Editorial
Hear the Ear: Gear up, Diabetes Care

Article
Soluble TNFR1 Levels in Type 2 Diabetes and its Association with Stages of Proteinuria

Article
Neurocognitive Disorders in HIV-positive Patients

Review Article
INDIaN Consensus on the mAnagemenT of cOugh at pRimary care setting (INDICATOR)

Review Article
Post-COVID-19 Cardiovascular Sequelae and Myocarditis

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10 Journal of The Association of Physicians of India, Volume 71 Issue 6 (June 2023)
Hear the Ear: Gear up, Diabetes Care

Sanjay Kalra1*, Navjot Kaur2

INTRODUCTION

Diabetes is a multifaceted and multisystemic disease. A broad spectrum of pathophysiological abnormalities interacts to create an equally complex array of clinical presentations. Experts have crafted taxonomic structures to understand the nosography of diabetic complications. Acute and chronic, metabolic and mitogenic, vascular-metabolic and visceral-metabolic, macrovascular and microvascular—these are some of the adjectives we use to list complications of diabetes in meaningful buckets. Taxonomy, however, is not foolproof. Even when we classify living entities as plants or animals, animals as vertebrates or invertebrates, and vertebrates as male or female, we acknowledge that there may be exceptions. This is true for diabetes as well. Not all cases of diabetes can be typed clearly, and not all complications can be classified uniformly.

One complication that defies a simple label is sensorineural hearing loss (SNHL). Hearing loss is known to occur more frequently in persons living with diabetes. As per available clinical data, the prevalence of hearing loss in people with long-duration of uncontrolled hyperglycemia in India can be as high as 85%. Another study from the United States has specifically depicted the weighted prevalence of low-frequency hearing loss (defined as the average threshold at 500, 1,000, and 2,000 Hz), and high-frequency hearing loss (average threshold at 3,000, 4,000, 6,000, and 8,000 Hz) to be 34.6, and 65.5%, respectively. The high prevalence is attributed to multiple risk factors and etiopathological mechanisms that explain the association between hearing loss and diabetes. The detrimental downstream effects of untreated hearing loss, such as dementia, are also well-reported. Yet, this crucial clinical entity is neither listed in the classic vascular complications of diabetes nor has been adequately addressed in novel concepts such as visceral-metabolic optimization of diabetes. The problem has also not been adequately prioritized as a significant risk in the World Health Organization Global Report on diabetes.

Multiple similarities, connections, and associations exist between diabetes and hearing loss (Table 1). Paradoxically, this complexity may preclude awareness and understanding of the importance of hearing loss in diabetes. Abraham et al., from Ludhiana, Punjab, India, address this gap by sharing data on the prevalence and clinical associations of hearing loss in type 2 diabetes. In their well-designed study of 200 adult participants living with type 2 diabetes, they assessed the status of distal peripheral sensory-motor neuropathy (DSPN) using the Michigan diabetic neuropathy score and hearing loss with pure tone audiometry. The study defined hearing loss as pure tone average >15-decibel hearing level (dBHL) in the worse ear. Clinically significant hearing loss (CSHL) was defined as pure tone average >25 dBHL in the worse ear. Pure tone average was defined as the average of 500, 1,000, and 2,000 Hz. The World Health defines hearing loss as a hearing threshold >20 dB in the better hearing ear. Hearing threshold refers to the minimum sound intensity that an ear can detect as an average of values at 500, 1,000, 2,000, and 4,000 Hz in the better ear. In this study, the prevalence of hearing loss was 81%, including 28.5% with CSHL. Further the authors reported that hearing loss was more frequent in persons with moderate/severe neuropathy (87.6%) and mild neuropathy (80.9%), compared to those without neuropathy (66.7%); hearing loss and hearing threshold correlated directly with the severity of neuropathy, and also with a degree of uncontrolled hyperglycemia, or glycated hemoglobin (HbA1c). Hearing loss was also more common in elder men and was significantly associated with reduced estimated glomerular filtration rate on univariate analysis. Hearing impairment was more in higher frequencies (2000, 4000, and 8000 Hz), and the correlation of hearing loss with neuropathy was also stronger in these frequencies.

The relationship between neuropathy and hearing impairment suggests that evaluation of auditory acuity must be included as a part of the screening and monitoring of neuropathy in diabetes. One may screen for hearing loss with simple validated tools such as the single question screening tool and Hearing Handicap Inventory for the Elderly–Screening version. Clinical tests like the whispered voice, finger rub, and tuning fork tests may also be used. Handheld audiometers are easy to use and interpret and can be utilized at different levels of diabetes care settings, including primary healthcare centers.

The Cinderella status of hearing loss, as a chronic vascular complication, of diabetes, may also be due to the perception that there are no specific treatments or interventions for it, this is not true. Reasonable glycemic control itself may prevent or retard the impairment of hearing. In persons with type 2 diabetes, for every 10% increase in HbA1c, a 32% increase in impaired speech perception and a 19% increase in high-frequency hearing loss have been noted. This means that glycemic control per se has an otoprotective effect. Metformin has been shown to decrease the probability of sudden SNHL in type 2 diabetes as well.

Aspirin, a drug frequently used to reduce the risk of atherosclerotic cardiovascular disease, is known to be ototoxic. It reduces cochlear emissions, damages the spiral ganglion neurons, and negatively impacts the central processing of hearing. Therefore, it should be used only when the indication is backed by evidence. Certain antibiotics, such as aminoglycosides, and anticancer drugs like cisplatin and carboplatin, can also impair hearing. These should be used cautiously in persons with, or at high-risk of, hearing loss. Excessive noise exposure is the leading cause of hearing loss, and this should be a focus of primordial and primary preventative strategies. Avoidance of substance abuse, especially tobacco, should also be highlighted.

Hearing loss is connected with other microvascular morbidities such as nephropathy and retinopathy. Considering this, it makes sense to explore the effect of glucagon-like peptide receptor agonists (GLP1RA), sodium-glucose cotransporter-2 inhibitors (SGLT2i), and linagliptin on auditory acuity. These drugs have a renoprotective impact and may be otoprotective as well. Another renoprotective drug, finerenone, reduces inflammation and fibrosis in the kidney through its mineralocorticoid receptor

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Hear the Ear: Gear up, Diabetes Care

Table 1: Diabetes and hearing loss—similarities, synapses, and solutions

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<tbody>
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<td>• Both diabetes and hearing loss are equally common.</td>
</tr>
<tr>
<td>• The prevalence of both syndromes is increasing worldwide.</td>
</tr>
<tr>
<td>• Both have more than one type of presentation.</td>
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<td>• Both conditions have well-described pre-disease states.</td>
</tr>
<tr>
<td>• A significant proportion of persons living with these diseases are unaware of their diagnosis.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Both may have a genetic origin.</td>
</tr>
<tr>
<td>• Both increase with age.</td>
</tr>
<tr>
<td>• Lifestyle is a major determinant of both—excessive noise contributes to hearing loss, and physical inactivity to diabetes.</td>
</tr>
<tr>
<td>• Dietary choices influence both glucose control and auditory health.</td>
</tr>
<tr>
<td>• Both can be iatrogenic—they can be precipitated by the use of drugs.</td>
</tr>
</tbody>
</table>

Etiopathogenesis

- The inner ear is one of the most densely vascularized structures in the body and is susceptible to vascular injury, which is common in diabetes.
- Microangiopathy, that is, microvascular dysfunction or endothelial dysfunction, can lead to hearing loss.
- The inner ear’s stria vascularis is a high-energy consumer with a high mitochondrial density and is susceptible to abnormalities in oxidative phosphorylation.
- Dysfunctional mitochondria, and the associated generation of reactive oxygen species, are essential pathophysiologic abnormalities in diabetes and hearing loss.
- Poor glycemic control is directly associated with hearing loss.

Management and prevention

- Lifestyle and dietary modification are important aspects of managing both conditions
- Early screening and diagnosis, as well as the regular follow-up, are mandated in both.
- Metformin has been shown to reduce the risk of hearing loss.
- GLP1RA, SGLT2i, and finerenone, which are nephroprotective, may be otoprotective as well.
- Imeglimin, through its mitochondrial-based mechanism of action, may improve auditory health as well as help manage glucose in type 2 diabetes.

Pragmatic proposals

- All persons with hearing loss, especially high pregnancy hearing loss, should be screened for diabetes.
- All persons with diabetes should be screened for hearing loss.
- Screening for hearing loss should be done along with screening for neuropathy, and/or retinopathy.
- Screening may be done earlier, or repeated more frequently, in persons with risk factors for, or established ear disease.
- Good glycemic control, along with the facilitation of a healthy lifestyle, and aids to enhance hearing, should be offered to all persons living with CSHL.

antagonist activity. Finerenone has been shown to improve renal outcomes and retinal health and reduce mortality. It is logical, therefore, that it may also exhibit oto-beneficial effects. Imeglimin, an oxidative phosphorylation inhibitor, is a new glucose-lowering drug that acts as an insulin secretagogue and sensitizer. Its effects on the mitochondrial structure and function and reduction of reactive oxygen species generation are unique. This leads one to hypothesize that imeglimin may help restore mitochondrial health in the inner ear and prevent hearing loss.

It is important to “hear the ear” and address this neglected issue. Not only does restoration of hearing acuity improves the quality of life, but it also facilitates interaction with all healthcare providers, encourages understanding of one’s condition, and improves adherence to therapy. Hearing loss is associated with social withdrawal and isolation and a higher risk of dementia. Early diagnosis and management of hearing loss can mitigate these psychosocial challenges and prevent dementia in persons at increased risk of the disease. We thank Abraham et al., and the Departments of Medicine and Endocrinology at Christian Medical College, Ludhiana, Punjab, India, for highlighting the heavy burden of hearing loss in persons living with type 2 diabetes. We join them in their call to tackle this significant complication of diabetes. As suggested by Jubbin Jacob and KVS Hari Kumar (personal communication), this research will kickstart a focus on aurocrinology or otocrinology. Based on their data, which shows a strong correlation between DSPN and hearing loss, we suggest that hearing loss be considered a part of neuropathy in diabetes. Further studies are warranted to generate evidence to support the premature onset of presbycusis (age-related hearing loss) in people living with diabetes, which would help to reduce hearing loss-associated morbidity. Strategies and structured formats for evaluating sensory neuropathy can be expanded to include the elicitation of symptoms and signs of hearing loss. Once we “gear up” to “hear the ear” and translate our words into action, diabetes care, and auditory health will improve.

References

always stay true to its values

Rx in Anaemia associated with

- Pregnancy & Lactation
- Menorrhagia
- Nutritional & Iron Deficiency
- Chronic Gastrointestinal Blood Loss
- General Weakness
- Chemotherapy-induced anaemia
- Lack of Appetite
- Chronic Kidney Disease
**Prevalence of Hearing Loss in Type 2 Diabetes Mellitus and Its Association with Severity of Diabetic Neuropathy and Glycemic Control**

Abin M Abraham¹, Jubbin Jagan Jacob², Ashish Varghese³

Received: 13 November 2022; Accepted: 13 February 2023

**Abstract**

**Objectives:** This study assessed the prevalence of hearing loss (HL) in patients with type 2 diabetes mellitus (T2DM) and its relationship with the presence and severity of diabetic neuropathy.

**Materials and methods:** Patients between the ages of 30 and 60 years (both ages inclusive) with T2DM were recruited and divided into three groups. Group I included patients without neuropathy. Group II had patients with mild neuropathy. Group III had patients with moderate and severe neuropathy. After informed consent hearing threshold was assessed using pure tone audiometry (PTA).

**Results:** Of the 200 patients recruited, the prevalence of HL was overall 81%. The prevalence was 66.7% in group I, 80.9% in group II, and 87.6% in group III (p = 0.009). Among patients with moderate to severe neuropathy (group III), 33.3% had clinically significant HL (CSHL) (p = 0.015). Age, gender, presence of neuropathy, and severity of neuropathy were associated with an increased risk of developing HL.

**Conclusion:** Among patients with diabetes, age, nephropathy, and neuropathy were associated with HL. The severity of HL worsened with the worsening severity of neuropathy and increase in glycated hemoglobin (Hba1c) levels. Patients with moderate to severe neuropathy might benefit from screening for HL.

**Introduction**

Type 2 diabetes mellitus (T2DM) is one of the major health problems with global estimates of more than 463 million affected individuals.¹ The increasing prevalence of T2DM is likely to result in an increased number of individuals with diabetes related complications. T2DM has been associated with hearing loss in several population-based studies.²⁻⁴ Hearing loss (HL) is an impairment that severely affects quality of life and has significant economic and emotional impact. It leads to social withdrawal, psychological alienation, anxiety, depression, cognitive decline and dementia among those who suffer from it. T2DM and hearing loss have been proven to be independent risk factors for the development of dementia. The risk of developing dementia is three fold in a patient with moderate hearing loss and five fold in a patient with severe hearing loss when compared to a person with normal hearing.⁵⁻⁶

Proposed pathophysiological mechanisms involved in the development of hearing impairment in T2DM include microangiopathy, neuropathy and mitochondrial damage.⁷ Angiopathy occurs in diabetes as a result of glycoprotein accumulation in the tunica intima and endothelial damage. Hyperglycemia induced overproduction of free radicals and superoxide leads to oxidative stress which plays a major role in endothelial dysfunction and diabetes related complications.⁸ There is reduction in dendritic branching, degradation of vasa vasonum of blood vessels supplying the vestibulo-cochlear nerve, reduction in the number of cochlear cells and cochlear microangiopathy. The stria vascularis has an abundant vascular supply and this makes it particularly vulnerable to diabetic Angiopathy.⁹⁻¹¹ There is substantial delay in auditory brainstem latencies of patients with T2DM which is suggestive of impaired neurological transmission in patients with diabetes.¹²⁻¹³

Strong evidence supports that timely diagnosis and use of hearing aids can significantly improve the quality of life, improve communication, and reduce depression and the rate of cognitive decline in patients with HL.¹⁴⁻¹⁵ Despite the prevalence and burden of HL in society, it is underdiagnosed and undertreated. This makes it important to identify the patients with T2DM who are at high risk for developing HL so that effective screening can be done for diagnosis and prompt initiation of treatment can then follow.

There are few published studies that assess the risk factors leading to HL among patients with diabetes. However, there has been no study comparing the association of HL with the presence of distal peripheral sensory-motor neuropathy (DSPN) and its severity. In this study, the prevalence of HL in patients with T2DM and its association with the presence of DSPN and its severity was studied. Identifying the potential risk factors and the association of neuropathy with HL can help in targeting the population that is at high risk of developing HL. This can help us in planning optimal strategies for screening and prompt treatment of patients with HL among patients with T2DM.

**Material and Methods**

**Setting**

This was a cross-sectional comparison conducted among patients with T2DM attending the outpatient clinics of the Department of Endocrinology, Christian Medical College and Hospital, Ludhiana, Punjab, India. The study was conducted from 1st November 2016 to April 2018.

**Subjects**

Consecutive patients between the ages of 30 and 60 years (both ages inclusive) who were diagnosed to have T2DM for at least 6 months were enrolled after informed consent. The participants in the study included patients from Punjab, India. Patients with a history of intake of ototoxic drugs, previous history of ear surgeries, recent infections in the ear, patients with a clinical history suggestive of Meniere’s disease (history of vertigo or
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...tinnitus in spells, patients with a past history of neurological diseases (stroke, multiple sclerosis, dementia, or central nervous system infections), patients with a past history of closed or open head injuries, patients with chronic overexposure of loud noises (90 dB for 8 hours a day, 5 days a week), patients unable to comprehend PTA assessment, and patients not willing to consent or not capable to consent were excluded. Demographic details were obtained from the subject’s clinical notes, followed by a clinical assessment of DSPN and an assessment of hearing using PTA.

Ethical Approval and Registration of Study Protocol
The Institutional Ethics Committee of Christian Medical College and Hospital approved the study protocol prior to any study-related activities, and the protocol was registered with the Baba Farid University of Health Sciences prospectively as part of the Doctor of Medicine thesis in general medicine for the first author and the principal investigator of the study under the supervision of the other two authors (https://www.bfuhs.ac.in/examination/PlanOfThesis/27-8-18/CMC-2016.pdf). Patients were recruited in the study after they provided informed consent in a language comfortable to them (English, Hindi, or Punjabi).

Sample Size
The prevalence of neuropathy in patients with diabetes was noted to be 50%. The sample size was calculated to be \( n = 200 \) by using the formula \( n = Z^2 \alpha/2 (1-p)/d^2 \), where \( Z = \alpha/2 \) is the critical value of the normal distribution at \( \alpha/2 \) (for our study, the confidence level of 95%, \( \alpha \) is 0.05 and the critical value is 1.96), \( p = 50\% \) is the proportion and \( d = 7\% \) is margin of error.

Assessment of Peripheral Neuropathy
Distal peripheral sensory-motor neuropathy (DSPN) among the participants of the study was assessed using the clinical Michigan Diabetic Neuropathy Score (MDNS). The MDNS score is calculated based on a neurological examination, and it is a validated tool for diagnosis and assessment of the severity of neuropathy in patients with DSPN, as discussed in the study by Feldman et al. Based on the MDNS score, recruited patients were divided into three groups. Group I included patients with no neuropathy (MDNS score of \( \leq 6\) ). Group II included patients with mild neuropathy (MDNS score of 7–13). Group III included patients with both moderate (MDNS score of 13–30) and severe neuropathy (MDNS score of \( \geq 30\) ).

Assessment of HL
Pure tone audiometry (PTA) was performed using Maico-MA 32 diagnostic audiometer in a soundproof compartment. Air conduction and bone conduction audiometric thresholds at 250, 500, 1000, 2000, 4000, and 8000 Hz were obtained using 5 dB steps. Hearing sensitivity for each ear was measured separately, and the severity of HL was assessed according to Goodman’s classification. Patients were classified into those with mild, moderate, moderately severe, severe, or profound HL accordingly.18 Severity of HL in the worse ear was considered for statistical analysis. In our study, HL was defined as pure tone average >15 dB hearing level (dBHL) in the worse ear. CSHL was defined as pure tone average > 25 dBHL in the worse ear. Pure tone average was defined as the average of 500, 1000, and 2000 Hz.

Statistical Analysis
Data was collected using a structured proforma. Data entry was done in Microsoft Excel spreadsheets. Mean, frequency, and standard deviation (SD) were calculated. The Chi-squared test was used to compare categorical variables between the groups. An independent \( t \)-test was used to compare the continuous data between two groups, and a one-way analysis of variance (ANOVA) was used to compare the continuous variables between more than two groups. ANOVA for repeated measures was used to find the change in PTA averages at different frequencies. Linear regression was used to find the significant predictors by taking the PTA average as the outcome for both the right and left ear. Bivariate logistic regression was used to find the significant predictors by taking an HL in any one ear as an outcome. A \( p \)-value of \<0.05 \) was considered statistically significant. Data analysis was done using Statistical Package for Social Sciences (version 21.0).

RESULTS
A total of 200 patients with T2DM were enrolled in the study, and the overall prevalence of HL was 81%. Among them, 152 patients had neuropathy, and 48 patients did not have neuropathy. The prevalence of HL was 66.7% among patients without neuropathy, 80.9% among patients with mild neuropathy, and 87.6% in patients with moderate to severe neuropathy (\( p \)-value = 0.004). The PTA values increased with an increase in the Hba1c levels. The flow of patients in the study is summarized in Flowchart 1.

Baseline Profile of Patients
The demographic, clinical, and biochemical profile of the patients is summarized in Table 1. Patients with neuropathy, males, and

Flowchart 1: Flow of patients in the study

| Patients with Type 2 DM with age between 30 to 60 years were identified |
| Grading of Peripheral sensory-motor neuropathy using Michigan Diabetic Neuropathy Score |
| Group 1: Patients without peripheral neuropathy were identified (n = 48) |
| Group 1: Patients with mild peripheral neuropathy were identified (n = 47) |
| Group 3: Patients with moderate and severe neuropathy were identified (n = 105) |

| ENT examination and Diagnostic Pure Tone Audiometry and Classification according to Goodmans classification |
| Patients without neuropathy: |
| Patients with mild neuropathy: |
| Patients with moderate to severe neuropathy: |

| Patients with hearing loss: n = 32 (66.7%) |
| Patients with hearing loss: n = 38 (80.9%) |
| Patients with hearing loss: n = 92 (87.6%) |

Results were analyzed according to protocol (n = 200)
older patients \((p = 0.003)\) had a higher risk of developing HL.

**Prevalence of HL and its Association with Neuropathy**

Figure 1A shows the prevalence of HL and CSHL among patients with and without neuropathy. The correlation was statistically significant for HL and CSHL \((p = 0.004\) and 0.016). Figure 1B shows the association of HL and CSHL with the severity of the neuropathy (MDNS Grade). The prevalence of HL and CSHL increased with the increase in severity of neuropathy (MDNS Grade), and the correlation was statistically significant \((p\text{-value 0.009 and 0.015, respectively})\).

**Hearing Loss (HL) in Speech Frequencies (Pure Tone Average)**
The clinical pure tone average (average of 500, 1000, and 2000 Hz) was found to be higher in patients with neuropathy, and the pure tone average increased with an increase in the severity of neuropathy \((p = 0.005)\). On univariate linear regression with PTA average as the dependent variable, age, severity of neuropathy (MDNS score and MDNS Class), and fasting plasma glucose (FPG) was found to have a significant positive correlation. The estimated glomerular filtration rate (eGFR) had a negative correlation with the PTA average.

**Association of MDNS Score/MDNS Class with Hearing Threshold in Various Frequencies**

Figure 2 shows the association of the severity of neuropathy with hearing threshold values at various frequencies in the right and left ears. In patients with neuropathy, the HL was found to be worse at higher frequencies like 2000, 4000, and 8000 Hz. With worsening grades of neuropathy, HL in the higher frequencies also worsened. The correlation was statistically significant in the higher frequencies like 2000, 4000, and 8000 Hz. The \(p\)-values were <0.001, 0.024, and 0.020 in the left ear. In the right ear, \(p\)-values were 0.005, 0.007, and 0.028 for these frequencies.

On comparing the MDNS score with the PTA hearing threshold, similar results were seen. The correlation was statistically significant for 2000, 4000, and 8000 Hz \((p = 0.001, 0.001,\) and 0.006 in the right ear and \(p = 0.001, 0.004,\) and 0.022 in the left ear).

**Association of HbA1c with HL or PTA**
The severity of HL in speech frequencies (pure tone average) had a significant correlation with HbA1c. The PTA values at 250, 500, 1000 Hz, and pure tone average increased with an increase in HbA1c levels, and the correlation was statistically significant \((p = 0.017, 0.004, 0.029,\) and 0.048, respectively). In the left ear,
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Patients with neuropathy were more likely to have HL, and the severity of HL increased with an increase in the severity of the neuropathy. The prevalence of CSHL was 20.8% in patients without neuropathy (group I), 25.5% in patients with mild neuropathy (group II), and 33.3% in patients with moderate to severe neuropathy (group III). The clinical pure tone average, which represents the average hearing threshold in speech frequencies, increased with increased severity of neuropathy. This was suggestive of worsening hearing impairment with an increase in the severity of neuropathy. It was noted that the hearing impairment was more in the higher frequencies, like 2000, 4000, and 8000 Hz, among patients with T2DM, and the correlation of HL with neuropathy was more in the higher frequencies. Age, gender, presence of neuropathy, and severity of neuropathy were associated with a significantly increased risk of developing HL.

Univariate and Multivariate Regression Analysis with HL in Any One Ear as an Outcome

On univariate analysis, age, gender, the severity of neuropathy (MDNS score and MDNS grade), and the presence of neuropathy were found to have significant correlations (Table 2). The prevalence of HL was higher in older patients ($p = 0.004$) and patients with neuropathy ($p = 0.006$). The risk of developing HL increased with the worsening severity of neuropathy ($p = 0.007$). Women had some protection against developing HL ($p = 0.033$). On multivariate analysis with AHL in any one ear as an outcome, age ($p = 0.018$), gender, and MDNS score ($p = 0.005$) were found to have a significant correlation.

Association of eGFR with HL

The mean eGFR for patients with HL and those without HL was $84.1 \pm 28.3$ and $91.8 \pm 3.4$, respectively ($p = 0.145$). With worsening renal function, there was worsening HL across all the frequencies. There was an increase in the PTA threshold across various frequencies as the eGFR decreased. At 2000 Hz, the increase in PTA threshold with the decrease in eGFR was found to be statistically significant ($p$-value of 0.034). However, the correlation was not significant in the other frequencies. The average PTA also increased with a decrease in eGFR (negative correlation); however, the correlation was not statistically significant ($p$-value > 0.05).

**Discussion**

Among the patients enrolled in our study with T2DM, the overall prevalence of HL was 81%, and the prevalence of CSHL was 28.5%.
2000 Hz) showed a significant correlation with the severity of neuropathy, age, and HbA1c. As speech sounds are more densely represented in the mid frequencies, the average of 500, 1000, and 2000 Hz signifies the involvement of speech frequencies. Clinical pure tone average had a significant association with MDNS score and MDNS grade. This was suggestive of worsening hearing impairment in speech frequencies with an increase in the severity of neuropathy. The pure tone average was higher in older patients and patients with higher HbA1c. Similar results were seen in the study by Austin et al. and Sugimoto et al., where higher HbA1c and uncontrolled blood glucose levels correlated with HL in patients with T2DM.20 Studies were done on diabetes in the higher frequencies among patients with T2DM.22–24 Patients with T2DM tend to develop HL in the higher frequencies; however, those with poorly controlled glucose levels had significant HL in the speech frequencies also. In a cross-sectional study conducted by Sugimoto et al., higher HbA1c and neuropathy were found to have some association with HL neuropathy, creatinine clearance, and retinopathy were found to have some association with HL.20 Pathophysiological changes seen in the auditory nerve and inner ear, which are similar to the changes seen in the peripheral nerves of patients with diabetic neuropathy, might explain the association of HL with neuropathy. In our study, HL had a negative correlation with eGFR, and this was consistent with other studies where patients with diabetic nephropathy were found to have a significant association with HL.20,21

It was noted in our study that HL was more prominent in the higher frequencies (2000, 4000, and 8000 Hz) for patients with T2DM. The correlation between hearing threshold and neuropathy was more in the higher frequencies. This suggests that patients with diabetic neuropathy are more likely to have hearing impairment in the higher frequencies. The HL in higher frequencies was more than the HL seen in speech frequencies. Similar results were seen in a study by Sugimoto et al. in which neuropathy correlated significantly with HL in the higher frequencies among patients with T2DM.25 Studies were done on diabetes and its association with HL, and a systematic review by Akinpelu et al. concluded that the severity of HL was higher in frequencies among patients with T2DM.26–28 Patients with HL in the higher frequencies have difficulty hearing when there is background noise or when they are in a group which can lead to social withdrawal and avoidance of social interactions. People with high-frequency HL tend to have difficulty in hearing certain consonants, like s, h, and f, which are uttered at a higher frequency than vowel sounds. This can result in speech sounding muffled, especially when talking on the phone, watching TV, or trying to have a conversation in background noise.

Among patients enrolled in our study with moderate to severe neuropathy, the prevalence of CSHL was 33.3%, while studies have reported that the prevalence of HL in a population of middle-aged adults is 14–20%.29 Even though the prevalence of CSHL was higher in our study group, none of them were evaluated for HL prior to our study or underwent any treatment for HL. Few studies showed some benefits of screening for HL among adults; however, there is no consensus regarding the high-risk groups who require screening for HL. In our study, it was seen that the prevalence of CSHL was significantly higher in patients with moderate to severe neuropathy compared to the prevalence of HL reported among middle-aged adults. Studies have shown that a 10 dB increase in PTA values was associated with 52% increased odds of social isolation and significant cognitive decline.26,27 Subclinical HL has also been independently associated with cognitive impairment and depressive symptoms. Due to the gradual onset of HL, many elderly individuals are unaware of their hearing impairment, and increasing age is associated with the underestimation of the severity of HL.4 With increasing age and cognitive decline, it becomes progressively difficult to use hearing aids. Delays in diagnosis can lead to an unwillingness to start treatment, poor compliance, improper maintenance of the hearing aids, and poor treatment outcomes.28,29 Diagnosis and initiation of treatment at the right time are important for the acceptance of treatment, adequate compliance, and optimal treatment outcome. Screening for HL in patients with diabetic neuropathy who are at a higher risk of developing HL can help in the timely diagnosis and treatment of these patients.

### Table 2: Univariate binary logistic regression with HL as the outcome

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Coefficient β</th>
<th>p-value</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.06</td>
<td>0.004</td>
<td>1.062</td>
<td>1.019-1.107</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>−0.802</td>
<td>0.033</td>
<td>0.448</td>
<td>0.214-0.938</td>
</tr>
<tr>
<td>MDNS score</td>
<td>0.093</td>
<td>0.002</td>
<td>1.097</td>
<td>1.035-1.163</td>
</tr>
<tr>
<td>MDNS grade</td>
<td>1.775</td>
<td>0.017</td>
<td>0.326</td>
<td>3.224</td>
</tr>
<tr>
<td>Neuropathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td></td>
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<td>1</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>1.045</td>
<td>0.006</td>
<td>2.843</td>
<td>1.344-6.012</td>
</tr>
<tr>
<td>Age</td>
<td>0.055</td>
<td>0.018</td>
<td>1.056</td>
<td>1.01-1.105</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>−1.143</td>
<td>0.006</td>
<td>0.319</td>
<td>0.141-0.723</td>
</tr>
<tr>
<td>MDNS score</td>
<td>0.107</td>
<td>0.005</td>
<td>1.113</td>
<td>1.041-1.191</td>
</tr>
</tbody>
</table>

American Speech-Language-Hearing Association recommends screening all adults, and World Health Organization’s guidelines on integrated care for older people recommend screening of elderly. As suggested by Nieman et al., although definitive recommendations have yet to be developed, the appropriate clinical practice would be to screen any person with perceived HL and persons with risk factors for developing HL.29 Studies have suggested that stimulation of the auditory system may reduce age-related degeneration, and using hearing aids might be beneficial in modifying the aging process in the auditory system.30 Hence screening of patients with moderate-severe diabetic neuropathy who are at high risk for developing HL should be considered to prevent the further worsening of quality of life-related to hearing impairment.

Single question screening, hearing handicap inventory for the elderly-screening version (HHIE-S), clinical tests like whispered voice tests, finger rub tests, and hand-held audiometers have been used for screening for HL in various studies. In single-question screening, the patient is asked a single screening question like “Do you have difficulty...
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with your hearing?” It has a sensitivity of 80% and a specificity of 74%. HHIE-S is a well-studied self-report questionnaire with 10 questions. It has a sensitivity of 68% and a specificity of 78%. These are simple tools that can be used by a physician or in a primary care center for screening. Poor quality of life due to Hearing impairment can be a potential preventable burden, and the only cost of the screening questionnaire consists of the time required by the patient and clinician.

Limitations
In a group of patients with severe neuropathy, the prevalence of CSHL might be higher than the prevalence reported in our study. Further studies, including more patients with severe neuropathy, can help in understanding the risk of HL in patients with severe neuropathy. Further studies using self-reported questionnaires can help in evaluating the efficacy of the questionnaires in screening these patients. Treatment and treatment outcomes of the patients diagnosed to have HL were not evaluated in our study. Further randomized control trials studying the treatment outcomes in patients with diabetic neuropathy who are diagnosed to have HL can help in better screening and treatment recommendations.

Conclusion
Among patients with T2DM, age, nephropathy, and diabetic neuropathy was associated with HL. The severity of HL worsened with the worsening severity of neuropathy and an increase in Hba1c levels. Patients with moderate to severe neuropathy might benefit from screening for HL using simple and cost-effective measures like self-reported screening questionnaires.

References
Patient-reported Outcome of Mild Coronavirus Disease 2019 Infection in Patients diagnosed from a Tertiary Care Center in Kerala: A 1-year Follow-up Study

Lisha Pallivalappil1*, Sajeena Jose Chittilapilly2, Imy Innies3

Received: 24 October 2022; Accepted: 03 March 2023

ABSTRACT
Background: The coronavirus disease 2019 (COVID-19) infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus had a huge burden on asymptomatic or mildly symptomatic persons who may have only briefly been associated with healthcare delivery systems during their illness. The knowledge about patient perception of disease outcomes is important in deciding future programs for dealing with pandemics in the community.

Materials and Methods: The objectives of the study were to determine patient-reported outcomes (PROs) 30 days and 1 year after the initial diagnosis of mild COVID-19 infection and to determine any factors associated with PROs. Patients who attended the fever screening clinic and were diagnosed with mild COVID-19 infection were contacted telephonically as they completed 30 days after their initial diagnosis, and their responses to the EuroQol five-dimensions 5-level (EQ-SD-5L) questionnaire were recorded. The patients were again contacted 1 year after the initial diagnosis and the same process was repeated.

Findings: A total of 237 patients were contacted telephonically and 167 patients responded to the call. The domain most affected at 30 days was usual activities, and at 1 year, it was anxiety and depression. The mean utility score at 30 days was 0.9347 and at 1 year was 0.9801. The factors associated with worse utility scores were age >45 years and comorbidities.

Interpretation: There is a significant proportion of patients who had restrictions in performing their usual activities 30 days after a mild COVID-19 infection, whereas the domain which showed the least improvement after 1 year was anxiety or depression. Even mild COVID-19 infection had an impact on the health-related quality of life (HRQOL) of people with the elderly and those with comorbidities affected more.

INTRODUCTION
The first official announcement of a novel coronavirus infection outbreak was made by the Chinese government in December 2019.1,2 The virus spread across the globe, causing illnesses ranging from asymptomatic or mild respiratory illness to severe pneumonia and acute respiratory distress syndrome, especially in a vulnerable subset of patients with comorbid illnesses. On January 30, 2020, the World Health Organization declared COVID-19 as a public health emergency of international concern and later declared a global pandemic.3,4 The disease brought about unparalleled economic, social, and political implications. The world had to adopt previously novel methods to protect the population from the medical and social, and economic effects of the disease. It was also a disease with a huge burden on asymptomatic or mildly symptomatic persons who have missed or only briefly associated with healthcare delivery systems during the course of their illness. Many people, after initial diagnosis of a mild infection, were referred for home isolation or treatment at home. Mild COVID-19 patients, after their diagnosis from COVID-19 clinics, were often lost to follow-up, especially in middle-income countries like India. And therefore, their disease outcome and the impact of disease on their QOL are poorly defined. The knowledge about patient perception of the disease and its outcomes is also important in deciding future programs for dealing with COVID-19 or other pandemics in the community. Thus, it becomes important to assess the outcomes of various treatment protocols from the point of view of the patient. For this, we are in need of structured and validated questionnaires. Patient-reported outcome measures (PROs) are validated questionnaires filled by patients describing their perspectives on their physical, mental, and social well-being. PROs have come to be an important tool in analyzing the fight against COVID-19.5 This study chose the EQ-SD-5L questionnaire developed by the EQ Research Foundation. EQ-SD is a standardized measure of health status developed by the EQ Group in order to provide a simple, generic measure of health for clinical and economic appraisal.6 Recently, EQ-SD utility score sets have been published for the Indian population.7 In this context, the current study focuses on PROs in patients affected by mild COVID-19 disease at 30 days and 1 year after COVID-19 infection.

MATERIALS AND METHODS
Study Design
The main objectives of the study were:

- Determine patient-reported outcome at 30 days and at 1 year after initial diagnosis of mild COVID-19 infection.
- Determine any factors associated with PROs at 30 days and at 1 year.

Study Subjects and Methods
This is a prospective observational cohort study conducted in a fever screening clinic of a tertiary care institute in Kerala. The study was conducted among patients attending the fever screening clinic during the delta wave of COVID-19 between March and May 2021. Consecutive cases were included in the study. The inclusion criteria were a positive confirmatory test for COVID-19 infection in patients aged 18 years or older in those attending the fever clinic and classified as mild according to the Indian Council of Medical Research (ICMR) guidelines.8 The definition of the mild case was COVID-19-positive by a confirmatory test with saturation at room air of 94% or more and a respiratory rate of 24 or more per minute. The patients are admitted to treatment areas or sent on home isolation according to the government guidelines for the same.9 Registers are

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Analysis
A descriptive analysis of the responses in each dimension at 30 days and at 1 year was done. A paired samples t-test was used to compare the mean utility scores at 30 days and 1 year. Independent samples t-test was used to compare the utility scores among various subgroups. A p-value of <0.05 was considered significant. The statistical analysis was done using IBM Statistical Package for the Social Sciences statistics version 26.

The study was approved by the Institutional Ethics Committee of the Amala Institute of Medical Sciences (Ref No 11/IEC/21/AIMS-41 dated 18/02/2021).

RESULTS
A total of 237 consecutive patients were identified from the register of the fever clinic. Demographic data were available for all these patients from the registers. When contacted telephonically, 48 patients did not answer the phone call. A total of 20 patients expressed unwillingness to participate in the study. A total of 167 patients were eligible for analysis at 30 days. At the end of 1 year, 162 patients responded to the phone call.

The demographic data are given in Table 1. The outcome according to hospitalization was as given in Table 2. The percentage of subjects in each of the five categories of the five domains at 30 days follow-up and 1-year follow-up is represented in Figures 1 to 5. The EQ-5D-5L level index was calculated at 30 days and at 1 year. The mean scores at 30 days and one year and the difference in scores are given in Table 3. A paired samples t-test for comparing utility scores at 30 days and 1 year was done, which showed a difference of 0.418 (0.257–0.579) between the 1-year score and the original score indicating significant improvement (Table 4).

