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HIV/AIDS and ART: Its Implications to Metabolic Abnormalities

Amar R Pazare

Introduction

Although HIV virus is known to mankind since the last four decades, there are many advances in understanding the virus, its manifestation, and its therapy. With the evolution in drug therapy for HIV, morbidity and mortality in people living with HIV/AIDS (PLHA) drastically reduced. Nowadays very few PLHA present with opportunistic infections and HIV/AIDS turned into chronic manageable disease from one of the dreaded diseases in the past.

As the longevity of PLHA increased drastically, they present with many chronic complications like malignancy, non-opportunist infections, cardiovascular diseases, and metabolic disorders.

Metabolic abnormalities include lipid abnormalities, insulin resistance, increased blood sugar, increased body mass index, lipodystrophy, hypertension, and increased waist circumference, and it is studied and published by many authors.

Lipid Profile

Lipid abnormalities can occur due to HIV infection itself or drugs used for treatment. Studies have shown that PLHA without antiretroviral therapy (ART) has low total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) but increased triglycerides. Increased level of interferon-α, C-reactive protein, and interleukin 6 (IL-6) is responsible for chronic inflammation which may cause an increase in the rates of basal lipolysis and hepatic lipid production.

Pallab Sinha, Nandini Chatterjee, Souvik Ghatak et al. in the present JAPI journal showed a lower level of TC in treatment-naive PLHA compared to PLHA on ART. They further clarified that TC is increased significantly in PLHA on protease inhibitor (PI) —based regime compared to non-PI-based regime.

Antiretroviral therapy, especially PIs, is responsible for low HDL-C, high LDL-C, and high TC. PIs inhibit adipocyte differentiation and lipogenesis and lower the hepatocyte chylomicrons clearance. It increases triglyceride synthesis in the liver.

Effect of ART Drugs on Lipid Profile

- All nucleoside reverse transcriptase inhibitors (NRTIs) except tenofovir increase LDL-C and triglycerides.
- Non-NRTIs, efavirenz increases TC and triglycerides, while nevirapine has little effect on lipid profile.
- Enfuvirtide did not have any effect on lipid levels.
- Entry inhibitors, maraviroc improves the lipid profile of patients with dyslipidemia.
- Integrase strand transfer inhibitors are safer for lipid profile compared with PI.

Hyperglycemia and Insulin Resistance

Many studies have shown that PLHA with or without ART developed hyperglycemia and insulin resistance over time. The prevalence of diabetes or milder glucose metabolism disorders in PLHA is 2–14%. The D:A:D: study (Data Collection of Adverse events on Anti-HIV Drugs), one of the largest studies on PLHA, showed an incidence of type 2 diabetes mellitus (T2DM) of 4.2 per 1000 person-years.

Multicenter AIDS Cohort Study (MACS) showed the incidence of T2DM was 14% in PLHA taking PI (ritonavir and indinavir) and NRTIs ( stavudine, zidovudine, and didanosine). In Veterans Aging Cohort Study (VACS), there is a correlation between diabetes and weight gain. For each 2.26 kg of weight gained, PLHA had a 14% increased risk of DM.

Low CD4 cell count and high levels of CRP and TNF receptors 1 and 2 are responsible for T2DM in these populations. Presence of lipodystrophy, HIV infection, coinfection with hepatitis C virus, decreased growth hormone, low CD4 count, and hepatic steatosis are responsible for insulin resistance. PLHA with lipodystrophy achieves lower insulin-stimulated glucose disposal, impaired glucose uptake by skeletal muscles, and increased intramyocellular lipids.

People living with HIV/AIDS on a PI-based regime developed insulin resistance and DM due to the inhibition of glucose transporter GLUT, and increased cytokines like adiponectin and leptins. Adiponectinemia is low in the PLHA population which is responsible for insulin resistance. NRTIs inhibit DNA polymerase-γ in mitochondria. Fat is not oxidized in the muscle and liver hence lipotoxic insulin resistance develops.

In the latest publication of the American Diabetes Association’s Standards of Medical Care in Diabetes (2016), advised blood glucose levels before and after 3 months of ART in PLHA.

People living with HIV/AIDS with lipodystrophy have increased levels of insulin and free fatty acids in the blood and over time may develop fatty liver disease.

Pallab Sinha, Nandini Chatterjee, Souvik Ghatak et al. in the present JAPI journal showed significantly higher fasting blood sugar in a PLHA in PI-based regime compared to non-PI-based regime.

ART and Lipodystrophy

Antiretroviral therapy can cause lipoatrophy or lipohypertrophy in the same patient. There is loss of peripheral fat (limbs and face) and deposited centrally (pot belly and buffalo hump). This is more marked in stavudine and zidovudine-containing regimen. Fat deposition also occurs in the liver and muscles. PLHA with longer duration of treatment, old patients, and low CD4 count are more prone to these complications.

Lipid Abnormalities and Heart Disease

One of the risk factors for atherosclerosis and coronary artery disease (CAD) is lipid abnormality. HIV itself can cause macrophage activation and endothelial dysfunction which may cause CAD. PLHA will have a 1.5–2-fold increased risk of CAD compared to HIV-negative individuals. They have a 4–5 fold increased risk of CAD at the end of 1 year.
Hypertension and Metabolic Syndrome

Many studies show that hypertension is more common in ART-treated than in ART-naive PLHA and HIV-negative subjects. Prevalence of hypertension may reach 96% in PLHA with metabolic syndrome. Aging, metabolic abnormalities, endothelial dysfunction, inflammation caused by HIV virus infection, and longer ART treatment may be responsible for hypertension in PLHA. PLHA on dolutegravir regime tends to get obesity and obesity increases the risk of hypertension and metabolic syndrome.\(^\text{18}\)

Nef, transcription protein (Tat), and glycoprotein 120 may have a link between metabolic syndrome and hypertension in genetically susceptible individuals. Inflammatory markers such as hsCRP and IL-6 are increased in PLHA with metabolic syndrome compared to PLHA without metabolic syndrome. This suggests that inflammation of metabolic syndrome has a role in the pathogenesis of hypertension in PLHA.\(^\text{18}\)

References

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An Observational Study on Metabolic Derangements in People Living with HIV

Pallab Sinha1, Nandini Chatterjee2, Souvik Ghatak3, Pranab Maity4*, Krisanko Das5, Sourin Mukherjee6, Avishek Guin7, Shantasil Pain8, Jyotirmoy Pal9

Revised: 20 July 2022; Accepted: 20 July 2022

ABSTRACT

Background: HIV infection is a global pandemic. The adult HIV prevalence in India is 0.22%. Successful therapy is transforming HIV into a chronic medical condition, and there are many metabolic complications. This study aimed to evaluate the metabolic abnormalities in people living with HIV (PLHIV) who were on antiretroviral therapy (ART) for at least 2 years and compare it with ART-naïve patients as well as the effect of protease inhibitor-based (PI-based) and non-protease inhibitor-based (non-PI-based) ART was assessed.

Methodology: Adult HIV-positive patients both ART-naïve and on ART for more than 2 years were included. Detailed history and clinical examination, including blood pressure and anthropometric measurements were done. This was followed by investigations like lipid profile including total cholesterol, triglyceride, high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), fasting plasma glucose, and hemoglobin A1c (HbA1c) estimation. Standard statistical tools were utilized to assess derangements and association to therapy.

Results: The study was conducted for 1.5 years in a tertiary care hospital. A total of 70% of the study population was male with mean age of participants being 43.2 years, 40% were ART-naïve, 37% received non-PI-based ART, and 23% PI-based ART.

The mean total cholesterol level and mean triglyceride value were significantly higher in the PI-based ART group than in the therapy-naive group. The ART-naïve group was seen to have more subjects with abnormally low HDL-C values. The PI-based ART study subjects were found to have a greater number of cases of glucose intolerance in relation to the rest of the two groups significantly (p-value < 0.001).

The LDL-C systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), and waist circumference had no association with the different ART regimens or with the HIV infection itself. CD4 T cell count at diagnosis in the three study groups was compared with all the variables of metabolic syndrome and no association was found.

Conclusion: Total cholesterol, triglycerides, and glucose levels are the main parameters found to be affected in PLHIV on therapy.

Journal of the Association of Physicians of India (2022): 10.5005/japi-11001-0109

INTRODUCTION

People living with HIV constitute an overwhelming 38 million individuals worldwide according to the Joint United Nations Programme on HIV/AIDS. The surveillance report published by National AIDS Control Organization (NACO) indicated the total number of PLHIV in India to be 23.49 lakhs in 2019. The adult PLHIV population of West Bengal in 2019 was reported to be 74,000.

Metabolic derangements are prevalent in a significant proportion of the population of PLHIV. These are due to HIV infection itself as well as seen due to its treatment with ART. Nucleoside reverse transcriptase inhibitor (NRTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), and PI all group of drugs are shown to be responsible for metabolic abnormalities seen in HIV, the extent being variable.

OBJECTIVES

- To study the metabolic abnormalities in PLHIV who are ART-naïve and compare with those who are on ART for at least 2 years.
- To compare the effect of PI-based and non-PI-based ART on metabolic parameters.

METHODOLOGY

Ours was a cross-sectional observational study. A total of 101 patients were selected from the ART center, ward, and outpatient department of a tertiary care hospital in eastern India in a span of one and a half years from February 2020 to October 2021. The study was approved by the Institutional Ethics Committee.

INCLUSION CRITERIA

Adult HIV-positive patients who gave informed consent. Diagnosis of HIV infection was done according to the diagnosis algorithm of NACO. Three groups were made:

- Antiretroviral therapy-naïve PLHIV.
- People living with HIV on ART for more than 2 years NNRTI based regimen—tenofovir lamivudine efavirenz (TLE).
- People living with HIV on ART for more than 2 years PI-based regimen—tenofovir lamivudine lopinavir/ritonavir (TLL/r).

EXCLUSION CRITERIA

Known patients of diabetes mellitus, hypertension, ischemic heart disease, dyslipidemia, metabolic syndrome at the time of diagnosis, known cases of liver disease, renal disease, nephrotic syndrome, and hypothyroidism.

Also, pregnant, very sick patients, and patients with opportunistic infections were excluded.

After screening the patients, according to the inclusion and exclusion criteria, those willing to give informed consent were enrolled. Detailed history and clinical evaluation including waist circumference, BMI, and blood pressure were recorded in the case report form. Reports of CD4 T cell count at diagnosis and fasting lipid profile including total cholesterol, triglyceride, HDL-C, LDL-C, fasting plasma glucose, and HbA1C were documented.

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Results were analyzed with proper statistical tests and methods to determine the significance level and power of the study.

**RESULTS**

A total of 101 participants were enrolled, 70% of whom were male with mean 2, 4, 6, 8, 10, 12 age being 43.2 ± 0.5 years. About 47.5% of patients belonged to the 41–50 years age group. Of these 40% were ART-naïve, 37% received non-PI-based ART, and 23% received PI-based ART (Fig. 1).

