors showed that both these were significantly greater in the nonsurvivor group. The CT score of nonsurvivors with T2D was significantly greater than survivors (17.3 ± 3.27 vs 13.72 ± 5.02; p = 0.0378).

Among the non-T2D patient group, the mortality was 6% (n = 3/50). Subgroup analysis of survivors and nonsurvivors in the diabetic group showed that the patients in the nonsurvivor group had significantly lower hemoglobin (12.65 ± 1.26 vs 11.03 ± 0.98; p = 0.03), lymphocyte (17.91 ± 6.26 vs 6.00 ± 3.46; p = 0.0022), neutrophil (77.66 ± 6.18 vs 89.00 ± 1.73; p = 0.003), NLR (5.08 ± 2.58 vs 17.90 ± 7.92; p < 0.0001), lactate dehydrogenase (306.39 ± 115.49 vs 636.67 ± 71.59; p < 0.0001), and D-dimer (452.97 ± 701.58 vs 5349.00 ± 3088.25; p < 0.0001) compared to survivors. Among non-T2D patients,
the BMI (31.63 ± 1.33 vs 22.47 ± 1.72; p < 0.0001) and the CT score (20.33 ± 1.15 vs 10.97 ± 5.42; p = 0.0048) in nonsurvivors was significantly greater compared to the survivors.

In the age-adjusted regression analyses for the total patient population, a CT score ≥18 [4.526 (1.215–17.522); p = 0.02], N > 80 [4.060 (1.115–17.478); p = 0.04], L < 20 [14.995 (2.598–286.418); p = 0.012], and HbA1c > 7 [28.830 (5.944–177.798); p < 0.001] was found to be statistically significant. In the multivariate regression analysis, a CT score ≥18 [17.706 (1.872–474.957); p = 0.028] and HbA1c > 7 [197.009 (9.517–21945.270); p = 0.005] were significant predictors of increased mortality risk. In the age-adjusted regression analyses for the T2D group, only HbA1c > 7 [58.268 (7.703–1263.426); p = 0.0006] and CRP > 41.4 [14.589 (2.194–294.669); p = 0.018] were found to be statistically significant.

**Conclusion**

Compared to patients without, patients with T2D may have a more severe clinical course as indicated by the biochemical, radiological, and clinical parameters assessed in our study and in accordance with previous clinical evidence. Further, a higher CT severity score and HbA1c at admission are negative prognostic markers for increased risk of mortality. Such patients should be categorized as high risk and treated appropriately.

**Ethics**

This study protocol was exempted from ethical review by the Institutional Review Board of Basaveshwar Teaching and General Hospital because the data analyzed did not contain any patient identifiable information.

**References**

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Switching from Telmisartan to Olmesartan offers responder rate improvement

COTO Study: 132 Diabetic patients

<table>
<thead>
<tr>
<th>Clinic BP</th>
<th>Home BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Baseline</td>
</tr>
<tr>
<td>TEL 40 mg</td>
<td>TEL 40 mg</td>
</tr>
</tbody>
</table>

Achievement rate for target BP (%)

- Telmisartan
- Olmesartan

- \( p<0.01 \)
- \( p<0.01 \)

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