Table 1: Demographic data

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>Age in years mean (SD)</th>
<th>Gender</th>
<th>Comorbidities</th>
<th>Symptomatology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>44</td>
<td>Male</td>
<td>Present</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>146 (61.6%)</td>
<td>95 (40%)</td>
<td>59 (25%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female</td>
<td>Absent</td>
<td>Fever</td>
</tr>
<tr>
<td></td>
<td></td>
<td>91 (38.4%)</td>
<td>142 (60%)</td>
<td>180 (76.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cough</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>141 (59.4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Absent</td>
<td>Rhinitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>142 (60%)</td>
<td>102 (43%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Anosmia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>142 (60%)</td>
<td>52 (22%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hemoptyosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>142 (60%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Loss of taste</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>142 (60%)</td>
<td>59 (25%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Received monoclonal antibody cocktail</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not received cocktail</td>
</tr>
</tbody>
</table>

Table 2: 30-day hospitalization data

<table>
<thead>
<tr>
<th>Outcome at 30 days</th>
<th>Did not require hospitalization</th>
<th>Hospitalized, ward admission</th>
<th>Hospitalized, ICU admission</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>146 (87.4%)</td>
<td>17 (10%)</td>
<td>3 (1.8%)</td>
<td>1 (0.01%)</td>
</tr>
</tbody>
</table>

Fig. 1: Comparison of mobility scores at 30 days and at 1 year
significant (Tables 10 and 11) (p-value = 0.571). Comparison of the difference in utility scores in persons above vs below 45 years of age showed that those above 45 years of age have a poor improvement in function compared to the younger age-group (Tables 12 and 13) (p-value = 0.003).

**Discussion**

Self-assessment of patient outcomes is central to COVID-19 research and future pandemic planning. We are only beginning to understand the long-term effects of SARS-CoV-2 infection. The symptoms have returned in some patients a few months postrecovery, while others have developed serious conditions such as Kawasaki-like disease. PROs might be used for long-term follow-up to assess the impact on a patient’s QOL and alert physicians to the development of potentially life-threatening complications. India had one of the largest populations of COVID-19-infected patients, and this should have led to a large cohort of patients suffering from various post-COVID-19 manifestations. In order to tackle the enormous surge during the delta wave, the country and the southern state of Kerala used a triaging system by ICMR which classified patients into mild, moderate, and severe infections based on the parameters of respiratory rate and saturation by pulse oximetry. The patients were sent for home isolation and advised to self-monitoring in case of mild infection. Many of these patients did not return to the healthcare system. So, a telephonic follow-up was considered ideal to understand their status both at 30 days and 1 year past diagnosis. The understanding gained by such a study can be used to focus future healthcare strategy planning on targeting this group of patients. Studies using validated and structured questionnaires to assess the patient’s version of the impact of COVID-19 infection have not been conducted in the South Indian state of Kerala. This is the first such study in this group discussing both short-term and long-term follow-up of this group of patients. Jyani et al. recently published the largest 5L version of the EQ-5D-5L valuation study conducted so far in the world. This is also the first valuation study in South Asia for use in the Indian population. The value set provided by these authors was used in the current study to provide utility scores to compare the EQ-5D-5L scores.

The current study showed that the mean utility score of subjects; 1 year after mild COVID-19 infection [0.9801, standard deviation (SD) 0.1243] was higher than the score; 1 month after diagnosis (0.9347, SD 0.0476). The scores showed that the subjects’ QOL was improving over the course of 1 year.
as the difference between the two scores was significant \( p\text{-value} = 0.001, \text{ confidence interval (CI) 0.257–0.579} \). But when we analyze the health status of the subjects in each of the domains, we can see that the domain most affected in the initial assessment at 30 days was the performance of usual activities. A total of 32% of patients had at least some limitations in usual activities. The reason behind this will have to be assessed by further investigations into people who visited the hospital at this time. We assume that the persistent COVID-19 symptoms may have been perceived as limiting daily activities in this group. At the end of 1 year, this domain showed significant improvement, with only 6% of people reporting at least some problem in performing usual activities. The next domain to be involved was anxiety and depression. A total of 24% of people experienced some severe anxiety or depression in the 1st month. This was interestingly the domain that showed the least improvement, with 17% of people still having at least some anxiety and depression at 1 year. A total of 23% of people also felt pain or discomfort at 1 month. This also showed a trend of persistence at one year since 19% of people had at least some discomfort at 1 year. A total of 23% of people also felt pain or discomfort at 1 month. This also showed a trend of persistence at one year since 19% of people had at least some discomfort at 1 year. The rather significant proportion of people with discomfort and anxiety 1 year after an initial diagnosis of mild COVID-19 infection is a significant finding of this study. The reason for this will also have to be analyzed by further clinical examinations and is not possible by telephonic communications alone. Mobility was the domain that was least affected, followed by limitations in self-care. In these two domains, only around 5% of people were affected in the initial 1 month, which came down to 2% at 1 year.

When this is compared to similar studies, we find that gender, occupation, and comorbidities exerted a major influence on EQ-5D scores in another population study from Tamil Nadu, which is a neighboring state of Kerala.\textsuperscript{10,11} While comparing such data from across the world, we can see that a varying proportion of patients had persistent symptoms post-COVID-19 infection is a significant finding of this study. The reason for this will also have to be analyzed by further clinical examinations and is not possible by telephonic communications alone. Mobility was the domain that was least affected, followed by limitations in self-care. In these two domains, only around 5% of people were affected in the initial 1 month, which came down to 2% at 1 year.

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**Table 3:** Mean utility scores at 30 days and at 1 year and the difference in scores

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Missing</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Utility score at 30 days</td>
<td>167</td>
<td>70</td>
<td>0.9347</td>
<td>0.984</td>
<td>0.1243</td>
</tr>
<tr>
<td>Utility score at 1 year</td>
<td>162</td>
<td>75</td>
<td>0.9801</td>
<td>1.000</td>
<td>0.0476</td>
</tr>
<tr>
<td>Difference in scores</td>
<td>162</td>
<td>75</td>
<td>0.0471</td>
<td>0.000</td>
<td>0.1125</td>
</tr>
</tbody>
</table>

**Table 4:** Paired samples t-test for comparing utility scores at 30 days and 1 year

<table>
<thead>
<tr>
<th>Statistics</th>
<th>Degree of freedom</th>
<th>p</th>
<th>Effect size</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Students t-test</td>
<td>5.31</td>
<td>&lt;0.001</td>
<td>Cohen's d</td>
<td>0.418</td>
<td>0.257–0.579</td>
</tr>
</tbody>
</table>

**Table 5:** Comparative assessment of utility scores for different groups at 30 days and at 1 year

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean utility score at 30 days (SD)</th>
<th>Utility score at 1 year (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age-group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Under 18</td>
<td>0.811 (0.294)</td>
<td>0.993 (0.019)</td>
</tr>
<tr>
<td>18–29 years</td>
<td>0.945 (0.063)</td>
<td>0.979 (0.042)</td>
</tr>
<tr>
<td>30–39 years</td>
<td>0.889 (0.178)</td>
<td>0.965 (0.069)</td>
</tr>
<tr>
<td>40–49 years</td>
<td>0.946 (0.677)</td>
<td>0.975 (0.051)</td>
</tr>
<tr>
<td>50–59 years</td>
<td>0.957 (0.969)</td>
<td>0.985 (0.368)</td>
</tr>
<tr>
<td>60–69 years</td>
<td>0.967 (0.049)</td>
<td>0.988 (0.023)</td>
</tr>
<tr>
<td>70 and above</td>
<td>0.973 (0.05)</td>
<td>0.997 (0.011)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.93 (0.143)</td>
<td>0.979 (0.044)</td>
</tr>
<tr>
<td>Female</td>
<td>0.941 (0.091)</td>
<td>0.981 (0.053)</td>
</tr>
<tr>
<td>Symptomatology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>0.945 (0.102)</td>
<td>0.978 (0.05)</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>0.931 (0.13)</td>
<td>0.981 (0.047)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nil</td>
<td>0.904 (0.159)</td>
<td>0.972 (0.058)</td>
</tr>
<tr>
<td>Present</td>
<td>0.969 (0.051)</td>
<td>0.989 (0.032)</td>
</tr>
<tr>
<td>Monoclonal antibody usage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.975 (0.044)</td>
<td>0.992 (0.023)</td>
</tr>
<tr>
<td>No</td>
<td>0.909 (0.148)</td>
<td>0.973 (0.057)</td>
</tr>
</tbody>
</table>
3 months after COVID-19 diagnosis, and impairments were more prominent in mental than physical well-being. The short form-36 questionnaire (SF-36-item Health Survey), Hospital Anxiety and Depression Scale, and Posttraumatic Stress Disorder Checklist-5 were used in this study. Similar findings were also reported from China in the study by Qu et al.15 Fatigue is the most common symptom reported in the post-COVID-19 period in various studies around the world.16,17 A review by Nandasena et al.18 found that a large majority of patients at various stages after discharge from the hospital had impacted their QOL. They also propose to study the domains in which the quality was impacted to plan future interventions for these people.

Compared to these cohorts, a lower percentage of patients reported symptoms when assessed by the EQ-5D-5L questionnaire in our study. The varying periods of follow-up make direct comparison difficult.

The persistent symptoms of depression and anxiety warrant the need for psychological evaluation and support in this group of patients. Detailed evaluation will also be needed to analyze the domain of pain and discomfort.

The next objective was to analyze the factors which led to worse utility scores. A subgroup analysis in the current study showed that the presence of any comorbidities, male gender, age >45 years, and use of a monoclonal antibody cocktail was associated with worse utility scores at the end of 1 year. The fact that the monoclonal antibody cocktail was given to the at-risk population with advanced age and multiple comorbidities may be acting as a confounding factor. A study by Chen et al.19 using SF-36 scores demonstrated a significant difference in HRQOL in patients with COVID-19 and age female sex, obesity, and length of stay associated with negative physical function and mental function. In the meta-analysis by Malik et al.,20 which included a total of 12 studies with 4,828 postacute COVID-19 syndrome patients, it was found that postacute COVID-19 syndrome was associated with poor QOL, persistent symptoms including fatigue, dyspnoea, anosmia, sleep disturbances, and worse mental health. Intensive care unit (ICU) stay was significantly associated with poor QOL. The meta-analysis by Qu et al.15 pointed out that in the 38 studies included, fatigue and dyspnoea were the most prevalent symptoms in acute post-COVID-19 and fatigue and sleep disturbance in chronic post-COVID-19 syndrome, respectively. They also opined that the available evidence is generally of poor quality, with considerable risk of bias, and is of observational design.

So, the need for further evaluation of the post-COVID-19 syndrome by a nuanced clinical evaluation is warranted. Our study is probably the first to analyze the chronic post-COVID-19 syndrome in the mild disease group patients and also one of the first to use a structured and validated questionnaire in this particular population of Southern India. The fact that the mild disease group is also not fully back to normal after one year of infection is to be noted and considered for further evaluation. We could concentrate more on the elderly population, male gender, and those with comorbidities to target further studies on the post-COVID-19 state.

The limitations of the study pertain to the nonavailability of the vernacular version of the telephonic questionnaire though we have tried to circumvent this by validating a translation of the questionnaire in Malayalam.
The recall bias of the respondents will have affected some of the data. The number of patients included in this study is also a limiting factor. However, this analysis of the acute and chronic post-COVID-19 state in the mild COVID-19 disease group gives valuable insights into the domains of life affected and will help plan targeted interventions in this group of subjects.

REFERENCES
### Soluble TNFR1 Levels in Type 2 Diabetes and its Association with Stages of Proteinuria

Raghul Lourdusamy, Kuppan Gokulakrishnan, Ezhil Nilavan, Nandagopal Balaji, Ramprasad Srivivasan

Received: 11 October 2022; Accepted: 03 March 2023

#### Abstract

**Aims:** Early identification of at-risk individuals for diabetic nephropathy would help in preventing or delaying end-stage renal failure. We measured the levels of circulating soluble tumor necrosis factor receptor 1 (sTNFR1) in various stages of proteinuria (MAC) to determine the association of this marker with diabetic nephropathy.

**Materials and methods:** The study was performed on 160 subjects, and a case-control methodology was employed. Type 2 diabetic subjects were recruited based on albuminuria and were grouped as (1) normalalbuminuria (NA); (2) microalbuminuria (MIC); (3) MAC; (4) normal glucose tolerance (NGT) subjects who served as healthy controls. sTNFR1 levels were measured by quantitative enzyme-linked immunosorbent assay (ELISA).

**Results:** Soluble tumor necrosis factor receptor 1 (sTNFR1) levels were highest in the MAC group, followed by the microMAC group. The sTNFR1 levels were not statistically different between the NGT and NA groups. On regression models, sTNFR1 was associated with MIC (odds ratio (OR)—6.491, 95% confidence interval (CI)—1.868–22.55 and MAC (OR per standard deviation—15.28; 95% CI—3.76–62.15; p < 0.001) even after controlling for all the possible confounding factors. Receiver operator curve (ROC) analysis revealed sTNFR1 cut-point of 1832 pg/mL had a C-statistic of 0.685 to discriminate MI from NA with 52% sensitivity. Whereas the sTNFR1 cut-point of 2050 pg/mL with a C-statistic of 0.8177 had 77% sensitivity for identifying MAC.

**Conclusion:** Soluble tumor necrosis factor receptor 1 (sTNFR1) is significantly associated with MIC and MAC group in type 2 diabetes, and this suggests a potential early diagnostic biomarker role of sTNFR1 for MAC among Asian Indians.

#### Introduction

Diabetes is a major risk factor for the development of end-stage renal disease (ESRD), and greater than 100,000 new subjects require renal replacement each year among Asian Indians. Microalbuminuria (MCR) is not satisfactory for early detection of diabetic kidney disease (DKD) since some patients with chronic kidney disease (CKD) have normal albuminuria despite underlying kidney damage. This phenotype is called normoalbuminuric-CKD, and the prevalence rate varies among populations ranging from 21–63%. Further, we have recently observed that the prevalence of rapid declines with a glomerular filtration rate (GFR) rate >5 mL/minute/1.73 m² was high at 19%. Serum creatinine is a late-stage marker and cannot be used during the early years of diabetes. Hence, a sensitive biomarker for a more accurate diagnosis of DKD is warranted, and a few biomarkers have been identified in this pursuit. Biomarkers such as urinary retinol-binding protein, fatty acid-binding proteins (FABP), kidney injury molecule-1 (KIM-1), and neutrophil gelatinase-associated lipocalin have been identified using a metabolomics approach. However, these markers have some limitations. KIM-1 levels vary with urinary volume and hence need to be adjusted with creatinine values, and FABP values are indicative of tubular damage but do not indicate whether the damage is caused due to diabetes.

The activation of inflammatory pathways such as tumor necrosis factor (TNF) is reported to be involved in the development of insulin resistance. The soluble forms of the receptors tumor necrosis factor receptor (TNFR) 1 and TNFR-2 with the spliced extracellular domain are found in blood and urine and possibly act as a decoy in the regulation of circulating TNF-α levels. The circulating levels of these soluble receptors, namely the STNFR-1, and STNFR-2, are increased in several disease states, including CKD. STNFR-1 and STNFR-2 have been demonstrated as a predictive marker for the development of ESRD among type 2 diabetes subjects predominantly in the Caucasian population. There is a paucity of data on the usefulness of STNFR1 biomarkers in the Asian Indian population, who are more prone to develop more insulin resistance and more susceptible to cardio-metabolic diseases and albuminuria.

Therefore, in this study, we sought to examine the relationship of sTNFR1 as a biomarker in diabetic kidney disease.

#### Materials and Methods

**Recruitment of Study Subjects**

This study was approved by the Institutional Ethics Committee of Sri Narayani Hospital & Research Centre. Type 2 diabetic subjects were recruited and categorized based on albuminuria into (1) NA (40); (2) MIC (40); (3) MAC (40); (4) NGT subjects (40) served as healthy controls.

**Anthropometric and Biochemical Measurements**

Anthropometric measurements, such as weight, height, and waist circumference, were obtained by using standardized methods and recorded. Body mass index (BMI) was calculated as weight (kg)/height (m)². Blood pressure (BP) measurements were recorded by standardized methods. Biochemical investigations were performed using an automated analyzer Beckman Coulter, AU480, United States of America. Diabetes was defined using World Health Organization consulting group criteria. Estimated GFR (eGFR) was calculated by using the CKD epidemiology collaboration equation.

**Soluble Tumor Necrosis Factor Receptor 1 (sTNFR1) Measurement in Plasma Samples**

Soluble tumor necrosis factor receptors 1 (sTNFR1) were measured using a quantikine ELISA kit purchased from R&D Systems, Minneapolis, Minnesota, United States of America, Cat# DRT100, according to manufacturer instructions. The coefficient of variation values for intraassay variation was 9.5%.

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and interassay variation were 4.4 and 6.1%, respectively.

**Statistical Analysis**

Data analysis was performed with Statistical Package for the Social Sciences (SPSS) statistical software (version 28.0.1; SPSS, Chicago, Illinois, United States of America). The Chi-squared test was used for categorical variables and Fisher’s exact test to compare proportions, and the comparison of means was carried out using analysis of variance/student’s t-test.

Standardized polytomous regression analysis was done to assess how incremental changes in sTNFR-1 were associated with MIC and MAC.

Receiver operating characteristic curves (ROC) were plotted for sTNFR-1 to identify MIC and MAC. C-statistic or area under the ROC (AUC) was estimated, and by interpolation from the area under the curve, the point closest to the upper-left corner, which maximized sensitivity and specificity, was selected as the optimal cut-point; this identified the highest number of subjects with or without MIC and MAC.18

**Results**

**Demographics and Biochemical Profile of Study Subjects**

There was no difference between the mean age and gender among the groups (Table 1). Total cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol levels were higher in the normal albuminuria group (p < 0.05). Diastolic BP was significantly higher in the MAC group (p < 0.05), whereas systolic BP was not statistically different between the groups.

**Soluble Tumor Necrosis Factor Receptor 1 (sTNFR1) Levels in Diabetic Kidney Disease**

Significantly higher in the MAC group (albuminuria group). Cholesterol levels were higher in the normal (HDL), and low-density lipoprotein (LDL) categories. Total cholesterol, high-density lipoprotein (HbA1c), and creatinine, and MIC. eGFR was negatively correlated with sTNFR1 levels (Table 2). There was no significant correlation between systolic BP, total cholesterol, HDL and LDL cholesterol, and serum triglycerides.

**Regression Analysis of Plasma sTNFR1 for MIC and MAC**

Standardized polytomous logistic regression analysis was performed with NA as the dependent variable and sTNFR1 as the independent variable. One standard deviation increase in sTNFR1 was independently associated with MIC (OR—4.11, 95% CI—1.694–9.983; p = 0.002). This association remained statistically significant even after adjusting for age, BP, glycated hemoglobin (HbA1c), urea, and serum creatinine (OR—6.491; 95% CI—1.868–22.55; p = 0.003). sTNFR1 was independently associated with MAC OR per standard deviation—9.679; 95% CI—3.804–22.62; p < 0.001.) Adjustment for age, BP, HbA1c, urea, and serum creatinine did not substantially change the association between sTNFR1 and MAC (OR per standard deviation—15.28; 95% CI—3.76–62.15; p < 0.001.)

**Soluble Tumor Necrosis Factor Receptor 1 (sTNFR1) Predicts Early Stages of Diabetic Kidney Disease**

Receiver operating characteristic curves (ROC) were constructed to derive the cut-point for sTNFR1 with the best sensitivity and specificity to identify MIC and MAC. Figure 2 shows the C-statistic for the sTNFR1 in predicting MIC and MAC. An sTNFR1 cut-point of 1832 pg/mL had a C-statistic of 0.648.

**Table 1: Baseline characteristics of study subjects**

<table>
<thead>
<tr>
<th>Description</th>
<th>nGT (n = 40)</th>
<th>NA (n = 40)</th>
<th>MIC (n = 40)</th>
<th>MAC (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>52 ± 7</td>
<td>51 ± 10</td>
<td>54 ± 7</td>
<td>54 ± 6</td>
</tr>
<tr>
<td>Sex; male</td>
<td>22 ± 24</td>
<td>23 ± 26</td>
<td>21 ± 23</td>
<td>24 ± 27</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>92 ± 12</td>
<td>160 ± 114*</td>
<td>60 ± 168</td>
<td>185 ± 81</td>
</tr>
<tr>
<td>Postprandial blood sugar (mg/dL)</td>
<td>115 ± 18</td>
<td>255 ± 60*</td>
<td>239 ± 95</td>
<td>281 ± 99</td>
</tr>
<tr>
<td>HbA1c% (mmol/mol)</td>
<td>5.7 ± 0.5</td>
<td>8.4 ± 1.6*</td>
<td>7.9 ± 1.8</td>
<td>9.2 ± 2.1</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>172 ± 31</td>
<td>196 ± 39*</td>
<td>166 ± 42</td>
<td>172 ± 49</td>
</tr>
<tr>
<td>Serum triglycerides (mg/dL)</td>
<td>145 ± 79</td>
<td>184 ± 75</td>
<td>175 ± 102</td>
<td>192 ± 128</td>
</tr>
<tr>
<td>Serum HDL cholesterol (mg/dL)</td>
<td>42 ± 8</td>
<td>45 ± 8</td>
<td>39 ± 9*</td>
<td>40 ± 11</td>
</tr>
<tr>
<td>Serum LDL cholesterol (mg/dL)</td>
<td>100 ± 27</td>
<td>115 ± 33</td>
<td>92 ± 31</td>
<td>94 ± 42</td>
</tr>
<tr>
<td>very-LDL cholesterol (mg/dL)</td>
<td>29 ± 16</td>
<td>37 ± 15</td>
<td>33 ± 17</td>
<td>39 ± 26</td>
</tr>
<tr>
<td>Blood urea (mg/dL)</td>
<td>21 ± 6</td>
<td>20 ± 5</td>
<td>25 ± 9</td>
<td>38 ± 17</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.98 ± 0.28</td>
<td>0.88 ± 0.36</td>
<td>0.93 ± 0.42</td>
<td>1.35 ± 0.58</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m2)</td>
<td>103 ± 20</td>
<td>107 ± 20</td>
<td>91 ± 23</td>
<td>94 ± 23</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>128 ± 15</td>
<td>132 ± 17</td>
<td>137 ± 27</td>
<td>140 ± 134</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>82 ± 9</td>
<td>82 ± 10</td>
<td>82 ± 10</td>
<td>94 ± 23</td>
</tr>
</tbody>
</table>

*p-value < 0.05 when compared to nGT; bp-value of <0.05 when compared to NA; #p-value of <0.05 when compared to NA; $p-value of <0.001 when compared to NA

**Table 2: Correlation analysis of sTNFR with metabolic risk factors in the study subjects**

<table>
<thead>
<tr>
<th>Variable</th>
<th>r-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.309**</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>0.278**</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>0.029</td>
<td>0.725</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>0.470**</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>0.173*</td>
<td>&lt;0.029</td>
</tr>
<tr>
<td>Postprandial plasma glucose</td>
<td>0.225**</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td>HbA1c</td>
<td>0.248**</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>−0.037</td>
<td>0.639</td>
</tr>
<tr>
<td>HDL</td>
<td>−0.014</td>
<td>0.857</td>
</tr>
<tr>
<td>LDL</td>
<td>−0.054</td>
<td>0.503</td>
</tr>
<tr>
<td>Serum triglycerides</td>
<td>0.027</td>
<td>0.732</td>
</tr>
<tr>
<td>Urea</td>
<td>0.454**</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.448**</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR</td>
<td>−0.473**</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MIC</td>
<td>0.424**</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**, p-value <0.001
sTNFR1 Levels in Diabetic Kidney Disease

Diabetic kidney disease (DKD) is characterized by glomerular apoptosis and is directly related to HbA1C and diabetic duration, and has been shown to be associated with an increase of proinflammatory cytokines such as TNF-α. Soluble forms of TNFR1 and TNFR2 are generated, possibly due to alternative splicing that results in the loss of the transmembrane and cytoplasmic domain. The underlying chronic proinflammatory state possibly results in the generation of sTNFR1, perhaps a way of counteracting the effects of TNF-α. In this context, we analyzed the relationship of plasma levels of sTNFR1 with different stages of DKD grouped by MAC. We found that levels of sTNFR1 were increased with the severity of diabetic kidney disease, with MIC showing high levels of sTNFR1 and MAC displaying very high levels. The mean sTNFR1 values among the Caucasians and in the current study were comparable with the mean levels in subjects with normal GFR at 1,613, and for CKD subjects with GFR between 60 and 30 mL/minute/1.73 m², it was 2,546, whereas in our study the values of sTNFR1 in these stages were 1,501 and 3,288, respectively.

There was a positive correlation with age and several other metabolic parameters with sTNFR1 and no correlation with lipids. This finding implies that hyperglycemia is central in the regulation of circulation sTNFR1 levels. There was a negative correlation of sTNFR1 with eGFR, indicating the association of sTNFR1 with renal decline. This is in contrast with a recently reported longitudinal study that did not find any correlation of sTNFR1 with eGFR but found a correlation with the albumin excretion ratio. This is possible due to the fact that the selected subjects in the study had advanced nephropathy, and the absolute change in eGFR was widespread, with a range of –2.22 to 0.73.

Studies support the potential role of sTNFR1 in predicting the severity of renal disease. In this context, we found a positive correlation between sTNFR1 and glycemic parameters, including fasting glucose and HbA1c. The correlation between sTNFR1 and established kidney injury markers such as serum creatinine and MIC suggest a diagnostic as well as prognostic value of sTNFR1. The significant negative correlation of sTNFR1 with eGFR also substantiates the role of sTNFR1 in assessing diabetic kidney injury. Interestingly, the association of sTNFR1 with MIC or MAC is significant even after adjusting the conventional risk factors for albuminuria and emphasizes a potential risk factor role of sTNFR1.

It is well known that ethnicity plays a definitive role in the development of diabetic kidney disease. It has been shown that Asian Indians are highly susceptible to the development of CKD than Caucasians. In this context, the increased sTNFR1 in patients with MIC and MAC in our study is an important finding. Additionally, our data suggest that an sTNFR1 cut point of 1832 pg/mL and 2050 pg/mL could be used to correctly identify 53% of MIC and 78% of MAC, respectively, in the study population.

To our knowledge, this is one of the very few studies that measure the sTNFR1 distribution from different stages of diabetes. The strength of the study is that the cases (MIC, MAC/NA) and controls (NGT) were classified using standard methods. One of the limitations of this study is that being a cross-sectional study, therefore, no cause-and-effect relationship between sTNFR1 and NA, MIC, or MAC could be established, for which prospective studies are needed.

In summary, we report that in Asian Indians, the sTNFR1 profile is higher in MIC and MAC, suggesting that it has the potential to be used as an early diagnostic marker for MIC or MAC.

**Authors’ Contribution**

RL—collected data, KG—performed the statistical analysis, EN—data collection and writing the manuscript, NB—analysis and writing the manuscript, and RS—writing and approval the manuscript.

**Consent**

Informed consent or a substitute for it was obtained from all patients for being included in the study.

**Ethics Statement**

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and/or with the Helsinki Declaration of 1964 and later versions. The study was approved by Sri Narayani Hospital & Research Centre Ethics Committee (IEC/IRB No: 48/19/02/19 dated 19th February 2019).

**References**

sTNFR1 Levels in Diabetic Kidney Disease


ANNOUNCEMENT

APPLICATION FOR YOUNG SCHOLAR IAG KOTA CHAPTER AWARD BY IAG SOCIETY KOTA

Indian Academy of Geriatrics (IAG) Society Kota registered under the Societies Act, formed by members of IAG Kota Chapter with the aim of welfare of senior citizens and promotion of research and medical education in the field of geriatric medicine announces the Young Scholar IAG Kota Chapter Award

About the Award: This yearly award is being started to promote young physician’s research, clinical and academic excellence in geriatric field.

Eligibility:
- The awardee has to present scientific deliberation during annual conference of the IAG. GERICON 2023 will be held at the National Centre of Ageing, All India Institute of Medical Sciences, New Delhi on 8th and 9th September 2023.
- Preferentially, it will be awarded to a member of IAG residing in India/Abroad who has made an outstanding contribution to the progress of geriatrics. Other applicants if score high on marking will not be solely rejected on the basis of IAG membership.
- Candidate should be of less than 45 years of age.
- The nominee for the award will be selected by a committee of three members appointed specifically for the purpose.
- The decision of the committee will be final.
- Once awarded, the nominee will have to give consent for delivering the deliberation. This is non-transferable.
- The award includes a medal, certificate and a cash prize money of ₹20,000. IAG Society shall not bear the travel and boarding/lodging of selected candidates.
- The awardee will have to register for the conference to avail other facilities of the conference.
- The selected candidate’s name will be announced in JIAG and website of IAG and JIAG.

How to Apply:
- The applicant has to submit the filled application form, link of Google Form is on the website and is https://forms.gle/4BxJJD5bQyuYUGEnS9
- Send the necessary and relevant documents and abstract (max of 250 words) of original work/research/unique idea/innovative social project/topic of presentation related to geriatric field to societykota@gmail.com on or before 31st July 2023 till 5 pm.
- Please visit http://indianacademyofgeriatrics.org OR www.jiag.in for application form.
- Selected candidates will be informed either through e-mail or phone.

For further enquiries, please contact:
Dr Meenaxi Sharda
Contact no.: 94141 88400
e-mail: meenakshisharda@gmail.com
Study of Correlation of Bone Mineral Density with Severity of Liver Cirrhosis

Vaibhav Shukla1*, Jalees Fatima2, Zeba Siddiqui3, Ruman Kugashiya4, Zia Ul Islam5

Received: 21 February 2022; Accepted: 10 March 2023

ABSTRACT

Introduction: Liver cirrhosis is a common ailment that is widely prevalent in our country and across the world. There are several manifestations of this disease. Metabolic bone disease also has an association with cirrhosis. The present study was designed to study the correlation between bone mineral density (BMD) and the severity of liver cirrhosis.

Materials and methods: This was a case-control study. A total of 35 diagnosed cases of liver cirrhosis and 35 age and sex-matched controls were included in the study. BMD was measured by dual-energy X-ray absorptiometry (DEXA) at the hip joint and lumbar spine. Child–Turcotte–Pugh (CTP) score was used for assessing the severity of liver cirrhosis.

Results: Out of the 35 cases of cirrhosis, 25 had either osteopenia or osteoporosis. The mean T-score at the hip joint in cases was −1.47 ± 1.62 and in controls, it was −0.56 ± 1.67 (p < 0.001). The mean T-score detected in the lumbar spine was −1.33 ± 1.66 and in controls −0.41 ± 1.67 (p < 0.001). There was a significant inverse correlation between CTP scores and BMD.

Conclusion: The present study revealed that abnormal BMD is highly prevalent in patients with liver cirrhosis. There is also a significant relationship between the severity of cirrhosis and BMD.

INTRODUCTION

Cirrhosis is a final stage of chronic liver disease that results in distortion of the normal liver architecture with the formation of extensive nodules, vascular reorganization, and deposition of an extracellular matrix. According to Global Burden of Liver Disease, roughly 1.03 million deaths per year in the world are estimated to be due to cirrhosis.1 Hepatic osteodystrophy (HO) is the term that defines the alterations in bone mineral metabolism that is found in patients with chronic liver disease.2 Individuals with chronic liver disease have been described to have a greater prevalence of osteopenia and osteoporosis and the studies performed in this regard have shown that this prevalence may vary in different populations. Patients with the cholestatic disease tend to have higher fracture incidence, varying from 13 to 22% according to the degree of liver dysfunction. Various studies reveal that up to 40% of patients with chronic liver disease may experience a fracture.1,4 Despite that, osteoporosis and osteopenia are often overlooked and very few cirrhosis patients are advised investigations to diagnose these bone abnormalities. We measure BMD by DEXA at a number of skeletal sites, most commonly the femoral neck and the lumbar spine. Osteoporosis is defined as a BMD in the hip and/or spine that is 2.5 standard deviations or more below the young adult’s mean value (T-score <−2.5).5 Osteopenia is defined as a T-score between −1 and −2.5.

The severity of chronic liver disease is assessed by two common scoring systems which are the CTP score and the model for end-stage liver disease. The CTP score is one of the most widely used scoring systems. The CTP scoring system takes into account the following parameters—serum albumin (ALB), serum bilirubin (BILI), prothrombin time (PT), ascites, and hepatic encephalopathy. The patients are classified into three classes I, II, and III.5

There are several studies dealing with the relationship between BMD and cirrhosis but the results of these studies are conflicting. Thus the present study was undertaken to assess the correlation between BMD and the severity of liver disease in patients with liver cirrhosis.

MATERIALS AND METHODS

The study population included cases and controls. Cases were patients >18 years of age diagnosed with liver cirrhosis. Age and sex-matched healthy individuals served as controls. There were 35 individuals in each group. Patients on drugs like steroids, estrogens, bisphosphonates, antiepileptic drugs, cytotoxic drugs, barbiturates, and lithium which affect bone metabolism were excluded. Patients with thyroid, adrenal, hypogonadal disorders, diabetes, chronic kidney disease, known cases of osteoporosis, fulminant hepatic failure, patients on regular intake of calcium and vitamin D supplements, and smokers were also excluded. After taking a detailed history and doing a thorough examination, biochemical investigations were done. BMD was assessed by DEXA at the lumbar spine and hip joint and results were expressed as T-score. A comparison of DEXA scores between cases and controls was done and results were analyzed.

RESULTS

The study was conducted on 70 individuals including 35 cases (adults diagnosed with liver cirrhosis) and 35 controls (age and sex-matched health individuals). There were 24 males and 11 females in the cases. A total of 10 cases were <40 years, 17 were between 40 and 60 years, and eight were >60 years.

The distribution of cases and controls into normal BMD, osteopenia, and osteoporosis are depicted in Table 1.

The majority of cases in class I had normal BMD, the majority in class II had osteopenia, and the majority of patients in class III had osteoporosis (Table 2).

When the mean T-scores were compared between cases and controls, cases had much lower T-scores, and the difference was found to be statistically significant (Table 3).

Serum vitamin D3 levels and ALB were reduced in cases as compared with controls and this difference was statistically significant. There was also a significant negative correlation between BMD and parathyroid hormone (PTH) levels (r = −0.389 and p = 0.0211) (Table 4).

There was a negative correlation between the CTP score and BMD value and this was statistically significant (Table 5).

There was a statistically significant difference observed with respect to the
Study of Correlation of BMD with Severity of Liver Cirrhosis

Table 6: T-score at two different sites and CTP class in cases

<table>
<thead>
<tr>
<th>CTP score</th>
<th>T-score (hip joint)</th>
<th>T-score (lumbar spine)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>−0.25 ± 1.75</td>
<td>−0.15 ± 1.77</td>
<td>p &gt; 0.05</td>
</tr>
<tr>
<td>Class II</td>
<td>−1.59 ± 1.37</td>
<td>−1.42 ± 1.49</td>
<td>p &gt; 0.05</td>
</tr>
<tr>
<td>Class III</td>
<td>−2.76 ± 0.27</td>
<td>−2.61 ± 0.29</td>
<td>p &gt; 0.05</td>
</tr>
</tbody>
</table>

Discussion

The determinants of BMD like genetic factors, age, gender, body mass index, exposure to sunlight, amount of physical activity, smoking and alcohol, dietary factors like consumption of salt, protein, and dairy products, use of medications, and prevalence of cirrhosis are variable in different parts of the world. The incidence of HO and fractures has been shown to be higher in patients with cirrhosis. Osteoporosis is unrecognized and hence untreated in several patients with liver cirrhosis. Hence the early diagnosis of HO is important in patients with chronic liver disease so that appropriate preventive and therapeutic strategies can be instituted.

A total of 70 patients were recruited in the present study with 35 patients each, in the case and control groups. Males dominated in both groups as 68.6% of the cases and 60% of the subjects in controls were males. Male: female ratio was 2.2:1 and 1.5:1 in cases and controls, respectively. There was no significant difference between the groups considering gender (χ² = 0.560 and p = 0.454). All the subjects were divided into three groups according to age—<40 years, 40–60 years, and ≥60 years. Both the groups had a higher number of mid-life (40–60 years) populations with 48.6% in the cases and 54.3% in the controls. There was no significant difference between the groups with regard to age group stratification (χ² = 0.2304 and p = 0.89). BMD declines in older people because of age-related bone loss. The exact age at which peak BMD is attained at different bony sites is not clear. It is also not known at what age this started happening. For the old subpopulation in the present study, the spine, as well as hip BMD, were found to be less in patients with cirrhosis than that in controls. However, for the younger age group, this difference was not seen (p > 0.05).

Screening for osteoporosis and osteopenia with single skeletal site measurements can underestimate the frequency and severity of the condition. The rate of renewal of bone is faster in the trabecular bone and therefore hips and vertebrae which are rich in trabecular bone are affected earlier. Hence the spine and hips will show evidence of osteoporosis and osteopenia earlier and the severity will also be more. In our study, the T-scores of the hip joint and lumbar spine were found to be lower in patients with chronic liver disease in...
comparison to age and sex-matched healthy controls. The mean T-score measured at the hip joint was $-1.47 \pm 1.62$ and $-0.56 \pm 1.67$ in cases and controls, respectively. While the mean T-score measured at the lumbar spine was $-1.33 \pm 1.66$ and $-0.41 \pm 1.67$ in cases and controls, respectively. There was a significant difference between cases and controls with regard to T-score ($p < 0.0001$). In a study by Turkeli et al., the patients with cirrhosis had a significantly lower BMD in the spine when compared with the BMD at the femoral neck.

The prevalence of osteopenia and osteoporosis has been variable in cirrhotic patients in different studies, ranging from around 11–48% for osteopenia and nearly 2–36% for osteoporosis. This heterogeneity can be attributed to the different methodologies adopted for the studies, patient characteristics, adoption of T or Z score as a measure of BMD, the etiology of cirrhosis, the severity of the disease, and factors like lifestyle and food habits. In the present study, 34.3% of the patients had alcohol-induced liver cirrhosis followed by 25.7% who had hepatitis B and 20% each with cryptogenic cirrhosis and hepatitis C. In our study irrespective of etiologies, the overall prevalence of osteoporosis and osteopenia was 22.9 and 37.1%, respectively. Around 14.3% of controls had osteoporosis while 34.3% had osteopenia. A total of 28.6 and 51.4% had normal BMD scores in cases and controls, respectively. There was no significant difference between the cases and controls with regard to HO ($\chi^2 = 4.690$ and $p = 0.0559$). In a study done by Soyulu et al., the prevalence of osteoporosis was 1.9% and that of osteopenia was 20% in patients with cirrhosis. In another study done by Ninkovic et al., the prevalence of osteoporosis was 36.6% and that of osteopenia was 48.8%. Sokhi et al. in their study demonstrated that 34.6% had osteopenia and 11.5% had osteoporosis. In the present study in the cirrhotic cases group, 31.4% had osteoporosis and 34.3% had osteopenia. There are several studies that show a high prevalence of abnormal BMD in patients with cirrhosis—Moschen et al. (37.8% osteopenia and 12.8% osteoporosis), Alcalde Vargas et al. (72% abnormal bone density), Goral et al. (osteoporosis 37%), and Diamond et al. (osteoporosis 16%).