**Total Cholesterol**

Of the total patients, 76 (75.2%) had total cholesterol level below 200 mg/dL. Mean total cholesterol among the naïve, non-PI group, and PI group were 157.3 ± 34.2, 173.3 ± 36.1, and 218.4 ± 52.3 mg/dL, respectively.

A significant association was present between the ART types and total cholesterol level (p-value 0.002), and mean total cholesterol level was significantly higher in the PI-based ART group (218.4 ± 52.3).

**Triglyceride**

A total of 18% of the study population had a high-fasting triglyceride value.

The mean fasting triglyceride in the naïve, non-PI group, and PI group were 109.4 ± 25.2, 116.6 ± 18.7, and 175.4 ± 59 mg/dL, respectively.

About 60.9% of patients in the PI-based ART group had raised triglyceride levels whereas it was only 7.3% and 2.7% in the other two groups, respectively. So abnormal triglycerides were significantly more seen with PI therapy (p-value < 0.001).

**HDL-C**

The ART-naïve group was seen to have more subjects with abnormally low HDL-C values. In treatment-naïve group, 58.5% had abnormal HDL-C, whereas in the treatment group it is 29.7% and 39.1% in non-PI group and PI group, respectively. Abnormal HDL-C is significantly greater in the naïve group (p-value 0.033).

**Fasting Glucose**

In the non-PI based group, 16.2% of patients had abnormal fasting glucose levels (FBS >100), and in the PI-based group, it was 65.2% of patients. The association of FBS with ART was found to be statistically significant (p < 0.001) (Table 1).

The LDL-C in our study appeared to have no significant association with the different ART regimens or with the HIV infection itself (p-value 0.151). SBP, DBP, BMI, and waist circumference had no association with the type of ART in the three study groups. Also, CD4 T cell count at diagnosis in the three study groups was compared with all the variables of metabolic syndrome. In our study, no association was found.

**DISCUSSION**

This was a cross-sectional observational study which was aimed at finding any association between metabolic derangements, HIV infection, and its therapy.

The natural course of HIV infection is associated with particular imbalances in lipid levels. There is an initial decline in HDL-C followed by a decline in LDL-C. In more advanced cases, the triglyceride levels increase.

HIV infection has been found to be associated with dyslipidemia, hypertriglyceridemia, glucose intolerance, insulin resistance, and lipodystrophy.4 HIV infection leads to the suppression of certain genes necessary to extinguish inflammation. Thus a dysregulated inflammatory response is generated. HIV-infected monocyctic cells suppress the expression of tyrosine kinase RON—a negative regulator of inflammation. This is mediated by a ubiquitin-proteasome pathway of degradation of the molecule. The long-term inflammatory state acts as a metabolic risk factor for further complications.5

**Table 1:** Comparison of fasting cholesterol, triglyceride, and glucose among the treatment-naïve, non-PI-based, and PI-based treatment groups

<table>
<thead>
<tr>
<th>Blood parameter</th>
<th>Treatment-naïve (%)</th>
<th>Non-PI-based treatment (%)</th>
<th>PI-based treatment (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol (&gt;200 mg/dL)</td>
<td>12.2</td>
<td>19</td>
<td>46.5</td>
<td>0.002</td>
</tr>
<tr>
<td>Fasting triglyceride (&gt;150 mg/dL)</td>
<td>2.7</td>
<td>7.3</td>
<td>60.9</td>
<td>0.001</td>
</tr>
<tr>
<td>FBS (&gt;100 mg/dL)</td>
<td>0.02</td>
<td>16.2</td>
<td>65.2</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Recently soluble urokinase plasminogen activator receptor is emerging as a predictor of dysmetabolism in HIV6.

Standard treatment of HIV involves the combination of at least three antiretroviral drugs, prescribed as a fixed-dose combination like TLE or TLL/r. At present dolutegravir has replaced tenofovir though this was not used in our regimens ART acts as a double-edged sword since it can both reduce the HIV-related complications and aggravate the potential metabolic side effects. Impairment in glucose metabolism has been shown in drugs including NRTIs—zidovudine, lamivudine, stavudine, and didanosine, and NNRTIs—efavirenz as well as PI—indinavir and lopinavir/ritonavir.8 PIs lead to metabolic derangement by impairing the conversion of retinoic acid to cis-9-retinoic acid (leading to impaired peripheral fat storage, sequestration of body fat to central adipocytes, and hyperlipidemia and by inhibiting low-density lipoprotein receptor-related protein.9 Another study has shown PIs to directly inhibit GLUT-4 mediated glucose uptake in the cells.10 Efavirenz and zidovudine induce some toxicity through endothelial dysfunction.11,12

A study which was conducted in western India in a tertiary care facility emphasizes the effect of ART on metabolic profile. As tenofovir and efavirenz are the widely used major components in the ART regimens in India, that cause metabolic derangements, this study shows that tenofovir-based therapy has a higher prevalence of metabolic syndrome.4 A study from Spain on metabolic disorders in PLHV on ART shows stavudine (d4T) and lopinavir/ritonavir were associated with metabolic syndrome after adjustment for age and BMI. It was noted that specifically protease inhibitor was significantly associated with metabolic syndrome.7 Stavudine or didanosine are no longer used in our regimens hence their effects could not be studied.

In our study, total cholesterol was found to have a significant positive association with the PI-based ART group (p 0.002). A significantly high mean triglyceride value in the PI-based ART group was also found, p-value being <0.001. Similar studies were conducted...
by de Matos Almeida et al. and Idiculla et al. regarding the metabolic changes in HIV-positive patients who are on ART.13,14 They showed that PI use was associated with higher odds of developing dyslipidemia and glucose intolerance (odds ratio = 3.1; 95% confidence interval [CI] = 1.4–7.1).

Kerr et al. also confirmed the above hypothesis in the Asian population in patients taking ritonavir-boosted indinavir.15 It was also noted that there was a significant association between HDL-C and the treatment-naïve group (p = 0.033). Thus, inference can be made that HDL-C values tend to normalize after being treated with ART, irrespective of the type of treatment. The effect of ART on HDL-C was conducted in a study by Pereira et al. which showed the beneficial effect of efavirenz on HDL-C. In this study, in patients with baseline HDL-C ≤40 mg/dL, an increase in HDL-C from 31 ± 1 to 44 ± 2 mg/dL (95% CI 5.9–21.9; p < 0.01) was observed and remained throughout the follow-up period.16 The mean FBS in the PI-based ART group (108.60) was significantly greater than the other two groups, mean values in naive and non-PI ART groups being 81.97 and 88.81, respectively, which were below the cutoff normal value. About 65.21% of the PI-based ART group and 16.21% of the non-PI-based ART group had glucose intolerance. This is in confirmation to the studies conducted by de Matos Almeida et al. regarding the lipid and glycemic changes in HIV-positive patients who are on ART.

A study by Nduka et al.17 showed that exposure to ART is significantly associated with increased SBP and DBP levels, and increased risk of hypertension, regardless of study-level sociodemographic differences. This inference differed from our study, though we need to further examine this by increasing the power and duration of our study. Bhagwat et al.’s patients showed higher waist circumference increases in the raltegravir arm compared with PIs in the seropositive patients. Here, naïve patients served as controls. In our study, we found no association of therapy with waist circumference with our regimen and integrase inhibitors were not used.18

**Limitations**

Small study population, selection bias due to convenient sampling, and single-center-based study are the main limitations of the study. Also, it could not differentiate between the effects of individual antiretroviral drugs. Insulin resistance could not be checked due to time constraints and lack of availability of testing. A prospective study would have been better to assess the development of metabolic alterations in the study group with a continuum of data.

**CONCLUSION**

In developed as well as developing countries, metabolic complications impart significant morbidity and mortality in PLHIV. HIV-infected people are being successfully treated with ART and living longer. In the spectrum of disease, morbidity is shifting primarily from opportunistic infections and immune dysfunction to metabolic complications.

This study concludes that ART as well as HIV itself, both are responsible for metabolic alterations. Not all the components of metabolic syndrome are affected in all cases, rather each medication in the ART regimen has a unique mechanism in modifying the metabolic profile of the patient. A better understanding of this condition by further large-scale multicentric studies would be beneficial for the effective management of the condition.

**REFERENCES**

Barrett’s Esophagus: A Comparison Study between Two Cohorts of Gastroesophageal Reflux Disease

Krishandas Devadas, Bony George, Jijo Varghese, Atul Hareendran, Nibin Nahaz, Tharun Tom Oommen, Rathan Cyriac Joseph, Vijay Narayanan

Received: 21 November 2021; Accepted: 25 May 2022

**ABSTRACT**

**Introduction:** Barrett’s esophagus (BE) is a complication of gastroesophageal reflux disease (GERD). It is seen among 15% of GERD patients as per a population-based study by Ronkainen et al. Barrett’s has malignant potential and annual progression to carcinoma depends on the presence or absence of dysplasia. There are various risk factors for the development of BE. We compared two symptomatic cohorts of GERD patients from the same geographical area who were evaluated for the presence of Barrett’s and various factors that can contribute to Barrett’s.

**Materials and methods:** Cross-sectional study. Two GERD cohorts, one from Kottayam and the other from Trivandrum were taken. The presence of Barrett’s and the factors contributing to the development of Barrett’s were analyzed between the two groups. Since biopsy data of all patients were not available, endoscopically suspected esophageal metaplasia (ESEM) was taken as Barrett’s.

**Results:** 415 patients were enrolled for the study (203 from Trivandrum and 212 from Kottayam). 192 females (99 from Trivandrum and 93 from Kottayam), and 223 males (104 from Trivandrum and 119 from Kottayam). Barrett’s esophagus and especially long-segment Barrett’s were significantly more common in Kottayam than Trivandrum (68 vs 22 and 36 vs 9) (p-value <0.001). Among the factors that were traditionally thought to contribute to the development of Barrett’s esophagus, age (>50 years) was not statistically significant among the two cohorts (mean age of Trivandrum was 48 years and Kottayam was 49 years). Duration of GERD symptoms was significantly more in the Trivandrum cohort compared to Kottayam (p-value <0.001). Hiatus hernia and body mass index (BMI) were more common in Kottayam. There were no statistically significant differences in erosive esophagitis and antral gastritis (%age?) between the two cohorts.

**Conclusion:** Both Trivandrum and Kottayam belong to the same geographical area and are separated by a distance of only 150 km. The Kottayam cohort is more prone to develop distal esophageal carcinoma as the BE is more in Kottayam. This data also suggests the need for GERD registries so that high-risk population can be targeted and early intervention can lead to a decrease in the incidence of distal esophageal carcinomas.

**BACKGROUND**

Gastroesophageal reflux disease (GERD) is defined by Lyon consensus as “identification of esophageal mucosal lesion or troublesome symptom caused by gastroesophageal reflux.” Barrett’s esophagus is a complication of GERD and is seen among 15% of GERD patients.²³ Barrett’s esophagus should be diagnosed when there is an extension of salmon-colored mucosa into the tubular esophagus extending ≥1 cm proximal to the gastroesophageal junction with biopsy confirmation of columnar metaplasia (British Society of Gastroenterology guidelines). Various factors can contribute to the development of Barrett’s esophagus. It includes tobacco use,⁴ male gender, more than 50 years of age, symptoms of GERD for more than 5 years, central obesity, Caucasian race,⁵ family history of GERD,⁶ hiatus hernia, and metabolic syndrome.⁷ And among Barrett’s patients, the chance of malignancy is more for long-segment Barrett’s (2 cm) than short-segment one. Now the incidence of distal adenocarcinoma is increasing and the increasing prevalence of Barrett’s is a cause for the same. Esophagitis in contrast to Barrett’s esophagus is more related to environmental factors than genetic factors. In a country like India, resources are limited and data on GERD are very few. It is important to find out high-risk populations for Barrett’s so that early treatment and surveillance can decrease the incidence of distal esophageal carcinoma. Our aim was to compare two cohorts of GERD from similar geographical areas separated by 150 km and to find out whether there is a statistical difference between the two cohorts for the presence and pattern of Barrett’s esophagus as well as the difference in presence of factors that contribute to Barrett’s esophagus.

**Aim and Objective**

• To compare two cohorts of GERD patients with regard to the presence and type of Barrett’s as well as factors contributing to the development of Barrett’s esophagus.

**Materials and Methods**

A cross-sectional study was conducted in the Department of Medical Gastroenterology, Medical College Kottayam and Trivandrum. Every consecutive patient undergoing UGI scopy with severe symptoms of GERD or duration of symptom more than 5 years or those with symptoms of GERD not severe or duration <5 years based on patient request who are willing to give consent were taken up for the study. Kottayam cohort was collected between 2014 and 2015 and Trivandrum cohort was collected between 2017 and 2019, and the exclusion criteria were:

- Patients who are not willing to give consent;
- Patients who had upper GI malignancy.

Patients underwent UGI scopy and looked for the presence of pathological GERD and minimum of eight biopsies were taken from ESEM of >2 cm to look for the presence of columnar metaplasia suggestive of Barrett’s esophagus. For ESEM of 1–2 cm, four biopsies will be taken from four quadrants of circumferential lesion and one biopsy per centimeter will be taken from the tongue of Barrett’s. Patients with esophagitis grades B, C, and D repeat UGI scopy done after 8–12 weeks of proton pump inhibitor to look for underlying Barrett’s. Since the biopsy data of all patients are not available, ESEM was taken as Barrett’s.

**Results**

A total of 415 patients were enrolled in the study (203 from Trivandrum and 212 from Kottayam). Out of which 192 were females (99 from Trivandrum and 93 from Kottayam), and...
223 were males (104 from Trivandrum and 119 from Kottayam) (Table 1).

Age of onset (>50 years) was among the variables that contribute to the development of Barrett’s esophagus. The mean age of the Trivandrum cohort and that of the Kottayam cohort was not statistically significant suggesting that the high incidence of Barrett’s in Kottayam is not due to the age of onset of the cohort (Table 2).

The percentage of Barrett’s esophagus among the Trivandrum cohort of GERD was 10.8% (15% GERD have Barrett’s according to American College of Gastroenterology guidelines on Barrett 2015) compared to 32.1% in the Kottayam cohort and that was statistically significant (p-value of <0.001) (Table 3 and Fig. 1).

Among males and females also Barrett’s esophagus was more in the Kottayam cohort compared to the Trivandrum cohort and that was statistically significant with a p-value of <0.001 (Table 4).

Duration of symptoms like heartburn and regurgitation (duration of more than 5 years) was among the variables that contribute to the development of Barrett’s esophagus. The mean duration of heartburn was 23.2 months in the Trivandrum cohort compared to the Kottayam cohort of 4.6 months and that was statistically significant with a p-value of <0.001 (Table 5). The mean duration of regurgitation was 14.8 months in the Trivandrum cohort compared to the Kottayam cohort of 5.1 months and that was statistically significant with a p-value of <0.001 (Table 6). Duration of symptoms was more in favor of the development of Barrett’s esophagus from the Trivandrum cohort.

Other variables favoring the development of Barrett’s were BMI and hiatus hernia. The mean BMI of the Trivandrum cohort was 24.7 compared to Kottayam of 29.5 and that was statistically significant with a p-value of 0.022 favoring the development of Barrett’s in the Kottayam cohort (Table 7).

The percentage of hiatus hernia among the Trivandrum cohort was 12.3% compared to 25.9% of Kottayam and that was statistically significant with a p-value of <0.001. Favoring the development of Barrett’s in the Kottayam cohort (Table 8).

Among the variables favoring the development of Barrett’s esophagus, hiatus hernia and BMI were statistically significant in the Kottayam cohort, and the rest of the variables like duration of symptom was more in the Trivandrum cohort and variables like age of onset were not statistically significant. So as to find whether Barrett’s in Kottayam is independent of favoring factors, binary logistic regression was done and found that Barrett’s among Kottayam was independently more common among the Kottayam cohort with a p-value of

---

**Table 1: Male-female composition of both study cohorts**

<table>
<thead>
<tr>
<th>Sex</th>
<th>Trivandrum</th>
<th>Kottayam</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N %</td>
<td>N %</td>
<td>N %</td>
</tr>
<tr>
<td>Male</td>
<td>99 49</td>
<td>93 44</td>
<td>192</td>
</tr>
<tr>
<td>Female</td>
<td>104 51</td>
<td>119 56</td>
<td>223</td>
</tr>
<tr>
<td>Total</td>
<td>203 100</td>
<td>212 100</td>
<td>415</td>
</tr>
</tbody>
</table>

**Table 2: Mean age of study population from the Kottayam cohort and the Trivandrum cohort**

<table>
<thead>
<tr>
<th>N</th>
<th>Age in years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean SD</td>
</tr>
<tr>
<td>Trivandrum</td>
<td>203 47.7 13.6</td>
</tr>
<tr>
<td>Kottayam</td>
<td>212 48.9 12.2</td>
</tr>
</tbody>
</table>

**Table 3: Barrett’s esophagus among the Kottayam and Trivandrum cohorts**

<table>
<thead>
<tr>
<th>HPR Barrett’s esophagus</th>
<th>Trivandrum</th>
<th>Kottayam</th>
<th>Total</th>
<th>χ² df p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N %</td>
<td>N %</td>
<td>N %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>22 10.8</td>
<td>68 32.1</td>
<td>90 21.7</td>
<td>27.541 1</td>
</tr>
<tr>
<td>No</td>
<td>181 89.2</td>
<td>144 67.9</td>
<td>325 78.3</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>203 100</td>
<td>212 100</td>
<td>415</td>
<td></td>
</tr>
</tbody>
</table>

**Table 4: Barrett’s esophagus among men and women of the Kottayam and Trivandrum cohorts**

<table>
<thead>
<tr>
<th>HPR Barrett’s esophagus</th>
<th>Trivandrum</th>
<th>Kottayam</th>
<th>Total</th>
<th>χ² df p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N %</td>
<td>N %</td>
<td>N %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male Yes</td>
<td>13 13.1</td>
<td>34 36.6</td>
<td>47</td>
<td>24.5</td>
</tr>
<tr>
<td>Male No</td>
<td>86 86.9</td>
<td>59 63.4</td>
<td>145</td>
<td>75.5</td>
</tr>
<tr>
<td>Female Yes</td>
<td>9 8.7</td>
<td>34 28.6</td>
<td>43</td>
<td>19.3</td>
</tr>
<tr>
<td>Female No</td>
<td>95 91.3</td>
<td>85 71.4</td>
<td>180</td>
<td>80.7</td>
</tr>
</tbody>
</table>

**Table 5: Mean duration of heartburn among the Kottayam and Trivandrum cohorts**

<table>
<thead>
<tr>
<th>Heartburn duration in months</th>
<th>Trivandrum</th>
<th>Kottayam</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N Mean SD</td>
<td>23.2</td>
<td>4.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Table 6: Mean duration of regurgitation among the Kottayam and Trivandrum cohorts**

<table>
<thead>
<tr>
<th>Regurgitation duration in months</th>
<th>Trivandrum</th>
<th>Kottayam</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N Mean SD</td>
<td>14.8</td>
<td>5.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Table 7: Mean BMI among the Kottayam and Trivandrum cohorts**

<table>
<thead>
<tr>
<th>N BMI p</th>
<th>Trivandrum</th>
<th>Kottayam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>203 24.7</td>
<td>212 29.5</td>
</tr>
</tbody>
</table>
Barrett’s Esophagus: A Comparison Study between Two Cohorts of GERD

Discussion

We found that there is a definite regional variation in BE between two geographically close areas separated by only about 150 kilometers as the crow flies. Even though traditional risk factors like duration of heartburn and regurgitation was lower in the Kottayam cohort, they had a higher distribution of Barrett’s esophagus in people with symptoms of GERD. We noted a significantly higher BMI in the Kottayam cohort which could have been a risk factor for the development of BE. Hiatus hernia was also higher in the Kottayam cohort which could have led to increased reflux and progression to BE.

However binary logistic regression could not find a relation of the abovementioned risk factors with the presence of BE. So other risk factors may be in action. One such could be genetic differences. However since a genetic analysis was not done, we are unable to say with any certainty that genetic factors are at play to explain the differences.

However erosive esophagitis was similar among both populations suggesting that environmental factors are less likely to contribute to Barretts. Similar was the case with antral gastritis suggesting that environmental factors are less likely to contribute to the difference in Barrett’s among the two cohorts.

Conclusion

Both Trivandrum and Kottayam belong to the same geographical area and are separated by a distance of only 150 km. The Kottayam cohort is more prone to develop distal esophageal carcinoma as the Barrett’s esophagus is more in Kottayam. This data also suggest the need for GERD registries so that high-risk population can be targeted and early intervention can lead to a decrease in the incidence of distal esophageal carcinomas.

References


HPR Barrett’s esophagus is an independent risk factor in Kottayam.

Esophagitis was analyzed among the two cohorts and found that it was statistically significant (p-value of 1.38) (Table 10). It was not significant among both males (p-value 0.159) and females (p-value 1.445) of both cohorts (Table 11).

Antral gastritis was also not statistically significant among both cohorts with a p-value of 1.569 (Table 12).