There may be several mechanisms that could contribute to the development of osteopenia and osteoporosis in patients with chronic liver disease. One of the mechanisms may be changes in the PTH levels. The development of HO has yielded conflicting results. Bonkovsky et al. Duarte et al., and Karan et al. did not find any association between PTH levels and the development of HO. On the contrary Crosbie et al. found a significant correlation between PTH levels and the development of osteoporosis and osteopenia.

We also found a significant negative correlation between BMD and PTH levels ($r = -0.389$ and $p = 0.0211$), which is in concordance with the above study as well a study by Turkeli et al. ($r = -0.111$ and $p = 0.496$). There was no statistically significant relationship between BMD and calcium, international normalized ratio (INR), hemoglobin (Hb), platelet count, or BILI. In the present study, a positive correlation was found between BMD and ALB in the cirrhotic patients’ group ($r = 0.56$ and $p = 0.001$) which is similar to the findings of Turkeli et al. who also reported a similar positive correlation ($r = 0.351$ and $p = 0.026$).

There are several studies dealing with reduced bone density and the CTP score. But these studies show conflicting results. In the present study, the BMD was related to the severity of liver cirrhosis and as the CTP score increased from class I to III, there was a linear increase from normal to low BMD suggesting osteopenia and osteoporosis. The majority of the class III subjects in the present study had osteoporosis (77.8%) while the majority of the subjects in class II had osteopenia (66.7%). Conversely, 63.6% of the subjects in class I had normal BMD. None of the subjects in class III had normal bone density while two patients in class I had osteoporosis and osteopenia. Patients with osteoporosis had a higher CTP class in comparison to patients with normal BMD ($p < 0.001$) and osteopenia ($p < 0.05$). The reduction in BMD revealed a significant correlation with the severity of the liver disease ($r = -0.683$ and $p < 0.0001$) just in line with Sokhi et al. but in contrast to a study by Chen et al.

There were certain limitations of the present study. This was a prospective study done in a single tertiary care center and had a small sample size due to the pandemic. A study with a much larger sample size can be planned to confirm or negate our observations.

**Conclusion**

In conclusion, HO is quite common in patients with cirrhosis. This study demonstrated that the severity of cirrhosis is inversely related to BMD. In the present study, higher CTP scores and lower vitamin D, and elevated PTH levels were significant risk factors for abnormal BMD in patients with cirrhosis.

**References**

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Diagnostic Approach to Extrapulmonary Tuberculosis by Cartridge-based Nucleic Acid Amplification Test

Saswati Chattopadhyay1, Tanusri Biswas2, Abhra Banerjee3, Nabamita Chaudhury4*, Raston Mondal5, Arghya Nath6

Received: 22 December 2022; Accepted: 03 March 2023

Abstract

Background: Tuberculosis (TB) is a highly infectious disease causing billions of cases worldwide. Though pulmonary TB is the most common form of infection, extrapulmonary cases are also very rampant and are responsible for a large number of cases. But the diagnosis of extrapulmonary cases is quite difficult because of varied manifestations and the paucibacillary nature of the infection. Cartridge-based nucleic acid amplification test (CBNAAT) is a simple, rapid test that is very efficient in the early diagnosis of these extrapulmonary cases [extrapulmonary TB (EPTB)].

Aim: A study was done to establish the usefulness of CBNAAT in the early diagnosis of EPTB cases.

Materials and methods: A comparative study was conducted in a rural tertiary care hospital in West Bengal, India, for 8 months (July 2021–February 2022). Samples were collected from different sites like pleural fluid, lymph nodes, cerebrospinal fluid (CSF), pus, ascitic fluid, and tissue aspirate and subjected to both CBNAAT and smear staining and examination under a fluorescent microscope. Positive samples were cultured, examined, and compared.

Result: From 593 samples collected from different sites in suspected cases of EPTB—52 samples were positive by CBNAAT, and six cases showed rifampicin resistance (RIF resistant). Smear staining of the samples by auramine–rhodamine stains and examined under the fluorescent microscope for acid-fast bacilli identifying 33 samples; the rest were negative. Slides showing acid-fast bacilli were cultured on Lowenstein–Jensen media.

Conclusion: Cartridge-based nucleic acid amplification test (CBNAAT) is a very useful assay for the early diagnosis of extrapulmonary cases as it can accurately identify false negative samples by smear microscopy.

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Introduction

Tuberculosis (TB) is an infection caused by the bacteria Mycobacterium tuberculosis (MTB)—when it affects the lungs—it is called PTB, and when the infection affects sites other than the lungs, it is called EPTB—the most common site of infection being lymph nodes followed by pleural effusion.

Tuberculosis is responsible for nearly 8.6 million cases globally, according to the report World Health Organization (WHO) Global TB. India is an endemic country for TB, and only cases from India add 26% to this global load; among the five countries contributing the maximum to this global load, India occupies the first position.

It is a great public health problem in India, leading to a large number of deaths, and hence is a great health hazard. Out of all the TB cases, 15–20% of cases are due to affection of extrapulmonary sites (EPTB), with nearly 50% of the cases being due to human immunodeficiency virus (HIV)–TB coinfection. In the worldwide scenario, of the 1,183,373 new TB cases annually, 234,029 (20%) are of EPTB origin.

To reduce all the complications and mortality due to it, early diagnosis is very important. Conventional or fluorescent microscopy and culture are very important in the early diagnosis of this infection. Culture is the gold standard of diagnosis, being able to diagnose both viable and drug-sensitive/resistant bacteria, but it is expensive, time-consuming, and requires a long time (about 6–8 weeks) to detect the bacilli and has sensitivity through high specificity.

In the same way, though conventional staining by Ziehl–Neelsen stain is simple, easy, cheap, and fast, it has low sensitivity and fails to identify a very low count of the bacteria (<10 bacilli/mL of the sample).

On the contrary, diagnosis of the infection can be done using fluorescent dyes—auramine–rhodamine dyes and seeing the stained smear under [light emitting diode fluorescence microscopy (LED-FMI)] light emitting diode fluorescence microscopy. The disadvantage of this method is that though it identifies about 5–10% more acid-fast bacilli (AFB), being more sensitive—the uptake of the dyes is slow, less specific, expensive, and decreased quality control procedures.

To overcome these limitations, CBNAAT or Xpert MTB/RIF assay, a fully automated real-time semi-nested polymerase chain reaction (PCR) system giving results within 2 hours, detecting RIF resistant gene was endorsed by WHO as the most rapid test for diagnosis of PTB in 2010 as a replacement for sputum smear microscopy. The assay has both high sensitivity and specificity but is expensive and can detect viable bacteria, including nontuberculous mycobacteria (NTM).

The high performance of Xpert MTB/RIF in TB samples is well established, and the same principle was applied to extrapulmonary cases where the diagnosis is difficult because of the paucibacillary nature of the infection and the presence of a variety of clinical features.

Aim

In our study, we aim to find whether CBNAAT is a useful tool in the diagnosis of EPTB and RIF resistance by subjecting all the samples collected from all the patients suspected to be suffering from EPTB to Ziehl–Neelsen stain, fluorescent stain with auramine dye, culture in Lowenstein–Jensen media and CBNAAT.

Materials and Methods

Type of the study and design: It was a hospital-based prospective cross-sectional study.

- Place of study: Culture and drug sensitivity testing (C&DST) laboratory under the Department of Microbiology, Burdwan Medical College & Hospital, Bardhaman, West Bengal, India.

1Associate Professor; 2Associate Professor and HOD, Department of Microbiology, Burdwan Medical College & Hospital, Bardhaman; 3Assistant Professor, Department of Microbiology, R.G. Kar Medical College and Hospital, Kolkata; 4Assistant Professor, Department of Microbiology; 5Associate Professor, Department of Community Medicine; 6Research Scientist-B, Department of Microbiology, Burdwan Medical College & Hospital, Bardhaman, West Bengal, India;

*Corresponding Author

Medical College & Hospital, Bardhaman, West Bengal, India.

- Period of study: July 2021–February 2022 following approval by the Ethics Committee.
- Study population: All nonrespiratory clinical samples from clinically suspected patients with symptoms of suspected EPTB attending the outpatient department or admitted in the chest ward or other departments—Medicine and Paediatrics Departments of Burdwan Medical & Hospital during this period were collected and sent to our C&DST laboratory for further processing.

**Inclusion Criteria**

All patients of both genders up to 80 years attending the hospital in this period with features of EPTB were included in the study.

**Exclusion Criteria**

- All sputum samples, blood, or urine.
- Patients not willing to give consent for the study.

**Sample Size**

A total of 593 extrapulmonary clinical samples collected from lymph nodes, pus, pleural fluid, CSF, ascitic fluid, and tissue aspirate from patients suspected of having EPTB were included in the study.

The samples were divided into two parts—one part was stained by Ziehl–Neelsen stain and auramine–rhodamine stain and examined under the conventional microscope under oil immersion (100×) magnification for 300 fields. Smears were similarly stained by auramine dye which enters the cell wall of the bacteria, making it glow golden-yellow when examined by fluorescence microscopy under ultraviolet (UV) light for AFB.

Samples from slides showing AFB were cultured on Lowenstein–Jensen media. Scrupping from positive culture was again stained by Ziehl–Neelsen stain and confirmed by finding AFB.

**Sample**

Two parts—first part stained by
- Ziehl–Neelsen stain—seen in conventional microscope under oil immersion (100×) magnification.
- Auramine–rhodamine stain—seen in a fluorescence microscope.

Positive slides—samples cultured in Lowenstein–Jensen media—stained by Ziehl–Neelsen stain and confirmed.

Second part—sample tested by CBNAAT—in universal falcon tubes (30 mL capacity) + sampling reagent (NaOH and isopropanol) at 2:1 ratio—kept for 15 minutes at room temperature with intermittent shaking—3 mL of this mixture was added to the CBNAAT cartridge—result read within 2 hours.

Cartridge-based nucleic acid amplification test assay—Cepheid, Sunnyvale, USA—is a closed, simple, rapid, cheap, disposable cost-effective cartridge system that does not require much expertise and is very useful in a TB endemic country like India where liquid C&DST is quite difficult. Being a closed system, there is very less chance of cross-contamination.

Cartridge-based nucleic acid amplification test (CBNAAT) identifies not only the TB bacilli but also the presence/absence of RIF resistance. It has a highly specific primer and five unique molecular probes which target the *rpoB* gene—identifying the TB bacilli and RIF resistance (as per the guidance given by the Central TB division, Government of India (RNTCP, 2013; RNTCP, 2012). The results read within 2 hours as MTB detected/MTB not detected with/without RIF resistance detected/not detected.

**Result**

A total of 593 samples of suspected EPTB were received in the study period from different extrapulmonary sites—with samples from lymph nodes being the highest (Fig. 1).

Of the lymph nodes, the cervical lymph node was the most affected site (13/22), followed by the axillary (06/22) and inguinal (03/22).

Of the 593 extrapulmonary samples processed, MTB was detected in 52 cases (8.77%) by CBNAAT, while 21 (3.5%) samples showed AFB by Ziehl–Neelsen stain, 33 samples (5.5%) were detected positive by fluorescent stain and the culture on Lowenstein–Jensen media detected AFB in 41 (6.9%) cases only (Table 1).

Smear microscopy by Ziehl–Neelsen stain could not detect 31 and fluorescent microscope 19 cases and falsely declared them to be negative, but CBNAAT being a very accurate test, detected the deoxyribonucleic acid (DNA) of TB bacilli in the samples and declared them to be positive (Tables 2 and 3). Culture in Lowenstein–Jensen media yielded positive results in 41 CBNAAT-positive cases but could not detect 11 CBNAAT-positive cases (Table 4).

The sensitivity and specificity of CBNAAT in comparison with Ziehl–Neelsen smear is (Table 5):

- Sensitivity = 21/21 + 0 × 100 = 100%
- Specificity = 541/572 × 100 = 94.58%

The sensitivity and specificity of CBNAAT on comparison with FM smear is:

- Sensitivity = 33/33 + 0 × 100 = 100%
- Specificity = 541/560 × 100 = 96.6%

The sensitivity and specificity of CBNAAT on comparison with culture results on Lowenstein–Jensen is:

### Table 1: Distribution of total extrapulmonary samples according to CBNAAT and microscopic findings

<table>
<thead>
<tr>
<th>Total EPTB sample</th>
<th>CBNAAT positive</th>
<th>CBNAAT negative</th>
<th>Microscopy ZN positive</th>
<th>Microscopy FM positive</th>
<th>Culture in LJ media positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>593</td>
<td>52</td>
<td>541</td>
<td>21</td>
<td>33</td>
<td>41</td>
</tr>
<tr>
<td>%</td>
<td>8.77</td>
<td>91.2</td>
<td>3.5</td>
<td>5.5</td>
<td>6.9</td>
</tr>
</tbody>
</table>

![Fig. 1: Distribution of the CBNAAT-positive EPTB samples from different sites](image)
Diagnosis of Extrapulmonary Tuberculosis by CBNAAT

- Sensitivity = 41/41 + 0 × 100 = 100%
- Specificity = 541/552 × 100 = 98%

Smear microscopy by auramine–rhodamine stain and examining them under a fluorescence microscope for AFB is a simple, rapid, cheap, but not very useful method with low sensitivity. Sputum culture on Lowenstein–Jensen media is a very sensitive and specific method, but it takes 6–8 weeks to give a positive result—so not very useful in a very infectious disease like TB where there is a great need for early diagnosis and treatment.

All the EPTB samples were subjected to Ziehl–Neelsen stain, FM stain culture in Lowenstein–Jensen media, and CBNAAT assay. The sensitivity and specificity of CBNAAT on comparison with culture results in FM smear-negative cases are:
- Sensitivity = 08/08 + 11 × 100 = 42.1%
- Specificity = 541/541 × 100 = 100%

Extrapulmonary samples were received from different sites like a lymph node, pus (22), pleural fluid (11), CSF (10), tissue aspirate (04), pus (03), ascitic fluid (01), and synovial fluid (01) but the maximum samples were from the lymph node followed by the pleural fluid.

The CBNAAT-positive samples were found more in females (27) than males (25) at a 1:08 ratio. The maximum number of cases was found in the age-group 21–30 years (32.70%), followed by the age-group 31–40 years of age (17.31%) (Table 6).

Among the 52 samples declared positive by CBNAAT, in six samples, RIF resistance was detected, and in the rest 46 samples, no RIF resistance was identified (Table 7).

### Discussion

Extrapulmonary TB accounts for approximately 25% of TB cases caused by Mycobacterium complex worldwide, thus being responsible to a great extent for the morbidity and mortality due to the bacteria. Because EPTB infection is usually deep-seated, biopsy by surgery is required to collect a sample for testing, making the diagnosis further difficult.

Culture by liquid media by mycobacteria growth indicator tube (MGIT) system is costly and needs a lot of expertise to do it by trained laboratory technicians.

Cartridge-based nucleic acid amplification test is a simple, rapid, closed system working on the principle of nested semi-quantitative nucleic acid amplification method, which can be done quite easily, giving early accurate results within 2 hours.

Cartridge-based nucleic acid amplification test is also useful in the diagnosis of EPTB, but its use in this aspect has not been used much, probably because of a lack of knowledge, and our study aims to highlight this fact.

A study by Denkinger et al. reported that samples from the lymph node were more sensitive (83%) than that from the pleural fluid (46%).

The same was also corroborated by Rai et al. and Penz et al., who also found that the sensitivity of the lymph node is much higher (87%) than that of pleural fluid (37%).

The same finding was also reported by us—MTB was isolated from the lymph node in 22 (42.31%) cases while that from the pleural fluid in 11 (21.16%) cases.

Tubercular pleural effusion was the most common form of EPTB in the study conducted by Mukherjee et al., being found in 58.17% of cases, followed by lymphadenopathy (22.71%).

The same was also corroborated by us—MTB was isolated more in the younger age-group, with MTB detected in 23 (34.3%) cases.

### Table 2: Comparison of results from CBNAAT and ZN smear

<table>
<thead>
<tr>
<th>CBNAAT status</th>
<th>ZN smear</th>
<th>Grand total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Smear positive</td>
<td>Smear negative</td>
</tr>
<tr>
<td>CBNAAT positive</td>
<td>21</td>
<td>31</td>
</tr>
<tr>
<td>CBNAAT negative</td>
<td>0</td>
<td>541</td>
</tr>
<tr>
<td>Grand total</td>
<td>21</td>
<td>572</td>
</tr>
</tbody>
</table>

### Table 3: Comparison of results from CBNAAT and FM smear

<table>
<thead>
<tr>
<th>CBNAAT status</th>
<th>FM smear</th>
<th>Grand total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Smear positive</td>
<td>Smear negative</td>
</tr>
<tr>
<td>CBNAAT positive</td>
<td>33</td>
<td>19</td>
</tr>
<tr>
<td>CBNAAT negative</td>
<td>0</td>
<td>541</td>
</tr>
<tr>
<td>Grand total</td>
<td>33</td>
<td>560</td>
</tr>
</tbody>
</table>

### Table 4: Comparison of results from CBNAAT and culture on LJ media

<table>
<thead>
<tr>
<th>CBNAAT status</th>
<th>Culture on LJ media</th>
<th>Grand total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Culture positive</td>
<td>Culture negative</td>
</tr>
<tr>
<td>CBNAAT positive</td>
<td>41</td>
<td>11</td>
</tr>
<tr>
<td>CBNAAT negative</td>
<td>0</td>
<td>541</td>
</tr>
<tr>
<td>Grand total</td>
<td>41</td>
<td>552</td>
</tr>
</tbody>
</table>

### Table 5: Comparison of CBNAAT results with culture on LJ media and FM smear-negative cases

<table>
<thead>
<tr>
<th>CBNAAT status</th>
<th>FM smear negative</th>
<th>Grand total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Culture positive</td>
<td>Culture negative</td>
</tr>
<tr>
<td>CBNAAT positive</td>
<td>08</td>
<td>11</td>
</tr>
<tr>
<td>CBNAAT negative</td>
<td>0</td>
<td>541</td>
</tr>
<tr>
<td>Grand total</td>
<td>08</td>
<td>552</td>
</tr>
</tbody>
</table>

*Among the total 52 extrapulmonary samples, the number of female patients outnumbered the male one*
In our study, we also found the maximum prevalence of MTB was in the age-group 21–30 years; 17 (32.70%) cases were closely followed by the age-group 31–40 years (13–25%).

Singh et al., in their study, found that MTB was found more in the cases of EPTB in males at the ratio of 3:2 male:female ratio.20

In our study, however, found that more EPTB cases were found in females than males (ratio 27/25—1.08).

In the study done by Singh et al. in 2020 detected RIF resistance by CBNAAT in 05 (6.8%) samples. They also found that out of 46 samples stained by Ziehl–Neelsen, which were negative, CBNAAT found MTB in 27 samples—thus proving the fact CBNAAT is a very sensitive test that could identify correctly false negative results given by Ziehl–Neelsen stain.21

In our study, CBNAAT gave RIF-resistant reports in six cases out of 52 positive samples (11.5%).

**Conclusion**

Cartridge-based nucleic acid amplification test is a very useful test able to diagnose a highly infectious disease like MTB rapidly within 2 hours, and hence treatment can be initiated very fast, thus preventing the development of resistant cases. India is a TB-endemic country, and increased use of CBNAAT for diagnosis of it—both pulmonary and extrapulmonary cases may act as a boon in disguise.

**Limitation**

A more detailed study for a span of over 1 year was not done.

**Author's Contribution**

- SC: Concept and design of the study, prepared the first draft of the manuscript, preparation of the manuscript, and revision of the manuscript.
- NC: Concept and design of the study, prepared the first draft of the manuscript.
- TB: Review of the literature and manuscript preparation.
- AB: Review of the literature and manuscript preparation.
- RM: Statistical analysis and their interpretation.
- AH: Preparation of manuscript and revision of the manuscript.

**References**

Neurocognitive Disorders in HIV-positive Patients

Prateek S Padole1, Rupal N Padhiyar2*, Dhirenda S Yadav3, Swati A Chavan4

Received: 27 July 2022; Accepted: 10 March 2023

Abstract

Human immunodeficiency viruses (HIV) associated neurocognitive disorders (HAND) encompasses a group of syndromes of various degrees of impairment in cognition and daily functioning of HIV-positive individuals. Although the widespread use of highly active antiretroviral therapy (HAART) has drastically reduced the prevalence of severe form of HAND, like HIV associated dementia (HAD), the prevalence of HAND and associated morbidity remains high.

Objectives: (1) To know the prevalence of HAND in HIV-infected patients of a multi-ethnic population. (2) To describe various types of neurocognitive impairment among patients of HAND and study the factors affecting HAND.

Study design: This study was a cross-sectional descriptive study conducted on 250 HIV-positive patients in outpatient department (OPD) of a tertiary care center in Mumbai, conducted over a period of 12 months. Patients with HIV-1 attending the OPD and having a minimal formal education of 4 years were included. Patients with comorbid delirium, any known central nervous system (CNS) disorder, any psychiatric disorder, and pregnant females were excluded. Outcome measures—the test batteries used were (1) International HIV Dementia Scale (IHDS) and (2) Addenbrookes cognitive examination-revised (ACE-R) scale.

Results: Of 250 subjects studied, 55.6% (139) were males and 44.4% (111) were females. The mean age of study population was 39.42 years. The mean years of education were 8.32 years. The mean duration of infection (diagnosis of HIV-positive state) was 64.49 months and the mean duration of HAART intake in our patients was 52.30 months. The mean cluster of differentiation 4 (CD4) counts of our subjects were 527.13 per cumm [standard deviation (SD) of 234.13]. The mean nadir CD4 counts were 224.35 per cumm (SD of 115.09). Using the ACE-R scale, the prevalence of HAND was 71.60%, of which 37.20% had an asymptomatic neurological impairment, 29.60% had mild neuropsychological impairment (ANI) and HIV-associated mild neurocognitive disorder (MND) to severe form of HAD. Although the prevalence of the dramatic forms such as HAD has decreased, there is an increased number of affected individuals with milder forms of HAND. Neurocognitive dysfunction, even in the mild form, not only has profound effects on daily living of the patients, but also affects employability. This, in the long term, can hamper the efforts carried out by various agencies to limit this pandemic. These patients may not be adherent with taking medications or can miss their appointments, may suffer psychiatric manifestations, and may have difficulty in using preventive measures for viral transmission. Certainly, survival rate of patients with HAND is lower than that of HIV-positive individuals without HAND.1,4 With increase in age of HIV-positive individuals, having lower nadir CD4 counts are at the highest risk of HAND. Memory, verbal fluency, and visuospatial abilities were the most commonly affected domains.

Conclusion: Human immunodeficiency viruses (HIV) associated neurocognitive disorders HAND is common in HIV-positive patients, most of whom are asymptomatic. Older patients with less education and severe disease, having lower nadir counts are at the highest risk of HAND. Memory, verbal fluency, and visuospatial abilities were the most commonly affected domains.

Introduction

Today, the widespread use of HAART has resulted in increased life expectancy of people living with HIV (PLHIV). This has led to rising concerns about the neurocognitive dysfunctions caused by the infection and its effect on the patient and the epidemic as a whole. Globally there were approximately 37.7 million,1 PLHIV at the end of 2020, and there were estimated 2.34 million PLHIV in India at the end of 2019.2 HAND is the CNS manifestation due to the virus itself. It consists of a group of syndromes of varying degrees of impairment in cognition and its associated functioning in HIV-infected people. The clinical spectrum of HANDS includes mild forms like asymptomatic neuropsychological impairment (ANI) and HIV-associated mild neurocognitive disorder (MND) to severe form of HAD. Although the effect on the patient and the epidemic as a whole, there were estimated 2.34 million PLHIV with ANI and MND to severe form of HAD. Although the prevalence of the dramatic forms such as HAD has decreased, there is an increased number of affected individuals with milder forms of HAND. Neurocognitive dysfunction, even in the mild form, not only has profound effects on daily living of the patients, but also affects employability. This, in the long term, can hamper the efforts carried out by various agencies to limit this pandemic. These patients may not be adherent with taking medications or can miss their appointments, may suffer psychiatric manifestations, and may have difficulty in using preventive measures for viral transmission. Certainly, survival rate of patients with HAND is lower than that of HIV-positive individuals without HAND.1,4 With increase in age of HIV-positive individuals, having lower nadir CD4 counts are at the highest risk of HAND. Memory, verbal fluency, and visuospatial abilities were the most commonly affected domains.
Neurocognitive Disorders in HIV-positive Patients

Exclusion Criteria
All those who did not consent to participation in the study. Patients having concomitant delirium, any known CNS disorder, use of psychoactive drugs, history of cerebrovascular accident, any psychiatric disorder, dementia with a known cause other than HIV, and pregnant females were excluded.

Participants
After applying the inclusion criteria, 250 patients were selected for the study. All these patients were assessed by the ART physician. HIV seropositive status was confirmed using the National AIDS Control Organization, Government of India guidelines and strategy. Demographic data like age, sex, address, education, and occupation were collected. Clinical information like other sexually transmitted infections, comorbidities like hypertension, diabetes, and dyslipidemia, and hepatitis B and C coinfection was obtained. Laboratory data included complete hemogram, liver and renal function tests, and electrolytes. Detailed information on current CD4 cell count, documented nadir CD4 cell count, length of time since diagnosis, and the antiretroviral therapy administered were also collected for the study purpose.

The participants were divided into three groups according to their CD4 cell counts (Centre for Disease Control and Prevention, 1992), that is, <200, 201–499, and >500 cells/mm³. Patients underwent a clinical and neurological evaluation before the study questionnaire.

Test Battery
Addenbrookes cognitive examination-revised (ACE-R)—the ACE-R is a cognitive test that assesses five domains of cognition, namely attention/orientation, memory, verbal fluency, language, and visuospatial abilities. Maximum score is 100, and higher the score, better is the cognitive functioning. At a cutoff score of 88, the sensitivity is 0.94 and the specificity is 0.89; while at a cutoff score of 82, the sensitivity is 0.84, and the specificity is 1.00. The Addenbrookes scale has been validated in various languages and has been effectively used as a screening tool for the early detection of dementia in various psychiatric clinics. We used the modified version of the ACE-R suitable to the Indian standards and language as is been validated by Mathuranath et al. The various domain specific cutoffs were also defined for our study to know the proportion of affected individuals. They were—attention <15/18, memory <20/26, verbal fluency <11/14, language <24/26, and visuospatial <14/16.5.

International HIV Dementia Scale (IHDS)—IHDS is a useful screening test to identify individuals at risk for HIV dementia in both the industrialized world and developing world. The IHDS has three subtests; motor speed, psychomotor speed, and memory recall. The maximum score is 12 points; a score of ≤10 is evidence of probable dementia. This cutoff score has been recommended to minimize false positives errors. IHDS was internationally validated of detecting HAND. Using a cutoff of ≤10, the sensitivity and specificity for HIV dementia with the IHDS were 80 and 57% respectively in a United States sample, and 80 and 55% respectively in a Ugandan sample. The IHDS can be a useful tool for HIV-positive individuals with or without a high school education. The cutoff for affected domain was ≤3 in our study.

Definitions
- Asymptomatic neurocognitive impairment (ANI)—Addenbrookes score of 83–88, both inclusive. Scores above 88 were considered normal.
- Mild neurocognitive dysfunction (MCD)—Addenbrookes score of 75–82, both inclusive.
- HIV associated dementia (HAD)—Addenbrookes score of <75.

Results
Demography
After applying the inclusion and exclusion criteria, our sample size was 250 patients. Of which 139 (55.60%) were males, and 111 (44.40%) were females. It corresponded to the gender distribution of HIV affected individuals in the general population and also in our ART OPD. The mean age of our patients was 39.42 years (SD = 9). There were 14% subjects below 30 years of age, 76.40% between 30 and 50 years of age, and 9.60% above 50 years of age. There were 14% subjects below 30 years of age, 76.40% between 30 and 50 years of age, and 9.60% above 50 years of age. The mean duration of infection (diagnosis to ART) was 5.30 years (SD = 4.89). The mean duration of ART intake was 52.30 months (SD = 34.42). The current CD4 counts of our subjects were 527.13 per cumm (SD = 234.13). The current CD4 (per cumm) was below 200 in 3.60%, between 200 and 500 in 47.20%, and above 500 in 49.20% of subjects.

Prevalence
The prevalence of HAND in our population using the ACE-R scale was found to be 71.60% (179/250) using the cutoff score of 89 and above as normal. The prevalence of HAND using the cutoff score of 10 in the IHDS Scale was 63.20% (158/250). ANI (score of 83–88 on ACE-R) was found in 37.20% (93/250). Mild cognitive dysfunction (score of 75–82) was found in 29.60% (74/250). HAD, as characterized by (symptoms of dementia and ACE-R score <75) was found in 4.80% (12/250) of the subjects.

Domain Affected
Using the ACE-R, we found that domain of memory was affected in 47.20%, visuospatial ability was affected in 43.20%, and verbal fluency was affected in 42% of the subjects. Domain of language and attention was not affected much in our study population (around 10%) (Table 2 and Fig. 1).

When domains of the IHDS were studied, almost all domains were significantly affected in our population, with memory recall being maximally affected (76.40%), psychomotor speed was affected in 63.2%, and motor speed as affected in 40.8% of patients (Table 3 and Fig. 2). The scores in all domains were significantly different in the normal and affected groups (p-value of <0.05). The difference in the mean scores of memory in both groups was the maximum.

Table 1: Demography and description of our population

<table>
<thead>
<tr>
<th>Study parameters</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>250</td>
<td>39.42</td>
<td>9.00</td>
</tr>
<tr>
<td>Years of education</td>
<td>250</td>
<td>8.32</td>
<td>2.81</td>
</tr>
<tr>
<td>Duration of infection (months)</td>
<td>250</td>
<td>64.49</td>
<td>40.77</td>
</tr>
<tr>
<td>On art since (months)</td>
<td>250</td>
<td>52.30</td>
<td>34.42</td>
</tr>
<tr>
<td>CD 4 current (/cumm)</td>
<td>250</td>
<td>527.13</td>
<td>234.13</td>
</tr>
<tr>
<td>CD 4 nadir (/cumm)</td>
<td>250</td>
<td>224.35</td>
<td>115.09</td>
</tr>
</tbody>
</table>
Asymptomatic neurocognitive impairment was seen in 37.20%, mild cognitive dysfunction in 29.60%, and HAD in 4.80%. A study from Southern India in 30 HIV-positive individuals with advanced HIV-1 infection with (clade C virus variant) reported that 56% of patients had cognitive deficits in two cognitive domains. The sample consisted of individuals with severe levels of immune deficiency. In our sample we had 250 HIV-1-positive patients. The tests used in the study were standardized and validated in the Indian population (Mathuranath et al.). Other Indian studies showed a similar prevalence as in the study by Muniyandi et al. (78%). Our study was carried out in a multi-ethnic population of Mumbai, consisting of a large number of subjects and gave similar results. The prevalence of HAD was comparatively higher in the Western world as compared to the Indian data. This may reflect the less neurovirulence of HIV clade C virus variant, which is a causative virus in 95% of infections in India.

HIV and neurocognition Indian literature—Indian literature about the neurocognitive deficit in HIV is limited. Kamat et al., compared 69 HIV-positive and 67 HIV-negative patients, who were asymptomatic, attending clinic in Chennai. They used the international neuropsychological test battery. Prevalence of HAND was significantly higher (33 vs 13%) in HIV-positive patients. About 90% of asymptomatic HIV-positive patients had some psychiatric illness in a study by Satapathy et al. The common diagnosis was adjustment disorders and depression. None of the patients were found to have cognitive defects in this study. The above differences in the parameters of the IHDS scale were also significantly different in both groups (p-value of <0.05).

Factors affecting HAND and their correlation with ACE-R scores—age is significantly and inversely correlated to the ACE-R score (p-value of <0.05; correlation coefficient = −0.148). As the years of education increase, the ACE-R score also improves. This is positively and significantly related (p-value of <0.05; correlation coefficient = 0.558). The correlation between nadir CD4 and ACE-R score was significant and positive (p-value of <0.05; correlation coefficient = 0.344). However, there seems to be no correlation between the duration of infection and the ACE-R scores, that is, the level of cognition (p-value of >0.05; correlation coefficient = −0.037) or between the current CD4 counts and the ACE-R scores (p-value of >0.05; correlation coefficient = 0.020) (Table 4 and Fig. 3).

**DISCUSSION**

Prevalence of HAND—the prevalence of HAND in our study was 71.60% according to the ACE-R scale and 63.20% according to IHDS.

**Table 2: Domains of ACE-R**

<table>
<thead>
<tr>
<th>Addenbrookes domain</th>
<th>Affected*</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention (&lt;15/18)</td>
<td>27</td>
<td>10.80%</td>
</tr>
<tr>
<td>Memory (&lt;20/26)</td>
<td>118</td>
<td>47.20%</td>
</tr>
<tr>
<td>Verbal fluency (&lt;11/14)</td>
<td>105</td>
<td>42.00%</td>
</tr>
<tr>
<td>Language (&lt;24/26)</td>
<td>26</td>
<td>10.40%</td>
</tr>
<tr>
<td>Visuospatial (&lt;14/16)</td>
<td>108</td>
<td>43.20%</td>
</tr>
</tbody>
</table>

*Standard cut-offs

**Table 3: Domains of IHDS**

<table>
<thead>
<tr>
<th>IHDS domain</th>
<th>Affected (≤3)</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor speed (4)</td>
<td>102</td>
<td>40.80%</td>
</tr>
<tr>
<td>Psychomotor speed (4)</td>
<td>158</td>
<td>63.20%</td>
</tr>
<tr>
<td>Memory recall (4)</td>
<td>191</td>
<td>76.40%</td>
</tr>
</tbody>
</table>

**Table 4: Comparison of the various cognitive domains in normal and affected groups**

<table>
<thead>
<tr>
<th>Study parameters</th>
<th>Addenbrook score ≤89 (normal) (N = 71)</th>
<th>Addenbrook score &lt;89 (affected) (N = 179)</th>
<th>Unpaired t-test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention (18)</td>
<td>N 71</td>
<td>Mean 17.21 SD 0.72</td>
<td>N 179</td>
<td>Mean 15.68 SD 1.03</td>
</tr>
<tr>
<td>Memory (26)</td>
<td>N 71</td>
<td>Mean 22.08 SD 1.59</td>
<td>N 179</td>
<td>Mean 18.61 SD 1.97</td>
</tr>
<tr>
<td>Verbal fluency (14)</td>
<td>N 71</td>
<td>Mean 11.93 SD 0.78</td>
<td>N 179</td>
<td>Mean 10.22 SD 1.21</td>
</tr>
<tr>
<td>Language (26)</td>
<td>N 71</td>
<td>Mean 25.65 SD 0.48</td>
<td>N 179</td>
<td>Mean 24.55 SD 1.22</td>
</tr>
<tr>
<td>Visuospatial (16)</td>
<td>N 71</td>
<td>Mean 13.83 SD 0.38</td>
<td>N 179</td>
<td>Mean 12.74 SD 1.86</td>
</tr>
</tbody>
</table>
Neurocognitive Disorders in HIV-positive Patients

studies were mostly clinical studies and neuropsychological tests were not carried out in all studies. It is impossible to recognize mild cognitive deficits with just clinical interview methods. A case-control study was conducted by Mandal et al., for cognitive impairment among 50 HIV-positive patients with stages I, II, and III in comparison to 50 control subjects utilizing digit span test, word association test, etc. They have shown that HIV-infected individuals had poor scores in all tests, and a statistically significant difference was noted in digit symbol substitution test, controlled word association test, and trail-making test.17

Factors affecting—we found that age positively correlated with the prevalence of HAND, while nadir CD4 and years of education strongly and negatively correlated with the prevalence of HAND. Duration of illness, duration of ART, gender, and current CD4 counts did not affect the presence of HAND, as there was no significant correlation between them. We didn’t find any correlation between the duration of HAART intake and presence of HAND. This can point towards a finding that there is no significant neurotoxicity of HAART, though detailed studies considering these two parameters are required. Also, gender or the present immunological status (current CD4) did not correlate with HAND, as was confirmed by all other studies. An important observation was the strong correlation between the years of education and the presence of HAND. This could be due to the protective effect of education on particular domains of cognition. This could also reflect the sociodemographic characteristic of the population and can confound the results and other parameters. We did a multivariate analysis to nullify the compounding effect of years of education and found that nadir CD4 count still had a significant correlation with the presence of HAND. We propose that the nadir CD4 count represents the virulence of the organism and the correlation confirms that highly virulent organisms are more likely to cause HAND. It was also demonstrated in Indian study by Muniyandi et al.14

Cognitive domains affected—the domains of cognition affected to determine the pattern of involvement in HAND. Domains studied were—attention and orientation, memory, verbal fluency, language and visuospatial abilities (ACE-R Scale) and motor speed, psychomotor speed, and memory recall (IHDS Scale). We found that the domains most affected in HAND were—memory, verbal fluency, and visuospatial abilities, while attention and language domain were relatively spared. Domains of IHDS scale were almost equally and universally affected with less affection to motor speed than to memory recall and psychomotor speed. Current concepts indicates predominant subcortical pattern of involvement among HAND patients, with bradykinesia and bradyphrenia being the characteristic features.18,19 Most common domains affected in HIV patients as per general consensus are abstraction/executive functioning, learning, motor functioning, and attention/working memory, whereas there is sparing of language and verbal functioning.18,20 In contrast, in our study, both cortical and subcortical functions were found to be commonly affected, which is similar to a recent study demonstrating cortical and subcortical neurodegeneration.21 Our study, we could not comment whether these effects are due to HAART, as has been suggested by other studies.22 A study done by Letendre et al., on CNS penetration-effectiveness of various ART drugs have observed that CNS penetration of different ART drugs varies in HAND patients and ART treatment strategies should include this aspect in their recommendations after validating it in clinical studies. Above study was a cross-sectional study and its interpretation was limited due to other confounding factors like duration and timing of ART initiation.23,24 Further studies should study the differences in the cognitive profile of HAND in patients on HAART and ART naïve patients. Some studies have reported similar deficits that support the involvement of subcortical and frontostriatal brain processes in clade B infection. The cognitive profile in the seropositive individuals in a study by Gupta et al., also suggest a frontostriatal pathology.25 The difference in cognitive functions of the healthy seronegative controls and the seropositive patients was in the domains of fluency, verbal working memory, and verbal learning and memory; thus cognitive deficits in these domains are associated with HIV1 infection. Earlier studies have shown evidence of working memory deficits in HIV-infected subjects supporting frontal lobe pathology in HIV infection.26,27 However, the type of cognitive dysfunction in South Asian patients with HAND does not fit into a discrete subcortical pattern, as shown in the study by Chan et al.24 Our study emphasize the importance of early diagnosis of neurological dysfunction among HIV patients to ensure that they are linked to comprehensive HIV care. Prior studies had used various neuropsychological assessment batteries for diagnosis of HAND.28,29 Our study has used a standardized mental assessment examination utilizing performance in various domain-specific parameters instead of total/recommended cutoff scores to provide a comprehensive cognitive assessment similar to the study done by Chan et al.24 Also, the IHDS scale was used as a study tool which allows comparisons with studies throughout the world. We hope that the results of this study will help to change the approach towards diagnosis, treatment, and management of HAND and sensitize physicians about this important topic.

Limitations of Study
Our study was a cross-sectional study, and thus, we could not keep follow-up subjects and could not study any intervention and its effects. The Neyman’s bias of selection could not be removed as not every HIV-affected individual visit the. We used the CD4 levels as the marker of immune suppression while HIV viral load was not done. We conducted the study only on the HIV-affected individuals and a control group was absent. However, we used cognitively normal HIV individuals as controls in our study to compare our results. Though the neuropsychological scales used are...
Neurocognitive Disorders in HIV-positive Patients

standardized and validated, there is a lack of published normative data on them. However, we have used demographically appropriate data wherever possible.

**Future Directions**

Future studies should concentrate on a follow-up cohort studying the effect of ART on the prevalence and manifestations of HAND. Also, studies on the effects of drugs on the molecular level should be conducted. There should be a consensus on the cognitive tools used to screen HAND and national guidelines for the same. Future studies should focus on the aspect of treatment as given by the providers, such that it can prevent the occurrence of HAND. This can affect the compliance to treatment, use of services, and decrease in morbidity of HIV-affected individuals.

**Conclusion**

The prevalence of HAND in our study is 71.6% using the ACE-R and standardized cut-offs. Asymptomatic neurocognitive impairment was seen in 37.20%, mild cognitive dysfunction in 29.60%, and HAD in 4.80%. Age has a significant correlation with the presence of HAND. As age increases, there is a decline in cognition, as evidenced by reduced scores on the neurocognitive scales. The years of education are also significantly and negatively correlated with the presence of HAND in our study. As the education level increases, the presence of HAND is less likely. Patients with lower nadir CD4 counts were more likely to be affected by HAND, showing a significant correlation.

The neurocognitive domains most affected in HAND were memory, verbal fluency, and visuospatial abilities. This suggests both cortical and subcortical involvement in HAND. Attention and language domains were relatively spared in HAND. The duration of infection, duration of consumption of ART, gender, and the current immune status (current CD4) do not have an effect on the presence of HAND.

**References**

Risk Factors associated with COVID-19 Patients in India: A Single Center Retrospective Cohort Study

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INTRODUCTION

The World Health Organisation (WHO) declared COVID-19 as a global pandemic on 11th March 2020. The disease is caused by severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2). China was the first country to be infected with the virus, and periodic testing and proper quarantine measures were imposed to contain the virus. Being highly contagious in <7 months, the virus spread to 214 other countries, causing the pandemic.1,2

The clinical presentation of COVID-19 is highly heterogeneous, ranging from asymptomatic to severe pneumonia with respiratory failure that could lead to acute respiratory distress syndrome or death. According to the WHO, 85% of infections cause a mild or moderate illness. In the remaining 10–15%, patients develop severe symptoms, which require hospitalization, and only about 5% of cases require intensive care. Recovery is dependent on the severity of the infection. For instance, patients with mild symptoms recover in 2 weeks, whereas those with severe symptoms recover in 3–6 weeks.3 This time to the events, here recovery is considered more critical as it can help establish the probability of the outcome and facilitate modification in treatment, if required, to achieve a more favorable result during a considerable duration of hospital stay. This time to recovery is usually estimated using a Kaplan–Meier survival curve, where the Y-axis indicates the survival and the X-axis denotes the time trend.4 Moreover, it can help to determine the duration of the hospital stay, availability of hospital beds in critical care, and recovery time of COVID-19 patients.5

Although a deeper understanding of the nature of the disease is acquired through literature, no definitive treatment has yet been proven to be effective in preventing the disease progression and the death of critical patients. This study, thus, aims to identify the risk factors for early warning and intervention using survival analysis by retrospectively analyzing the characteristics and outcomes of patients associated with mortality among COVID-19 patients admitted to Seven Hills Hospital Reliance facility, a dedicated COVID-19 care hospital in Mumbai, Maharashtra, India.

MATERIALS AND METHODS

The study was conducted at Seven Hills Hospital Reliance facility, Mumbai, Maharashtra, India, under the approval of the ethics committee at Sir HN Reliance Foundation Hospital (RFH) and Research Centre.

Study Design

It is a retrospective, observational analytical study without any control group for COVID-19-positive cases. COVID-19 diagnosis was performed as per the WHO interim guidelines.6 Since the study did not involve any intervention in patient care, the requirement for written informed consent was waived by the institutional Ethics Committee (IEC).

Study Population

The study population included all adult patients aged 18 years and above with reverse transcriptase quantitative polymerase chain reaction (RT-qPCR)—confirmed SARS-Cov-2 infection admitted to the hospital within the study period of March–June 2020. The diagnosis was confirmed by a positive result of RT-qPCR assay from nasal and pharyngeal swab specimens. Only those patients who were admitted for >24 hours were included in this study. Patients transferred to other facilities for further care were excluded.

Design and Data Extraction

Data including epidemiological history, demographics, clinical symptoms and signs, comorbidities, radiological assessments,
laboratory findings upon admission, treatments, and clinical outcome were extracted from electronic medical records. The primary endpoint of the outcome was time to death.

**Study Variables**

Data were extracted from the electronic medical record system. Baseline demographic data, arterial oxygen pressure (PaO\textsubscript{2})/fraction of inspired oxygen (FiO\textsubscript{2}) ratio, sequential organ failure assessment (SOFA) score comorbidities, medication history, category of COVID-19 disease—mild, moderate, and severe were noted. Clinical characteristics such as time from the onset of symptoms to hospitalization, symptoms on presentation, radiological investigation using HRCT and chest X-ray findings were also recorded in addition to abnormal laboratory parameters (low lymphocyte count) and inflammatory marker levels (serum C-reactive protein (CRP; <0.5 mg/dL), D-dimer (0–250 ng/mL), ferritin (30–400 ng/mL), lactate dehydrogenase (LDH; ≤250 U/L), and interleukin (IL-6; 0–7 pg/mL)). Treatment therapies as per Sir HN RFH COVID-19 treatment protocol and overall complications during hospitalization were also noted. Clinical outcomes, including in-hospital mortality (defined as the proportion of patients with COVID-19 who died in the hospital), ICU admission, use of noninvasive or mechanical ventilation, total hospital length of stay, and ICU length of stay, were all considered while performing data analysis.

**Statistical Analysis**

Data was entered in MS Excel (Microsoft\textsuperscript{©}, USA) and converted to Stata version 15.1 (\textsuperscript{©}StatCorp, College Station, Texas, United States of America). The mean and standard deviation (SD) or median and interquartile range (IQR) were estimated for all continuous variables. The proportions were identified for categorical variables.

Mean values across groups were compared using the Independent Samples t-test, and median values were compared using the Mann–Whitney U test. The proportions were compared using the Chi-squared test or Fisher’s exact test for low expected cell counts. Both these parameters were estimated for the whole study population using clinical and demographic characteristics as well. The difference between the two survival curves was determined using the log-rank test. We then created a multiple regression model using Cox proportional hazards regression modelling to estimate the risk factors associated with COVID-19 mortality. We also included demographic and clinical variables in the model. p-values of <0.05 were considered statistically significant.

**Results**

The mean (SD) age of the patients (N = 565) was estimated to be 51.6 (16.4) years. Of these, 368 (65.3%) were men and 196 (34.8%) were women.

Out of 565 patients, 516 (91.3%) patients were discharged and 49 (8.7%) patients died. Overall, 119 (20%) patients required ICU admission, of which 70 (58%) patients survived. Patients required noninvasive or mechanical ventilation for an average duration of 6 or 8 days, respectively. The average total hospital length of stay was 11 days, whereas the ICU length of stay was 9 days. On admission to the ICU, patients with a PaO\textsubscript{2}/FiO\textsubscript{2} ratio of <200 and a SOFA score of >6 were at a high risk of mortality (41%).

The general mortality rate was estimated to be 0.81/100 person-days [95% confidence interval (CI): 0.61, 1.07/100 person-days], 0.96/100 person-days for men, and 0.50/100 person-days for women. Upon comparing the characteristics of survived and deceased, the deceased was older than or equal to 60 years (17.4%; p < 0.001) and were mostly men [10.6 vs 5.1% (men vs women); p = 0.028]. The most prevalent comorbidities were determined to be hypertension, diabetes mellitus, heart disease, thyroid and neurological diseases, chronic kidney disease, and lung disease (Table 2).

**Clinical Characteristics**

**Symptoms**

In total, 565 patients presented COVID-19 symptoms, which included constitutional symptoms (fever, rhinorrhea, sore throat, myalgia, fatigue, and anosmia), respiratory and cardiac symptoms (breathlessness, cough, and chest pain), abdominal symptoms (diarrhea, vomiting, and abdominal pain), and neurological symptoms (headache, altered sensorium, hemiplegia, convulsions, and coma) (Table 3). The median duration from the onset of symptoms to hospital admission was 5 (3/7) days. The duration from the onset of symptoms to death and that from hospital admission to death were 15 (11/25) and 10 (5/18) days, respectively.

**Complications**

The most common complication associated with COVID-19 was found to be sepsis [30 (5.3%)], followed by acute kidney injury [28 (5%)]. Other complications included thrombosis [19 (3.4%)], followed by cardiac [17 (3%)] and respiratory complications such as acute lung injury, pulmonary hemorrhage, and barotrauma [16 (3%)].

---

**Table 1: Categorization of COVID-19 severity based on the symptoms**

<table>
<thead>
<tr>
<th>Severity</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>Nil</td>
</tr>
<tr>
<td>Mild</td>
<td>Respiratory symptoms:</td>
</tr>
<tr>
<td></td>
<td>• Cough, cold, throat pain, and fever.</td>
</tr>
<tr>
<td></td>
<td>• Nausea, vomiting, and diarrhea.</td>
</tr>
<tr>
<td></td>
<td>• Room air oxygen saturation (SpO\textsubscript{2}) &gt; 95%.</td>
</tr>
<tr>
<td></td>
<td>• No hypotension.</td>
</tr>
<tr>
<td></td>
<td>• Clear sensorium or mild gastrointestinal symptoms but no comorbidities.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Dyspnea.</td>
</tr>
<tr>
<td></td>
<td>• Tachypnea.</td>
</tr>
<tr>
<td></td>
<td>• SpO\textsubscript{2} &lt; 95% on room air.</td>
</tr>
<tr>
<td></td>
<td>• Confusion/drowsiness.</td>
</tr>
<tr>
<td></td>
<td>• Normotensive.</td>
</tr>
<tr>
<td></td>
<td>• Worsening vomiting/diarrhea, but no hypotension or multiorgan dysfunction, and no comorbidities.</td>
</tr>
<tr>
<td>Severe</td>
<td>Dyspnea.</td>
</tr>
<tr>
<td></td>
<td>• Tachypnea.</td>
</tr>
<tr>
<td></td>
<td>• SpO\textsubscript{2} &lt; 95% on supplemental oxygen using a nonrebreathing mask with oxygen at 10 LPM.</td>
</tr>
<tr>
<td></td>
<td>• Confusion/drowsiness.</td>
</tr>
<tr>
<td></td>
<td>• Hypotension or shock.</td>
</tr>
<tr>
<td></td>
<td>• Worsening vomiting/diarrhea and/or severe extrarespiratory symptoms and/or hypotension/shock and/or multiorgan dysfunction or failure, and epidemiological risk factors present.</td>
</tr>
</tbody>
</table>
Mortality-associated Risk Factors in COVID-19

Table 2: Demographics and clinical characteristics of our study group

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Deaths</th>
<th>Survivors</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>565 (100)</td>
<td>49 (8.7)</td>
<td>516 (91.3)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–39</td>
<td>153 (27.1)</td>
<td>2 (1.3)</td>
<td>151 (98.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>40–59</td>
<td>217 (38.4)</td>
<td>15 (6.0)</td>
<td>202 (94.0)</td>
<td></td>
</tr>
<tr>
<td>≥60</td>
<td>195 (34.5)</td>
<td>34 (17.4)</td>
<td>161 (82.6)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>368 (65.3)</td>
<td>39 (10.6)</td>
<td>330 (89.4)</td>
<td>0.028</td>
</tr>
<tr>
<td>Female</td>
<td>196 (34.8)</td>
<td>10 (5.1)</td>
<td>186 (94.9)</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>162 (28.7)</td>
<td>21 (13.0)</td>
<td>141 (87.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>No</td>
<td>403 (71.3)</td>
<td>28 (6.9)</td>
<td>375 (93.1)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>210 (37.2)</td>
<td>30 (14.3)</td>
<td>180 (85.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>355 (62.8)</td>
<td>19 (5.4)</td>
<td>336 (94.7)</td>
<td></td>
</tr>
<tr>
<td>Lung disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>24 (4.3)</td>
<td>5 (20.8)</td>
<td>19 (79.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>No</td>
<td>541 (95.8)</td>
<td>44 (8.1)</td>
<td>497 (91.9)</td>
<td></td>
</tr>
<tr>
<td>Dialysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>30 (5.3)</td>
<td>14 (46.7)</td>
<td>16 (53.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>535 (94.7)</td>
<td>35 (6.5)</td>
<td>500 (92.5)</td>
<td></td>
</tr>
<tr>
<td>Heart disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>44 (7.8)</td>
<td>6 (13.6)</td>
<td>38 (86.4)</td>
<td>0.22</td>
</tr>
<tr>
<td>No</td>
<td>521 (92.2)</td>
<td>43 (8.3)</td>
<td>478 (91.8)</td>
<td></td>
</tr>
<tr>
<td>Neurological disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>27 (4.8)</td>
<td>4 (14.8)</td>
<td>23 (85.2)</td>
<td>0.28</td>
</tr>
<tr>
<td>No</td>
<td>538 (95.2)</td>
<td>45 (8.4)</td>
<td>493 (91.6)</td>
<td></td>
</tr>
<tr>
<td>Thyroid disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>32 (5.7)</td>
<td>3 (9.4)</td>
<td>29 (90.6)</td>
<td>0.75</td>
</tr>
<tr>
<td>No</td>
<td>533 (94.3)</td>
<td>46 (8.6)</td>
<td>487 (91.4)</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8 (1.4)</td>
<td>1 (12.5)</td>
<td>7 (87.5)</td>
<td>0.52</td>
</tr>
<tr>
<td>No</td>
<td>557 (98.6)</td>
<td>48 (8.6)</td>
<td>509 (91.4)</td>
<td></td>
</tr>
<tr>
<td>Posttransplant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2 (0.4)</td>
<td>0 (0)</td>
<td>2 (100)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>No</td>
<td>563 (99.7)</td>
<td>49 (8.7)</td>
<td>514 (91.3)</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Outcomes

Association of Comorbidities and Severity with Mortality

Mortality among all COVID-19 patients was significantly associated with increased age (p = 0.001), hypertension (14.3 vs 5.4%; <0.001), lung disease (p = 0.03), and in patients with chronic kidney disease and are on dialysis (46.7 vs 5.4%; p < 0.001). Furthermore, a significant association of mortality was observed with male gender (p = 0.028) and diabetes mellitus (p = 0.02) (Table 2).

Association of Symptoms and Disease Severity with Mortality

Based on the severity of the disease, mortality was found to be significant in patients with severe COVID-19 symptoms (59 vs 0%; p < 0.001). Other symptoms, such as breathlessness (p < 0.001) and seizure (p = 0.048), were found to be significantly associated with mortality (Table 3). Patients requiring ICU admission (41.1 vs 0%; p < 0.001) were found to be at an increased risk of mortality.

Association of Laboratory and Radiological Investigations with Mortality

Out of 565 patients, 205 (37.1%) patients had low lymphocyte on admission, of which 38 (18.5%) patients died. Low lymphocyte count (p = 0.001) and severe disease on HRCT analysis (p = 0.001) were significantly associated with death. Among 49 patients who died in the hospital, HRCT was performed on 35 patients and severe disease was identified in them. In addition, high levels of CRP, LDH, ferritin, and IL6 were detected in COVID-19 patients; however, these parameters were not found to be significantly associated with mortality (Table 4).

The Kaplan–Meier survival curve showed a significant association of COVID-19 infection with age (≥60; p = 0.008) (Fig. 1), hypertension (p = 0.03) (Fig. 2), dialysis (p = 0.0001) (Fig. 3), lung comorbidities (p = 0.01) (Fig. 4), breathlessness (p = 0.0001) (Fig. 5), severe disease upon HRCT analysis (p = 0.0001) (Fig. 6), ICU admission (p = 0.0001) (Fig. 7), and lymphocyte count at admission (p = 0.0001) (Fig. 8). Cox proportional HRs demonstrated that a significant increase in mortality risk was associated with hypertension (HR 2.56; 95% CI 1.04–6.29), whereas patients with normal lymphocyte count were at low risk of mortality with HR 0.28 (95% CI 0.13–0.62, p = 0.001).

Association of Therapies with Mortality

Based on the Indian Council of Medical Research guidelines and RFH COVID-19 treatment protocol, all patients were treated with HCQ and azeza on admission. However, as 52 patients were contraindicated for HCQ, 513 patients were treated with HCQ and azeza, of which 478 (93.2%) patients survived. Of these 513 patients, a 100% survival rate was observed in asymptomatic (N = 24), mild (N = 358), and moderately symptomatic (N = 77) patients. However, out of 65 patients with severe COVID-19 infection, only 29 (45%) patients survived. Of the 36 patients who did not survive, the average time from the onset of illness to ICU admission was 8 days. Of these 36 patients, 14 patients were transferred from outside the hospital, patients with severe COVID-19 infection were direct admissions, and 15 patients were transferred from wards. Patients with cytokine storm who were treated with tocilizumab were observed to
have significantly higher mortality rates (47.7 vs 3.6%; p < 0.001), whereas treatment with HCQ and azee showed a low risk of mortality (6.8% vs 26.9%; p < 0.001) (Table 4).

The Kaplan–Meier survival curve results showed similar findings wherein mortality due to COVID-19 was significantly associated with patients not receiving HCQ + azee (p = 0.0001) (Fig. 9) and in patients receiving...
With the medications. Of the 139 patients, 123 (88.5%) patients survived, and 16 (11.5%) patients died. Out of 565 patients, 56 patients who received convalescent plasma therapy, 21 (37.5%) patients died. Steroids in the form of methylprednisolone or dexamethasone were used to treat 77 patients with moderate to severe disease. Of these, 53 (69%) patients survived, and 24 (31.1%) patients died.

Risk of mortality (Cox proportional HR = 0.27, 95% CI 0.09–0.83, \( p = 0.02 \)). Patients with moderate to severe symptoms were treated in an awake prone position along with tocilizumab (\( p = 0.0001 \)) (Fig. 10). Treatment with HCQ + azee was identified as a predictor of good prognosis because patients treated with this combination of drugs were at low risk of mortality (Cox proportional HR = 0.27, 95% CI 0.09–0.83, \( p = 0.02 \)).

### Table 4: COVID-19 investigations and management

<table>
<thead>
<tr>
<th>Clinical Symptoms</th>
<th>Total</th>
<th>Deaths</th>
<th>Surivors</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Severity*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>24 (4.3)</td>
<td>0 (0)</td>
<td>24 (100.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mild</td>
<td>371 (65.7)</td>
<td>0 (0)</td>
<td>371 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>87 (15.4)</td>
<td>0 (0)</td>
<td>87 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>83 (14.7)</td>
<td>49 (59.0)</td>
<td>34 (41.0)</td>
<td></td>
</tr>
<tr>
<td>Chest X-ray (NA)</td>
<td>427 (75.6)</td>
<td>14 (3.3)</td>
<td>413 (96.7)</td>
<td></td>
</tr>
</tbody>
</table>

*As per WHO guidelines

### Figure 4: Kaplan–Meier survival estimates by lung involvement

### Figure 5: Kaplan–Meier survival estimates by breathlessness experienced by COVID-19 patients.

### Figure 6: Kaplan–Meier survival estimates by COVID-19 severity on HRCT

aze, azithromycin; CRP, C-reactive protein; HCQ, hydroxychloroquine; HRCT, high-resolution computed tomography; IL-6, interleukin 6; LDH, lactate dehydrogenase; *chest X-ray (NA) is not available; the p-value is only for the rows in which we could categorize the severity of COVID-19 based on the radiological findings.
Survival analysis results showed an overall survival rate of 0.98, 0.96, 0.91, 0.83, and 0.71 on days 3, 7, 14, 21, and 28, respectively. Based on the survival model, patients above 60 years of age showed a decline in survival (0.96–0.59). Similarly, patients on dialysis also showed a decline in survival (1.00–0.35) during the 28-day study period (Table 5). Additionally, a decline in survival probability was observed for patients who were brought into the hospital from other facilities and directly transferred to the ICU (0.81 on day 3 to 0.42 on day 28).

**Discussion**

The present study was an attempt to identify the determinants of mortality in COVID-19 patients who were admitted to a tertiary care hospital using survival analysis. Our initial preliminary analysis results showed that the deceased were older male patients with diabetes and hypertension as comorbidities and on dialysis. Survival analysis is the data analysis of the outcome variable till the event occurs, and this event could be recovery, relapse, or death, with the time to the event being called survival time. The inclusion of censored data facilitating covariates makes this analysis more reliable.5

The Kaplan–Meier plots demonstrated a decrease in overall survival from 0.98 to 0.71 from day 3 to 28, and the risk of mortality was associated with increased age (above 60 years), hypertension, lung involvement, dialysis, breathlessness and severe disease on HRCT analysis, and low lymphocyte count on admission.

Gender hegemony is a probable cause of COVID-19 infection among men as men tend to go outside of the house more frequently than their female counterparts due to work or migration, making them more susceptible to the virus.
Mortality-associated Risk Factors in COVID-19

The pooled estimates showed that HCQ treatment did not significantly affect survival at 14 and 28 days in COVID-19 patients when compared with the control population (relative risk (RR): 1.003, 95% CI: 0.983–1.022). HCQ treatment also resulted in the alleviation of symptoms at day 10 (RR: 1.044, 95% CI: 0.911–1.196). However, COVID-19 patients with comorbidities were successfully treated with HCQ (RR: 1.058, 95% CI: 1.035–1.082), resulting in negative reverse transcription polymerase chain reaction (RT-PCR) results from positive RT-PCR results on day 6 (RR: 1.123, 95% CI: 1.041–1.212). Patients receiving HCQ treatment were at a higher risk of developing cardiac side effects (RR: 2.012, 95% CI: 1.428–2.833) and gastrointestinal side effects (RR: 1.318, 95% CI: 0.730–2.380). Severe infections are treated with more invasive pharmacotherapeutic agents such as remdesivir, biologicals, convalescent plasma, and anticoagulant therapy, whereas inflammation caused due to infection is treated with steroids.

Contrastingly, Koya et al. demonstrated decreased survival from the time of the onset of symptoms among young adults without any comorbidities. However, the authors suggested that further studies must be carried out to investigate the involvement of any other factors in these patients. In addition, hypothryoidism was reported as COVID-19-associated morbidity. Shang et al. reported that diabetic patients requiring insulin had a shorter survival time than non-diabetic patients when infected with COVID-19, thereby contributing considerably to the mortality rate, which was consistent with the findings of our study. The survival time of diabetic patients was reduced when compared with that of non-diabetic patients (0.97–0.66), suggesting the association of diabetes with COVID-19-related mortality. Guzik et al. concluded that preexisting heart conditions were also associated with an increased risk of mortality. In the present study population, decreased survival was found to be associated with hypertension (0.97–0.70), kidney complications (1.00–0.35), and lung involvement (0.96–0.62). Similar to our findings, worldwide literature had adjusted estimates from cohort analyzes wherein increased age, male population, hypertension, diabetes, and chronic obstructive pulmonary disease or major cardiovascular diseases were found to be associated with enhanced risk of mortality or the severity of the disease among COVID-19 patients.

The initial strategy is to promote control measures to reduce transmission and enhance the use of non-pharmacological interventions, including quarantine and self-isolation. This is done to reduce hospital admission and optimize hospital capacity.

Conclusion

Thus, the present study on survival analysis revealed a decrease in survival probabilities of patients with increasing age, male gender, hypertension, diabetes, dialysis, and lung involvement. Furthermore, patients presenting with low lymphocyte count and breathlessness demonstrate the severity of the disease or the dysfunction of other organs and are considered at equal risk. Population variation in terms of treatment needs to be considered, wherein treatment with HCQ + azee gave positive results, thereby pointing toward pharmacogenomic influence. Lastly, the exact stage at which immunomodulators such as tocilizumab should be administered in patients must be studied in detail via conducting hardcore analysis.

Ethics

- Ethics Committee approval: Institutional Review Board approved the study with the IEC protocol number HNH/IEC/2021/ OCS/CCM/55.
- Informed consent: The requirement for written informed consent was waived by the IEC.

References


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Intermittent Use of Continuous Glucose Monitoring: A New Paradigm in Treatment of Type 2 Diabetes

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ABSTRACT

Objectives: To suggest how continuous glucose monitoring (CGM) may be used intermittently in individuals with type 2 diabetes (T2D).

Materials and methods: The use of CGM is largely in those with type 1 diabetes (T1D), in whom it makes sense to use CGM continuously as CGM provides a valuable tool to not only adjust their insulin doses but also to match it with their diet, physical activity, and other lifestyle modifications. In the case of T2D, however, especially for those not on insulin, the use of CGM may not be needed on a continuous basis. The use of CGM on an intermittent basis is rarely discussed in the literature. This article tries to provide clinical situations where CGM can be used intermittently.

Results: Intermittent use of CGM defined as the “use of CGM once in 2 or 3 months or a fixed frequency” and may be useful in several situations in those with T2D. We suggest the following indications for the intermittent use of CGM in T2D—newly diagnosed patients where treatment is being started, uncontrolled diabetes where treatment is being altered, starting intensive lifestyle modification, during infections, during preoperative control, in children and adolescents with T2D, as a motivational tool to improve behavioral modification, after metabolic surgery, and in patients on steroids, apart from other indications.

Conclusion: Intermittent use of CGM in T2D can be useful in special situations and can also be cost saving particularly in resource-constrained regions of the world.

INTRODUCTION

A doption of CGM in the treatment of patients with diabetes has been increasing globally as it addresses many limitations inherent to glycated hemoglobin (HbA1c) testing and self-monitoring of blood glucose (SMBG).1 However, the vast majority of CGM studies to date have been done in persons with T1D,2,3 and studies on CGM in T2D are limited.4–10 Even in these studies in T2D, the use of CGM has been mostly restricted to T2D patients on insulin, and its use in those not on insulin is rarely discussed.

There are several potential barriers to patient acceptance that impede the propagation of CGM on a wider scale. User burden associated with the currently existing systems, high cost, reimbursement issues, pain, allergy, and unfamiliarity with the system were identified as reasons among patients for not using CGM in developed countries.11 Given these barriers, using CGM on a temporary or intermittent basis increases the benefits and possibilities of its use in T2D patients. Indeed, intermittent use of CGMs allows its allocation to suitable patient groups and indications, especially in limited-resource settings.12 Intermittent use of CGM could provide economic flexibility, rather than not using it at all. However, there is a need for clarity on the frequency of the intermittent use of CGM which undoubtedly has to be individualized for T2D patients depending upon their stage of the disease and multiple other factors like the presence of comorbidities and complications of diabetes. In this review, we discuss the use of the intermittent use of CGM and its benefits and suggest ways to more effectively use CGM intermittently.

USE OF CGM IN T2D

Continuous glucose monitoring (CGM) has been shown to produce a significant reduction in HbA1c levels in T2D patients.3 One study reported the utility of CGM use in T2D patients in revealing glycemic fluctuations, which could otherwise go undetected in routine SMBG.13 Use of CGM has helped clinicians and patients to make appropriate treatment changes.

Continuous glucose monitoring (CGM) can be a great tool to ensure adherence to lifestyle and behavioral modifications. Retrospective data which includes trends, ambulatory glucose profile, and time in range (TIR) facilitate better exercise adherence and reduced caloric/carbohydrate intake in patients with T2D.13–15 There are some studies that have looked at the cost-effectiveness of CGM in T2D.16

WHAT IS THE INTERMITTENT USE OF CGM?

Intermittent use of CGM may be defined as “the use of CGM, once in 2 or 3 months or a fixed frequency in T2D.” According to a recent review, “intermittent use of CGM systems is any planned and agreed use that is intended not to be continuous or all-the-time use but for predefined periods of time or situations.”12 In a real-world setting, adherence to CGM remains suboptimal irrespective of technological advancements, patient education, and support programs.17 Depending upon the financial resources and personal choices,

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some patients may choose intermittent use of CGM as an educational and/or motivational tool, rather than a permanent or continuous diabetes management strategy. Therefore, clinicians should explore the potential of intermittent use of CGM as an option for particular patient groups and situations from this angle. The guidelines of the Endocrine Society recommend the intermittent use of CGM for short-term retrospective analysis in the following groups of patients:

- Pediatric patients with nocturnal hypoglycemia, dawn phenomenon, and postprandial hyperglycemia.
- Patients with hypoglycemia unawareness.
- Patients experimenting with important changes to their diabetes regimen.
- Adult patients with T2D (not on prandial insulin) with HbA1c > 7% and who are willing and able to use the device.

Intermittent CGM can be used for specific events or situations such as pregnancy and hypoglycemia or hyperglycemia during certain life events. Healthcare personnel could utilize CGM judiciously at periodic intervals in order to assess and adapt the therapy provided.

**Clinical Evidence of the Efficacy of Intermittent Use of CGM**

Intermittent short-term use of real-time CGM (rtCGM) as clinically indicated has been shown to produce greater improvement in A1c in T2D patients compared to non-CGM users. Ehrhardt et al. randomized subjects to rtCGM in an intermittent manner (2 weeks on, 1 week off) over 12 weeks compared to SMBG four times per day. It was observed that HbA1c reduction occurred even without treatment intensification or increased incidence of hypoglycemia, which underscores the advantages of rtCGM in T2D in a lifestyle intervention. Yoo et al. demonstrated that the rtCGM use (3 days at a time for 3 months) can induce better glycemic outcomes (compared to SMBG) by helping to bring about modifications in diet and exercise in patients with poorly controlled T2D. Kesavadev et al. utilized CGM intermittently to analyze its effect on glycemic control in T2D patients, on a wide range of treatment regimens and based on these, consensus guidelines have also been developed in some countries like India. Simonson et al. showed that the use of a professional CGM in primary care used along with a doctor or registered nurse was effective in lowering A1c, increasing TIR, and reducing hypoglycemia.

### Possible Indications for Intermittent Usage of CGM in T2D Patients

We suggest that clinicians could explore using CGM intermittently in the following situations in T2DM. These are summarized in Table 1 and described in detail below.

#### Newly Diagnosed Patients where Treatment is being started

Wherever a newly diagnosed patient is started on treatment (especially if diabetes is severe at the onset with glucolipotoxicity and either short-term insulin or a combination of oral drugs is used), it is useful to initiate intermittent CGM to see the response to therapy and to avoid hypoglycemia.

#### Case Study

A 19-year-old obese boy presented with symptoms of polyuria, polydipsia, and weight loss of 3 kg. Both his parents had T2D. His weight was 92.4 kg, height was 178 cm, and body mass index was 29.2 kg/m². Fasting plasma glucose was 297 mg/dL (16.5 mmol/L), postprandial plasma glucose was 412 mg/dL (22.8 mmol/L), and HbA1c was 12.6% (114.2 mmol/mol). There was no ketosis. He had marked acanthosis nigricans. His waist circumference was 97 cm and he had dyslipidemia with elevated serum triglycerides (300 mg/dL) and a low high-density lipoprotein (32 mg/dL). C-peptide assay showed reduced, but detectable pancreatic β-cell reserve (fasting—0.8 pmol/mL, stimulated—1.4 pmol/mL). In view of the glucolipotoxicity, a CGM was initiated which showed the following (Fig. 1).

As can be seen, the TIR was 0% and all of the readings above range [Time above range (TAR) = 100%]. He was started on a long-acting basal insulin analog at bedtime (glargine—12 units) along with a combination of a dipeptidyl peptidase-4 inhibitor (sitagliptin) and metformin. The sugars started responding well by the 4th day and by the end of the 2nd week, the sugars were under fairly good control. The insulin was continued in a reduced dose for another 2 weeks during which time the TIR was 98% and the TAR was 0% (Fig. 2). There was no significant hypoglycemia. At the end of 4 weeks, the insulin was withdrawn. Later, sitagliptin was also withdrawn and he was stabilized with just metformin. After 3 months, his fasting plasma glucose had decreased to 92 mg/dL, postprandial plasma glucose to 134 mg/dL, and HbA1c to 6.4%. His fasting C-peptide improved to 1.8 pmol/mL and stimulated C-peptide to 3.4 pmol/mL. The CGM was withdrawn at this stage.

The use of intermittent CGM, in this case, was helpful to see the response to the therapy and to note whether there were any hypoglycemic reactions during the initial phase of aggressive treatment with insulin plus oral agents.

#### Uncontrolled Diabetes where Treatment is being Altered

Intermittent use of CGM can be efficiently used to track the glucose response after changes in therapy regimen and can support patients and physicians to decide whether the insulin adjustments were appropriate. In addition, patients have more glucose data to guide them in adjusting their insulin dosing at mealtimes. Intermittent use of CGM can also be suggested for patients with T2D who are currently on oral antidiabetic drugs or insulin to see whether their TIR is within recommended guidelines.

#### Starting Intensive Lifestyle Modification

Yoo et al. showed that intermittent use (3 days of rtCGM every month for 12 weeks) generated a significant decrease in calorie consumption, an increase in physical activity, an improvement of weight, and a 1% decrease in HbA1c in poorly controlled patients with T2D. A community-based study in India used retrospective CGM with two sessions over 3 months in 181 T2D patients. The study observed a 0.6% reduction in HbA1c and noted that 67.6% of participants made dietary changes and 48.6% made exercise modifications accordingly. Vigorsky et al. conducted a trial of 100 T2D patients intermittently using CGM (2 weeks on, 1 week off) over 12 weeks and compared the results to patients using

### Table 1: Suggested indications for intermittent use of CGM

1. Newly diagnosed patients where treatment is being started
2. Uncontrolled diabetes where treatment is being altered
3. Starting intensive lifestyle modification
4. Infections
5. Perioperative control
6. Gestational diabetes mellitus and diabetes complicating pregnancy
7. Children and adolescents with T2D
8. As a motivational tool to improve behavioral modification
9. After metabolic surgery
10. Patients on steroids (e.g., during COVID–19 and other pandemics)
Fig. 1: CGM graphs of a newly diagnosed T2D patient during first 2 weeks of treatment

Fig. 2: CGM graphs for next 2 weeks after starting treatment
Use of Continuous Glucose Monitoring

SMBG four times per day. They reported that HbA1c reduction occurred in the absence of medication intensification or increased hypoglycemia, and this indicates that one of the benefits of intermittent use of rCGM in T2D is behavior and lifestyle modification. There are anecdotal instances of severe hypo occurring after a sudden increase in physical activity. These can be avoided by using intermittent CGM.

Infections

In the presence of infections, glucose levels tend to fluctuate widely. Also, insulin may be given for a short time to cover this period. Intermittent CGM use is ideal in this situation.

Perioperative Control

Perioperative hyperglycemia is considered to be an independent marker of poor surgical outcomes. Strict glucose control is beneficial for accelerating wound healing, reducing infection rates, reducing the number of days of hospital stay, and reducing postoperative mortality. Maintaining glucose control in perioperative patients often is a great challenge for physicians. Here, intermittent use of CGM before and after surgery can be an excellent tool to monitor glucose levels closely and this helps to improve patient outcomes.

Gestational Diabetes Mellitus (GDM) and Diabetes complicating Pregnancy

There are several studies that have shown the usefulness of CGM in GDM and diabetes-complicating pregnancy. The intermittent use of CGM in pregnant women with pregestational diabetes or GDM has been shown to improve pregnancy outcomes. CGM has provided relevant perspectives about neonatal glucose metabolism and there is an increasing interest in its use, especially in preterm infants where glucose management is difficult. Intermittent CGM application can reduce the number of blood tests required and improve long-term outcomes in neonates. A systematic review has compiled all studies on the use of CGM in pregnancy.

Children and Adolescents with T2D

In children where frequent finger pricks can be difficult, intermittent CGM offers an excellent tool to detect nocturnal hyps or unexpected peaks of blood glucose.

As a Motivational Tool to improve Behavioral Modification

Physical activity and meals exert a great influence on glycemic variability and are often difficult to manage, but intermittent use of CGM enhances diabetes knowledge and awareness about glycemic fluctuation and is useful in the education and motivation of patients with T2D. Kesavadev et al. have demonstrated that intermittent use of CGM produces actionable data that helps and motivates patients for diabetes self-care practices, leading to improvement in glycemic control. Fonda et al. revealed that intermittent use of CGM may be suitable for motivating or helping avoid burnout in T2D patients.

After Metabolic Surgery

After metabolic (bariatric) surgery, glucose levels can suddenly drop and postprandial hypoglycemia is a major complication after gastric bypass surgery and bariatric surgery. Intermittent use of CGM can be effectively applied to diagnose this condition and to adjust diet and therapy postoperatively. This application also helps in the prediction of diabetes remission.