Long-segment Barrett’s was more among Kottayam compared to Trivandrum (36 vs 9) and it was statistically significant with a p-value of <0.001 (Table 13).
Barrett’s Esophagus: A Comparison Study between Two Cohorts of GERD


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A Retrospective Observational Study of Neurological Manifestations in COVID-19 (SON-CoV)

Neetu Ramrakhiani1, Neeraj Bhutani2*, Deepak Chaudhary3, Pooja Parab4, Karni Singh5, Priya Agrawal6, Vikas Gupta7

Received: 08 February 2022; Accepted: 29 June 2022

Abstract
Objectives: Coronavirus disease 2019 (COVID-19) has neurologic manifestations associated with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This study aimed to retrospectively analyze SARS COVID-19 patients with neurological manifestations and identify patterns of presentation including the site of neuroaxis involvement, neuroimaging, and associated systemic involvement.

Methods and subjects: This retrospective observational study was conducted at two tertiary care hospitals in western Rajasthan. Data on age, sex, presenting symptoms, and comorbidities (hypertension, diabetes, cardiac, cerebrovascular disease, and cancer) were collected from 28th February 2020 to 31st December 2020 through medical records, discharge summaries, and radiological studies. Verbal/written patient consent was obtained due to the prevailing COVID-19 norms at the time of the first wave. All neurological manifestations were reviewed by at least two neurologists and were divided into central nervous system (CNS) and peripheral nervous system (PNS) manifestations. Systemic features and their temporal relationship with neurological features were recorded. Various other specialized assessments and therapeutic interventions were conducted.

Results: The mean age was 57.32 years for the CNS group and 40 years for the PNS group (p = 0.025). Age was significantly lower in the PNS group than in the CNS group (p = 0.025). Anemia, leucocytosis, and elevated serum creatinine were more commonly seen in the CNS group, although the difference was not statistically significant. The most common CNS manifestations were stroke (41.8%), which included ischemic stroke constituted 83% of cases, followed by seizure (22%), encephalopathy (20.9%), headache (15.1%), and vertigo (3.8%). The most common PNS manifestation was neuropathy (57%), which included Guillain–Barré syndrome (GBS), critical illness neuropathy, and autonomic neuropathy.

Conclusion: CNS symptoms of COVID-19 are more common than PNS symptoms. Stroke is the most frequent (46%) COVID-CNS symptom, which occurs in people of age above 35 years and is associated with high mortality.

Introduction
Coronavirus disease 2019, which resulted in a global pandemic, originated in the Wuhan province of China. Although initially believed to be predominantly a disease with respiratory presentation, it is clear now that the disease incurs multisystem manifestations. Neurological manifestations are also seen, and we discuss our experience with tertiary care centers in western Rajasthan. The study aimed to evaluate common patterns of presentation and outcomes of patients presenting with COVID-19. Data were retrospectively collected after the outbreak of COVID-19. Data were collected with the active collaboration of two centers in western Rajasthan.

The first case of a COVID-positive patient in Rajasthan was detected on 28th February 2020. He was an Italian national who visited Rajasthan as a tourist and had respiratory tract symptoms. Since then, approximately 5,000 patients with COVID-19 have been treated in total at both centers.

Most (94%) of the participants in this study were inpatients to neurology services of the centers for neurological symptoms. Hospital ethics committee approval was granted to conduct this study.

Subjects and Methods
Data were collected from 28th February 2020 to 31st December 2020 through medical records, discharge summaries, and radiological studies on age, sex, presenting symptoms, and comorbidities (hypertension, diabetes, cardiac, cerebrovascular disease, cancer, or chronic renal disease). Verbal consent of the patient/surrogate was taken due to prevailing COVID-19 norms at the time of the first wave. Major inclusion criteria were as follows:

- Age >18 years.
- Written or verbal consent of patient or surrogate.

Exclusion criteria included the following:

- Isolated computed tomography (CT) of the thorax suggestive of COVID pneumonia with a negative COVID-19 PCR test.
- Lack of consent for participation in the study.

We defined severe COVID-19 in patients with the following characteristics: SpO2 <94% on room air or requirement of ventilation, a respiratory rate >30 breaths/min, lung infiltrates exceeding 50%, and requirement of ventilation. Patients in our study included those admitted primarily for neurological complaints. They were divided into COVID-19 or post-COVID-19 groups, depending on the duration from clinical presentation (>14 days and COVID-19 negative after initial positive report) or the presence of COVID-19.
antibodies after 14 days following symptom onset, which occurred after 30 days of initial presentation. The groups were divided according to ages (in years) >34, 35–49, and >50. All neurological manifestations were reviewed by at least two neurologists and were divided into manifestations of the CNS and PNS. CNS manifestations included stroke, encephalopathy, seizures, headache, and dizziness or vertigo. PNS manifestations included impaired taste and smell, neuropathy, myopathy, myalgia, and creatine phosphokinase (CPK) values >200. Systemic features included fever, cough, diarrhea, and fatigue. Further, the temporal relationship of the systemic features with neurological features was recorded. Therapeutic interventions and outcomes of both neurological illness and systemic disease were recorded when feasible. Impaired consciousness and encephalopathy included changes in the level of consciousness (stupor, coma, somnolence, delirium, and changes in the content of consciousness). All strokes were diagnosed by a combination of clinical findings and neuroimaging [CT, magnetic resonance imaging (MRI), magnetic resonance venography, and computerized tomography venography] as appropriate, depending on the demand in a clinical context.

Guillain–Barré syndrome was defined according to standard clinical criteria. Anosmia, ageusia, and headaches were recorded per patient history. For the diagnosis of myopathy in patients, a clinical examination with objectively recorded weakness and/or raised CPK (more than 200 IU) was considered.

**RESULTS**

A total of 95 patients with a confirmed COVID-19 infection were included in this study. Twelve of these patients were excluded from analysis in either the CNS or PNS category if COVID-19 positivity was thought to be incidental and unrelated to clinical syndromes such as organophosphorus poisoning–1, unexplained urinary retention–1, tetany–1, degenerative ataxia, and normal pressure hydrocephalous1 or compressive myelopathy due to malignancy, etc. After the exclusion of

<table>
<thead>
<tr>
<th>CNS</th>
<th>PNS</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>77</td>
<td>6</td>
<td>83</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>57.32</td>
<td>40</td>
<td>0.385</td>
</tr>
<tr>
<td>Age up to 35 years</td>
<td>13</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>36–60 years</td>
<td>29</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>35</td>
<td>1</td>
<td>36</td>
</tr>
<tr>
<td>Male</td>
<td>53</td>
<td>4</td>
<td>57</td>
</tr>
<tr>
<td>Female</td>
<td>24</td>
<td>2</td>
<td>26</td>
</tr>
<tr>
<td>Hypertension</td>
<td>33</td>
<td>2</td>
<td>35</td>
</tr>
<tr>
<td>Diabetes</td>
<td>30</td>
<td>1</td>
<td>31</td>
</tr>
<tr>
<td>CKD</td>
<td>5</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>CAD</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Thyroid disorders</td>
<td>6</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Other comorbidities</td>
<td>33</td>
<td>1</td>
<td>34</td>
</tr>
<tr>
<td>Respiratory symptoms</td>
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<td>2</td>
<td>19</td>
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<tr>
<td>Gastroenterological symptoms</td>
<td>16</td>
<td>0</td>
<td>16</td>
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<tr>
<td>Systemic symptoms</td>
<td>17</td>
<td>3</td>
<td>20</td>
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<tr>
<td>Raised D-dimer</td>
<td>30</td>
<td>3</td>
<td>33</td>
</tr>
<tr>
<td>Raised ferritin</td>
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<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Anemia</td>
<td>34</td>
<td>3</td>
<td>37</td>
</tr>
<tr>
<td>Leucocytosis</td>
<td>19</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Raised LDH</td>
<td>12</td>
<td>1</td>
<td>13</td>
</tr>
</tbody>
</table>

CNS, central nervous system; PNS, peripheral nervous system; CKD, chronic kidney disease; CAD, coronary artery disease; LDH, lactate dehydrogenase; NS, not significant

Fig. 1: Distribution of patients
these patients, 83 patients were included in the final analysis (Fig. 1 and Table 1).

Patient demographics and clinical characteristics are presented in Table 1. The mean age was 57.32 for the CNS group and 40 for the PNS group ($p = 0.025$). Of these patients, at least 28 patients had diabetes, 32 had hypertension, five had chronic kidney disease, four patients had coronary artery disease (CAD), and one patient had malignancy. A total of 46 patients had more than one comorbidity, and 20 had none. CNS manifestations were more common than PNS manifestations. Age was significantly lower in the PNS group than in the CNS group ($p = 0.025$). No significant differences in sex were observed. Anemia, leucocytosis, and elevated serum creatinine were more commonly seen in the CNS group, although the difference was not statistically significant.

The most common CNS manifestations were stroke (41.8%), followed by seizure (22%), encephalopathy (20.9%), headache (15.1%), and vertigo (3.8%). The most common PNS manifestation was neuropathy (57%), which included GBS, critical illness neuropathy, and autonomic neuropathy. This was followed by myositis (14%) and anosmia (28%). Systemic manifestations of fever, malaise, and changes in appetite were observed in 18.2% of the patients. Of the patients, 21.5% had associated respiratory symptoms and 15% had associated gastrointestinal (GI) symptoms (Tables 1 and 2).

Seizures and COVID-19
Fifteen patients presented with seizures, of which two were known cases of epilepsy, and the rest had new-onset seizures. Comorbidities included hypertension in five patients, diabetes in six patients, chronic stroke in two patients, CAD in one patient, and chronic obstructive pulmonary disease in one patient. Anemia was found in seven patients and leucocytosis in four patients.

Evidence of stroke was found in four patients, three patients demonstrated normal imaging, and another three demonstrated nonspecific imaging findings.

Headache and COVID-19
Headache was the most prominent clinical feature in 11 patients (13.2%). In most of the patients, headache was a feature of ongoing COVID-19 infection (8/11), although in a minority of the patients (3/11) it could be a new-onset headache in the post-COVID-19 phase. Neuroimaging was performed in 8 out of 11 patients, which was normal in six patients and showed nonspecific changes in two patients. Anemia was frequently associated with headaches in 7 out of 11 patients.

Stroke and COVID-19
Stroke was the most common manifestation and constituted 43.3% (36/83) of the patients in our study. The mean age was 63 years and most of the patients were male. Most patients had their stroke during an ongoing COVID-19 infection (32/36), and a minority (4/36) had a stroke in the post-COVID-19 phase. Of these patients, the majority consisted of ischemic stroke (81.0%) and intracranial hemorrhage (16.2%), and one case of venous thrombosis (2%) was recorded in our series. Five (13.8%) of these patients had a chest CT, which was typical for COVID-19, and another five had some nonspecific findings on chest CT. Large vessel occlusion was found in five of the eight patients in whom angiographic studies were performed. Mortality was recorded in two of the 36 patients with stroke. Six of the 36 patients had additional GI features, and 10 of the 37 patients had additional respiratory features alongside stroke. Anemia was found in most of these patients (15/36). A D-dimer level >500 was found in a minority of patients. Therapeutic interventions such as antiviral agents (14/36), antibiotics (11/36), and antithrombotic agents were used in a large majority of the patients (22/36). All patients with ischemic stroke received antplatelet therapy. The use of an antithrombotic agent was statistically significant in the stroke subgroup.

COVID-19 and Encephalopathy
Twelve patients presented with COVID-19 encephalopathy. The mean age of the patients was 57.17 years out of which 75% of these patients were men. Nine patients had encephalopathy in their COVID-19 phase and another three had encephalopathy in the post-COVID-19 phase. Nonspecific MRI brain changes were seen in three patients, and chronic stroke was found in one patient. A total of 4 out of 17 patients (23%) had additional systemic features, and another four (23%) and two (11.5%) patients had

<p>| Table 2: Clinical laboratory and radiological characteristics of patient with CNS manifestations of SARS COVID-19 |
|---------------------------------|-----------|----------------|----------------|----------------|----------------|</p>
<table>
<thead>
<tr>
<th>Headache</th>
<th>Vertigo</th>
<th>Seizure</th>
<th>Encephalopathy</th>
<th>Stroke</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
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<td>3</td>
<td>15</td>
<td>12</td>
<td>36</td>
</tr>
<tr>
<td>Mean age</td>
<td>47.82</td>
<td>50.67</td>
<td>52.13</td>
<td>57.17</td>
<td>63</td>
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<tr>
<td>Male/female</td>
<td>7/4</td>
<td>1/2</td>
<td>11/4</td>
<td>9/3</td>
<td>25/11</td>
</tr>
<tr>
<td>During COVID</td>
<td>8</td>
<td>3</td>
<td>9</td>
<td>9</td>
<td>31</td>
</tr>
<tr>
<td>Post-COVID-19</td>
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<td>0</td>
<td>6</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>HTN</td>
<td>4</td>
<td>0</td>
<td>5</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>DM</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>4</td>
<td>18</td>
</tr>
<tr>
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<td>1</td>
<td>0</td>
<td>2</td>
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<tr>
<td>CKD</td>
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<td>0</td>
<td>1</td>
<td>4</td>
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<td>0</td>
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<td>1</td>
<td>9</td>
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<td>12</td>
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<tr>
<td>Anemia</td>
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<td>5</td>
<td>15</td>
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<tr>
<td>Raised TLC</td>
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<td>3</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Raised D-dimer</td>
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<td>8</td>
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<td>11</td>
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<tr>
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<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
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<td>0</td>
<td>5</td>
<td>2</td>
<td>4</td>
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<tr>
<td>Typical COVID-19</td>
<td>0</td>
<td>0</td>
<td>3</td>
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<td>5</td>
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<tr>
<td>Atypical COVID-19</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
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<td>0</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Normal</td>
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<td>0</td>
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<tr>
<td>Acute infarct</td>
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<td>0</td>
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<td>0</td>
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<tr>
<td>Chronic infarct</td>
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<td>0</td>
<td>3</td>
<td>1</td>
<td>1</td>
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<tr>
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<td>0</td>
<td>1</td>
<td>0</td>
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<td>0</td>
<td>0</td>
<td>1</td>
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<tr>
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<td>0</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Normal</td>
<td>6</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; CKD, chronic kidney disease; TLC, total leucocyte count; LDH, lactate dehydrogenase; CVT, cerebral venous thrombosis; NS, not significant.
GI and respiratory features, respectively. Agitation was a common feature in most of these patients.

**COVID-19 and PNS Manifestations**

As our study groups mostly had hospitalized patients with COVID-19, PNS manifestations were likely underrepresented. We had only six patients with PNS symptoms, with neuropathy occurring in 66% of those patients. This included two patients with GBS, one with autonomic neuropathy, and one with critical illness myoneuropathy (Tables 3 and 4).

**Discussion**

The COVID-19 pandemic caused by the SARS-CoV-2 has predominant respiratory manifestations, although it is increasingly recognized that neurological manifestations can be an important component of clinical presentation. The neurotropic and neuroinvasive capabilities of the coronavirus are well described. The earliest publications from the epicenter of infection in Wuhan, China by Mao et al. found neurological manifestations in 36.4% of the patients. It was also noted in this study that neurological manifestations were more common in patients with severe infections. There are multiple mechanisms through which viruses can enter various parts of the nervous system. Hematogenous dissemination by entering lymphocytes through a trojan horse mechanism is one such described mechanism. Another mechanism consists of the retrograde transmission of the virus into the brain from the nasal mucosa to the peripheral nerve terminals followed by the olfactory groove, as illustrated by MRI imaging showing hyperintensities in the olfactory groove. SARS-CoV-2 has been isolated from the CSF of patients with encephalitis, supporting the theory of viral invasion. Autopsy reports have also demonstrated brain tissue edema and neuronal degeneration in affected patients. At the cellular level, the binding of the spike protein on the surface of SARS-CoV-2 to the ACE2 receptor on the host cell is central to infection. ACE2 receptors are crucial for SARS-CoV-2 cellular tropism in humans.

The ACE2 receptors are expressed in the airway, lung parenchyma, small intestine, kidney, endothelium of blood vessels, and CNS. Recent reports indicate that ACE2 is expressed in neurons, astrocytes, and oligodendrocytes, as well as in the substantia nigra, ventricles, middle temporal gyrus, posterior cingulate cortex, and olfactory bulb.

While symptoms such as headache are common as observed in our study, symptoms with other neurological manifestations are also observed frequently. The neurological symptoms associated with COVID-19 infection can be broadly divided into three categories. The first category consists of patients with systemic manifestations due to severe COVID-19, resulting in secondary sepsis, encephalopathy, or hypoxia, further leading to neurologic sequelae. The second category consists of diseases in which COVID-19 infection itself would lead to the new-onset of neurological symptoms such as encephalopathy, new-onset seizures, stroke, and hyposmia due to viral pathology or a postinfectious disease such as GBS. The third category may consist of individuals who are by and large asymptomatic for COVID-19; however, symptoms would result from another source, such as in the case of patients with tuberculous meningitis presenting with a comorbid COVID-19 infection or spinal metastasis with paraparesis combined with positive COVID-19 results, these symptoms are often atypical for COVID-19 but may have aggravated the underlying disease or not very similar to a COVID-19 infection, which may have aggravated due to the underlying disease or may have been acquired due to multiple hospital visits and patient contact. Most (87%) of our patients belong to the first and second categories. The patients in our study mainly demonstrated CNS manifestations of COVID-19 infections. Most patients who presented with either stroke or new-onset seizures were elderly and often had secondary risk factors for stroke. None of them had a previous history of stroke, which led us to postulate that COVID-19 infection had a pathogenic role in triggering these stroke events or acting as a catalyst on the fertile ground of vascular risk factors. Patients presenting with PNS involvement were younger (mean age: 40), with symptoms of neuropathy. D-dimer levels were found to be much more significantly elevated in patients presenting with CNS manifestations. 95.2% of the patients

**Table 3:** Clinical and radiological characteristics of patients with PNS manifestations of SARS COVID-19

<table>
<thead>
<tr>
<th></th>
<th>GBS</th>
<th>Autonomic neuropathy</th>
<th>Anosmia ageusia</th>
<th>Myositis</th>
</tr>
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<tbody>
<tr>
<td>Total number</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
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<td>Mean age</td>
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<td>24</td>
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</tr>
<tr>
<td>Male</td>
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<td>0</td>
<td>0</td>
</tr>
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<td>Female</td>
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<td>1</td>
<td>1</td>
</tr>
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<td>COVID-19</td>
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<tr>
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<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

**Table 4:** Treatment and outcome details in patients with CNS and/or PNS pathology in SARS COVID-19 infection

<table>
<thead>
<tr>
<th></th>
<th>CNS18</th>
<th>PNS19</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
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<td>6</td>
<td>0.313</td>
</tr>
<tr>
<td>Recovered</td>
<td>47</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Same status</td>
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<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>Antiviral</td>
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<td>Antibiotic</td>
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<td>0.084</td>
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<tr>
<td>Antithrombotic</td>
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<td>0.398</td>
</tr>
<tr>
<td>Steroids</td>
<td>21</td>
<td>2</td>
<td>0.359</td>
</tr>
</tbody>
</table>

CNS, central nervous system; PNS, peripheral nervous system.
had a good outcome; however, four deaths were recorded in our cohort. Stroke was the most common neurological manifestation of COVID-19 infection. 83.3% of these strokes were ischemic. 37% of the patients received specific antiviral agents (remdesivir and favipiravir), steroids, and antithrombotic agents. In hospital mortality was greater in the CNS group compared to the PNS group, although this difference was not statistically significant.

One of the limitations of this study was that it was a retrospective study. Further, the dominant population for this study consisted of inpatient neurology patients, leading to an underrepresentation of PNS manifestations, which may be more common in the community. We may have only chosen severe PNS manifestations like GBS and critical illnesses like myoneuropathy for observation. Also, minor neurologic manifestations like anosmia and ageusia may be overshadowed by manifestations like stroke and critical illness neuropathy. A further prospective study is planned to overcome this limitation in the near future.

**Authors’ Contributions**

Dr Neetu Ramrakhiani: concepts, design, definition of intellectual content, literature search, clinical studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, manuscript review, guarantor. Dr Neeraj Bhutani: design, definition of intellectual content, literature search, clinical studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, manuscript review, guarantor. Dr Deepak Chaudhary: design, definition of intellectual content, data analysis, statistical analysis, manuscript preparation, manuscript review. Dr Pooja Parab: data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript review. Dr Karni Singh: clinical studies, data acquisition, data analysis, manuscript review. Dr Priya Agarwal: clinical studies, data acquisition, data analysis, manuscript review. Dr Vikas Gupta: clinical studies, data acquisition, data analysis, manuscript review.

**Ethics Statement**

Approval from Institutional Ethics Committee was taken (Ref No.: FEHJ/IEC/21/07). Informed consent from study subjects was taken.

**Acknowledgments**

I would like to acknowledge Devang Sharma and Dr Akshay Kumar Jaimini for their contribution in preparation of this manuscript.

We would like to thank Editage for their English language editing services.

**References**

Technology and Medical Care in India: Growth of Telehealth Awareness during the COVID-19 Pandemic

Ragul Ganesh1, Koushik Sinha Deb2, Arunkumar Subbiah3*

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ABSTRACT

Background: COVID-19 pandemic has highlighted the importance of telemedicine in healthcare delivery worldwide. However, the true success of telemedicine depends on patients’ acceptance, which in turn is decided by their interest in telemedicine. In this study, we aim to assess the population interest in telemedicine services across India during the COVID-19 pandemic.

Methods: We measured national-level public interest in “telemedicine” using terms related to telemedicine in Google Trends during the years 2019 and 2020. The relationship between population search volume for telemedicine (composite score) and the number of COVID-19 cases in the early phase of COVID-19 was analyzed. The literacy rate and relative interest in telemedicine in the states were analyzed to assess the impact of education on telemedicine interest.