Patients on Steroids (e.g., during COVID–19 and Other Pandemics)

Intermittent CGM can produce superior outcomes for patients on steroids by enabling appropriate therapy adjustment. This is particularly relevant during these times of COVID–19 when steroids are given for a few days to weeks. CGM can be used to adjust insulin doses during these brief periods of very severe hypoglycemia especially during some times of the day when the steroids push up the sugar levels.

Suggested Timing of Intermittent CGM use in the Outpatient Clinic

Evaluation of glycemic control in a patient with T2D requires the judicious and integrated use of all available tools such as HbA1c, SMBG readings, lab blood tests, and CGM at the most appropriate times, as each of these provides information on different aspects of the patient’s glycemic profile. Most diabetes clinics in developing countries assess patients’ glycemic control utilizing a combination of HbA1c and lab blood glucose tests, with only a few patients performing SMBG on a regular basis. The need of the hour, therefore, is to integrate intermittent CGM into the existing assessment paradigm so that the “blind spots” of the conventional tests can be removed.

Proposed Strategies for Intermittent CGM Use

We propose that three strategies can be utilized for integrating intermittent CGM into the routine diabetes clinic assessment (Fig. 3).

- Strategy 1: The patient can be initiated on CGM after he/she has reported for a routine clinic visit and has had his/her HbA1c (and blood glucose) estimated. The clinician would have made alterations to the therapeutic regimen based on these results and the CGM (usually read after a week or 15 days) will help to assess the adequacy of these alterations.
- Strategy 2: Patients can initiate the CGM 15 days in advance of the clinic visit so that the clinician has a clear idea about the patient’s glycemic excursions along with the HbA1c result. This will help in adjusting the dose of antidiabetic drugs that is tailored to the patient’s glycemic profile. This is an excellent example of precision diabetes monitoring.
- Strategy 3: The patient can be initiated on CGM 1 week (i.e., 7 days) prior to the clinic visit.

Fig. 3: Proposed strategies for intermittent use of CGM—diagrammatic representation
intermittent use of CGM could be a new paradigm in the therapy of T2D and certainly, it would make it more affordable, especially in developing countries. Obviously, randomized clinical trials are needed to prove both the short-term and long-term efficacy of this method of monitoring diabetes control as well as its cost-effectiveness.

**References**


**Table 2: Frequency of CGM use in T2D at two diabetes centers in India over a 3-year period**

<table>
<thead>
<tr>
<th>Frequency of sensor use</th>
<th>Chennai (DMSC) n (%)</th>
<th>Ahmedabad (Diacare) n (%)</th>
</tr>
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<tbody>
<tr>
<td>Total no. of sensors used</td>
<td>18,321</td>
<td>1,864</td>
</tr>
<tr>
<td>Once</td>
<td>17,060 (93.1%)</td>
<td>1,576 (84.5%)</td>
</tr>
<tr>
<td>Twice</td>
<td>1,051 (5.7%)</td>
<td>206 (11.1%)</td>
</tr>
<tr>
<td>Thrice</td>
<td>159 (0.9%)</td>
<td>60 (3.2%)</td>
</tr>
<tr>
<td>Four or more times</td>
<td>51 (0.3%)</td>
<td>22 (1.2%)</td>
</tr>
</tbody>
</table>

**Barriers to the Use of CGM**

An early discontinuation rate of 27% and a nonadherence rate of 13.9–31.1% were observed within 12 months of CGM initiation. Therefore, it is essential to identify the factors that influence nonadherence and early discontinuation to improve treatment adherence and reduce healthcare resource waste. Tanenbaum et al. identified the cost of supplies, accuracy issues, user burden of the device, pain, and nonuser-friendliness as the top reasons for patients to discontinue CGM use. Another interesting study observed that 75% of youth who stopped using hybrid closed-loop systems also suspended the use of CGM due to poor CGM accuracy, failed sensor calibrations, and sensor errors. Such repercussions underscore the need for assessing individual barriers to CGM use. Intermittent use of CGM can address many of these barriers, especially the cost issues as it is associated with significant cost savings as compared to continuous use. If the patient is initiated on intermittent CGM quarterly, he/she is required to purchase only four sensors per year, as compared to 26 (if the CGM needs to be continued without a break for the entire year) and this translates to 75% reduction in the cost of use.

**Challenges to Implementation of Intermittent Use of CGM**

As already discussed, the large-scale implementation of CGM technology especially for continuous use continues to be a major challenge. Very few physicians have developed or implemented a systematic approach to interpret CGM data, although comprehensive guidelines have been published for the same. There is also a lack of training support for the physicians and the patients on the appropriate use of CGM. Although intermittent CGM is definitely less expensive than continuous CGM, it is still not within the reach of many people if they have to pay “out of pocket.” Lack of reimbursement options, patient support programs, the cost of insulin, and other medicines might impede the widespread adoption of CGM which could be perceived to be “nonessential” when one has limited resources. Most importantly, there are no established clinical guidelines to define the intermittent use of CGM and these are urgently needed. Rodbard has elegantly reviewed the success, challenges, and opportunities of CGM use. We argue that in situations where continuous use of CGM remains a challenge, at least its intermittent use could be considered.

In summary, intermittent use of CGM could be a new paradigm in the therapy of T2D and certainly, it would make it more affordable, especially in developing countries. Obviously, randomized clinical trials are needed to prove both the short-term and long-term efficacy of this method of monitoring diabetes control as well as its cost-effectiveness.
Abridged Prescribing Information

Active Ingredients: Metformin hydrochloride (as sustained release) and glimepiride tablets. Indication: For the management of patients with type 2 diabetes mellitus when diet, exercise and single agent (glimepiride or metformin alone) do not result in adequate glycemic control. Dosage and Administration: The recommended dose is one tablet daily during breakfast or the first main meal. Each tablet contains a fixed dose of glimepiride and Metformin Hydrochloride. The highest recommended dose per day should be 8 mg of glimepiride and 2000mg of metformin. Due to prolonged release formulation, the tablet must be swallowed whole and not crushed or chewed. Adverse Reactions: For Glimepiride: Hypoglycaemia may occur, which may sometimes be prolonged. Occasionally, gastrointestinal (GI) symptoms such as nausea, vomiting, sensations of pressure or fullness in the epigastrium, abdominal pain and diarrhea may occur. Hepatitis, elevation of liver enzymes, cholestasis and jaundice may occur; allergic reactions or pseudo allergic reactions may occur occasionally. For Metformin: GI symptoms such as nausea, vomiting, diarrhea, abdominal pain, and loss of appetite are common during initiation of therapy and may resolve spontaneously in most cases. Metallic taste, mild erythema, decrease in WBC absorption, very rarely lactic acidosis, Hemolytic anemia, Reduction of thyrotropin level in patients with hypothyroidism, Hypomagnesemia in the context of diarrhea, Encephalopathy, Photosensitivity, hepatic fibrosis. Warnings and Precautions: For Glimepiride: Patient should be advised to report promptly exceptional stress situations (e.g., trauma, surgery, febrile infections), blood glucose regulation may deteriorate, and a temporary change to insulin may be necessary to maintain good metabolic control. Metformin Hydrochloride may lead to Lactic acidosis; in such cases metformin should be temporarily discontinued and contact with a healthcare professional is recommended. Sulfonylureas have an increased risk of hypoglycemia. Long-term treatment with metformin may lead to peripheral neuropathy because of decrease in vitamin B12 serum levels. Monitoring of the vitamin B12 level is recommended. Overweight patients should continue their energy-restricted diet, usual laboratory tests for diabetes monitoring should be performed regularly. Contraindications: Hypersensitivity to the active substance of glimepiride & Metformin or to any of the excipients listed. Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis, diabetic pre-coma). Severe renal failure (GFR <30 ml/min). In pregnant women. In lactating women. Acute alcohol intoxication; alcoholism.

Use in a special population:

Pregnant Women: Due to a lack of human data, drugs should not be used during pregnancy. Lactating Women: It should not be used during breastfeeding. Pediatric Patients: The safety and efficacy of drugs has not yet been established. Renal impairment: A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months. Additional information is available on request.

Last updated: March 13, 2023

* In case of any adverse events, kindly contact: pv@usv.in          For the use of registered medical practitioner, hospital or laboratory.*
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1. Ritesh K A et. al, JCSSR.2023;6(3):2010-17
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INDIan Consensus on the mAnagemenT of cOugh at pRimary care setting (INDICATOR)


Accepted: 28 March 2023; Received: 10 May 2023

Article: INDIndian Consensus on the management of cough at primary care setting (INDICATOR)

Journal of the Association of Physicians of India (2023): 10.5005/japi-11001-0275

ABSTRACT

Background: Cough has a prevalence of 9.6% globally and 5–10% in India. Though it is a reflex action, it affects an individual’s quality of life (QoL) when uncontrolled. There was a need to create an integrated guidance document on managing cough with primary care physicians in the Indian setting. This consensus intends to bridge this gap by providing clinical recommendations to diagnose and manage cough in primary healthcare in India.

Materials and methods: The modified Delphi method was used to arrive at a consensus on clinical statements. The panel comprised 10 experts, including pulmonologists, otolaryngologists, a pediatrician, and a general physician. The statements were discussed under the following domains: definition, etiology, diagnosis, and treatment.

Results: A total of 11 clinical statements were framed, with 75 reaching consensus, 13 reaching near consensus, and 21 reaching no consensus. The experts recommended empiric use of nonopiod antitussive agents for symptomatic relief of acute dry cough. The use of oral antihistamines, oral decongestants, or mucocutaneous agents as a part of fixed-dose combinations (FDCs) in cough associated with rhinitis or upper airway cough syndrome (UACS) can be considered for symptomatic relief. Maintaining good hydration is important to manage a productive cough. Cough preparations are to be considered as last resort in patients with an unexplained chronic cough when other treatments have failed. Additionally, insights were captured on red flag signs, nonpharmacologic therapy, special populations, and referral to higher centers. Experts have also proposed a management algorithm with an integrated care pathway approach for acute, subacute, and chronic coughs.

Conclusion: The present consensus fills the existing need and may guide the physician to successfully diagnose and manage cough in the primary healthcare setting in India.

INTRODUCTION

Globally, the most common symptom leading to a medical consultation is a cough. An acute cough is typically caused by a common cold. Cough is triggered by a neuronal hypersensitivity reflex, and it functions as a protective response in the respiratory passages. It also has a role in transmitting infectious diseases. Moreover, chronic cough negatively affects the QoL.1

Acute cough has a prevalence of 9–64%, whereas chronic cough has a prevalence of greater than 10% (7.2–33%) in most countries.2 Regional differences have been found with a higher prevalence in Western countries than in Eastern countries, probably due to gastroesophageal reflux disease (GERD) and obesity. However, in the general population, it is more common among males who smoke.3 In India, the prevalence of cough ranges from 5 to 10%.4

The initial diagnosis of cough is made in the primary healthcare setting. Specialist care is needed when the symptom persists and the cause is elusive. Furthermore, the presence of comorbidities requires a multidisciplinary approach and may complicate both diagnosis and treatment.5 Chronic cough affects the QoL more than acute cough.6 Acute cough results in transient illness caused by upper respiratory tract infections (URTIs), and this leads to absenteeism from work or school.7 Chronic cough results in breathlessness, fatigue, insomnia, impaired speech, vomiting, and rarely chest pain, rib fracture, and hernia. It may cause urinary incontinence (UI) more often in women, and cough syncope commonly in men.8 Chronic cough also impairs daily activities and affects relationships with family.9

Previous guidelines on acute cough have emphasized that though a wide variety of approaches exist in managing cough, there is a scarcity of robust evidence backing them. Therefore, guidelines help the physician in differential diagnosis and identification of etiology and provide evidence-based treatment strategies.10 The international guidelines on cough may not address the region-specific needs of primary care settings. Moreover, tropical countries have different etiologic and risk factors than other regions. Guidelines may help overcome the time lag between a patient’s first outpatient department (OPD) visit and the diagnosis and management of a cough.11

This Delphi-based consensus was undertaken to address important areas in the management of cough. A wide spectrum of potential causes of cough can cause a dilemma in the diagnosis in primary care.12 Symptomatic management of cough at primary care is not uniform. Many FDCs are marketed for dry and productive cough.13 Chronic cough, especially undiagnosed, usually requires a multidisciplinary and integrated approach to care; however, this does not often happen in clinical practice.14,15 This consensus aimed at guiding clinicians to improve the standard of care in the management of patients with cough and devise a consensus encompassing all aspects regarding the diagnosis and management of cough in India.
Indian Cough Consensus

Objective
The objective of the current consensus is to devise clinical statements guiding the diagnosis and management of cough in the primary healthcare setting in India.

Materials and Methods
The modified Delphi method was used to develop this consensus document with a geographically diverse panel of experts. Several iterations took place from April 2022 to September 2022 to arrive at the final consensus statements. A panel of 10 experts was chosen based on clinical experience, academic achievements, and engagement in clinical research in respiratory medicine, which included three experts who were a part of the core panel for preparing and reviewing the clinical statements. An electronic search of PubMed and Embase databases was conducted to develop statements for the current consensus. A rigorous literature search identified the relevant articles written in English and published over the last 15 years between 1st January 2007, and 1st August 2022, using the keywords “cough,” “general practice,” and “primary care.” The results of the literature search were disseminated among the expert panel in the electronic full-text version. Core experts reviewed these articles to identify the gaps in evidence and unmet needs in diagnosing and managing cough in the primary healthcare setting in India to assist in developing clinical statements.

The experts conducted two Delphi rounds to arrive at the consensus statements (110 clinical statements in the first round and 36 clinical statements in the second round via email with a Likert scale [9-point]). The first round of the Delphi survey consisting of 110 statements, was disseminated on SurveyMonkey®. This was followed by a virtual meeting with the experts, during which results from the first round were discussed, and statements for which near or no consensus was reached were deliberated in depth to determine whether they should be reformulated for the next Delphi round or omitted completely. Also, a proposal to add some uncovered topics was made by a few experts. A total of 36 clinical statements were taken for Delphi round two, including reformulated and new ones. A total of 10 experts participated in the first and second rounds of the Delphi survey. Finally, algorithms for the diagnosis and management of acute, subacute, and chronic coughs were designed. The class of recommendation was based on a Likert scale (9-point) and was as follows:

- Consensus: Statements with a mean score of ≥7.00 with no greater than one outlier.
- Near consensus: Statements with a mean score of ≥6.50 with no greater than two outliers.
- No consensus: Statements did not meet either of the above criteria.13

Statistical Analysis
The chair and staff liaison collected and analyzed the responses to the survey from both rounds. Descriptive statistics, mean scores, and outliers were calculated for all statements. A rating ≥2 Likert points from the mean in either direction was considered an outlier. Statements were further grouped into the corresponding class of recommendation.

As a modified Delphi-based method was used, ethics committee approval was not necessary; however, all experts who participated in this consensus process were informed of the objectives of the study, and the participants were also informed that this consensus document would be utilized for publication purposes. Participant consent was taken before the dissemination of the survey. Participants provided independent responses on the Delphi survey depending on their clinical experience. The responses of all participants were analyzed to calculate the mean and outliers for each consensus statement.

The steps employed in formulating the current consensus are given in Figure 1.

The modified Delphi method allows for interaction between experts.4 This method facilitates clarification of issues and justification of viewpoints by members of the panel. The first survey was created with SurveyMonkey® (online). A Likert scale (9-point) was used to measure agreement, with the following anchors—strongly agree (9), agree (7), neutral (5), disagree (3), and strongly disagree (1). Statements were concise and clear to avoid leading language that might bias responses. The consensus statements addressed predetermined topics such as definition, diagnosis, evaluation, and treatment. Statements were limited to expert views and did not include any recommendations for action (such as should do, must do, and may do).13

Results
A total of 110 statements were formulated initially. After reframing the statements, after round 1 and 2, there were a total of 109 statements, with 75 reaching consensus, 13 reaching near consensus, and 21 reaching no consensus. The final statements are provided in Table S1. A table is presented with the key consensus statements in Table 1.
Table 1: Summary of key consensus statements

<table>
<thead>
<tr>
<th>Sr No</th>
<th>Statement Definition</th>
<th>Mean</th>
<th>Outlier</th>
<th>Consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>In clinical practice, estimating the duration of a cough is the first step in narrowing the list of potential diagnoses.</td>
<td>8.12</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>2</td>
<td>URTI and bronchiolitis caused by viruses are to be looked at as the common cause of acute cough in an OPD setting.</td>
<td>9.11</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>3</td>
<td>The common cold is to be looked at as the common cause of acute cough in an OPD setting.</td>
<td>7.67</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>4</td>
<td>Asthma is to be looked at as the common cause of chronic cough in an OPD setting.</td>
<td>9.22</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>5</td>
<td>GERD is to be looked at as the common cause of chronic cough in an OPD setting.</td>
<td>8.44</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>6</td>
<td>UACS secondary to rhinosinus diseases to be looked at as the common cause of chronic cough in an OPD setting.</td>
<td>8.89</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>7</td>
<td>NAEB is to be looked at as the common cause of chronic cough in an OPD setting.</td>
<td>7.44</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>8</td>
<td>Postinfectious cough is to be looked at as the common cause of subacute cough in an OPD setting.</td>
<td>8.78</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>9</td>
<td>Exacerbations of underlying diseases such as asthma, COPD, and UACS to be looked at as the common cause of subacute cough in an OPD setting.</td>
<td>8.22</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>10</td>
<td>A dry cough usually indicates a noninfectious etiology.</td>
<td>7.33</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>11</td>
<td>A productive cough usually indicates infectious etiology.</td>
<td>7.67</td>
<td>2</td>
<td>Near consensus</td>
</tr>
<tr>
<td>12</td>
<td>We recommend hearing cough sounds as it is a critical part of patient evaluation.</td>
<td>9.67</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>13</td>
<td>We recommend additional/aggressive investigation in patients presenting with cough and red flag signs to rule out pneumonia, severe exacerbation of asthma/ COPD, pulmonary embolism, and heart failure.</td>
<td>8.67</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>14</td>
<td>We do not recommend routine assessment of QoL in chronic cough.</td>
<td>5.7</td>
<td>7</td>
<td>No consensus</td>
</tr>
<tr>
<td>15</td>
<td>We recommend the assessment of QoL in patients with chronic idiopathic cough.</td>
<td>8</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>16</td>
<td>We recommend first-line workups such as chest X-ray, spirometry, and complete blood count evaluation to be done for patients with chronic cough.</td>
<td>8.67</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>17</td>
<td>We recommend first-line workups such as chest X-ray, spirometry, and complete blood count evaluation to be done for patients with subacute cough.</td>
<td>8.44</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>18</td>
<td>We recommend asking for HRCT in patients who are not responding to treatment with chronic coughs.</td>
<td>8</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>19</td>
<td>We recommend using HRCT only when the common causes of chronic cough have been excluded, in the presence of bibasilar velcro-like crackles, or in suspected cases of bronchiectasis, even if the chest X-ray is normal.</td>
<td>8.78</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>20</td>
<td>We recommend suspecting UACS in patients presenting with increased nasal discharge, frequent throat clearing, and postnasal discharge.</td>
<td>8.11</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>21</td>
<td>We recommend suspecting CVA in patients presenting cough as a predominant symptom without wheezing.</td>
<td>8.44</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>22</td>
<td>We recommend continuing symptomatic treatment till the symptoms last in acute dry cough.</td>
<td>7.7</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>23</td>
<td>We recommend the use of dextromethorphan as the preferred antitussive in patients with acute dry cough.</td>
<td>7</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>24</td>
<td>We recommend using one of the nonopioid antitussive drugs in acute dry irritating cough.</td>
<td>7.6</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>25</td>
<td>We recommend not using codeine-based preparation in patients with acute cough.</td>
<td>7.67</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>26</td>
<td>We recommend not using codeine-based preparation in patients with subacute cough.</td>
<td>7.78</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>27</td>
<td>We recommend not to use one of the nonopioid antitussive drugs in subacute dry irritating cough.</td>
<td>4.4</td>
<td>2</td>
<td>No consensus</td>
</tr>
<tr>
<td>28</td>
<td>We recommend the use of levocetirizine as the preferred antihistamine in the treatment of dry cough.</td>
<td>6.56</td>
<td>1</td>
<td>Near consensus</td>
</tr>
<tr>
<td>29</td>
<td>We do not recommend the routine use of decongestants in the treatment of dry cough.</td>
<td>7.5</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>30</td>
<td>We recommend using monotherapy for the management of cough, whereas FDCs can be preferred in situations where the role of additional agent/s is justified.</td>
<td>7.3</td>
<td>1</td>
<td>Consensus</td>
</tr>
</tbody>
</table>

Contd...
Indian Cough Consensus

**Discussion**

Cough has a significant psychological, physical, and social impact. It may be associated with exhaustion, chest pain, lightheadedness, dizziness, UI, sleep disturbance, rib fracture, and work absenteeism. Furthermore, the etiology of cough is difficult to diagnose. A survey has highlighted the challenges in diagnosing and managing chronic cough. Most of the participants (70%) consulted more than three doctors, and only 53% received a proper diagnosis. A mere 30% felt that their cough had been adequately managed, with 57% finding limited usefulness and 36% having no effect of medications.

**Clinical Classification of Cough**

The expert panel agreed with generally accepted definitions of cough in adults in terms of duration, namely acute (≤3 weeks), subacute (between 3 and 8 weeks), and chronic (>8 weeks), for guiding the management of patients in routine clinical practice. However, in children, a cough persisting for >4 weeks is considered a chronic cough. These definitions of cough agree with those published by the expert panel report in 2018, American College of Chest Physicians (CHEST) guidelines, and clinical practice guidelines given by the Chinese Thoracic Society (CTS) Asthma Consortium. However, World Allergy Organization-Allergic Rhinitis and its Impact on asthma recognizes patients presenting with cough for 4–8 weeks either as prechronic cough or as cough observed in those recovering from acute cough-associated illness. Though arbitrary, cough duration informs about likely etiologies and requires diagnostic workup.

Eliciting the nature of the cough is a part of good history-taking. The nature of cough can be “wet” productive, “dry” nonproductive, or mixed. Knowledge of the nature of cough aids in the differential diagnosis. In the case of a wet cough, the sounds have features indicating mucus. When perceivable wetness is absent, the cough is called dry. When the cough is wet on occasion and dry on other occasions, it can be labeled as mixed. However, diagnosing using cough sounds is a subjective method. Although a wet cough is usually associated with an infectious etiology, some studies have also suggested that “moist cough” is not of physiological significance and is subjective. Dry cough is caused by seasonal allergies (hay fever) and viral infections. Describing the nature of a cough is an important part of recording a good history of cough; however, the nature of a cough alone is not of diagnostic significance.

**Causes of Cough**

Knowledge of common causes of cough is essential for diagnosis and empiric treatment. Around 90% of acute cough is due to URTI, mainly caused by viruses. Other reasons for acute cough are allergens, exposure to irritants (aerosols, tobacco smoke, and pollutants), and dry or cold air. Acute cough may rarely be due to life-threatening causes like severe pneumonia or pulmonary embolism. It is usually dry in nature. Notably, acute rhinosinusitis is suspected if symptoms of URTI (except cough) last >10 days. Subacute cough is a grey area in the classification of cough, and usually, it is infectious or postinfectious in nature.

Diagnosing and managing chronic cough is challenging due to underlying causes such as respiratory disease (upper airway disease and asthma), nonrespiratory conditions (GERD), and uncertain multifactorial etiologies. Furthermore, cough hypersensitivity syndrome (CHS), with a central mechanism of cough reflex hypersensitization, complicates both diagnosis and treatment. Considering the various underlying etiologies of chronic cough, unresponsive or undiagnosed patients need a coordinated and integrated multidisciplinary approach. The implementation of such an approach is usually limited at the primary care level.

Experts highlighted the common causes of cough according to duration, which can serve as a guide to general practitioners. Viral URTI, bronchiolitis, and the common cold are common for acute cough. Exacerbations

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<table>
<thead>
<tr>
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<th>Outlier</th>
<th>Consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>We recommend the short-term use of either ambroxol or bromhexine in the treatment of productive cough.</td>
<td>7.2</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>32</td>
<td>We recommend the short-term use of either N-acetylcysteine or guaifenesin in the treatment of productive cough.</td>
<td>7.4</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>33</td>
<td>We recommend patients presenting with cough-associated red flag signs be referred to a higher center.</td>
<td>8.44</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>34</td>
<td>We recommend using morphine/gabapentin/amitriptyline in chronic refractory cough under a specialist’s supervision.</td>
<td>7.8</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>35</td>
<td>We recommend ruling out medication history, such as ACE inhibitors, in patients with chronic dry cough.</td>
<td>8.2</td>
<td>0</td>
<td>Consensus</td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme; COPD, chronic obstructive lung disease; CVA, cough variant asthma; FDC, fixed-dose drug combinations; GERD, gastroesophageal reflux disease; HRCT, high-resolution computed tomography; NAEB, nonasthmatic eosinophilic bronchitis; OPD, outpatient department; QoL, quality of life; UACS, upper airway cough syndrome; URTI, upper respiratory tract infections

**Recommendations:** Generally accepted definitions of cough in adults in terms of duration are acute (≤3 weeks), subacute (between 3 and 8 weeks), and chronic (>8 weeks), and these guide the management of patients in routine clinical practice. A cough that does not expel mucus or phlegm from the respiratory tract is called a productive cough. However, the nature of a cough is not to be interpreted in isolation in clinical practice. A dry cough is indicative of a noninfectious etiology, whereas a productive cough may indicate an infectious etiology.
of conditions such as chronic obstructive pulmonary disease (COPD), asthma, and UACS should also be in mind for acute cough. Nonasthmatic eosinophilic bronchitis (NAEB), UACS secondary to rhinosinusitis, GERD, and asthma are common causes of chronic cough. Postinfectious cough, pertussis, and postviral rhinosinusitis are the frequent causes of subacute cough. Acute cough due to viral infections in some cases may take >3 weeks for resolution.

Experts suggested ruling out a drug-induced cough. It refers to a chronic cough due to certain drugs. In addition to angiotensin receptor blockers and angiotensin-converting enzyme inhibitors, there are cases reported with drugs such as omeprazole and leflunomide. Table 2 provides lists of drugs associated with cough.15

One of the most common symptoms of coronavirus disease-19 (COVID-19) is cough. In around 10–20% of patients, persistent cough may be observed for weeks or months following recovery from the acute phase of infection. This is also observed in severe acute respiratory syndrome coronavirus 2 infections in 2–42% of cases. A study demonstrated that among COVID-19 patients, clinical or hospitalization-related factors were not associated with post-COVID-19 cough 11 months after their discharge from the hospital. Song et al. have suggested that post-COVID-19 cough is due to vagal sensory nerve activation, leading to neuroinflammatory events and cough hypersensitivity in the brain.23

### Recommendations: There are certain common causes of cough according to duration, which can serve as a guide to general practitioners. Viral URTI, bronchiolitis, and the common cold are common for acute cough. Exacerbations of conditions such as COPD, asthma, and UACS should also be in mind for acute cough. NAEB, UACS secondary to rhinosinusitis, gastroesophageal reflux disorder, and asthma are common causes of chronic cough. Postinfectious cough, pertussis, and postviral rhinosinusitis are the frequent causes of subacute cough. In some cases, acute cough due to viral infections may take >3 weeks to resolve. Certain drugs, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, omeprazole, and leflunomide, may cause a drug-induced chronic cough.

### Quality of Life (QoL)

There was no agreement against routinely assessing the QoL in chronic cough using validated tools such as the visual analog scale, cough QoL questionnaire, cough severity diary, Leicester cough questionnaire, and Pulmonary Function Questionnaire. The panel was split in their decision, with half of them in favor and the other half against the use of QoL assessment for chronic cough in clinical practice. Expert panel reports and CHEST guidelines supported the use of validated tools for the assessment of cough severity or QoL.17,12 A study found that objective and subjective assessments of cough were moderately related to one another, and subjective assessments measured different aspects than objective assessments. They highlighted the relevance of using both tools in the assessment of patients with cough.15 Clinical evaluation generally suffices along with taking a history for acknowledging impaired QoL. Poor QoL is reflected if the cough is leading to UI, syncope, or fractured ribs. A consensus was reached on using QoL assessment in chronic idiopathic cough cases. By using a cough-specific questionnaire to assess the QoL, the psychosocial, mental, and physical effects of chronic cough have been demonstrated. The cough-related QoL status was found to be worse in women than in men, probably due to UI, that is, more commonly seen in older women.30

### Recommendations: Quality of life (QoL) assessment is recommended specifically for chronic idiopathic cough but not for the routine assessment of chronic cough.

### Diagnosis

Watchful waiting of up to 8 weeks has been suggested by German guidelines before initiating the full diagnostic assessment if there are no alarming signs or symptoms. According to the guidelines, acute cough due to acute viral infections is mild and self-limiting (within 9–12 days), and no additional diagnostic measures are necessary.1

The first step in patient evaluation is taking the medical and clinical history with an emphasis on the history of rhinorrhea, exposure to pollutants, smoking, allergy, and medication history. Appreciating differences between dry and wet cough sounds also helps the clinician in diagnosis.24

The recommendation to perform a physical examination of the sputum before sending it to the laboratory for examination reached no consensus. This is in contrast with the Chinese Cough Guidelines given by the CTS Asthma Consortium, which suggested that examining sputum characteristics, volume, and purulence can help in arriving at a diagnosis.18 However, experts did recommend performing microscopic and cultural sputum examinations in chronic productive cough where bacterial infection is suspected. Pulmonary tuberculosis is to be ruled out in all cases of subacute or chronic cough. GeneXpert Ultra is recommended to rule out suspected cases of *Mycobacterium tuberculosis* as it has high sensitivity and specificity.

In patients with cough with red flags, additional investigations will rule out heart failure, COPD, pulmonary embolism, severe exacerbation of asthma, and pneumonia. Radiologic and laboratory investigations need not be used routinely for acute cough in the absence of red flag signs. However, chest radiographs, spirometry, and complete blood counts are to be carried out in patients with chronic coughs.

Though the majority (60%) of experts favored the recommendation of avoiding high-resolution computed tomography (HRCT) when chest radiographs and physical examinations were found to be normal, 40% did not agree with this. However, there was consensus on recommending HRCT in chronic cough refractory treatment after common causes have been excluded, in case of bilateral velcro-like crackles are present, or bronchiectasis is suspected despite a normal chest radiograph. The expert panel believed HRCT is important when suspecting specific conditions such as emphysema, hemoptysis, rheumatic disease, or interstitial collagen disease. Therefore, its use depends upon the situation, the clinical setting, and the type of patients visiting the OPD. This agrees with the results of a study that emphasized that before special investigations such as HRCT can be considered for chronic cough, one must exclude the common etiologies of cough.31 The European Respiratory Society (ERS) guidelines regarding diagnosing and managing chronic cough recommend not to perform computed tomography scans when findings after chest radiography and physical examination are normal,12 and the ACCP guideline recommends HRCT following 4–6 weeks of recall visits and only...
for chronic cough not responsive to adequate treatment. A near consensus was reached in not recommending 24-hour pH monitoring in all patients with chronic coughs suspected to be caused by GERD. Seven of 10 experts agreed with not performing pH monitoring even when the patient has GERD. Furthermore, no consensus was arrived at for performing pH monitoring before prescribing long-term (>8 weeks) proton pump inhibitors (PPIs) in patients with chronic cough suspected of having GERD. The German Cough Guidelines recommend an impedance pH probe for chronic cough of unclear etiology after other diagnostic tests to detect undiagnosed GERD have been conducted. The CTS cough guidelines mention that the nonavailability of 24-hour impedance monitoring (multichannel) for esophageal pH in most hospitals poses a difficulty in formulating guidelines regarding the test. The Lyon consensus on the management of GERD has stated that pH monitoring (wireless) is expensive and laborious to interpret, and neither wireless pH monitoring nor impedance monitoring is easily available.

In around 59% of individuals, evidence-based diagnostic and management strategies prove to be refractory, or the reason for the cough remains unexplained. This is termed a refractory or unexplained chronic cough. The complications of chronic refractory cough are UI, anxiety, depression, social disruption, and sleep disturbance.

Patients with chronic refractory or idiopathic cough whose symptom increases with triggers, such as ambient temperature or cold air, or the smell of perfume, most likely have CHS. Identification of this new category of CHS requires physicians to address the unmet need to choose suitable therapies for this condition. This is caused by peripheral and central mechanisms. Broadly, CHS is associated with the following—(1) low level of thermal, mechanical, or chemical exposure with negative full etiologic workup that triggers troublesome cough; and (2) low levels of thermal, mechanical, or chemical exposure–associated respiratory disease or with positive etiologic workup that triggers troublesome cough, which either responds to etiologic treatment or is refractory to etiologic treatment.

The panel recommended the following investigations:

- Sinus imaging in patients presenting with cough and signs and symptoms of chronic sinusitis or nasal hypertrophy.
- Cardiac workup (electrocardiography, echocardiography, and Holter test) in patients suspected of having cough of cardiac origin.
- Spirometry, bronchoprovocation challenge, allergy evaluation, and fractional exhaled nitric oxide (FeNO) testing in patients suspected of having asthma, cough-variant asthma (CVA), or NAEB.
- Bronchoscopy with bronchoalveolar lavage, in the absence of sputum, when infection or interstitial lung disease is suggested.
- Laryngoscopy in patients with chronic cough suspected to be of upper airway etiology.

### Recommendations: Pulmonary tuberculosis

Pulmonary tuberculosis is to be ruled out in all cases of subacute or chronic cough. Gene Xpert Ultra is recommended to rule out suspected cases of Mycobacterium tuberculosis as it has high sensitivity and specificity.

In patients with cough with red flags, additional investigations will rule out heart failure, COPD, pulmonary embolism, severe exacerbation of asthma, and pneumonia. Radiologic and laboratory investigations need not be routinely used for acute cough without red flag signs. However, chest radiographs, spirometry, and complete blood counts are to be carried out in patients with chronic coughs.

High resolution CT (HRCT) is recommended in chronic cough refractory to treatment after common causes have been excluded, in case bibasilar velcro-like crackles are present or bronchiectasis is suspected despite a normal chest radiograph. HRCT is also recommended when suspecting specific conditions such as emphysema, hemoptysis, rheumatic disease, or interstitial collagen disease.

Patients with chronic refractory or idiopathic cough whose symptoms increase with triggers such as ambient temperature, cold air, or the smell of perfume most likely have CHS.

### Treatment

#### Acute Cough

In acute mild cough, a near consensus was obtained for no pharmacologic intervention. However, in cases of worsening acute cough, the panel was in favor of pharmacologic intervention. As per the CHEST expert panel recommendation, in children with acute cough, honey can be used, than no treatment. Experts acknowledged the strategy of watchful waiting and active surveillance but also cautioned about carelessness.

The experts did not recommend the use of nonpharmacologic therapies for acute cough.

Nonpharmacologic therapies, especially honey and ivy leaf extract, have been shown to provide symptomatic improvement in postviral acute cough, but many natural components have not been sufficiently investigated. Additionally, they are not found to be better than pharmacologic options. The CHEST expert panel report does have a recommendation for the use of honey to manage cough due to common colds between the ages of 1 and 18 years for symptomatic relief. The results of the present consensus agree with the CTS cough guidelines, where the emphasis was given to symptomatically managing acute cough.

Therapeutic interventions aimed at the elimination of the underlying etiology of cough. However, managing cough often necessitates symptomatic approaches.

### Recommendations: Watchful waiting and active surveillance are recommended with caution in acute cough. It is recommended that acute cough be treated symptomatically with pharmacologic therapies.

#### Antitussives

Empiric management with antitussive agents may be necessary for symptomatic relief in acute cough. Nonopioid antitussives are preferred in managing acute cough. The present consensus recommends using dextromethorphan as the preferred antitussive in patients with acute dry cough. A near consensus was reached for the use of levodropropizine as a preferred antitussive for acute dry cough. Moreover, the use of nonopioid antitussive drugs for acute and subacute dry irritating cough reached near consensus.

Recommendation for dextromethorphan comes from a wide experience of its use in clinical practice by experts. When objective measurements such as bouts of cough, cough effort, and cough count were used, dextromethorphan was the only medication that could significantly suppress acute cough. A study examined the drug of choice in the management of dry cough in India—dextromethorphan ranked the highest, and levodropropizine ranked the least in its effectiveness in suppressing dry cough.

Levodropropizine (an orally administered nonopioid) demonstrates an antitussive action peripherally by modulating levels of sensory neuropetide in the respiratory tract.
Evidence from trials to practice guidelines has demonstrated that levodropropizine (peripherally acting), when compared with dextromethorphan (centrally acting), has favorable effects in managing cough.\(^\text{40}\) A meta-analysis demonstrated that levodropropizine was significantly better than central antitussive drugs in reducing nocturnal awakenings and the intensity and frequency of cough in both children and adults.\(^\text{42}\) Experts opined against using codeine-based preparations in acute and subacute cough. Recent studies do not support the use of codeine for suppressing acute cough.\(^\text{40}\)

Similarly, the German Respiratory Society guidelines also recommend dextromethorphan in both acute and subacute cough; however, they emphasize that evidence supporting its use for subacute cough was inadequate.\(^\text{1}\) The CTS cough guidelines do not recommend using dextromethorphan or codeine as monotherapy in acute cough caused by a common cold but suggest combining them with first-generation antihistamines.\(^\text{18}\)

### Antihistamines

The use of levocetirizine, as a preferred antihistamine, for dry cough received a near consensus. A significantly impaired QoL is observed in the common cold associated with acute cough. It was found (internet survey) that cough lasted for a longer duration than other symptoms associated with cold in 69% of respondents.\(^\text{43}\) Centrally penetrant histamine type 1 receptor (H1) antagonists exert antitussive action by binding nonhistaminergic receptors in the central nervous system and by controlling cough excitability and mucus secretion. The efficacy of a sedating antihistamine has been demonstrated in cough due to UACS.\(^\text{44}\)

The Korean guidelines mention antihistamine use in managing UACS.\(^\text{45}\) However, the CTS cough guidelines do not recommend first-generation antihistamines as a monotherapy. They suggest combining them with decongestants to improve symptoms such as sneezing, cough, and nasal discharge.\(^\text{18}\) The combination of antihistamines and decongestants for the management of cough is also mentioned in the German cough consensus.\(^\text{1}\) The guidelines by Japanese, Korean, Australian, and Chinese societies recommend using H1 antagonists in chronic cough. Clinical trials have shown the benefit of oral antihistamines in a subgroup of patients, especially patients with atopy or seasonal allergic rhinitis-associated cough.\(^\text{46}\)

**Recommendations:** Empiric management of cough using antitussives is recommended, particularly with nonopioid antitussives. Dextromethorphan is the preferred antitussive in acute dry cough. Codeine-based preparations are not recommended for acute and subacute cough.

### Decongestants

The panel did not recommend routine use of decongestants in managing dry cough; however, their use as a part of FDCs with antitussive or antihistamine in cough associated with rhinitis or cold can be considered for short periods for symptomatic relief. FDCs were recommended by experts in certain situations, such as where the role of additional agents is justified. Three studies demonstrated the benefits of combining a decongestant, an antihistamine, and a placebo on cough reduction. Two trials have shown equivocal findings. The quality of studies and variations in patient characteristics necessitate a careful interpretation of the results.\(^\text{47-51}\)

Combinations of dextromethorphan with expectorants, antihistamines, and decongestants in antitussive preparations may provide symptomatic relief with a cough that interferes with daily activities in patients.\(^\text{52}\)

The CTS cough guidelines supported the use of antitussives, antihistamines, and decongestants for patients with severe short-term cough.\(^\text{18}\)

**Recommendations:** The routine use of decongestants in the treatment of dry cough is not recommended; however, the use of decongestants as a part of FDC with antitussive or antihistamine in cough associated with rhinitis or cold is recommended for a short period for symptomatic relief.

### Mucoactive Drugs (Mucolytics/ Mucokinetics/Expectorants)

Respiratory diseases that present with the clinical complication of mucus hypersecretion are managed with mucoactive agents. They work by decreasing mucus hypersecretion and increasing the ability to expectorate the sputum. It includes drugs under mucolytic, expectorant, and mucokinetic categories.\(^\text{53}\) By increasing the chloride concentration in airway secretions, reducing airway tachykinins, and decreasing cough reflex hypersensitivity, N-acetylcysteine (a mucolytic) may decrease mucus viscosity. Additionally, there is a promotion in the diffusion of antibiotics and improved mucociliary function in chronic bronchitis cases due to changes caused in the mucus rheology.\(^\text{53}\) Guaifenesin (an expectorant) acts by increasing the bronchial secretion volume and exerting an influence on the cholinergic innervation in airway mucous glands. The decrease in the quantity of thick and viscous secretions is one of the main benefits of using guaifenesin expectorant to symptomatically manage the cough. However, randomized controlled trials (RCTs) have not proven guaifenesin as being clinically effective in managing cough.\(^\text{53}\)

Bromhexine (a mucokinetic) and ambroxol (a metabolite of bromhexine) decrease mucus secretion by inducing hydrolytic depolymerization in mucoprotein fibers. An RCT demonstrated the efficacy of ambroxol and N-acetyl cysteine in symptom control and in making the mucopurulent sputum more serous.\(^\text{54}\) The coadministration of antibiotics with bromhexine have shown to amplify the actions of the antibiotic.\(^\text{55}\) The CTS cough guidelines recommend the use of mucolytics in patients with acute tracheobronchitis who find it hard to expectorate the sputum. They recommend sustained-release guaifenesin to manage acute respiratory infections. Patients with chronic sinusitis also benefit from mucolytics.\(^\text{18}\) The German guidelines recommend the use of mucolytics in acute viral bronchitis.\(^\text{1}\)

The short-term use of ambroxol or bromhexine is recommended by this panel to manage productive cough, and so is the use of either N-acetylcysteine or guaifenesin. The experts felt that ambroxol or bromhexine has an additional anti-inflammatory effect. Similar anti-inflammatory and antioxidant effects of ambroxol and N-acetyl cysteine have been mentioned in the German Cough Guidelines. The German guidelines also emphasize the role of guaifenesin in managing cough associated with acute bronchitis.\(^\text{1}\) Guaifenesin or N-acetylcysteine can be used in individuals with difficulty in expectorating. The experts had no preferences on the type of mucolytic agent and mentioned that they must be used judiciously over a short period of time.

**Recommendations:** The short-term use of ambroxol or bromhexine is recommended to manage productive cough, and so is the use of either N-acetylcysteine or guaifenesin.
Demulcents

Demulcents consist of honey, lozenges, linctus-containing syrup (glycerol and licorice), and menthol. They increase swallowing and saliva production and therefore interfere with the cough reflex or coat the peripheral sensory receptors responsible for triggering a cough. Cough receptor irritation in the pharynx is also reduced. They usually are effective for 20–30 minutes, which is related to the amount of time the sugar is bound to the receptor. Demulcents are safe on oral or topical administration at low doses. An RCT in adults demonstrated the safety and efficacy of glycerol in reducing dry cough. The evidence on the safety and efficacy of menthol in managing acute cough is low to moderate in quality. A faster initiation of action and greater effectiveness is observed when antitussive drugs are formulated as syrups than as tablets or capsules. Experts reached a near consensus on recommending the use of demulcents such as lozenges in acute dry cough; however, they disagreed on its use in chronic cough patients. The panel refrained from making any recommendation over the preferred formulation type, tablet or liquid, although they opined that it is more of a patient preference than a physician’s choice.

**Recommendations:** Demulcents are recommended for acute dry cough but not for chronic cough.

Hydration

Dehydration leads to the synthesis of proinflammatory mediators, which affects airway caliber, especially in asthma, whereas normal hydration promotes mucociliary clearance and protects the airway epithelium. Experts strongly recommended maintaining good hydration as an important part of management, especially in productive cough.

**Recommendations:** Maintaining good hydration is strongly recommended in managing cough, particularly in productive cough.

Oral Bronchodilators

A near consensus was achieved for not recommending the use of oral bronchodilators in managing productive cough. However, the experts encouraged the qualified use of inhaled bronchodilators. The ERS guidelines on chronic cough and the Korean Cough Guidelines mention that there is a role of inhaled bronchodilators in improving the cough symptoms in CVA. The CTS cough guidelines mention inhalation of hypertonic saline, mannitol, and bronchodilators, as a combination, to improve cough clearance. The panel recommended the treatment of acute exacerbations of asthma or COPD with short-acting β-agonists (SABAs) and short-acting muscarinic antagonists, corticosteroids, and antibiotics. The Korean Cough Guidelines recommend inhaled SABA, theophylline, inhaled corticosteroids (ICS), and codeine in cough associated with chronic bronchitis and decreased lung function.

**Recommendations:** Short-acting β-agonists, short-acting muscarinic antagonists, ICS, and antibiotics are recommended to manage acute exacerbations of asthma or COPD.

Antibiotic Use

The experts recommended symptomatic treatment without antibiotics for acute and subacute coughs. Antibiotics are used in productive cough or when purulent sputum is present. In subacute cough, antibiotics are used if the cough is due to a bacterial infection. A consensus was reached for prescribing the antibiotic for the average duration of 5–10 days. Similarly, the CTS cough guidelines recommend using antibiotics for patients with nasal mucus discharge or purulent sputum. They also suggest antibiotics not be used in chronic coughs unrelated to infection. Macrolides provide relief from symptoms and have a reduced risk of bacterial resistance and long-term adverse effects. The German guidelines recommend macrolide antibiotics in the exudative stage of infection lasting up to 10 days. The guidelines recommend the use of antibiotics in the presence of green or yellow sputum, indicating a secondary bacterial infection. They mention that antibiotics have no role in cough associated with postviral rhinosinusitis. This point agrees with the Korean Cough Guidelines, which mention postinfectious cough to be the most common reason for subacute cough and recommend symptomatic management in these patients without antibiotics. However, no consensus was reached for prescribing azithromycin for a month in patients with a chronic or persistent cough.

**Recommendations:** Antibiotics are recommended for 5–10 days in productive cough when purulent sputum is present or in subacute cough due to a bacterial infection.

Special Populations

The expert panel did not reach a consensus on altering the dose of cough medications in the elderly and agreed on similar doses to elderly patients as that of adults. They agreed on exercising caution in the elderly while prescribing antihistamines, centrally acting drugs, and expectorants. The Malaysian consensus recommends avoiding sedating antihistamines in the elderly population.

A consensus was reached for the use of mucolytics and antitussives during pregnancy and lactation. Bromhexin is a United States Food and Drug Administration pregnancy category A drug; therefore, it is generally safe to use during pregnancy. Guaifenesin, an expectorant, is commonly used in over-the-counter cough medicines and is generally considered safe to use during pregnancy, though studies have been limited. Experts agree regarding its safety during pregnancy within the dosage limits.

In pregnant or lactating women, codeine must be avoided. Dextromethorphan is the preferred antitussive during both pregnancy and lactation due to its equivalence to codeine as an antitussive in pregnancy. Bronchodilators in cough syrups are not suited extensively for pregnancy and have limited or no evidence; hence, they are best avoided in pregnancy. Pregnancy category B drugs include chlorpheniramine, diphenhydramine, and loratadine. There are a number of potential risks associated with taking antihistamines during pregnancy, including polydactyly (diphenhydramine), cleft palate (diphenhydramine or loratadine), uterine contractions (diphenhydramine), and retrolental fibroplasia. To reduce the risk of teratogenicity, the Malaysian consensus on antihistamines advises against using antihistamines during the first trimester of pregnancy. Sedating antihistamines is also discouraged during pregnancy and breastfeeding. Experts in our consensus also advised against using antihistamines during pregnancy.

A consensus was reached on not giving dextromethorphan to patients below 4 years of age. In general, antitussive medications are avoided in children below the age of 2 years. Codeine for cough and cold is strictly contraindicated among children below 12 years. Dextromethorphan is approved for use beyond 4 years of age and is in line with the consensus by the experts. Experts also reached a consensus on using terbutaline in patients above 6 years, but no consensus was reached on avoiding levosalbutamol in patients below 4 years. An Indian expert closed-group discussion report on children notes that bronchodilators are commonly prescribed beginning at the age...
of two. Even though there is little to differentiate between terbutaline and levosalbutamol syrup, in children <5 years of age, levosalbutamol is preferred, and in children 6 years or older not responding to levosalbutamol, terbutaline is preferred.\textsuperscript{18}

Furthermore, no consensus was reached on the use of mucolytics as the only treatment for pediatric patients with a productive cough and not recommending antihistamines routinely in children with acute dry cough. The CTS consensus mentions using pseudoephedrine with caution in pediatric patients and is against the use of antitussive agents in infants.\textsuperscript{18}

**Recommendations:** The dose of cough medications recommended for the elderly is the same as that for adults; however, caution must be exercised while prescribing antihistamines, centrally-acting drugs, and expectorants. During pregnancy and lactation, mucolytics and antitussives are recommended to manage the cough. Codeine, oral bronchodilators, and antihistamines are not recommended during pregnancy. Dextromethorphan is recommended in children above the age of 4 years, and terbutaline is recommended in children above the age of 6 years.

**Referral to Higher Centers**

The panel recommends that patients with cough and red flag signs at presentation, or those with a persistent cough for >14 days despite treatment, be referred to higher centers. Hemoptysis, prominent dyspnea, especially at rest, vomiting, hoarseness, and systemic symptoms (fever, weight loss, and peripheral edema with weight gain) are all red flags that require referral. In addition to these, experts advised considering cough syncope and UI while coughing as potential red-flag signs. If the underlying cause is ambiguous, a referral to a pulmonologist is recommended as the first step.

**Chronic Cough Drugs**

The experts recommend codeine preparation in patients with an unexplained chronic cough when other treatments have failed (caution must be exercised due to undesirable side effects and highly variable interindividual metabolism of the drug). With its antitussive, analgesic, and sedative properties, codeine is useful in a variety of situations, as noted by Eddy et al. When the cough is accompanied by pain, an analgesic effect is helpful, and when the cough is the result of anxiety or central stimuli, a sedative effect is beneficial.\textsuperscript{56} An opioid antitussive, such as codeine, is reserved as a last resort in a cough not controlled with any other medications. This is like the CTS guidelines, which recommend codeine in severe, unexplained dry cough or irritating refractory dry cough, especially if associated with chest pain.\textsuperscript{18}

The experts also recommended a therapeutic trial of gabapentin in adults with unexplained cough and the use of morphine, amitriptyline, or gabapentin for chronic refractory cough under a specialist’s supervision. However, no consensus was reached on the use of a trial dose of low-dose morphine (5–10 mg twice a day) in adult patients with chronic refractory cough. Similar recommendations have been made by the Korean cough consensus. The German consensus recommends low dose (10 mg) morphine once or twice daily for distressing cough and mentions that side effects, such as addiction, respiratory depression, constipation, and sedation, need to be considered. The guidelines also recommend that chronic idiopathic cough be treated as a neuropathy with the administration of gabapentin.\textsuperscript{1} The CTS cough guidelines stress the temporary use of morphine only when all other treatments have failed.\textsuperscript{18}

The panel also recommends the use of PPIs in chronic cough with concomitant typical reflux symptoms. The recommendation highlights the use of PPIs for at least 2 months where GERD is suspected as the etiology for chronic cough and symptoms are suggestive of reflux disorder. Similar recommendations were made in the German and the Chinese cough consensus. The German consensus suggests a twice-daily, high-dose PPI therapy for 60–90 days in patients with positive results for comprehensive reflux assessment. The CTS cough guidelines recommend a standard or intensive dose of PPI for at least 2 weeks.\textsuperscript{1,18,45}

The panel also recommends the use of ICS with or without inhaled bronchodilators as a therapeutic choice for managing patients with chronic cough with a high suspicion of bronchial asthma and the addition of an antileukotriene agent (like montelukast) when there is an incomplete response to ICS. ICS is the mainstay in managing asthma. Experts emphasized following GINA guidelines in these cases. A subcategory of asthma, CVA, typically presents with only a cough and no other symptoms such as wheezing or dyspnea. This also agrees with the Korean, German, and Chinese consensus, which recommends ICS with or without leukotriene receptor antagonists or long-acting bronchodilators in CVA.\textsuperscript{1,18,45}

**Recommendations:** Codeine preparations are recommended in patients with unexplained chronic coughs when other treatments have failed. A therapeutic trial of gabapentin is recommended for adults with unexplained coughs. The use of morphine, gabapentin, or amitriptyline under a specialist’s supervision is recommended for chronic refractory cough. In chronic cough with concomitant typical reflux symptoms, PPIs are recommended. In chronic cough with suspected bronchial asthma, inhalational corticosteroids are recommended; additionally, antileukotriene agents are recommended in patients not responding to inhalational corticosteroids adequately.

**Other Therapeutic Options**

The panel reached a near consensus on a trial of speech/voice therapy and cough suppression physical therapy in patients with unexplained chronic cough. Speech therapy is suggested as a nondrug-based option for managing unexplained cough, in which the person is taught to suppress the urge to cough, which is also a technique for reducing the cough trigger. Similarly, cough suppression therapy (CST) educates patients about various counseling, cough suppression techniques, and breathing exercises. The CST has been shown to reduce cough symptoms,
cough reflex hypersensitivity, and cough frequency in RCTs.67

The Korean consensus and the German Cough Guidelines recommend speech therapy in case of laryngeal dysfunction syndrome or laryngeal hypersensitivity with irritating chronic cough.13,65 The ERS guidelines also recommend physiotherapy or speech therapy to improve QoL in patients with chronic refractory cough.13 The CTS cough guidelines recommend physical therapy in addition to speech therapy to reduce cough hypersensitivity and the frequency of cough.18

A consensus was not reached for a 1-month-long trial of macrolides in patients with cough due to chronic bronchitis refractory to other treatments, considering local guidelines on antimicrobial stewardship. Expert recommendations from India on the use of macrolides in respiratory disease mention that though macrolides are used often as the first-line treatment in respiratory infections, caution must be exercised as long-term use can lead to antimicrobial resistance.68

There are many pathophysiological processes and potential causes underlying chronic cough. A systematic and careful evaluation is needed to identify factors provoking cough, such as medications, asthma, GERD, rhinosinusitis, and eosinophilic bronchitis, and eliminate serious pathologies, such as undiagnosed malignancy as causative factors for cough.13,15 Experts emphasized ruling out angiotensin converting enzyme (ACE) inhibitor use as the etiology. In some individuals, the use of ACE inhibitors increases the sensitivity to the cough reflex. The other drugs that induce cough are amiodarone, β-blockers, methotrexate, bleomycin, mitomycin C, busulfan, gliptins, ICS, ipratropium, tiotropium, disodium cromoglycate, β2-adrenergic, nedocromil, pentamidine, secretolytics, zanamivir, fentanyl, and mycophenolate mofetil.3

The panel reached a consensus on cough syncope and stress incontinence being red flag signs. Incontinence is mainly seen in women and significantly affects health-related QoL.12 Charcot, in 1876, first described the loss of consciousness after an episode of coughing.69 An important and commonly overlooked complication of cough is cough syncope. Cough syncope, a temporary loss of consciousness while coughing, is a distressing condition that could be fatal if it occurs while driving.34 However, there is a dearth of literature, consensus statements, or guidelines on investigating and managing patients with cough syncope. Markedly elevated intrathoracic pressure due to coughing results in post-tussive syncope. Subsequently, there is a reduction in the decreased cardiac output and venous return, leading to syncope. The baroreceptors get stimulated by the alterations in the intrathoracic pressure, and this triggers hypotension and peripheral vasodilation. These complex mechanisms result in the loss of consciousness. There are currently no guidelines on the investigation of cough syncope; King et al. proposed a primary set of tests for excluding differential pathologies, which included a detailed history and examination for ruling out possible neurological causes where symptoms of limb weakness, visual disturbance, headache, or paresthesia are present. Additionally, various medications may contribute to cough. All patients who experience cough syncope must undergo investigations such as cardiac event monitoring and electrocardiography.34

Urinary stress incontinence occurs during activities such as exercising, coughing, or sneezing, leading to the leakage of a small quantity of urine. In females, UI associated with chronic cough has a much higher incidence than that in males. The reasons for this are a weaker sphincter tension and a shorter urethra in females. However, both men and women can have UI. They exercise to strengthen the pelvic floor, controlled coughing, and the airway clearance technique can help reduce the amount of leakage.70,71 Counseling is important for those with UI.72

The panel recommended a brief counseling session for patients presenting with psychogenic cough. Severe psychological issues lead to psychogenic cough, which is mostly seen in children. Usually, when a cough due to other conditions is ruled out, psychogenic cough is the diagnosis considered. This is managed in children by psychological counseling and suggestive therapy and in
adults with anxiolytics, antidepressants, and psychological interventions.\textsuperscript{18}

**Recommendations:** Speech therapy is recommended as a nondrug-based option to manage the unexplained chronic cough. CST is recommended to reduce cough symptoms and frequency and cough reflex hypersensitivity. A brief counseling session is recommended for patients presenting with psychogenic cough.

Based on the consensus statements, algorithms have been developed. The algorithms for acute cough, subacute cough, and chronic cough are given in Figures 2 and 3, respectively.

**Conclusion**

Cough is a bothersome symptom routinely observed in clinical practice. There are several challenges in accurately diagnosing and managing cough in India. Routinely managing cough, in turn, has mainly focused on empiric and over-the-counter drugs. The lack of adequate integrated evidence necessitates devising a consensus by a team of experts. The current consensus covers a wider range of topics, such as the definition, diagnosis, evaluation, and treatment of cough. It has been framed by a group of experts, which include pulmonologists, otolaryngologists, a pediatrician, and a general physician. This consensus has made recommendations to aid in both diagnosing and managing cough in primary healthcare settings in India.

**Author Contributions**

PPD has contributed to the study Design. SBB, SP, HB, PPD, VJ, SB, and PJ have contributed to Literature Search. PPD, PKT, and NA have contributed to the preparation of the consensus statement. PPD, PKT, NA, and PJ have contributed to the review of the consensus statement. PPD, SBB, and SP have contributed to the interpretation of results. SBB, SP, and PPD have contributed to the draft manuscript preparation. All authors have contributed to the critical review of the manuscript.

**Acknowledgment**

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**References**

12. Rosenfeld RM, Nnacheta LC, Corrigan MD. Clinical consensus statement development
Table S1: Summary of consensus statements

<table>
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<th>Sr. No</th>
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<th>Mean</th>
<th>Outlier</th>
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<td>An unexplained chronic cough is defined as a cough that persists longer than 8 weeks and remains unexplained despite extensive assessment for a common and uncommon condition.</td>
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<tr>
<td>8</td>
<td>In clinical practice, estimating the duration of the cough is the first step in narrowing the list of potential diagnoses.</td>
<td>8.12</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>9</td>
<td>URTI and bronchiolitis caused by viruses are to be looked at as the common cause of acute cough in an OPD setting.</td>
<td>9.11</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>10</td>
<td>The common cold is to be looked at as the common cause of acute cough in an OPD setting.</td>
<td>7.67</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>11</td>
<td>Exacerbations of underlying diseases such as asthma, COPD, and UACS should also be considered as the cause of acute cough in an OPD setting.</td>
<td>9.00</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>12</td>
<td>Asthma is to be looked at as the common cause of chronic cough in an OPD setting.</td>
<td>9.22</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>13</td>
<td>Gastroesophageal reflux disease is to be looked at as the common cause of chronic cough in an OPD setting.</td>
<td>8.44</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>14</td>
<td>UACS secondary to rhinosinus diseases to be looked at as the common cause of chronic cough in an OPD setting.</td>
<td>8.89</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>15</td>
<td>NAEB is to be looked at as the common cause of chronic cough in an OPD setting.</td>
<td>7.44</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>16</td>
<td>Postinfectious cough is to be looked at as the common cause of subacute cough in an OPD setting.</td>
<td>8.78</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>17</td>
<td>Exacerbations of underlying diseases such as asthma, COPD, and UACS to be looked at as the common cause of subacute cough in an OPD setting.</td>
<td>8.22</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>18</td>
<td>Seasonal allergies/hay fever are to be looked at as the common cause of dry cough in an OPD setting.</td>
<td>8.00</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>19</td>
<td>Viral infection is to be looked at as the common cause of dry cough in an OPD setting.</td>
<td>8.33</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>20</td>
<td>A dry cough usually indicates a noninfectious etiology.</td>
<td>7.33</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>21</td>
<td>Lower respiratory tract infections such as bronchitis and pneumonia are to be looked at as the common cause of productive cough in an OPD setting.</td>
<td>8.33</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>22</td>
<td>The productive cough usually indicates infectious etiology.</td>
<td>7.67</td>
<td>2</td>
<td>Near consensus</td>
</tr>
<tr>
<td>23</td>
<td>Medical history—we recommend undertaking medical or clinical history, such as a preceding history of cold/rhinorrhea, smoking, environmental/occupational pollution exposure, allergy, or medication history, as the first step in patient evaluation.</td>
<td>9.11</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>24</td>
<td>Clinical pointers—we recommend additional/aggressive investigation in patients presenting with cough and red flag signs to rule out pneumonia, severe exacerbation of asthma/COPD, pulmonary embolism, and heart failure.</td>
<td>8.67</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>25</td>
<td>We recommend routinely assessing cough QoL or cough severity with validated tools such as the Punum ladder.</td>
<td>5.67</td>
<td>0</td>
<td>No consensus</td>
</tr>
<tr>
<td>26</td>
<td>We do not recommend routine assessment of QoL in chronic cough.</td>
<td>5.70</td>
<td>7</td>
<td>No consensus</td>
</tr>
<tr>
<td>27</td>
<td>We recommend the assessment of QoL in patients with chronic idiopathic cough.</td>
<td>8.0</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>28</td>
<td>We recommend hearing cough sounds as it is a critical part of patient evaluation.</td>
<td>9.67</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>29</td>
<td>Laboratory investigations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>We recommend not to use radiologic and laboratory investigations routinely for acute cough unless there are red flag signs.</td>
<td>8.11</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>31</td>
<td>We recommend first-line workups such as chest X-ray, spirometry, and complete blood count evaluation to be done for patients with chronic cough.</td>
<td>8.67</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>32</td>
<td>We recommend not using HRCT as a second-line investigation in patients with chronic cough who display both normal physical examination and chest X-ray.</td>
<td>7.78</td>
<td>4</td>
<td>No consensus</td>
</tr>
<tr>
<td>33</td>
<td>We recommend asking for HRCT in patients who are not responding to treatment in patients with chronic coughs.</td>
<td>8.0</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>Sr. No</td>
<td>Statement</td>
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<td>Consensus</td>
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</tr>
<tr>
<td>34</td>
<td>We recommend using HRCT only when the common causes of chronic cough have been excluded, in the presence of bibasilar velcro-like crackles, or in suspected cases of bronchiectasis, even if the chest X-ray is normal.</td>
<td>8.78</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>35</td>
<td>We do not recommend performing 24-hour pH monitoring in chronic cough suspected due to GERD.</td>
<td>6.70</td>
<td>2</td>
<td>Near consensus</td>
</tr>
<tr>
<td>36</td>
<td>We recommend performing 24-hour pH monitoring before prescribing long-term (&gt;8 weeks) PPI treatment for chronic cough in a suspected case of GERD.</td>
<td>6.20</td>
<td>2</td>
<td>No consensus</td>
</tr>
<tr>
<td>37</td>
<td>We recommend sinus imaging in patients presenting with cough and signs/symptoms suggestive of chronic sinusitis or nasal hypertrophy.</td>
<td>8.22</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>38</td>
<td>We recommend entire cardiac workups such as ECG, ECHO, and Holter in patients presenting with cough suspected of cardiac origin.</td>
<td>8.22</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>39</td>
<td>We recommend spirometry, bronchoprovocation challenge, allergy evaluation, and FENO in patients suspected of asthma/CVA/NAEB.</td>
<td>8.22</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>40</td>
<td>We recommend suspecting UACS in patients presenting with increased nasal discharge, frequent throat clearing, and postnasal discharge.</td>
<td>8.11</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>41</td>
<td>We recommend suspecting CVA in patients presenting cough as a predominant symptom without wheezing.</td>
<td>8.44</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>42</td>
<td>We recommend performing a physical examination of sputum before sending it to the laboratory for examination.</td>
<td>6.50</td>
<td>3</td>
<td>No consensus</td>
</tr>
<tr>
<td>43</td>
<td>We recommend using microscopic and cultural sputum examination in cases of chronic productive cough if a bacterial infection is suspected.</td>
<td>9.00</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>44</td>
<td>In the absence of sputum, we recommend using bronchoscopy with bronchoalveolar lavage may be indicated in the presence of high suspicion of infection or interstitial lung disease.</td>
<td>8.89</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>45</td>
<td>We recommend performing laryngoscopy in patients with chronic cough who have suspected upper airway etiology.</td>
<td>7.11</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>46</td>
<td>We recommend ruling out pulmonary tuberculosis in all cases of subacute or chronic cough.</td>
<td>8.33</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>47</td>
<td>Treatment approach—In the absence of clinical signs of a specific etiology of a cough, we do not recommend any drug, and patients are advised to watch and wait.</td>
<td>5.33</td>
<td>4</td>
<td>No consensus</td>
</tr>
<tr>
<td>48</td>
<td>In acute mild cough, we do not recommend any treatment, and patients are advised to watch and wait.</td>
<td>6.50</td>
<td>2</td>
<td>Near consensus</td>
</tr>
<tr>
<td>49</td>
<td>In acute worsening cough, we do not recommend any treatment, and patients are advised to watch and wait.</td>
<td>3.20</td>
<td>1</td>
<td>No consensus</td>
</tr>
<tr>
<td>50</td>
<td>We recommend the use of nonpharmacological treatments such as honey and ivy leaf in the treatment of acute cough caused by a URTI or allergen.</td>
<td>6.10</td>
<td>1</td>
<td>No consensus</td>
</tr>
<tr>
<td>51</td>
<td>We recommend symptomatic therapy in patients with comorbidity in acute cough without red flag signs.</td>
<td>6.70</td>
<td>1</td>
<td>Near consensus</td>
</tr>
<tr>
<td>52</td>
<td>We recommend continuing symptomatic treatment till the symptoms last in acute dry cough.</td>
<td>7.70</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td></td>
<td>Antitussives</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>53</td>
<td>We recommend the use of dextromethorphan as the preferred antitussive in patients with acute dry cough.</td>
<td>7.00</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>54</td>
<td>We recommend the use of nonopioid antitussive drugs as the preferred antitussives in patients with subacute dry cough.</td>
<td>6.67</td>
<td>1</td>
<td>Near consensus</td>
</tr>
<tr>
<td>55</td>
<td>We recommend using one of the nonopioid antitussive drugs in acute dry irritating cough.</td>
<td>7.60</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>56</td>
<td>We recommend not using codeine-based preparation in patients with acute cough.</td>
<td>7.67</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>57</td>
<td>We recommend not using codeine-based preparation in patients with subacute cough.</td>
<td>7.78</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>58</td>
<td>We recommend the use of levodropropizine as the preferred antitussive in patients with acute dry cough.</td>
<td>6.67</td>
<td>0</td>
<td>Near consensus</td>
</tr>
<tr>
<td>59</td>
<td>We recommend not to use one of the nonopioid antitussive drugs in subacute dry irritating cough.</td>
<td>4.40</td>
<td>2</td>
<td>No consensus</td>
</tr>
<tr>
<td></td>
<td>Antihistamines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>We recommend the use of levocetirizine as the preferred antihistamine in the treatment of dry cough.</td>
<td>6.56</td>
<td>1</td>
<td>Near consensus</td>
</tr>
<tr>
<td>61</td>
<td>We do not recommend the routine use of antihistamines in the treatment of acute dry cough.</td>
<td>6.30</td>
<td>3</td>
<td>No consensus</td>
</tr>
<tr>
<td>62</td>
<td>We do not recommend the routine use of antihistamines in pediatric patients with acute dry cough.</td>
<td>6.30</td>
<td>2</td>
<td>No consensus</td>
</tr>
<tr>
<td></td>
<td>Decongestants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>63</td>
<td>We do not recommend the routine use of decongestants in the treatment of dry cough.</td>
<td>7.50</td>
<td>1</td>
<td>Consensus</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Statement</th>
<th>Mean</th>
<th>Outlier</th>
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<tbody>
<tr>
<td>Other class</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>64</td>
<td>We do not recommend demulcants like lozenges in the management of dry cough.</td>
<td>5.89</td>
<td>2</td>
<td>No consensus</td>
</tr>
<tr>
<td>65</td>
<td>Lozenges are routinely used in patients with acute dry cough.</td>
<td>6.50</td>
<td>2</td>
<td>Near consensus</td>
</tr>
<tr>
<td>66</td>
<td>Lozenges are routinely used in patients with chronic cough.</td>
<td>5.90</td>
<td>4</td>
<td>No consensus</td>
</tr>
<tr>
<td>67</td>
<td>We recommend using monotherapy for the management of cough, whereas FDCs can be preferred in situations where the role of additional agent/s is justified.</td>
<td>7.30</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>68</td>
<td>We do not recommend menthol in the management of dry cough.</td>
<td>7.33</td>
<td>4</td>
<td>No consensus</td>
</tr>
<tr>
<td>69</td>
<td>The type of formulation is a matter of patient preference, and the panel would not like to make any recommendations with respect to tablet/liquid preparation.</td>
<td>7.0</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>70</td>
<td>We recommend the short-term use of either ambroxol or bromhexine in the treatment of productive cough.</td>
<td>7.20</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>71</td>
<td>We recommend short-term use of either N-acetylcysteine or guaifenesin in the treatment of productive cough.</td>
<td>7.0</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>72</td>
<td>We do not recommend maintaining good hydration as an important part of management in productive cough.</td>
<td>7.40</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>73</td>
<td>We do not recommend the routine use of bronchodilators in the treatment of productive cough.</td>
<td>6.50</td>
<td>2</td>
<td>Near consensus</td>
</tr>
<tr>
<td>74</td>
<td>We recommend treating acute exacerbation of asthma/COPD with SABA/SAMA + corticosteroid ± antibiotics.</td>
<td>7.40</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>Antibiotic use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75</td>
<td>We recommend symptomatic treatment without antibiotics for acute cough.</td>
<td>8.56</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>76</td>
<td>We recommend symptomatic treatment without antibiotics for a subacute cough.</td>
<td>8.11</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>77</td>
<td>We recommend antibiotics to be used in purulent sputum or productive cough.</td>
<td>8.78</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>78</td>
<td>We recommend using antibiotic therapy to be initiated in subacute cough due to bacterial infection.</td>
<td>9.00</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>79</td>
<td>We recommend a 1-month trial of azithromycin in patients with chronic/persistent cough.</td>
<td>3.44</td>
<td>0</td>
<td>No consensus</td>
</tr>
<tr>
<td>80</td>
<td>We recommend the average duration of antibiotic use to be around 5–10 days.</td>
<td>8.78</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>Special population</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>81</td>
<td>We recommend that dose alteration is not required routinely in elderly patients—they can be prescribed the same dose as adults.</td>
<td>5.22</td>
<td>1</td>
<td>No consensus</td>
</tr>
<tr>
<td>82</td>
<td>We recommend exercising caution while using antihistamines/centrally acting drugs/expectorants in elderly people.</td>
<td>7.80</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>83</td>
<td>We recommend dose alteration is not required in immunocompromised patients—they can be prescribed the same dose as adults.</td>
<td>7.11</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>84</td>
<td>We recommend against the use of oral bronchodilators during pregnancy and lactation.</td>
<td>7.20</td>
<td>2</td>
<td>Near consensus</td>
</tr>
<tr>
<td>85</td>
<td>Mucolytic/antitussive can be used in pregnancy and lactation.</td>
<td>7.10</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>86</td>
<td>We recommend dextromethorphan should be avoided in pediatric patients below 4 years of age.</td>
<td>7.11</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>87</td>
<td>We recommend levosalbutamol should be avoided in pediatric patients below 4 years of age.</td>
<td>5.11</td>
<td>0</td>
<td>No consensus</td>
</tr>
<tr>
<td>88</td>
<td>We recommend terbutaline can be used safely in pediatric patients over 6 years of age.</td>
<td>6.89</td>
<td>1</td>
<td>Near consensus</td>
</tr>
<tr>
<td>89</td>
<td>We recommend mucolytics should be the only treatment given to pediatric patients presenting with productive cough.</td>
<td>5.44</td>
<td>0</td>
<td>No consensus</td>
</tr>
<tr>
<td>90</td>
<td>We do not recommend the routine use of antihistamines in pediatric patients with acute dry cough.</td>
<td>6.30</td>
<td>2</td>
<td>No consensus</td>
</tr>
<tr>
<td>Persistent cough</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>91</td>
<td>We recommend patients presenting with cough-associated red flag signs at presentation should be referred to a higher center.</td>
<td>8.44</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>92</td>
<td>We recommend patients with a persistent cough, despite treatment for more than 14 days, should be referred to a higher center.</td>
<td>8.78</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>Chronic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>93</td>
<td>We recommend PPIs for patients with chronic cough who display concomitant typical reflux symptoms.</td>
<td>9.11</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>94</td>
<td>We recommend a twice-daily standard dose of PPI for at least 2 months where GERD is the cause of chronic cough.</td>
<td>8.56</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>95</td>
<td>We recommend the use of ICS with/without bronchodilators as a therapeutic choice for the treatment of patients with chronic cough with high suspicion of bronchial asthma.</td>
<td>9.11</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>96</td>
<td>We recommend considering the addition of an antileukotriene agent (e.g., montelukast) when the response to ICS is incomplete.</td>
<td>7.11</td>
<td>1</td>
<td>Consensus</td>
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<tbody>
<tr>
<td>98</td>
<td>We recommend codeine preparation to patients with an unexplained chronic cough only when other treatments have failed because of the drug's highly variable interindividual metabolism and undesirable side effect profile. Other options in therapy</td>
<td>8.00</td>
<td>2</td>
<td>Consensus</td>
</tr>
<tr>
<td>99</td>
<td>We suggest a trial of speech therapy and cough suppression physical therapy in patients with unexplained chronic cough.</td>
<td>6.89</td>
<td>2</td>
<td>Near consensus</td>
</tr>
<tr>
<td>100</td>
<td>We suggest a trial of speech therapy in patients with unexplained chronic cough.</td>
<td>6.60</td>
<td>1</td>
<td>Near consensus</td>
</tr>
<tr>
<td>101</td>
<td>We suggest a therapeutic trial of gabapentin in adult patients with unexplained chronic cough.</td>
<td>7.00</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>102</td>
<td>We recommend a trial of low-dose morphine (5–10 mg BD) in adult patients with chronic refractory cough.</td>
<td>6.11</td>
<td>3</td>
<td>No consensus</td>
</tr>
<tr>
<td>103</td>
<td>We recommend using morphine/gabapentin/amitriptyline in chronic refractory cough under specialist's supervision.</td>
<td>7.80</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>104</td>
<td>We recommend a 1-month trial of macrolides in patients with cough due to chronic bronchitis refractory to other therapy, considering local guidelines on antimicrobial stewardship.</td>
<td>6.00</td>
<td>2</td>
<td>No consensus</td>
</tr>
<tr>
<td>105</td>
<td>We recommend considering cough hypersensitivity syndrome in patients with chronic refractory/idiopathic cough whose symptom increases with triggering events such as a change in ambient temperature or cold air, or perfume smell.</td>
<td>7.40</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>106</td>
<td>We recommend ruling out medication history, such as ACE inhibitors, in patients with chronic dry cough.</td>
<td>8.20</td>
<td>0</td>
<td>Consensus</td>
</tr>
<tr>
<td>107</td>
<td>We recommend considering cough syncope as a red flag sign.</td>
<td>8.001</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>108</td>
<td>We recommend considering stress incontinence as a red flag sign.</td>
<td>7.70</td>
<td>1</td>
<td>Consensus</td>
</tr>
<tr>
<td>109</td>
<td>We recommend a brief counseling session for patients presenting with psychogenic cough.</td>
<td>8.40</td>
<td>0</td>
<td>Consensus</td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme; COPD, chronic obstructive lung disease; CVA, Cough variant asthma; ECG, electrocardiography; ECHO, echocardiography; FDC, fixed-dose drug combinations; FeNO, fractional exhaled nitric oxide; GERD, gastroesophageal reflux disease; HRCT, high-resolution computed tomography; ICS, inhaled corticosteroids; NAEB, nonasthmatic eosinophilic bronchitis; OPD, outpatient department; PPI, proton pump inhibitors; SABA, short-acting β-agonists; SAMA, short-acting muscarinic agonist; QoL, quality of life; UACS, upper airway cough syndrome; URTI, upper respiratory tract infections
Post-COVID-19 Cardiovascular Sequelae and Myocarditis

Lakshmi Chakradhar Yarlagadda¹, Debasis Ghosh², Ullash Basak³, Manab Senapati⁴, Monalisa Das⁵, Rajdeep Ghosh⁶*

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ABSTRACT

Background and aim: Post coronavirus disease 2019 (COVID-19) cardiovascular (CV) pathological changes, myocarditis, and myocardial infarctions (MIs) are major public health issues. This review discusses acute and chronic COVID-19 cardiac manifestations.