Results: The interest in telemedicine in the year 2020 is higher compared to the year 2019 (U = 269.5, z = −7.943, p < 0.001). The search trends for telemedicine increased consistently during the early phase of the COVID-19 pandemic. The greatest search volume was seen in Andhra Pradesh. There was a strong correlation (r = 0.65, p < 0.001) between the initial increase in the number of COVID-19 cases and population-level interest in telemedicine over time. The relative interest in telemedicine for the year 2019 showed a significant direct relationship with the literacy rate (r = 0.47, p = 0.04). However, the relative interest in telemedicine for the year 2020 showed no relationship with the state’s literacy rate signifying the spread of telemedicine across literacy barriers.

Conclusion: Population interest in telemedicine was higher in the year 2020 compared to the previous year and remained high even after the easing of lockdown. The COVID-19 pandemic has played an important role in increasing the Indian public’s interest in telemedicine.

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INTRODUCTION

Telemedicine uses information and communication technology to provide diagnostic and management consultations irrespective of geographical and functional distance.1 The importance of telemedicine lies in the fact that people living in less developed areas especially rural areas can receive state-of-the-art medical consultation from experts worldwide. The COVID-19 pandemic and the ensuing travel restrictions necessitated medical care to be provided to patients in their place of stay. This could be accomplished only by teleconsultation which apart from providing timely care reduced the risk of unnecessary exposure to infection. Telemedicine has helped public health care delivery during earlier emergencies too.2

The Government of India (GOI) initiated various telemedicine services including National Teleconsultation Centre (CoNTec) and National Medical College Network to boost the medical response to COVID-19.3 The state governments adopted the “stay home OPD” launched by the GOI for providing teleconsultations.4 The national telemedicine practice guidelines were subsequently released to decrease the ambiguity in the practice of telemedicine.

India has over 560 million internet users accounting for one-half of our population.3 With the available technological advances and governmental support, the major limiting factor for telemedicine and teleconsultation is the interest evinced by the general public. Internet search remains the primary mode for acquiring health information by the general public. At present, Google Search is the most widely used search engine in India and worldwide. We hypothesized that analyzing the search trends in Google would help us get an idea of the need and overall popularity of telemedicine in India. The entire catalog of searches performed can be assessed through Google Trends. The search volume in Google Trends is used as a proxy measure of population interest and demand.

In this study, we investigated the relationship between nation-level population interest assessed by internet search trends for telemedicine with the spread of the COVID-19 pandemic across the country. We also compared the proportion of interest in telemedicine for the years 2019 and 2020 in each state to understand the role of the present pandemic in augmenting the population interest in telemedicine.

METHODS

All internet searches made through Google are indexed and this can be assessed through Google Trends. Google Trends provides a relative search volume (RSV) or search volume index ranging from 0 to 100 for each search terminology. This represents the search interest for that particular term relative to the overall search volume for the given geographic area, population size, and search period. The peak search activity for the term is scored as 100%, while a value of 50 means that the term is half as popular at the time of assessment. We used this search volume data to measure the population interest in telemedicine.

We used the search terms “telemedicine,” “telehealth,” “teleconsultations,” and “online consultations” in Google Trends, for a period of 2 years from 1st January 2019 to 31st December 2020. This particular period was chosen so that the change from the pre-COVID period can be tracked and compared to the period of pandemic spread. The search interest in the year 2019, being the pre-COVID period, could show the pre-existing interest in telemedicine in India. The search interest in the year 2020 could show the effect of the pandemic. We also assessed the relative awareness about telemedicine in different states by calculating the RSV of each state for telemedicine. The relationship between the literacy rate and relative interest in telemedicine in the states for the years 2019 and 2020 was assessed to understand the impact of education on telemedicine adoption in various areas. The association of

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population search volume for telemedicine (composite RSV score) with daily cumulative numbers of COVID-19 cases in India during the study period was determined.

The Google Trends data were accessed on 28th February 2021. The data on the number of COVID-19 cases in India has been obtained from the Ministry of Health and Family Welfare’s official website. All the data were managed on an Excel sheet and analysis was conducted using SPSS version 21. Normality distribution was checked using Shapiro–Wilk test. Descriptive statistics using mean, standard deviation (SD), median, and interquartile range (IQR) were used to describe the study sample. Interferential statistics using nonparametric tests were conducted to study the relationship between continuous variables. The level of statistical significance was set at a p-value of less than 0.05.

**Results**

The mean RSV in Google Trends for the aforementioned search terms for the overall study period from 1st January 2019 to 31st December 2020 was 26.5 (±25.8). The mean RSV for the year 2019 was 13.6 (SD 5.2), while the median was 12.0 (IQR 9–17). The mean RSV for the year 2020 was 41.6 (SD 22.9), while the median was 40.0 (IQR 22.2–61.5).

In the year 2020, the RSV values gradually increased and the peak RSV of 100 was reached on 17th April 2020, subsequently, the RSV values decreased. When assessed with the daily number of COVID-19 cases in India till 17th April 2020, it was seen that the population interest in telemedicine increased as the number of COVID-19 cases increased. There was a strong correlation between the number of COVID-19 cases reported and interest in telemedicine (Pearson’s correlation: r = 0.65, p < 0.001) (Fig. 1). The telemedicine interest during the national lockdown from March to May 2020 (median = 71; IQR = 64–81) was higher compared to the telemedicine interest from June to December 2020 (median = 40.5; IQR = 28–49.25), corresponding to gradual ease of lockdown. We observed that the Mann–Whitney test showed a significant difference (U = 23.0, z = −4.179, p ≤ 0.001) in the population interest in telemedicine between the lockdown phase and the unlock phase.

The population interest in telemedicine in the year 2020 was significantly higher than in the year 2019 (U = 269.5, z = −7.043, p < 0.001) as evaluated by the Mann–Whitney test. We compared the RSVs of each of 52 weeks in the year 2020 with that of the previous year 2019. We found that the RSV scores of most of the weeks in 2020 were significantly higher than the RSV score of corresponding weeks in 2019 (T = 1257, z = −5.981, p < 0.001) by Wilcoxon signed-rank test. The RSV scores of corresponding weeks in 2019 and 2020 are depicted in Figure 2.

Telemedicine awareness in different states was assessed for the study period. Seventeen states and two union territories (Delhi and Chandigarh) had RSV scores indicating interest in telemedicine (Table 1). The top five states with maximum telemedicine interest in 2019 were Tamil Nadu, Kerala, Haryana, Telangana, and...
and Delhi. While the states like Andhra Pradesh, Kerala, Telangana, Odisha, and Tamil Nadu showed maximum interest in 2020. The relative interest in the states for the year 2019 did not show any relationship with that of 2020. We observed that the relative interest in telemedicine in the states for the year 2019 showed a significant direct relationship with the literacy rate ($r = 0.47, p = 0.04$). However, the relative interest in telemedicine in the states for the year 2020 showed no relationship with the state literacy rate.

**Discussion**

The COVID-19 pandemic is an unprecedented global catastrophic event with far-reaching consequences for the physical and mental well-being of the entire population. The pandemic has brought to fore the importance of telehealth as an integral part of health care delivery. Telemedicine has assisted clinicians in identifying patients requiring in-person health care services and thereby reducing overcrowding in hospitals. Though queries have been raised about patient satisfaction by teleconsultation, the Cochrane review by Bunn et al. showed that teleconsultations reduce the direct contact between health care providers and patients, without affecting patient satisfaction.6 During pandemics like the present one, hospital visits have to be reduced by both patients and caregivers, and the advantage provided by telemedicine is expected to give the much-needed fillip for the growth of telemedicine across the country.7 Though the growth of telemedicine was expected in this time period, we need to know if this will continue once normalcy is restored. The prerequisite for the success of telemedicine services would be public interest and Google Search is at present the best available modality to understand this interest.

Telemedicine is a giant yet essential leap for health care delivery to remote areas, especially in developing countries. Moreover, in developing countries like India, rural areas suffer from dearth of trained specialists, inadequate transportation facilities, need to travel long distances for specialized consultations, and difficulty in taking time off from work. Telehealth services may be the much-needed panacea to circumvent all these problems for this deserving population. Various tools such as smartphone apps, videoconferencing, text messaging, and emails have been used effectively for the delivery of teleconsultations. With the widespread acceptance of telemedicine, advances in video consultations are bound to happen soon.

Our study showed that the interest in telemedicine increased during the period of the pandemic compared to the previous year. There was an increased awareness in telemedicine at the population level with the increase in the number of COVID-19 cases in India as shown by the direct correlation between the search volume values and the number of COVID cases per day. These findings are similar to the study in developed countries wherein there was an increase in interest in telehealth services with the increase in the number of COVID cases.8 Though there was a modest increase in interest in telecommunication services during the initial part of the pandemic, a drastic increase was observed as the lockdown was enforced across the country. It also showed the interest was maximum during the period of national lockdown due to various physical restrictions. However, even after the easing of lockdown, the interest in telemedicine in the latter half of the year 2020 was higher compared to the previous year. This is a promising trend and shows acceptance of telemedicine in our country.

The systematic review by Ekeland et al. has shown that telemedicine is effective in various health services including online psychological interventions, telemonitoring of respiratory conditions, preventive health, cognitive behavioral therapy for the treatment of anxiety disorders, etc. Also, patient information was clearly and reliably interpreted allowing for correct teleconsultations.9 This should ease our concern about issues in interpreting patient concerns and medical issues in a virtual manner.

One rational query about telemedicine would be about the educational qualification of those seeking teleconsultation. It would be plausible to expect that those who are better educated would be more likely to use this service. Hence, we tried to determine the relation between teleconsultation interests and the state’s literacy rate. We observed a direct correlation between the relative interest in telemedicine in the states for the year 2019 and the literacy rate. However, we did not find a correlation between the two for the year 2020. This highlights the impact of the COVID pandemic on telemedicine interest. The rapid growth of telecommunication, the decline in data costs, and the penetration of mobile internet services across the country have made health care delivery possible using telemedicine in remote areas irrespective of education status.

The GOI developed various mobile health services in response to COVID-19. CoNTec telemedical system has been set up to evaluate and treat the patient without an in-person patient visit. A study by Mishra showed that during the COVID-19 outbreak, telemedicine was perceived to be better suited and useful for the delivery of health care services.10 One more notable aspect was that patients are not intimidated by technology. This would help in the growth of technology in the long run.