Methods: The devastating impact of COVID-19 on global healthcare and economies has likely been one of humanity’s deadliest calamities in recent decades, as multiple literature and databases were searched from 2020 to 2022.

Results: As of April 2022, we identified 73 articles in various electronic databases that discussed the details of COVID-19 and cardiac manifestations. Cardiometabolic risk factors should now, more than ever, be a top priority for clinicians, as their potent role in exacerbating COVID-19 illness severity has been conclusively demonstrated.

Conclusion: This review discusses cardiac pathology changes, CV consequences of acute COVID-19, microvascular injury and cardiac complications linked with SARS-CoV2, COVID-19 linked with chronic CV disease, therapeutic drug effects on heart used in COVID-19, and possible investigational approaches and management strategies for post-COVID-19 CV consequences.

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HIGHLIGHTS

- Microvascular injury and cardiac complications: Linked with SARS-CoV2.
- COVID-19 linked with chronic CV disease.
- Therapeutic drug effects on heart used in COVID-19.
- Possible investigational approaches and management strategies for post-COVID-19 CV consequences.

INTRODUCTION

The COVID-19 pandemic has infected 466 million people and resulted in 6 million deaths. This crippled the public health infrastructure and the lives of people. COVID-19 patients present with a spectrum of symptoms—asymptomatic, flu symptoms (fever, muscle aches, shortness of breath, headache, altered sensation of taste and smell) to severe complications like acute respiratory distress syndrome, acute kidney injury, thromboembolism, and myocarditis.¹² The complications are instigated and driven by cytokine storm—immunological reaction by macrophages which release proinflammatory cytokines (Interferon (IFN) α, IFN-γ, Interleukin (IL) 1β, IL-6, IL-12, IL-18, IL-33, tumor necrosis factor (TNF) α, transforming growth factor β, etc.) and chemokines (CCL/CXCL) (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc.) which damage the epithelial cells lining the blood vessels of various organs leading to organ failures.³⁴ COVID-19 affects the cardiac system by destabilizing the atherosclerotic plaque through severe inflammatory reactions and microvascular thromboembolic events. Many reports have widely reported poor prognosis in COVID-19 patients with CV complications; this further shows a strong link between COVID-19 and the CV system.⁵⁶ Cardiac complications of COVID-19 virus infection include myocarditis,⁸ acute coronary syndrome (ACS), and MIs,⁹ which is strongly supported by biochemical,¹⁰¹¹ biopsy,¹² and autopsy findings. It was reported that myocardial injury due to COVID-19 was attributed to nearly 7% of mortality rates in an early case study.¹²

In this article, we review several clinical studies, articles, and case studies and provide a detailed account of the mechanisms of myocardial injury in COVID-19 patients and its resulting clinical manifestations, and impact on chronic CV patients and further explore myocarditis caused by COVID-19 mRNA vaccine. We have also emphasized different investigation models and management approaches specifically for each case.

CARDIAC PATHOLOGY CHANGES: EFFECT OF COVID-19

Coronavirus disease 2019 (COVID-19) CV problems extend from angina to several carditis and arrhythmias. The majority of problems develop within the first 2 weeks of the presentation. ACS and myocarditis are both major cardiovascular problems that frequently have a poor prognosis as well as a high death rate. Cardiovascular connection in COVID-19 has been attributed to a variety of pathways, including cytokine storm-induced proinflammatory state, direct viral attack to myocytes, hypercoagulable condition with the thromboembolic event, coronary plaque unsteadiness, or a demand-supply disparity contributing to ACS (Fig. 1).¹³

Cardiac symptoms are not confined to the active phase of COVID-19 infection but can also arise during the convalescent phase. During the convalescent phase, affected individuals are at a higher menace for ACS, particularly post-COVID-19 MI may arise as an outcome of coronary plaque unsteadiness caused by persistent inflammation. Furthermore, a chronic hypercoagulable state or endothelial dysfunction following infection with the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can be a proposed explanation for an ACS to develop also after healing from coronavirus infection.¹⁴ As previously thought, myocardial inflammation is not exclusively associated with severe COVID-19 as well as symptomatic COVID-19 instances. Puntmann et al.¹⁴ used cardiac magnetic resonance imaging (MRI)/cardiac MRI (CMR) to show persistent myocardial inflammation in 60/100 individuals who had to get well from COVID-19 infection in a recent German cohort. On EMB, three individuals with considerable cardiac involvement revealed active lymphocytic inflammation. Following the remission of their lung problem along with a negative real-time PCR test following a minimum of 2 weeks from the

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Post-COVID-19 Cardiovascular Sequelae and Myocarditis

Patients with post-COVID-19 cardiac syndrome have a hypercoagulable state with continuous inflammation, which manifests as ischemia or as sequelae of myocarditis together with left ventricular dysfunction and constant myocardial inflammation, resulting in arrhythmias or heart failure. Information from the earlier SARS pandemic also revealed a long-standing consequence following the SARS coronavirus infection. Patients with post-COVID-19 cardiac syndrome have a hypercoagulable state with continuous inflammation, which manifests as ischemia or as sequelae of myocarditis together with left ventricular dysfunction and constant myocardial inflammation, resulting in arrhythmias or heart failure. Information from the earlier SARS pandemic also revealed a long-standing consequence following the SARS coronavirus infection.

Figs 1A and B: (A) Direct myocardial damage—occurring because of entry of virus to the cardiac cells by ACE 2 causing inflammatory changes and destruction of myocardial cells; (B) Indirect injury—downregulation of ACE 2 leads to vasoconstriction, endothelial dysfunction, inflammatory changes, and initiation of the coagulation routes associated with microvascular thrombosis; the immune system activation leads to a systemic inflammatory response that finally causes myocardial infarction (created by the mechanism of development.com)

initial diagnosis, all of these individuals underwent a CMR. The majority of these individuals were silent or had slight-to-moderate signs, as well as those with serious cardiac manifestations, were omitted. All this indication alludes to continuing heart inflammation (peri-myocarditis) even during the disease’s convalescent phase.

This persistent myocardial inflammation, edema, and ventricular dysfunction may be one of the causes of symptoms like chest pain also shortness of breath in the post-COVID-19 convalescent phase. Furthermore, persistent inflammation can cause myocardial scarring and also create a breeding ground for lethal ventricular arrhythmias, particularly in the aged and persons with comorbidities.

All of this has far-reaching implications, given the large number of recovered cases, as well as persistent cardiac inflammation or subclinical myocardium dysfunction that may manifest later in life. This necessitates better menace categorization in individuals who are aged or have many comorbidities, as well as the prudent use of CMR in affected individuals with increased biomarkers to find out persistent myocardial inflammation.

This demands better risk categorization in individuals who are elderly or have many comorbidities utilizing biomarkers such as cardiac troponins, as well as the prudent use of CMR in affected persons with high biomarkers to identify persistent myocardial inflammation. Furthermore, the application of cardioprotective treatments such as statins or sodium-glucose cotransporter-2 inhibitors has the potential to reduce long-term consequences in these individuals. Previous research has linked worse outcomes to a greater New York Heart Association functional class, immunohistological markers of inflammation, viral genome detection, or CMR characteristics of active inflammation.

Subsequent healing from COVID-19 infection, other significant CV consequences include the emergence of thromboembolic events, including venous thromboembolism (VTE). Single-center research of 163 patients from the United States of America found VTE in 2.5% of well again patients 30 days after
discharge, with most of them being segmental lung embolism, intracoronary thrombus, and ischemic stroke.15 Similarly, VTE rates of 4.8 and 7.2% in individuals with subsequent COVID-19 infection were described in retrospective investigations from the United Kingdom.19,20 The recurrence of lung thromboembolism after remission from COVID-19 illness can be fatal, especially if it is combined with hemodynamic instability. Because COVID-19 infection is linked with a hypercoagulable condition, there is an increased risk of VTE during the disease’s convalescent phase. The recurrence of pulmonary thromboembolism after healing from COVID-19 infection can be fatal, especially if it is combined with hemodynamic instability. Because COVID-19 disease is associated with a hypercoagulable condition, there is an increased risk of VTE during the disease’s convalescent phase. This was noted in a recent study of a 52-year-old lady suffering from acute pulmonary thromboembolism after recovering from COVID-19.21

### Mechanism of Development of CV Consequences in Acute COVID-19: Including Autopsy Studies

The impact of angiotensin-converting enzyme (ACE) 2 receptors in SARS-CoV-2 heart participation is now well understood. Numerous mechanisms, together with direct cytotoxic injury22 dysregulation of the renin-angiotensin-aldosterone system,23 endothelitis as well as thrombo-inflammation, and associated alterations in the immune response to cytokine release, have been suggested to cause the myocardial injury.24

The sequence of myocardial damage after SARS-CoV-2 infection obtained from autopsy reviews is biased due to referral bias, although it has specified preliminary pathophysiological clues. Only four affected individuals (5%) had assumed cardiac damage in an initial autopsy series of 80 back-to-back SARS-CoV-2 polymerase chain reaction (PCR) positive cases.25 Two deaths occurred from sudden cardiac arrest due to comorbid conditions. One patient had a serious MI, and the other had right-sided ventricular lymphocytic infiltrates. These preliminary findings implied that wide myocardial impairment as a predominant reason for mortality might be uncommon.

Basso et al.26 considered the hearts in 21 chosen autopsies in a subsequent multicenter autopsy study. Myocarditis (characterized as lymphocytic infiltration as well as myocyte necrosis) was seen in 14% of the cases, infiltration of interstitial macrophage in 86%, and pericarditis as well as right-sided ventricular damage in 19%. Halushka and Vander Heide27 reviewed 22 publications that described the autopsy outcomes of 277 affected individuals. Lymphocytic myocarditis was mentioned in 7.2% of cases, but only 1.4% met the firm histopathological criteria28 for myocarditis, implying that exact myocarditis was uncommon. Lindner et al. found COVID-19 viral elements in the cardiac muscles of 24 out of 39 (5%) back-to-back autopsies; the viral load was medically important in 16/39 (41%). Notably, viral elements were separated in interstitial cells, such as macrophages and pericytes, rather than cardiomyocytes. The elevated virus load in certain conditions was also not aligned with inflammation, which is consistent with autopsy studies showing a low prevalence of myocarditis.25

### Microvascular Injury and Cardiac Complications: Linked with SARS-CoV2

Cardiac troponin levels in COVID-19 patients are frequently elevated,29 suggesting myocardial damage or ischemia. The exploration of Bois et al.30 gives the idea to boost the impression of COVID-19-associated microthrombi. In a little group of 15 people, the authors discovered that postmortem fibrin microthrombi were much more usual (80%) than serious ischaemic damage (13%) and myocarditis (33%), implying a part for thrombosis in exacerbating the myocardial impairment.

Fox and Heide31 have theorized the wide range of pathophysiological progressions that underpin myocardial impairment. Hypoxia and microvascular harm in the lungs, according to the authors, may result in right heart stress as well as myocyte necrosis. Limited microvascular outcomes, endotheliosis,32 related microthrombi, and varied renin-angiotensin homeostasis may all contribute to this.33 Elevated cytokines,34 for example, IL-1, IL-16,17,22, IFN-γ, and TNF-α may also make a significant contribution to myocardial damage by triggering dysfunction of endothelium, platelet stimulation, recruitment of neutrophils, and ultimately activating a hypercoagulable situation (Fig. 1).

### Consequences after Acute and Chronic COVID-19 Illness

The mechanisms underlying persistent cardiac impairment following serious illness are even now unknown. One potential clarification is a long-lasting inflammatory reaction elicited by constant viral reservoirs in the muscles of the heart after the serious infection,25 which may be worsened by obesity-accompanying inflammatory signaling driven in part by perivascular adipose tissue through the discharge of adipokines such as monocyte chemoattractant protein-1 as well as adjusted upon initiation, Normal T cell expressed, and presumably discharged, CCL/CXCL that worsen endothelial.36 Insidious tissue harm, followed by long-lasting myocardial fibrosis, would be an unintended after-effect of such courses, resulting in worsened ventricular compliance, deficient myocardial perfusion, augmented myocardial stiffness, diminished contractility, and possible arrhythmias.

An autoantibodies reaction to cardiac antigens via molecular mimicry is a second mechanism for late damage.35 Wang et al. high-throughput proteome analysis has discovered a variety of autoantibodies to humoral and tissue antigens in COVID-19 patients. Individuals with chronic fatigue syndrome have also been found to have autoantibodies to cholinergic as well as adrenergic receptors.35,36 Several longitudinal cytokine profiling and proteomic studies37,38 have recently revealed an increase in the appearance of prothrombotic factors (e.g., factor VIII, plasminogen activator inhibitor-1, prothrombin) following the serious infection. It is consistent with the growing number of reports of late embolic difficulties.25 The elevated prevalence of vascular thrombosis in the lung (5–30%),39,40 especially in patients with hospitalization, is predictable to increase the threat of pulmonary hypertension with thrombo-embolism in the future.40 Dysfunction of the endothelium31 and its difficulties may establish in affected individuals, with findings of lasting impairment found in younger people 3–4 weeks later SARS-CoV-2 contamination.42

Countless of these problems are similar to those experienced by survivors of extra epidemics such as SARS, Middle East respiratory syndrome, and H1N1A, emphasizing the importance of recognizing the effect of respiratory viral infections on CV health, formerly highlighted by Xiong et al.43 in a previous review.

Explaining cardiac participation in the framework of multisystem health can offer observations into procedures of ongoing damage by identifying distinct patterns of tissue injury (e.g., inflammatory deviations or embolic changes). Ramam et al.44 performed multi-organ MRI on 58 posthospitalized COVID-19 patients and 30 matched controls and found tissue aberrations in the lungs (60%), heart (26%), liver (10%), kidneys (29%), and brain (11%). MRI irregularities in nearly every organ were linked to inflammatory...
indicators, implying that long-lasting inflammation could impair healing. Following this, the posthospitalisation-COVID-19 survey found that failure to heal from multi-organ manifestations was linked to symbols of permanent inflammation.22 Dennis et al.23 examined the frequency of multi-organ destruction among primarily nonhospitalized affected individuals in another study of 201 affected individuals and discovered that signs of long COVID-19 huddled amongst those with multisystem damage on MRI. Dysfunction of the endothelium, dysfunction microvascullarly as well as prothrombotic tendencies may all promote multi-organ impairment.23 Perfusion imbalances in the heart, as well as lungs (Patelli et al. and Kotecha et al.) of COVID-19 patients, have been observed in preferred studies using advanced imaging modalities such as positron emission tomography, CT, and MRI at 40–60 days after infection.

Multi-organ MRI showed indications of small vessel illnesses (9.3%) and ischemic changes (3.7%) in the brain (9.3%), and 1.9% had a MI 2–3 months after infection in one survey of hospitalized individuals.46 Some other reports of 104 hospitalized patients found that inducible myocardial perfusion abnormalities were usual in affected individuals with medium to serious disorders but did not fluctuate in burden when contrasted to comorbidity and hazard factor matched controls. Numerous studies are presently being conducted to describe a load of vascular and thrombotic difficulties25 and also to survey the possible benefits of continuous antithrombotic (extended thromboprophylaxis) as well as vascular protecting treatments (e.g., statins, risk-factor management) in postacute COVID-19 affected individuals, as shown in Table 1 and Figure 2.

**COVID-19 Linked with Chronic CV Disease**

Up to a third of COVID-19 patients have a history of chronic CV disease.1, 47 Indoor patient mortality, the hazard of thrombo-embolism, and septic shock incidence are all related to the presence of concomitant cardiac illness.25 Individuals with a history of heart failure have a two to four-fold chance of decompenation and death even in the postacute phase. An increasing incidence of heart failure aggravation may appear even after 30 days following SARS-CoV2 infection; according to25 the discontinuation of guideline-based medical therapy throughout serious illness is one factor for the increasing epidemic of postdischarge heart failure episodes.

Researchers from the TRED-HF study previously established that stopping heart failure therapy had a deleterious impact on individuals with cured dilated cardiomyopathy, leading to recurrence and poor consequences.25 Successful resumption and optimization of heart failure remedies may thus be critical in preventing heart failure readmissions following an acute COVID-19. COVID-19 has a cardiometabolic profile that is similar to that of cardiac illnesses, suggesting that COVID-19 may have a role in the destabilization of preclinical disorders (e.g., heart failure and coronary artery disease). This could clarify the elevated rate of type 2 MI in people with severe COVID-19, as well as the rise in ‘newly’ diagnosed CV diseases.25 Alteration of the renin-angiotensin-aldosterone system, endothelial dysfunctions,48,49 renal injury,50 and steroid use are all possible contributors.

Fig. 2: Mechanism of development of cardiac changes due to COVID-19 (created by the mechanism of development.com)
<table>
<thead>
<tr>
<th>Category/National clinical trials (NCT) number</th>
<th>Title</th>
<th>Used drugs or intervention</th>
<th>Outcome or result of the trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV NCT04324463</td>
<td>Anticoronavirus therapies to prevent progression of COVID-19 trial (ACT COVID-19)</td>
<td>Aspirin, Colchicine, Rivaroxaban</td>
<td>In the colchicine versus control study, hospitalization for 45 days was associated with mortality, disease progression, and a composite of MACE. Aspirin versus placebo—45-day composite of death and hospitalization, progression of the disease, and MACE composite. Aspirin and rivaroxaban versus the control group—45-day composite of death and hospitalization, disease progression, and MACE composite.</td>
</tr>
<tr>
<td>CV NCT04381936</td>
<td>Randomized evaluation of COVID-19 therapy (RECOVERY)</td>
<td>Aspirin, Colchicine, Steroid, Empagliflozin, Anakinra</td>
<td>The primary and secondary consequence measures are death within 28 days, the need for mechanical ventilation, and hospital stay. A second outcome evaluates the risky outcome of a thrombotic event up to 6 months after randomization.</td>
</tr>
<tr>
<td>CV NCT04662684</td>
<td>Medically Ill hospitalized patients for COVID-19 thrombosis extended prophylaxis with rivaroxaban therapy: the MICHELLE trial</td>
<td>Rivaroxaban</td>
<td>The main outcome indicators are VTE 35 days later hospital discharge and VTE-related mortality. Secondary outcome measures include bleeding 35 days after hospital discharge and a composite of myocardial ischemia, stroke, arrhythmias, heart failure, and death from any cause.</td>
</tr>
<tr>
<td>CV NCT04406389</td>
<td>Anticoagulation in critically ill patients with COVID-19 (the IMPACT trial)</td>
<td>Unfractionated heparin, Enoxaparin, Angiotroban, Fondaparinux</td>
<td>Death within 30 days is the primary outcome measure; secondary outcomes include the occurrence of VTE at 6 months, length of intensive care unit (ICU) stay, and incidence of serious vascular events.</td>
</tr>
<tr>
<td>CV NCT04486508</td>
<td>Intermediate-dose vs standard prophylactic anticoagulation and statin vs placebo in ICU patients with COVID-19 (INSPIRATION)</td>
<td>Unfractionated heparin, Enoxaparin, Atorvastatin, Matched placebo</td>
<td>The primary outcome measure is the 30-day composite of serious VTE, arterial thrombosis, death, and extracorporeal membrane oxygenation treatment. Secondary outcome measures consist of 30-day major adverse CV events (MACE), arrhythmia, death, major bleeding, decreased platelet count, elevated liver enzymes, and atrial fibrillation.</td>
</tr>
<tr>
<td>CV NCT04900155</td>
<td>Evaluation of the effect of long-term lipid-lowering therapy in STEMI patients with coronavirus infection COVID-19 (CONTRAST-3)</td>
<td>Atorvastatin, Ezetimibe</td>
<td>The primary outcome measures are a 96-week lipid profile, electrical instability, ventricular rhythm disturbance, autonomic regulation, myocardial deformation, left ventricular systolic function, and MACE.</td>
</tr>
<tr>
<td>CV NCT04460651</td>
<td>Prevention and treatment of COVID-19 with EPA in subjects at risk-intervention trial (PREPARE-IT)</td>
<td>Icosapent ethyl, Placebo</td>
<td>The primary outcome measures are SARS-CoV-2 positivity at 60 days and COVID-19 hospitalization; secondary endpoints include CRP, triglycerides, COVID-19-related hospital stays, nonfatal myocardial infarction, and stroke at 28 days.</td>
</tr>
<tr>
<td>CV NCT04505098</td>
<td>A pragmatic randomized trial of icosapent ethyl for high-CV risk adults (MITIGATE)</td>
<td>Icosapent ethyl</td>
<td>The main outcome indicator is the proportion of individuals with a moderate to severe viral upper airway infection and a worsening clinical status. Mortality at 12 months, MACE, as well as heart failure were secondary outcome measures.</td>
</tr>
<tr>
<td>CV NCT04350593</td>
<td>Dapagliflozin in respiratory failure in patients with COVID-19 (DARE-19)</td>
<td>Dapagliflozin, Placebo</td>
<td>30-day organ dysfunction, ventricular tachycardia, respiratory decompensation, renal replacement therapy and vasopressor therapy are the primary outcome measures. Upon 30 days in the hospital, days alive without respiratory decompensation is a secondary outcome measure.</td>
</tr>
<tr>
<td>Cardiac ISRCTN11721294</td>
<td>Rehabilitation for cardiac arrhythmia</td>
<td>Rehabilitation</td>
<td>Autonomic function was measured with a 12-lead ECG Holter device for 10 minutes and 24 hours at baseline and after the rehabilitation program (6 weeks).</td>
</tr>
</tbody>
</table>
Therapeutic Drug Effects on Heart used in COVID-19

The vast majority of CV problems that persist after COVID-19 are caused by tissue injury acquired during acute sickness. Further research into the influence of critical treatments on long-standing CV health is needed. Anti-inflammatory medicines like dexamethasone and tocilizumab have been known as significant weapons in the COVID-19 therapeutic arsenal. Though, the amount to which they impact long-term cardiopulmonary healing is unknown, and data on heart damage rates are not yet generally available. Further research is needed to see if continued inflammation in long-standing COVID-19 patients reflects a rebound event in dexamethasone- or tocilizumab-cured individuals. Anticoagulation’s intricate role in patients demands considerable thought. In the serious phase, mounting evidence suggests that aspirin has no benefit in dropping mortality between hospitalized patients and nonhospitalized outpatients.

The degree of sickness (noncritical hospitalized affected individuals benefiting the most) is a major factor of medication achievement, according to data in confirmation of therapeutic dosage anticoagulation. A multiplatform adaptive randomized controlled clinical trial combining data from the studies such as REMAP-CAP, ACTIV-4a, and ATTACC found that therapeutic dose heparin enhanced survival until hospital discharge as well as organ support-free days in relatively ill individuals but not in critically ill patients. Other investigations (the ACTION, INSPRIATION, and RAPID trials) on the other hand, found no variance in main endpoint measures between ill individuals taking therapeutic vs preventive dosage anticoagulation. The ACTIV-4B242 study found no difference in the 45-day existence between nonhospitalized individuals who received aspirin, minimal dose, or maximum dose apixaban vs placebo. In addition, to comprehend the long-standing advantages of anticoagulation in ill individuals, more research is required.

Possible Investigational Approaches and Management Strategies for Post-COVID-19 CV Consequences

Although the real extent of postacute COVID-19 CV damage is unknown, cardiac symptoms appear to be common in this stage. Proof in favor of cost-effective techniques to rule out substantial CV pathology is urgently needed. Some experts believe this method is reasonable. Some experts believe that screening elevated-risk patients for constant cardiac connection, such as those with irregular cardiac tests during the serious period, newly diagnosed CV changes in post-COVID-19 cases, and sports, is a reasonable method.

A complete history, physical and general examinations, along with a blood test panel (C-reactive protein (CRP), B-type natriuretic peptide (BNP)/natriuretic pro BNP, troponin I and glycated hemoglobin, and lipids), electrocardiogram (ECG), with transthoracic echocardiography at least 8–12 weeks later infection could be used to screen high-risk people. Additional testing is advised for people who have clinically significant anomalies after the screening. Following screening studies, noninvasive procedures such as stress single positron emission computed tomography, CMR, Holter, and coronary computed tomography angiography may be investigated; invasive coronary angiography may be investigated; invasive coronary angiography or endomyocardial biopsy (EMB) may be directed for elevated-risk people. Where appropriate, referral to specialty clinics [e.g., arrhythmia clinic, postural orthostatic tachycardia syndrome (POTS), or psychiatric assistance] should be measured. Ill individuals with long-lasting CV illnesses should be queried about their past exposure to COVID-19 and the status of vaccination when they come in for a routine follow-up. For particular affected individuals who report persistent symptoms, a short-term evaluation of physical, mental, and cognitive well-being may be mandatory, as this could smooth timely referral to suitable support rehabilitation, occupational therapy, psychology, physiotherapy, and social and welfare support associated with reducing the burden of ill patients. Numerous proposals have been made by consensus societies about athlete return-to-play guidance. Although previous standards were conservative, the latest findings of professional and college sportsmen have directed a change in proposals. As per the 2019 position announcement of the Sports Cardiology Unit of the European Association of Preventive Cardiology, graded resumption of sports and exercise is recently taken into account for minor infections, while a limit of exercises for three months is even now suggested for individuals with assumed myocarditis (Table 2).

The treatment of postexposure COVID-19 with persistent myocarditis is still a hotly debated topic. The European Society of Cardiology (ESC)55 and American Heart Association (AHA)55 have proposed EMB for patients with complex (non-COVID-19 individuals) myocarditis (i.e., unexplained dilation of left ventricle associated with significant dysfunction, critical tachy, and bradyarrhythmia, troponin leak continuation) to help guide particular medication options (e.g. antivirals vs immunomodulatory therapy).

There are currently no COVID-19 guidelines on this; however, countless reviews are being conducted to determine the best effective managing technique. The effectiveness of oral nonsteroidal anti-inflammatory medications and also colchicine for COVID-19-associated pericarditis is also being investigated.

Patients with postexposure COVID-19 ACS are usually handled according to the AHA and the ESC recommendations, which were published in 2014 and 2020 separately. Likewise, heart failure medication is focused on making the best use of available medications at the time they are needed, according to recommendations. There are presently no available studies on the effectiveness of long thromboprophylaxis after serious COVID-19; still, several interventional studies (e.g., STIMULATE ICP, HEAL-COVID-19) are presently in progress to fill this void.

The management of protracted COVID-19 is essentially supportive once major CV, as well as other organ pathology, has been ruled out given the substantial link between obesity and extended COVID-19, calorie restriction, nutrition, targeted categorized exercise, decreased stress, and excellent sleep hygiene may be advantageous in the lengthy run. There’s mounting evidence that it can help with vascular dysfunction, systemic inflammation and metabolic syndrome. In addition, a pragmatic, comprehensive approach that is focused on symptom relief may be required. Nonpharmacological treatments for dyspnea include pulmonary rehabilitation,61 respiratory exercises,62 and alternative therapies64 (for example, singing therapy,65 body rotation, acupuncture, and stretching). Individuals who are sent back to work may advantage from a phased arrival, which allows them to gradually rejoin work after a period of mental and physical rehabilitation. Initial medical appointments for mental well-being assessment behavioral therapy may be advantageous to certain patients, provided that psychosocial issues are a key indicator of partial healing. Dysautonomia and POTS can be debilitating for sufferers.66–69 Correcting reversible sources (heat, dehydration), optimizing long-lasting illness management, and educating patients are all important aspects of POTS care. β-blockers may be beneficial in the treatment of palpitations in some patients.
After prolonged bed rest and graded exercise programs, urging patients to adopt an erect position may help to alleviate postural complaints. Reduced peripheral venous pooling may relieve symptoms of orthostatic hypotension with compression pantyhose-style stockings with a 30–40 mm Hg counter pressure. Pharmacological therapy (such as fludrocortisone, ivabradine, midodrine, com

<table>
<thead>
<tr>
<th>Table 2: Summary of all the relevant cardiac investigations and roles in post-COVID-19 management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mode of investigation</strong></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
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<tr>
<td>Echocardiography</td>
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<td>MRI</td>
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<tr>
<td>Cardiopulmonary exercise test</td>
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<td>CT pulmonary and coronary angiography</td>
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<tr>
<td>Cardiac single photon emission CT</td>
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<tr>
<td>ECG monitor</td>
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<tr>
<th>Table 3: Examples of vast (n &gt; 400) prospective observational analyses evaluating COVID-19-related cardiovascular effects throughout short and long periods</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NCT number</strong></td>
</tr>
<tr>
<td>NCT04465552</td>
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methylidopa, and clonidine may be used if symptoms continue despite adherence to the aforementioned procedures.25

**CONCLUSION**

Our existing knowledge of pathophysiologic causes and medications of choice is inadequate, but there is reason to be hopeful. Numerous international and national research endeavors are underway to unravel the disease’s intricacies. The significant prevalence of cardiac symptoms, as well as other organ presentations, emphasizes the importance of multispecialty input, a strategy that is expected to benefit other chronic diseases as well. Patients’ fears and anxieties could be alleviated by proactive screening and investigation, if necessary.

Various rehabilitation programs (face-to-face and telemedicine) for the medications for breathing difficulties, fatigue, and cognitive decline, as well as the cognition-targeted therapeutic way (e.g., transcranial stimulation), metabolic modulators (like niagen), immunomodulatory medications (e.g., tocilizumab, steroids, atorvastatin, laranilubmab, colchicine), antifibrotic managements (e.g., pirfenidone and apixaban). Further, 730 reports interrelated to COVID-19 are listed on ClinicalTrials.gov and the World Health Organization. Around >80 place a high priority on long-term CV results. Table 3 lists a few research with 400 or more participants as examples.

To ensure long-term service running in these difficult economic periods, significant efforts must be made to obtain the correct balance between patient benefits and cost-effective investigations. Finally, lengthy COVID-19 will amplify the massive inequalities in healthcare facilities shown by COVID-19, a challenge that necessitates worldwide humanitarian labor to boost and fund fair approach to healthcare, social as well as welfare backing, and vaccinations around the world. The devastating impact of COVID-19 on global economies and healthcare has probably been one of humanity’s deadliest calamities in recent decades. COVID-19 survivors are in the hundreds of millions worldwide, with some claiming inadequate recovery months after the serious illness, which is known as long COVID-19. Chest pain, exhaustion, brain fog, breathlessness, headaches, and palpitations are all continual reminders of the virus’s destruction and the need to be cautious of any long-term effects. Cardiometabolic risk factors should now, more than ever, be a top main concern for medical doctors, as their potent role in exacerbating COVID-19 ailment acuteness has been conclusively demonstrated. The explanation of long COVID-19, the epidemiology of manifestations of cardiopulmonary consequences in the framework of long COVID-19, the pathophysiological ways for chronic and acute CV injury ancillary to SARS-CoV-2 infection, management, as well as directions for further future study are all discussed in this review.

**STATEMENT OF DECLARATION**

**Consent to Participate**

All the authors mutually agree to participate in this work.

**Consent for Publication**

All the authors mutually agree to submit the manuscript for publication.

**Authors’ Contributions**

Conceptualization—Debasish Ghosh, Rajdeep Ghosh; Formal analysis and investigation—Ullash Basak, Lakshmi Chakradhar Yarlagadda, Rajdeep Ghosh; Writing—original draft preparation—Ullash Basak, Lakshmi Chakradhar Yarlagadda, Debashish Ghosh, Manab Senapati, Rajdeep Ghosh; Writing—review and editing—Ullash Basak, Rajdeep Ghosh; Supervision—Rajdeep Ghosh.

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**References**

Post-COVID-19 Cardiovascular Sequelae and Myocarditis

In hypertensive patients with CAD

Initiate with

**Tazloc-Beta 25**

Telmisartan 40 mg + Metoprolol Succinate 25 mg PR

**Assured Control on Sympathetic Over Activity**

74% HCPs Prefer the Combination of Telmisartan + Metoprolol

- Control over Heart Rate
- 24 Hour BP Control

1. Data on file

In hypertensive patients with CAD

**Tazloc-Beta 50**

Telmisartan 40 mg + Metoprolol Succinate 50 mg PR

**Superior Cardiovascular Protection**

In Post PCI

METOPROLOL & TELMISARTAN

Reduces risk of

- MACE
- Recurrent MI

In patients with hypertension & diabetes,

**Tazloc®-AM**

Telmisartan 40/80 mg + Amlodipine 5 mg

**The Complete Protection**

**AMLODIPINE** reduces 48% urine micro-albumin levels within 12 weeks

---

*In comparison to other anti-hypertensive drugs*

<table>
<thead>
<tr>
<th>Microalbumin (mg/day)</th>
<th>Before treatment</th>
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<td>AMLODIPINE</td>
<td>18.39</td>
<td>8.96</td>
</tr>
<tr>
<td>OTHER ANTIHYPERTENSIVE DRUGS</td>
<td>9.23</td>
<td>8.91</td>
</tr>
</tbody>
</table>

CONSENSUS STATEMENT

Scoring System for the Use of Nebulizers in the Primary Care Settings: An Expert Consensus Statement

Surinder K Jindal1, Shrikant Pawar2, Ashfaq Hasan3, Aloke Ghoshal4, Raja Dhar5, Subodh K Katiyar6, K S Satish7, Deepak Talwar8, Sundeep Salvi9

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ABSTRACT

Background: The use of nebulizers is an important and useful method for delivering drugs to the lungs in patients with various airway and lung parenchymal disorders. They are primarily used in patients with acute symptoms and in a selected group of patients for maintenance treatment. Its use has increased, especially during the coronavirus disease 2019 (COVID-19) pandemic. To ensure the appropriate use of nebulizers by primary care physicians and to guide them, we aimed to develop a simple nebulizer use score.

Methods: An expert working group (EWG) of pulmonologists were formed who using a semi-Delphi method, developed a list of variables and a cut-off score to decide when to use nebulizers. We started with a total of 55 variables that were developed through an exhaustive review of the literature. These were further reduced to smaller numbers that had the maximum score as well as concordance with the EWG. The scores ranged from 1 to 10 (completely disagree to completely agree), and only those above 7.5 were selected.

Results: A total of 8 variables with the highest scores were selected (Table 1), which had a total maximum score of 40. A score of <15 was suggested to indicate no use of nebulizer and >20 to suggest definite use of nebulizer. A score between 15 and 20 was suggested for physician judgment. A separate table of 12 conditions was made where the use of nebulizers was mandatory.

Conclusion: This first-of-its-kind nebulizer score can be used by primary care physicians to decide which patients should be put on nebulizer treatment.

INTRODUCTION

The inhalation route is the most natural route of drug delivery to the lungs. It is the safest, fastest, and most effective route and constitutes the cornerstone for treating patients with a variety of respiratory conditions. Various devices have been developed to deliver the drug directly to the lungs, which include pressurized metered-dose inhalers (pMDIs), dry powder inhalers (DPIs), breath-actuated metered-dose inhalers (MDI), and nebulizers. Inhalation therapy is primarily recommended for all patients with asthma and chronic obstructive pulmonary disease (COPD) (bronchodilators and corticosteroids), but is also used to treat pneumonia and cystic fibrosis (antibiotics), surfactant deficiency (surfactant) and other lung diseases.

Nebulization is an important and useful route of delivering drugs to the lungs in patients with various airway and lung parenchymal disorders. They are primarily used in the treatment of acute exacerbations of asthma and COPD because of their ease of use in patients who are breathless. However, they are also used in the maintenance treatment of obstructive airway diseases, both in the hospital setting as well as at home in a selected group of patients. Some drugs can be delivered only by the nebulization route and have no alternatives. In patients, it is important to ensure that the nebulizers are not misused (either underused or overused).

During the COVID-19 pandemic, home nebulization has gained increased popularity as it has been relatively easy to make people learn its use than the use of a MDI with a spacer, especially on teleconsultation without physically meeting the patient. Nebulization requires minimal or no direct cooperation from the patient and can be administered by a caregiver or a family member. During this COVID-19, the surge in the use of nebulizers has been somewhat worrisome because of the fear of increased transmission of infection due to the spread of the virus in the environment during nebulization. However, this perceived risk is not supported by any objective evidence. Moreover, a systematic review of 22 studies reported no conclusive evidence of viral transmission by the nebulizer.

We considered it important to clearly define the indications when nebulization can be safely employed in both non-COVID-19 and COVID-19 patients. Deciding the key conditions for the rationale use of nebulizers would prevent their overuse and thereby the ill effects. We attempted to define a method based on the assessment of a simple clinical score that could be utilized in primary-care practice to decide whether to use the nebulized drugs or to avoid them.

Nebulizers are misused in clinical practice (both overuse or underuse) largely because of a lack of guidelines as to when nebulizers can or should be used in place of pMDIs or DPIs. The aim of this exercise was to develop a list of key conditions and a scoring system that could help general practitioners assess the requirement of domiciliary nebulization and help them decide which patients are likely to benefit from the use of nebulized medications.

METHODOLOGY

This document was developed as a clinical expert consensus statement by a panel of nine experts from the field of respiratory medicine. It reflects key conditions and scoring for the use of a nebulizer both during an epidemic/pandemic situation or otherwise. We first performed an extensive literature review of a total of 729 articles. Please refer to the link for more details.

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published in Pubmed, Google Scholar, and Google on the conditions that determine the use of nebulizers at domiciliary and hospital setups. Out of 729 articles whose full text we reviewed, 63 articles were found relevant to the topic that listed variables that could be used for deciding the need for nebulization.