<table>
<thead>
<tr>
<th>Indian states</th>
<th>RSV 2020</th>
<th>RSV 2019</th>
<th>Literacy rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andhra Pradesh</td>
<td>100</td>
<td>36</td>
<td>67.66</td>
</tr>
<tr>
<td>Assam</td>
<td>30</td>
<td>18</td>
<td>73.18</td>
</tr>
<tr>
<td>Bihar</td>
<td>10</td>
<td>12</td>
<td>63.82</td>
</tr>
<tr>
<td>Chandigarh</td>
<td>85</td>
<td>22</td>
<td>86.43</td>
</tr>
<tr>
<td>Delhi</td>
<td>44</td>
<td>52</td>
<td>86.34</td>
</tr>
<tr>
<td>Gujarat</td>
<td>21</td>
<td>33</td>
<td>79.31</td>
</tr>
<tr>
<td>Haryana</td>
<td>28</td>
<td>63</td>
<td>76.64</td>
</tr>
<tr>
<td>Karnataka</td>
<td>42</td>
<td>51</td>
<td>75.6</td>
</tr>
<tr>
<td>Kerala</td>
<td>61</td>
<td>74</td>
<td>93.91</td>
</tr>
<tr>
<td>Madhya Pradesh</td>
<td>20</td>
<td>28</td>
<td>70.63</td>
</tr>
<tr>
<td>Maharashtra</td>
<td>29</td>
<td>43</td>
<td>82.91</td>
</tr>
<tr>
<td>Odisha</td>
<td>57</td>
<td>29</td>
<td>73.45</td>
</tr>
<tr>
<td>Punjab</td>
<td>29</td>
<td>35</td>
<td>76.68</td>
</tr>
<tr>
<td>Rajasthan</td>
<td>22</td>
<td>27</td>
<td>67.06</td>
</tr>
<tr>
<td>Tamil Nadu</td>
<td>54</td>
<td>100</td>
<td>80.33</td>
</tr>
<tr>
<td>Telangana</td>
<td>59</td>
<td>56</td>
<td>67.66</td>
</tr>
<tr>
<td>Uttar Pradesh</td>
<td>24</td>
<td>32</td>
<td>69.72</td>
</tr>
<tr>
<td>West Bengal</td>
<td>40</td>
<td>47</td>
<td>77.08</td>
</tr>
</tbody>
</table>

Table 1: Population interest in telemedicine and literacy rate in various states of India
Our study was limited to English language searches in Google. This limits our result from assessing interest levels among the non-English speaking population which is widespread in our country. Google is the primary search engine in over 98% of the Indian population and hence, may reflect the overall search preference of the majority. The interest levels among the rural public could not be assessed separately and hence may under-represent rural area interests. Despite these limitations, Google Trends data is a valuable tool to assess patient preferences as the success of any initiative is inherently dependent on individual interest. Patient satisfaction is paramount for the success of any new initiative and this has to be assessed in the future. This would help in the formulation of health policies that are actively supported and utilized by the general public.

With the rapid growth of mobile internet services, computer literacy, and cost-effective telecommunication technologies, telemedicine is bound to be a game-changer for medical care in India.

**CONCLUSION**

The rapidly spreading pandemic and the ensuing public health measures posed significant challenges for continuing the delivery of health care services through conventional modes and resources. During this period of the COVID-19 pandemic, telemedicine helped in providing health care services. Telemedicine may be the panacea we are looking for to minimize the imbalances between urban and rural medical care. Population interest is significantly in favor of telemedicine expansion and the onus is on the public and private health agencies to rise to the occasion and extend services even after the present pandemic settles.

**REFERENCES**

Comparison of Outcomes of Clinical Teaching Station and Traditional Bedside Teaching among the Final Year Medical Students

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ABSTRACT

Background: Teaching clinical skills is generally done by bedside teaching (BT). Clinical teaching stations (CTSs) are specially designed for the final year medics.

Methods: The aim was to evaluate and compare the impact of CTS with BT on the final year medical undergraduates. Evaluation of the effectiveness of CTS among the participants was the primary objective with a % change in academic performance.

A teaching program was conducted in two phases with each phase having two sessions, covering respiratory system (RS), gastrointestinal tract (GIT), cardiovascular system (CVS), and central nervous system (CNS). In the first phase, RS and GIT and in the second phase CVS and CNS were taught by TS and BT methods. Each session lasted for 2 weeks.

Results: Thirty participants were grouped into two. The total mean ± SD score was 22.57 ± 3.86 and 24.4 ± 4.32 for BT and TS, respectively. Mean scores were higher in students who were taught by CTS but were statistically not significant (p > 0.05) in both phases.

There was no significant gender difference in the impact of the two teaching methodologies. The number of students who excelled was more with TS whereas, the scores were moderate with BT. All (100%) participants unanimously agreed that CTS is more effective and interactive and helped in better understanding of the subject.

Conclusion: TS as a teaching tool is realistic with repeatable clinical scenarios and objective assessment. BT provides students with the required clinical skills, TS can enhance the knowledge and application. TS can be used as a supplementary tool along with BT.

INTRODUCTION

There have been efforts to bring new methodologies in teaching to create and increase students' interest, establish a positive learning environment, promote better understanding, retention and recall of the subject learned, foster self-directed independent learning, and assess the assessor/teacher for a positive change.

These methodologies allow appropriate autonomy to the learner and the assessor and help to balance teaching and clinical work. Most importantly, it specifies the learning objectives, what must be learned and done (essential, desirable), and adjusts to learner needs, which is modifiable. It creates an environment for interactions and ask questions to promote learning by providing clear explanations. Its adaptability by adjusting teaching to diverse settings including coaching in clinical and technical skills. Teaching in medical schools must elicit thought-provoking process in the learner, incorporate research data, develop clinical reasoning/diagnostic skills along with teaches effective patient management and communication skills. However, the implementation of these methodologies is still in its infancy.

Teaching in a medical school is a dynamic and integrated process. Teaching clinical skills to medics is generally by BT, a traditional, unidirectional, and teacher-centric method unless the teacher engages the students by interaction. CTS is specially designed for the final year MBBS students and medical postgraduates where they are trained considering the student’s core abilities. Application of the medical knowledge they learned, the ability to demonstrate clinical skills, develop investigational and therapeutic clinical plans for the disease, and demonstrate professional behaviors and attitudes at a level expected of a physician in independent practices are the expected outcomes. Majumder et al. have reported that objectively structured CTS is well perceived by the students, though it was stressful and more difficult. This type of educational tool was found to be feasible, acceptable, can be successfully implemented in medical colleges, and helpful in predicting the clinical skills and performance of medical students.

We introduced and evaluated the impact and utility of clinical stations as a teaching tool in teaching general medicine to the final year MBBS students.

MATERIALS AND METHODS

This prospective, cross-over study was conducted by the Department of General Medicine of a tertiary care teaching hospital. The study was initiated after obtaining approval from the Institutional Ethics Committee and prospective participants were included after obtaining a written informed consent. The aim of the study was to evaluate and compare the impact of CTS with BT method on the final year medical undergraduates. Evaluation of the effectiveness of CTS on the final year medics was the primary objective of the study with a % change in academic performance in the respective topics. To comprehend the perception of the students regarding CTS was the secondary objective.

Thirty medics in the final year of MBBS, who consented to participate were included in the study and were grouped into two. A teaching program was conducted in two phases with each phase having two sessions, covering the four body systems (RS, GIT, CVS, and CNS). In the first phase, RS GIT and in the second phase CVS and CNS were taught by TS and BT methods. Each session lasted for 2 weeks. Study procedures are depicted in Figure 1.

Participants in both groups were assessed after the completion of a topic. Test scores were compared.
Results

Of 30 participants, there were 11 (37%) males and 19 (63%) females.

The total mean ± SD score was 22.57 (±3.86) and 24.4 (±4.32) for BT and TS; mean scores were higher in students who were taught by CTS compared to traditional BT but was statistically not significant (p > 0.05) in both the phases (Table 1).

There was no significant difference in the means of the scores among the participants (Table 2).

There was no significant gender difference in the impact of the two teaching methodologies reflected by mean (Table 3) and mean change (Table 4).

The number of students who excelled was more with CTS whereas, the scores were moderate with BT (Table 5).

All (30, 100%) participants unanimously agreed that the TS is more effective and interactive and helped them a better understanding of the subject.

Discussion

Teaching in a medical school is a more responsible job as the teacher is accountable not only to impart medical skills and knowledge to students and treating patients but also to regulatory agencies (in terms of accreditation and self-regulation), hospitals/universities, and funders. Quality of medical education has a direct impact on the delivery of health-care, which depends not only on the teachers but also on teaching methodologies, techniques, and learner’s interests and capabilities. Deficit in the clinical and practical skills among the medical students is a concern, hence, repeated assessments of the student is necessary.

With declining clinical skills among students and increasing dependency on investigations, it is necessary that students be equipped with adequate diagnostic skills. A comprehensive approach is needed for holistic management, which requires logical thinking, clinical evaluations, and correlations. Though BT is an effective teaching and learning methodology, the use of CTS has been useful in the assessment of clinical conditions by promoting independent critical thinking, recall, and application of clinical knowledge. It promotes the feeling of responsibility among students, helps in improving technical and problem-solving skills, goal setting in terms of must learn and desire to learn, and interaction...
Clinical Teaching Station and Bedside Teaching

and communicative skills. Development of situational awareness, which is most required in general medicine, can be promoted by clinical stations. Hence, its use in teaching medical subjects is highly supported and recommended.

Use of CTS is useful in enhancing learning medical subjects and makes it less stressful. It helps the students to identify their deficiencies and lacunae and promote active learning.\(^7\) Use of objective structured stations was well perceived and accepted by students for pre and para clinical subjects,\(^8,10\) but not by those in the final year MBBS.\(^12\) As general medicine is an extensive subject, it is difficult for an undergraduate student to remember all aspects of diseases, and becomes more stressful. Use of clinical stations may offer some help in reducing stress and improving students’ performance. CTS also helps in fetching more marks, which can be considered rewarding. Studies have shown that it can help in the theoretical knowledge to assess, manage real-time medical problems, and implementing these additional teaching tools can improve the skills of medical students.\(^12\)

In general medicine, every step in patient management is important and calls for evaluating the student in the same. Hence, CTS including history taking, clinical examination, clinical and laboratory investigations, differential diagnosis, and treatment options can be of immense value in increasing the competency of the student.\(^13\) As there is no exit exam after the mandatory rotational internship, it is necessary that the final year MBBS student be made capable of independently evaluating and managing the patient.

Though these methodologies have been accepted and incorporated into the curriculum, there are negative reviews on the same; there is a concern if these really have a positive influence on students’ learning and if the scores are reflective of clinical skills.\(^1\) We noticed that TS was well perceived, skills improved among our students, and is an effective teaching methodology. Fun-filled, team learning helped to build reasoning and active involvement of every member encouraged questioning. Team discussions proved helpful in better communication.