A list of 55 "key conditions" deciding the nebulizer use and related information was extracted, which mainly covered the conditions related to: (1) the patient’s disease and its severity; (2) presence of comorbid conditions; (3) age; (4) physical and mental condition of the patient; (5) the need of aerosolized drug delivery system and their limitations to using the pMDI, DPI, and nebulizers. The 55 key conditions/criteria were further combined, and those that seemed to have the highest value (as evaluated by SKJ, SP, and SS) were further reduced to 20 key conditions. All the 20 conditions were then sent to the expert panel to score on a Likert scale from 1 to 10 using the following criteria: 1–2 strongly disagree, 3–4 mostly disagree, 5–6 agree, 7–8 mostly agree, and 9–10 completely agree. Expert members were encouraged to score them as single points (Flowchart 1). An additional five questions were developed by SKJ based on disease type and severity score, which also underwent the same process as above.

An internal review was performed on the selection of the most appropriate “key conditions” which would help to decide the use of a nebulizer. The review resulted in the identification of 20 key conditions with the scores for respective conditions.

In the second stage, both the list of key conditions and scoring separately developed were shared with all the expert members using the Delphi process (Flowchart 1). At the end of the Delphi process, the comments from all the experts were reviewed and collated for discussion during the consensus meeting. The average score was computed and was ranked from the highest score (strongly agree—score 10) to the lowest score (strongly disagree—score 1), and the same was used to develop three tables based on consensus from all panelists. Finally, the panel agreed upon an 8-point clinical score to decide the use of nebulizers based on the total score.

After the completion of the Delphi process, the consensus meeting was held online using the Zoom platform. The outcome of the Delphi process was discussed and finalized.

The clinical scoring system consisted of 8-point criteria with different weights amounting to a total of 40 score points (Table 1). The total points given to a patient need to be added to reach a total score. It was decided by consensus to keep the cut-off score of 20. A patient with a score of 20 or more would most likely benefit from nebulization whenever inhalational treatment is required. On the other hand, one may avoid nebulization for a patient who has a total score of <15 points. A nebulizer can be used depending on the clinical judgment of the medical practitioner and the disease severity of patients if the total score is between 15 and 20. At the end of this article, we have listed five case scenarios explaining how the scoring system can be used to decide whether nebulization therapy would be appropriate or otherwise.

We also listed clinical conditions where there is no alternative to nebulization whenever inhalational treatment is required (Table 2). Similarly, we made a list of drugs that can only be given by the nebulization route (Table 3).

**Discussion and Conclusion**

Inhalational administration of drugs is an essential mode of therapy for several lung diseases, particularly for emergency use for sick patients. pMDIs, DPIs, and nebulizers have their own advantages and disadvantages. Nebulization is an effective method of drug delivery to the airways and the lungs but generally requires a larger dose of drugs than with inhalers. Nebulizers are not recommended where pMDIs and DPIs are clinically preferred, for example, for conditions like mild–moderate asthma and COPD.

Nebulization is generally reserved for either severe and acute conditions or when inhalers cannot be used for various reasons. There has been an obvious lack of clarity on the safe use of domiciliary nebulizers without increasing the risk of dissemination of infection from contagious diseases, especially during an epidemic. Unlike all aerosol-generating procedures, which are recommended not to be used or to be used...
with caution during the current COVID pandemic, nebulizers are believed to be very useful, especially in the management of acute respiratory conditions. There are algorithms that have been developed to guide medical practitioners who practice in primary care settings on when to use the nebulization of drugs as the preferred mode of inhalational therapy. A previous consensus document on home nebulization has been published for the maintenance treatment of obstructive airway diseases. Nebulizers are often the drug delivery route of choice used in the hospital or clinic setting to manage severe and acute exacerbations of asthma and COPD. Nebulizers can also be used at home for maintenance therapy in patients who cannot use inhalers.

### Table 1: Scoring criteria with different assigned scores

<table>
<thead>
<tr>
<th>No.</th>
<th>Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Disease-specific</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Asthma</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>COPD</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>Disease severity (asthma or COPD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mild-to-moderate</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>Patient previously using inhalers with the benefit</td>
<td></td>
</tr>
<tr>
<td></td>
<td>pMDI, pMDI + spacer, and DPI</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Nebulizer</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>Noncompliance with the use of pMDIs with spacer and DPI or persistent use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>of nebulizers, despite best efforts to encourage the use of pMDIs or DPIs</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>in patients</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Distressing or disabling breathlessness despite maximal therapy with</td>
<td></td>
</tr>
<tr>
<td></td>
<td>inhalers and feels better with a nebulizer</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>Severe coexisting COPD in patients with lung cancer</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>Inability to inhale quickly and deeply using a DPI despite best efforts</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>to train patients in DPI usage</td>
<td></td>
</tr>
</tbody>
</table>

Only for patients with COVID-19/other viral infections.

8   COVID-19 positive/patients with other contagious viral infections.

*If the patient is already on a pMDI or DPI and uses it correctly and is happy to continue with that, we should encourage them to use that.

Total maximum score 40

Recommended cut-off scores: <15, nebulizer will not be necessary/useful; >20, nebulizer will likely be necessary/useful; 15–19, a nebulizer can be used depending on clinician judgment

### Table 2: Conditions where nebulizers must be used (no need for scoring)

| 1   | Drugs whose inhalational forms can be delivered only by the nebulizer route (Table 2). |
| 2   | Acute exacerbations of asthma or COPD requiring hospitalization.                  |
| 3   | Altered mental state/cognitive decline/confused state requiring inhalation therapy. |
| 4   | Patients who are inadequately controlled on DPIs or MDIs need high doses of inhaled bronchodilators or corticosteroids. |
| 5   | Lack of coordination while using pMDI despite best efforts to train in the pMDI technique. |
| 6   | Visual factors that may limit the ability to use DPIs and pMDIs, such as macular degeneration, cataracts, or glaucoma. |
| 7   | Dexterity issues such as Parkinsonism or stroke.                                  |
| 8   | Hand arthritis in elderly patients (the use of pMDI or DPI use should be encouraged if assisted inhalation for pMDI or DPI is possible through caregivers). |
| 9   | Non-CF bronchiectasis in patients requiring inhaled antibiotics.                 |
| 10  | Bronchiolitis in patients requiring inhaled epinephrine or antiviral drugs.      |
| 11  | Cystic fibrosis (antibiotics and mucolytics).                                    |
| 12  | Pulmonary arterial hypertension in patients requiring inhaled nitric oxide and prostacyclin. |

Although nebulizers generate aerosols, they do so from the nebulization chamber containing the drug, and unless that is contaminated with the virus, it will not transmit the severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) infection to others. Concerns were earlier raised for aerosols being generated from the patient’s cough following the use of nebulizers as a potential source of viral transmission. However, a systematic review of 22 articles, including seven case series and seven simulation-based studies, reported that although case series reported concerns of transmission risk and droplet dispersion with virus recovery, there was no conclusive evidence to suggest that the use of nebulizers increases the transmission of coronavirus. The Centers for Disease Control, United States of America, recommends appropriate safety measures to be followed during the use of the nebulizer, such as the use of an N95 mask, eye protection, gloves, and a gown for the healthcare provider (HCP) in the acute emergency setting in the hospital. Visitors or relatives should not be present during the nebulization process, and the room surfaces and nebulizer equipment should be properly disinfected after use. Also, patients do not need to be transferred to a higher level of care solely for the purpose of providing nebulizer treatment. HCPS should also follow appropriate hand hygiene measures when helping patients remove nebulizers and oxygen masks.

The scoring system described in the present study is based on the review of the literature and a Delphi process with experts from across the country in the field of respiratory medicine. None of the experts had any conflicts of interest to declare. The scoring does not apply to the use of drugs, such as surfactants, inhaled antibiotics, and mucolytics, which can only be delivered by the nebulized route (Table 3).

In conclusion, the scoring system derived through a structured consensus process for deciding nebulization therapy is simple to use for general practitioners for the selection of patients with obstructive airway diseases such as asthma and COPD, both during the COVID as well as non-COVID periods.

### Case Scenarios

- A 68-year-old male shopkeeper has known COPD for over 10 years. During the COVID-19 pandemic, he develops acute exacerbation with fever and breathlessness. He was found to be COVID-positive (SARS-CoV-2) on a throat swab real-time reverse transcription polymerase chain reaction (RT-PCR) test. He was admitted to the local health center.
He had been previously admitted twice in the last year and frequently required nebulization. His oxygen saturation was 87%. Besides standard treatment, he required bronchodilator administration with the help of nebulization, but the physician was afraid of nebulization for fear of dissemination at home. How will you decide, and what decision will you make on this issue?

Answer: The patient has an acute exacerbation of COPD, presenting with breathlessness and requiring hospitalization. According to Table 2, point No. 2, this is an indication where nebulization is not required. For his hospital stay, he needs to be put on a nebulizer. No need to do the scoring here.

However, if the patient is now discharged home and the rest of the information remains the same, we could now use the scoring method as follows:

- Disease specific, COPD = 2
- Disease severity, severe = 4
- Previous use of nebulizers = 4
- Do not comply with MDIs = 6
- Better with inhalers = 7
- COVID-19 positive = 3


A 62-year-old businesswoman had poorly controlled diabetes for over 5 years. He suddenly developed a fever and breathlessness and was sick and air-hungry with arterial oxygen saturation of around 80% with features of sepsis. He was admitted to the local health facility. His airway secretion grew Pseudomonas aeruginosa sensitive to colistin. In addition to parenteral colistin, will you give colistin through the inhaled route?

Answer: Giving colistin through the inhaled route is off-label. According to Table 3, if the physician thinks it’s necessary, inhaled colistin can be given only by the nebulizer route. Therefore, there is no need to do the scoring here.

A 55-year-old female police officer with a history of asthma developed a fever and irritating cough for 2–3 days. Her oxygen saturation was stable at above 92%. She had previously been maintained on budesonide/formoterol DPI but had recently stopped treatment. She was found to be COVID-negative on a throat swab RT-PCR test. She was asked to restart her inhaled corticosteroids (ICS) and bronchodilators at home in addition to other drugs. The physician was wondering whether to give ICS/bronchodilators by nebulization. How will you decide, and what decision will you make on this issue?

Answer: Calculate the nebulization score as follows:

- Disease specific = 1.
- Disease severity = 1.
- Previous use of nebulizers = NA.
- Do not comply with DPIs = NA.
- Better with inhalers = 0.
- COVID-19 positive = 0.

Total score = 2. Nebulization = not required. Even if she had tested covid positive, the score would have gone up to 5, which meant nebulization was not required.

A 78-year-old farmer had a history of chronic cough and breathlessness for over 15 years. He also had Parkinsonism symptoms. He develops acute worsening of his condition with fever, cough, and breathlessness. He was found to be COVID-positive (SARS-CoV-2) on a throat swab RT-PCR test. His oxygen saturation was low—around 86%. He was admitted to the local health center. Besides standard treatment, he required inhaled bronchodilator administration. The physician was skeptical of nebulization for fear of dissemination in the surroundings. How will you decide, and what decision will you make on this issue?

Answer: Calculate the nebulization score.

Patient score:

- Disease specific, COPD = 2.
- Disease severity, severe = 6.
- Previous use of nebulizers = 7.
- Do not comply with MDIs = 6.
- Better with inhalers = 0.
- COVID-19 positive = 0.

Total score = 9. Nebulization = not required.

References:

Monosodium Glutamate (MSG) Symptom Complex (Chinese Restaurant Syndrome): Nightmare of Chinese Food Lovers!

Minal Shastri¹, Darshankumar M Raval², Vaishnavi M Rathod³

Received: 21 October 2022; Accepted: 05 February 2023

ABSTRACT
Chinese food, containing the ingredient monosodium glutamate (MSG) as the main additive agent, results in a variety of symptoms in susceptible individuals. The spectrum of symptoms ranges from headache, sweating, abdominal pain, and urticaria to angioedema in severe cases. This group of symptoms is known as MSG symptom complex or Chinese restaurant syndrome (CRS). We reported one such case with unique dermatological manifestations in a young male, developed on the consumption of Chinese food, noticed first-time as per our knowledge. An adolescent male presented to the Emergency Department with high-grade fever, cough, shock, congested throat, and generalized skin rashes. After giving the history of ingestion of Chinese food prior to symptom onset, we suspected him of a case of CRS; our diagnosis was further supported by raised absolute eosinophil count (AEC) and immunoglobulin E (IgE) levels in the blood. The patient was given intramuscular adrenaline and intravenous corticosteroid in the emergency department for anaphylaxis, followed by oral antihistaminic.

INTRODUCTION
Chinese food contains a particular ingredient as the major additive agent, MSG—a monosodium salt of glutamic acid, which is used in the dish to enhance the savour flavour known as Umami in Japanese. As glutamate is the main agent carrying flavor to the dish, MSG is used in several other food products such as canned foods, crackers, chips, etc.¹ Although recognized as a safe product by the Food and Drug Administration to be used in food items, some susceptible individuals are more prone to exhibit a group of symptoms within a few hours of the consumption of MSG. The presenting features range from headache, sweating, abdominal pain, giddiness, urticaria, as well as angioedema in severe cases. This group of symptoms is often called MSG symptom complex.²,³ In 1968, MSG—the food flavor-enhancer, was first linked to a series of benign and transient features through case reports, collectively known as the CRS.⁴ Here, we have reported a similar case in a young male who presented to us with angioedema and unusual dermatological manifestations.

CASE DESCRIPTION
An adolescent male with no significant past, medical, family or personal history presented to our tertiary care hospital with complaints of high-grade fever, cough, with expectoration, cold, change in voice, vomiting, and generalized rashes for the last 3 days. There were no complaints of chest pain, breathlessness, sore throat, diarrhea, abdominal pain, headache, burning micturition, altered sensorium, blurring of vision, or history of recent vaccination/insect bite.

On presentation to the Emergency Department, the patient had warm extremities with a nonrecordable pulse and blood pressure (Table 1). Considering the patient was in a state of shock (by excluding fluid overload), intravenous fluids were started along with intravenous antipryetic, antihistaminic, and antibiotic. Once the patient improved vitally (Table 1), further general and systemic examinations were carried out, suggestive of a congested and edematous posterior pharyngeal wall with edematous uvula, generalized rashes with peeling of skin (Figs 1 to 7), extensive ronchi in both lung fields, and normal other system examination with the absence of neck rigidity and Kerning’s sign. Therefore, considering this case as anaphylaxis, intramuscular adrenaline (0.5 mg—0.5 mL of 1:1000 solution) and intravenous corticosteroid (hydrocortisone 100 mg) were given in the emergency department.

Investigations
The routine investigations were suggestive of a high total count and raised C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) (Tables 2A and B). After stabilizing the patient, further history was evaluated, which revealed the patient had consumed Chinese food a day before the onset of the symptoms. Therefore, we suspected this case was a food allergic reaction, and further investigations were conducted to support our diagnosis. The subsequent investigations showed raised AEC and serum IgE levels, high creatinine kinase (CK) total and CK in skeletal muscle (CK-MM) levels, indicating an allergic reaction (Table 2C). When dermatology reference was sought for skin lesions, lesions were diagnosed as allergic rashes with miliaria crystallina.

Treatment
From history, general and systemic examination, investigations, and temporal association with the ingestion of Chinese food, we came up with the diagnosis of food allergic reaction, namely MSG symptom complex—CRS.

After giving a single dose of adrenaline and hydrocortisone, the patient improved and did not require further doses. On account of the high total count, the patient was treated with intravenous antibiotics along with oral antihistaminic for an allergic reaction for 5 days and was kept in observation. The dermatologist prescribed oral antihistaminic and local antibiotic ointment for the skin lesions.

After 5 days of hospitalization, the patient improved clinically with the resolution of skin rashes and with improvement in laboratory parameters, thus discharged with advice to avoid food causing this allergic reaction and contact the healthcare facility in case of further episodes.

Outcome and Follow-up
During the stay in the hospital, the patient improved clinically and did not develop a further episode of allergic reaction or anaphylaxis. His skin rashes were resolving without the development of new lesions. The patient was counseled about the nature of his disease and to avoid food items susceptible to causing him further such episodes. As this was

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Monosodium Glutamate Symptom

Table 1: Vital parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>On presentation to emergency room</th>
<th>After 1 hour</th>
<th>After 3 hours</th>
</tr>
</thead>
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<tr>
<td>Temperature (°F)</td>
<td>101.3</td>
<td>100.3</td>
<td>99.1</td>
</tr>
<tr>
<td>Extremities</td>
<td>Hot</td>
<td>Warm</td>
<td>Warm</td>
</tr>
<tr>
<td>Pulse (per minute)</td>
<td>Not palpable</td>
<td>134</td>
<td>96</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>Not recordable</td>
<td>90/50</td>
<td>100/60</td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td>Not recordable</td>
<td>95</td>
<td>98</td>
</tr>
</tbody>
</table>

Discussion

Chinese food products commonly contain a salt—MSG, as a flavor-enhancing ingredient. A susceptible person is prone to exhibit clinical features reactionary to MSG consumption, which includes headache, diaphoresis, flushing, tachycardia, palpitations, numbness, paresthesia, fatigue, and dizziness. These symptoms develop as early as 20 minutes following the consumption of Chinese products and last 24–48 hours. Physician consultation is required if the symptoms do not resolve after 48–72 hours or worsen, such as difficulty in swallowing, speaking, or breathing, and drooling of saliva, as severe cases of angioedema have also been reported.

The New England Journal of Medicine (1968) elaborates on the symptoms, such as the sensation of either burning or numbness at the back of the neck, spreading to both upper limbs and occasionally to the front of the thorax, which may be associated with

Fig. 1: Dermatological manifestations of CRS showing skin exfoliation on the nape of the neck

Fig. 2: Dermatological manifestations of CRS showing skin exfoliation on the anterior aspect of the neck

Fig. 3: Dermatological manifestations of CRS showing skin exfoliation in the left axilla

Fig. 4: Dermatological manifestations of CRS showing skin exfoliation in the right axilla

Fig. 5: Dermatological manifestations of CRS showing erythematosus and hyperpigmented lesions in the lower limb.

Fig. 6: Miliaria crystallina on the back

Fig. 7: Dermatological manifestations of CRS showing erythematous lesion on the neck
Monosodium Glutamate Symptom

Table 2A: Hematological, biochemical and serological investigations

<table>
<thead>
<tr>
<th>Investigations</th>
<th>On admission</th>
<th>On day 3</th>
<th>On day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (gm%)</td>
<td>14.8</td>
<td>12.4</td>
<td>12.1</td>
</tr>
<tr>
<td>Total count (per cumm)</td>
<td>19100</td>
<td>15,800</td>
<td>11,700</td>
</tr>
<tr>
<td>Differential count (N/L/E/M%)</td>
<td>87/8/0/1</td>
<td>72/23/4/1</td>
<td>70/28/1/1</td>
</tr>
<tr>
<td>(4% band cell present)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count (per cumm)</td>
<td>304,000</td>
<td>258,000</td>
<td>225,000</td>
</tr>
<tr>
<td>Urea (mg/dL)</td>
<td>35.1</td>
<td>36</td>
<td>38</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.97</td>
<td>0.93</td>
<td>0.75</td>
</tr>
<tr>
<td>Serum glutamic pyruvic transaminase (IU/L)</td>
<td>45</td>
<td>36</td>
<td>28</td>
</tr>
<tr>
<td>Serum glutamic-oxaloacetic transaminase (IU/L)</td>
<td>51</td>
<td>44</td>
<td>37</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU/L)</td>
<td>105</td>
<td>99</td>
<td>98</td>
</tr>
<tr>
<td>Bilirubin (T, D, ID) (mg/dL)</td>
<td>1.3, 0.4, 0.9</td>
<td>1.2, 0.4, 0.8</td>
<td>0.6, 0.2, 0.4</td>
</tr>
<tr>
<td>Urine routine and micro</td>
<td>NAD</td>
<td>–</td>
<td>NAD</td>
</tr>
<tr>
<td>Random blood sugar (mg/dL)</td>
<td>96</td>
<td>108</td>
<td>91</td>
</tr>
</tbody>
</table>

NAD, No Abnormality Detected

Table 2B: Serological and inflammatory markers

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR (mm/hour)</td>
<td>20</td>
</tr>
<tr>
<td>CRP (microl/mL)</td>
<td>12 (Positive)</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>132</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.6</td>
</tr>
<tr>
<td>Ionized calcium (mmol/L)</td>
<td>1.18</td>
</tr>
<tr>
<td>Total protein (gm/dL)</td>
<td>4.6</td>
</tr>
<tr>
<td>Serum albumin (gm/dL)</td>
<td>2.4</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>4.8</td>
</tr>
<tr>
<td>Antistreptolysin O</td>
<td>Negative</td>
</tr>
<tr>
<td>Serum widal</td>
<td>Negative</td>
</tr>
<tr>
<td>Dengue NS-1 antigen</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Table 2C: Specific investigations

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Result</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK–total (U/L)</td>
<td>618</td>
<td>Male—55–170 Female—30–135</td>
</tr>
<tr>
<td>CK-MM (U/L)</td>
<td>598</td>
<td>20–200</td>
</tr>
<tr>
<td>AEC (thou/ cumm)</td>
<td>400</td>
<td>0.02–0.50</td>
</tr>
<tr>
<td>IgE (IU/mL)</td>
<td>179.40</td>
<td>0–100</td>
</tr>
</tbody>
</table>

CRS, Chinese restaurant syndrome; NAD, No Abnormality Detected

Palpitation and generalized weakness as well, within 20 minutes of eating of MSG-containing food items. Tightening of the temporalis and masseter, raised pressure in the infraorbital region, headache, and other symptoms were also observed in the consumption of high concentrations of MSG in liquid items such as soups.

After two colleagues from Albert Einstein College of Medicine made sure that the clinical features were due to MSG, used liberally while making Chinese food, this finding was further supported by the analyzing group of students of medical school at New York University School of Medicine, who reproduced the features in volunteers through ingestion of tomato juice/broth rich in MSG. While conducting a study on 530 participants

with antihistaminic, which can also be used as prophylaxis, without the need for any specific treatment. However, severe cases, such as angioedema leading to difficulty in swallowing, speaking, or breathing, are treated with intravenous corticosteroids and intramuscular adrenaline, as similarly in our patient. History, general and systemic examination, investigations, and temporal association with the ingestion of Chinese food helped us to arrive at our diagnosis of CRS, which could have been missed otherwise.

Learning Points/ Take Home Messages

- Given the increased consumption of Chinese food, especially in the young generation, it is important to recognize CRS with a detailed history, general and systemic examination, and appropriate investigations in susceptible individuals presenting with symptoms and signs peculiar to the syndrome.

- Early recognition and appropriate treatment are necessary as severe reactions have been reported, which may result in fatal outcomes if not treated in time.

- Our patient presented with similar symptoms upon consumption of Chinese food, with raised AEC and serum IgE levels in the blood, with unique dermatological manifestation, which is not described in the literature on CRS as far as we are aware.

References

C A S E  R E P O R T

Dyke-Davidoff-Masson Syndrome with Recurrent/Refractory Seizures: A Rare Case in Adult

Sunil D Bhaisare1*, Abhijeet Gaikwad2, Gopal Gholap3, Aneesh V4, Balram Yadav5

Received: 30 November 2022; Accepted: 26 December 2022

A B S T R A C T

A 26-year-old left-handed female presented in the emergency ward with three to four episodes of convulsion, which started focally with secondary generalization. She had froth through the mouth, tongue bite, and mild postictal confusion for 1 day before hospitalization. She had a past history of stroke with hemiplegia right 23 years back with partial recovery. About 3 months after hemiplegia, she also had seizures, and since then taking medications for seizures. She had mild mental retardation with poor scholastic performance and left school after the fourth standard. On computed tomography (CT)—brain evaluation, he was found to have imaging features of Dyke-Davidoff-Masson Syndrome (DDMS). It is one of the rare causes of recurrent and refractory seizures in adults.

I N T R O D U C T I O N

D yke-Davidoff-Masson Syndrome (DDMS) presents as seizures, hemiplegia or hemiparesis, and mental retardation. However, mental retardation not always be present. The classical radio imaging feature described is hemiatrophy of the cerebrum, ventricular dilatation, and calvarial changes along with or without shift of midline structure to the affected side depending on whether brain insult was in utero or after the birth of a baby. This was first described by Dyke–Davidoff–Masson in 1933.1

Since then, only a few cases of DDMS have been reported in late childhood and adults.2–4

C A S E  D E S C R I P T I O N

A 26-year-old, left-handed female presented in the emergency ward with three to four episodes of recurrent convulsion starting on the right upper and lower limb, followed by secondary generalization. She had froth through her mouth, tongue bite, and mild postictal confusion for 1 day before hospitalization. She had a past history of mild mental subnormality with poor scholastic performance and left school after the fourth standard. She was receiving tab valproate 200 mg twice a day (BD), tab carbamazepine 200 mg BD, tab phenytoin 100 mg three times daily (TDS), and tab frisium 10 mg HS along with folic acid 5 mg once daily. There was no CT-brain report available of her childhood hemiplegia.

Clinically her hemodynamic and vital parameters were stable. Both carotids were felt and equal. No sebaceous nodules over the face, no nevus, no ash-leaf rash, or shagreen patch over a body part. She had right supranuclear facial palsy and hemiparesis with 4/5 power in the upper limb and 3/5 in the lower limb. Deep tendon reflexes on the right side were exaggerated, and the plantar was extensor. The left side was normal. The coordination and sensory examination were normal. Cardiovascular, respiratory, and abdominal system examination was normal. A routine investigation like complete blood count, kidney function test, liver function tests, serum sodium, serum potassium, and serum calcium were normal. Serum calcium was 6.1 mg/dL (reduced). TDM level of valproate was reduced to 26.47 (50–100). CT-brain revealed left cerebral atrophy and ventricular dilatation with no shift of midline structures which is suggestive of DDMS (Fig. 1). CT-angiography reveals no vascular occlusion or malformation. Along with the correction of calcium, we gave her intravenous (IV) levpirl 500 mg TDS, IV valproate 500 mg TDS, oral carbamazepine through RT 200 mg TDS, and tab. Frisium 10 mg Hs along with folic acid 5 mg daily. With this treatment also, for the first 3–4 days, she used to get two to three episodes of seizures, and then on the 5th day, she became seizure-free.

Fig. 1: Computed tomography (CT) brain showing left cerebral atrophy with right lateral ventricular dilatation with no shift of midline

D I S C U S S I O N

The first description of DDMS dates back to 1933 when Dyke–Davidoff–Masson described the plain skull radiographic and pneumoencephalographic change in a series of nine patients presenting with hemiparesis, seizures, facial asymmetry, and mental retardation.1 DDMS is caused by the cerebral insult that may occur in utero when the maturation of calvarium has not been completed or during early life (during birth or postnatally first 2–3 years) due to brain damage (usually traumatic).2 The etiological factors for DDMS have been postulated as trauma, inflammation, vascular malformations, or occlusion.2–4

When the insult occurs in utero, there is a shift of midline structures towards the side of the disease, and the sulcal prominence replacing the gliotic tissues is absent.5 This feature differentiates it from cerebral hemiatrophy, which occurs in early life. The atrophied cerebral hemisphere will have

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prominent sulcal spaces if the insult occurs after birth or after the end of sulcation.\(^7\) But in our patient, we were not able to postulate the exact cause for hemiatrophy as CT-angiography was normal, and there is no clear history of prenatal or postnatal insult. When the insult occurs \textit{in utero}, it could be due to gestational vascular occlusion primarily involving the middle cerebral artery (MCA) territory. Decreased carotid artery blood flow due to coarctation of the aorta can also cause cerebral hemiatrophy.\(^3\) Garg et al.,\(^6\) reported febrile seizures as a possible etiological factor for cerebral hemiatrophy, while MCA stroke by Sener and Jinkis.\(^7\)

Approximately one-third of patients with seizures/epilepsy present as refractory, requiring multiple antiepileptic drugs.\(^8\) Juvenile myoclonic epilepsy, Lennox–Gastaut syndrome, tuberous sclerosis, and bilateral cerebral palsy are some of the disorders which can present with mental retardation and refractory seizures. DDMS is one of the rare conditions presenting with recurrent/refractory seizures. Proper clinical history and CT-magnetic resonance imaging (CT-MRI) will provide a correct diagnosis. Inadequate therapy and precipitating factors like hyponatremia, hypocalcemia, hypomagnesemia, and hypoglycemia should also be considered in refractory seizures, as in our patient, she had hypocalcemia and a low therapeutic level of valproate. We corrected hypocalcemia and increased the dose of valproate, and subsequently, she responded.

Dyke-Davidoff-Masson Syndrome (DDMS) should be differentiated from basal cell germinoma, Sturge–Weber syndrome, linear nevus syndrome, Fishman syndrome, Silver–Russell syndrome, and Rasmussen encephalitis.\(^9\) Proper clinical history and CT-MRI findings will help in clinching the correct diagnosis.

The treatment is symptomatic and should target convulsion, hemiplegia/hemiparesis, and learning difficulties. The prognosis is better if hemiparesis occurs after the age of 2 years and in the absence of prolonged or recurrent seizures. Intractable disabling hemiplegia or seizures are the potential candidates for hemispherectomy, with a success rate of 85% in carefully selected cases.\(^10\)

Dyke-Davidoff-Masson Syndrome (DDMS) should be suspected in adults who have a past history of hemiparesis due to vascular, traumatic, or infective causes during early childhood. Radio imaging with CT- or MRI-brain usually reveals characteristic features of DDMS.

**References**


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DECT: A Novel Window in Gout Imaging

Shruti Bajad1, Dhaval Tanna2, J N Durga Rao Yadavalli3, Rajiva Gupta4

Received: 14 August 2019; Accepted: 06 February 2023

A 37-year-old hypertensive and diabetic male was presented with polyarthritis and nodular soft swellings over multiple joints of upper and lower limbs along with podagra. The patient had a strong history of taking alcohol around 100 mL/day on a regular basis. He was being treated for rheumatoid arthritis in view of rheumatoid factor positivity with disease-modifying antirheumatic drugs without any significant relief and underwent right total knee and left total hip replacement. His anticitrullinated peptide antigen was negative. His X-ray of both hands and feet showed multiple deformities with erosions (Fig. 1). His ultrasound sonography on both hands and feet showed variable-sized echogenic soft tissue nodular deposits with internal calcific foci with posterior acoustic shadowing seen around elbows, wrist, knee, and dorsal surface of bilateral first metacarpophalangeal joints. His dual-energy computed tomography (DECT) of both hands and feet showed numerous large urate tophi (green) along the whole extent of both wrists and hands (Figs 2 and 3).

Dual-energy computed tomography (DECT) is a new modality in the armamentarium of gout imaging which has witnessed a huge surge in its usage and availability. It is a noninvasive method of seeing monosodium urate (MSU) crystal deposits, especially in early gout. It works on the principle of differentiating material on individual absorption of X-rays at different photon energy levels (typically at 80 and 140 kVp).1

Data from a recent 40 patients study has determined its specificity of 0.83 [95% confidence interval (CI): 0.68–0.93] and the sensitivity to be 0.90 (95% CI: 0.76–0.97).2 Subclinical MSU deposits can also be detected in asymptomatic hyperuricemic patients.3 However, its use in follow-up of such patients is still questionable and it is important to locate true crystals and eliminate artifacts that are observer-dependent.

Fig. 1: X-ray of both hands showing multiple erosions and deformity

Fig. 2: Dual-energy computed tomography (DECT) of both feet showed numerous large urate tophi (green) along the whole extent of both feet

Fig. 3: Dual-energy computed tomography (DECT) of both hands showed numerous large urate tophi (green) along the whole extent of both wrists and hands

REFERENCES
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Walter Hess and Interbrain

Jayant Pai-Dhungat¹, Geeta Gore²

Walter Rudolf Hess (1881–1973), born in Northern Switzerland, and received his medical degree from the University of Zurich in 1906. Hess was trained as a surgeon and earned his PhD in 1908. He was also trained as an ophthalmologist and opened his own private practice in Switzerland. During these years, he developed the “Hess screen” for studying ocular imbalance. He left his lucrative practice as an ophthalmologist and went into research in physiology in 1912 under Justus Gaul (1849–1939). Hess was appointed Professor of Physiology and Director of Physiology at the University of Zürich in 1917 and later Director of the Physiological Institute, where he served until his retirement in 1951.

Hess became interested in the study of the autonomic nervous system; these nerves originate at the base of the brain (diencephalon) and extend throughout the spinal cord, controlling autonomic functions like digestion, respiration, and excretion. Diencephalon forms the central core of brain tissue (interbrain), which extends from the brain stem to the cerebrum and surrounds the third ventricle. It includes the thalamus, hypothalamus, and epithalamus (pineal region). Hypothalamus is a highly organized structure with many nuclei reflecting numerous important functions. It controls and integrates activities of ANS and is closely associated with the limbic system, and responds to complex stimuli such as stress.

Walter Hess used brain stimulation techniques with fine 0.25 mm diameter electrodes to stimulate or destroy specific areas of the brain in conscious cats that moved freely. He discovered that the seat of autonomic function was in the hypothalamus. Hess mapped the control centers for each function to such a degree that he could induce the physical behavior pattern of a cat confronted by a dog simply by stimulating the proper points on the animal’s hypothalamus. This way, Hess could induce behaviors from excitement to apathy, depending on the region of stimulation. When stimulating the anterior lateral part of the hypothalamus, he induced a fall in blood pressure, slowing of respiration and responses such as hunger, thirst, micturition, and defecation. On the other hand, stimulation of the posterior ventral part led to extreme excitement and angry behavior.

He also found that he could induce sleep in cats, a finding that was highly controversial at the time but later confirmed by other researchers. Hess’s mapping and localization of diencephalic function ultimately led to its use in treating patients with surgery for certain motor and psychological disturbances.

Walter Hess received the 1949 Nobel Prize for Physiology or Medicine, which he shared with neurosurgeon Egaz Moniz. Hess’s contribution was mentioned as—“For his discovery of the functional organization of the interbrain as a coordinator of the activities of the internal organs.”

Hess died in 1973 at the age of 92.

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Sensory Ataxic Neuropathy with Dysarthria and Ophthalmoplegia (SANDO): A Multisystem Mitochondrial Disorder

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\(^1\)Resident; \(^2\)Assistant Professor; \(^3\)Professor; \(^4\)Department of Neurology, Stanley Medical College, Chennai, Tamil Nadu, India

Mitochondrial diseases are clinically heterogeneous and have complex inheritance patterns resulting in incorrect or delayed diagnosis.\(^1\) We report a case of mitochondrial cytopathy with ataxic sensory neuropathy, dysarthria, and ophthalmoplegia in a middle-aged female.

A 36-year-old lady presented with insidious onset, gradually progressive neurological illness in the form of distal, symmetrical, flail weakness of both upper limbs and lower limbs (lower limbs > upper limbs) of 8 years duration, associated with numbness and paresthesias in all four limbs of 6 years duration.

Neurological examination revealed mild dysarthria, mild ptosis in the left eye, restriction of eye movements in all directions without double vision, absent deep tendon reflexes in lower limbs, and glove and stocking pattern of graded sensory loss for all modalities of sensations in all four limbs. Romberg's sign was positive.

Laboratory investigations revealed normal blood parameters without muscle/liver enzyme elevation. Vitamin B12 levels were normal. The vasculitic workup was negative. Nerve conduction test demonstrated severe sensory motor axonal neuropathy of all four limbs. Needle electromyography showed features of chronic denervation. Magnetic resonance imaging brain was normal. Muscle biopsy of peroneus brevis muscle, demonstrated ragged red fibers and COX-negative fibers, features suggestive of mitochondrial myopathy. Superficial peroneal nerve biopsy shows features of severe axonal neuropathy.

The term “sensory ataxic neuropathy with dysarthria and ophthalmoplegia” syndrome is characterized by an adult-onset severe form of ataxic sensory neuropathy, dysarthria, and chronic progressive external ophthalmoplegia,\(^2\) results from mitochondrial dysfunction and is due to mitochondrial deoxyribonucleic acid depletion in muscle and peripheral nerve. The phenotype is largely variable.\(^3\) Mitochondrial disorders should always be considered in the differential diagnosis of neurological diseases with multiaxial involvement (Fig. 1).

Experience in Conducting a National Course in Advanced Clinical Epidemiology from a Superspeciality Tertiary Healthcare Institute

Tushar Prabhakar\(^5\), Kanica Kaushal\(^5\)

\(^5\)Senior Resident; \(^5\)Assistant Professor, Institute of Liver & Biliary Sciences (Deemed to be University), Delhi, India

Clinical epidemiology is an integral part of the widely accepted evidence-based system of healthcare delivery. However, to ensure the utilization of the full potential of epidemiological research in guiding public health policies and thus saving lives in the future, it is important that all those related to the healthcare system are acquainted with the broad concepts of clinical epidemiology.\(^7\) With this intent, the Department of Clinical Research and Epidemiology at the Institute of Liver and Biliary Sciences (ILBS), New Delhi, India, organized a 3-day virtual short course on “advanced clinical epidemiology.”

The course was aimed at young faculty members in public health, community health specialists, as well as researchers, epidemiologists, scientists, medical officers, PhD scholars, residents of medicine, and allied health professionals.

It primarily included four-course modules, namely study designs and bias, randomized controlled trials, statistical significance and summarizing data, and observational studies and diagnostic test studies. It also included advanced topics like literature search strategy and an introduction to the Grading of Recommendations Assessment, Development, and Evaluation approach. These encompassed a total of 10 didactic, interactive lectures and discussions that were taken up by distinguished speakers from ILBS, Delhi, India; Postgraduate Institute of Medical Education and Research, Chandigarh, India; University College of Medical Sciences, Delhi, India; All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India; INCLEN Trust International, Delhi, India; and National Institute of Epidemiology, Chennai, Tamil Nadu, India.

Over 800 participants from over a hundred institutes across the country enrolled themselves for the short course. The lectures were conducted online via the Zoom platform, and each was followed by either a hands-on exercise, online polls, or discussion using the

Fig. 1: Restriction of eye movements in all directions (external ophthalmoplegia)
live chat feature of Zoom or Google survey forms. A live screen showing poll results in real-time helped in identifying potential lacunae in knowledge.

Feedback showed an overall appreciation for the choice of topics and their critical significance in their respective fields. Overall, the varied participation and their steady interest throughout the duration of the course reiterated the fact that concepts of clinical epidemiology provide a foundation for clinical observation and interpretation that lead to valid conclusions in order to improve medical decision-making.²

REFERENCES
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