Objective TSs though have been promising with a positive impact, its impact on pass percentage has been disappointing and failed to predict the performance of the students; despite this, it was previewed as useful.\(^14\) We observed that it can help in identifying poor performers early, who need extensive training and distinguish those who can excel. Objective CTSs are useful tools as predictors of poor performers particularly in the essay questions.\(^15\)

Objective structured tools have shown to increase the pass percentage,\(^3\) but we noticed that it helped the students with basic knowledge and passed the test to excel. Hence, BT which imparts basic clinical skills is a must for medical students. Previous studies have stated it to be an effective way of teaching medical and medicine management to future doctors,\(^16\) our study supports this observation.

We have done the study in two phases, with cross-over. Being a single-centered study with a small sample size was the major limitation of the study. We tested only the clinical skills, but not the procedural skills, which, however, were not assessed in undergraduate medics. Involving senior students in teaching and assessing the junior students, in group discussions can benefit both. Implementing this educational tool from the 1\(^{st}\) year till the internship period is worthwhile.

Our study indicates that CTS can be complimentary to the traditional BT and can enhance the performance of those students.

### Table 3: Gender-wise comparison of mean scores of those who passed the test

<table>
<thead>
<tr>
<th>Subject</th>
<th>Gender</th>
<th>Teaching method</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>SE of mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>RS</td>
<td>Female</td>
<td>10</td>
<td>26.20</td>
<td>3.36</td>
<td>1.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>9</td>
<td>24.22</td>
<td>4.06</td>
<td>1.35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CTS</td>
<td>7</td>
<td>25.14</td>
<td>5.46</td>
<td>2.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>9</td>
<td>21.00</td>
<td>3.32</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>BT</td>
<td>8</td>
<td>21.88</td>
<td>4.52</td>
<td>1.60</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>21.00</td>
<td>2.68</td>
<td>1.10</td>
</tr>
<tr>
<td>Phase II</td>
<td>CVS</td>
<td>Female</td>
<td>7</td>
<td>25.14</td>
<td>5.46</td>
<td>2.06</td>
</tr>
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<td></td>
<td></td>
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<td>21.00</td>
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<td>1.11</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
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<tr>
<td></td>
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<td>6.03</td>
<td>2.46</td>
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<tr>
<td>Phase II</td>
<td>CNS</td>
<td>Female</td>
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<td></td>
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<td>22.11</td>
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<td>3.73</td>
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<tr>
<td></td>
<td></td>
<td>Male</td>
<td>6</td>
<td>22.50</td>
<td>4.76</td>
<td>1.95</td>
</tr>
</tbody>
</table>

PTA, posttest assessment; SE, standard error

### Table 4: Gender-wise comparison of mean difference in the scores

<table>
<thead>
<tr>
<th>Subject</th>
<th>Gender</th>
<th>Teaching method</th>
<th>n</th>
<th>Mean</th>
<th>STD</th>
<th>SE of mean</th>
<th>95% CI</th>
<th>t-value</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td>Phase I</td>
<td>RS</td>
<td>Female</td>
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<td>0.950</td>
<td></td>
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</tr>
<tr>
<td></td>
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<td>Male</td>
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33
who have attained basic knowledge and skills through latter, but at this stage cannot replace it. It is been observed that reasoning aptitude and skills, which is of utmost importance in clinical practice,17 needs to be developed in medical students in which CTS can prove helpful. CTS is a worthy learning tool, can assess student’s in-depth knowledge and make them better skilled medical professional. It may find use in the preparation for exams, improve reasoning capacity; focus on micro skills is an advantage. We need to address other aspects such as proper history taking, and accurate record keeping. Involving students in the preparation of CTS can help in increasing reasoning capacity, bring improvement in the weaker areas.

CONCLUSION
Clinical teaching station as a teaching tool are realistic with repeatable clinical scenarios, which are assessed objectively. BT though provides students with the required clinical skills, CTS can enhance the knowledge and application as indicated by better posttest scores in groups exposed to CTS. CTS can be used as a supplementary tool along with BT, but cannot replace it, at least for now. There is space for significant improvement in the area of clinical education and numerous strategies can be implemented.

REFERENCES

Table 5: Posttest scores with BT and CTS

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Role of Itolizumab in the Treatment of COVID-19 Patients, Admitted to ICU at a Tertiary Care Hospital

Nalini Kurri¹, Bhumesh Tyagi², Atul Kaushik³, Nikhil Gupta⁴, A K Agarwal⁵, B M Singh⁶

Received: 18 January 2022; Accepted: 20 July 2022

ABSTRACT

Background: Clinical studies have correlated severe deterioration of COVID-19 patients due to excessive and uncontrolled production of cytokines. There is a pressing need to explore therapies, which could prevent the cytokine storm rather than terminating it.

Aims and objectives: The aim of the study is to evaluate the effect of itolizumab on clinical outcomes of patients with moderate-severe COVID-19 disease admitted to ICU. The primary aim of the current study is to find out any mortality benefit in 14 days. The secondary aim is to assess the morbidity outcomes in terms of reduction in inflammatory markers and also the duration of hospital stays to assess the prognostication.

Materials and methods: It is a retrospective case-control study in which laboratory-confirmed COVID-19 patients admitted to ICU were taken. A total of 62 patients were recruited, 31 patients received itolizumab (cases/treatment group) and 31 patients didn’t receive itolizumab (designated as controls).

Results: Among the total patients recruited, 68% of the study population was male and 32% were female. A total of 12 patients expired among cases and 13 expired among controls. Overall mortality in both groups was noted to be almost similar. The control group showed mortality at lower computed tomography (CT) scores compared to the cases. There is a significant reduction in inflammatory markers, like interleukins-6 (IL-6) and D-dimer in cases compared to the control group.

Conclusion: In conclusion, treating patients with cytokine storms before they require intubation/mechanical ventilation is crucial to preventing deaths. Itolizumab has shown no clinical benefit in critically ill COVID-19 patients, however, timely initiation of itolizumab therapy may serve as a key therapeutic option in preventing the mortality and morbidity outcomes in moderate-severe COVID-19 patients.

INTRODUCTION

Irrespective of the type of variant and its replication potential, the cytokine storm, which needs to be addressed with promptness contributes the ultimate severe illness. Cytokine storm is characterized by the abnormal release of circulating cytokines such as IL-1β, IL-2, IL-4, IL-6, IL-7, IL-8, IL-9, IL-10, IFN-γ, GM-CSF, TNF-α. These are five types of cytokines, which include interferons (IFNs), ILS, tumor necrosis factors, chemokines, and colony-stimulating factors. ILs are proinflammatory and are involved in the growth and differentiation of leukocytes. Corticosteroids and therapeutic monoclonal antibodies targeting the proinflammatory cytokines, such as IL-6 have been trailed to dampen the cytokine storm, but COVID-related mortality seems to be still very high with the existing therapies. Hence, it is very crucial to target the inflammatory cascade ahead of the cytokine storm in order to prevent its dire consequences. Itolizumab, is an anti-CD6 humanized immunoglobulin G1 (lgG1) monoclonal antibody, which acts early in the inflammatory cascade.

MATERIALS AND METHODS

The present study is based on data retrieved from the medical records of adult patients who were admitted to ICU at Sharda Hospital and School of Medical Sciences and Research, Greater Noida, Uttar Pradesh. This is a level III designated COVID-19 facility working under the aegis of the Uttar Pradesh Government. A total of 62 patients were recruited, 31 patients received itolizumab (treatment group) and 31 patients could not receive itolizumab (control group). Corticosteroids, heparin, and remdesivir were given to both groups as standard care.

Inclusion Criteria for both the Groups

- All patients aged >18 years.
- Patients with a positive RT-PCR for COVID-19.
- Moderate/severe COVID-19 infection as defined below:
  - Cases: Patient getting at least one dose of itolizumab iv.
  - Controls: Patients not getting itolizumab iv.

Exclusion Criteria for both the Groups

- Pregnancy or breastfeeding.
- Patients with known active infections.
- Known allergies with a previous history of anaphylaxis.

WHO Case Severity Definitions³

Critical COVID-19

Defined by the criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions that would normally require the provision of life-sustaining therapies such as mechanical ventilation (invasive or noninvasive) or vasopressor therapy.

Severe COVID-19

Defined by any of:

- Oxygen saturation <90% on room air.
- In adults, signs of severe respiratory distress (accessory muscle use, inability to complete full sentences, respiratory rate >30 breaths per minute).

Nonsevere COVID-19

Defined as the absence of any criteria for severe or critical COVID-19.

Study Conduct and Design

It is a hospital-based retrospective observational study, the study was conducted over 2 months, from 1st April 2021 to 30th May 2021. Itolizumab, therapy was initiated at 1.6 mg/kg, infused at 25 mL/hour for the first hour. If well-tolerated, it was increased to 50 mL/hour to infuse the remaining amount. The infusion was completed over 5–6 hours. Clinical improvement was evaluated by assessing the posttreatment

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mortality outcomes, inflammatory markers, and radiological findings.

**Statistical Methods**

All the data obtained were analyzed statistically using Microsoft Excel, Statistical Package for Social Sciences (SPSS) software ver. 21.0. Categorical variables were expressed in numbers and percentages (%). Continuous variables were compared by Student’s t-test or Mann–Whitney U test. The categorical variables were compared by the Chi-square method and Fisher exact test. A p-value of less than 0.05 is considered significant.

**Results**

The age of the patients ranged from 27 to 81 years in both groups. The mean age of patients is 53 years in the treatment group and 50 years in the control group, the median age was 52 years and 48 years, respectively with the overall majority being male (68%). There are six females and 25 males in the cases while 15 females and 16 males are among the controls. Most of the patients presented with fever, cough, myalgia, and loss of smell, while all patients had complaints of difficulty in breathing.

Patients’ comorbid conditions included diabetes (43%), hypertension (29%), others (58%) in the treatment group, and diabetes (43%), hypertension (12%), and others (54%) in the control group. About 41% of patients in the treatment group and 45.16% in the control group reported having no comorbidities, that is, both the groups were comparable in terms of co-morbidities with an insignificant p-value of 0.7972.

A single case of infusion-related reaction was reported with chills and rigors. The patient received symptomatic treatment with chlorpheniramine 20 mg IV, as he is already on steroids, but it was abated by extending the period of infusion. Repeat doses were not given to any patients.

Figures 1 and 2 depict posttreatment inflammatory markers: the mean IL-6 value declined by 67.12%, and the mean D-dimer declined by 76.96% compared to predose values, with a significant p-value of 0.003 and 0.003, respectively in comparison to the control group. Reduction in mean C-reactive protein (CRP) (59%) and Ferritin (77%) was observed in a posttreatment group compared to predose values, but their p-values are not significant when compared to the control group. A significant reduction in proinflammatory biochemical parameters such as IL-6 and D-dimer was observed in the treatment group as shown in Table 1.

Figure 3 depicts pretreatment radiological findings: A mean CT severity score of 15.68, in the treatment group with a standard deviation (SD) of 4.10, and among controls, CT severity score is 13.68 with an SD of 4.11. Both groups were comparable in terms of CT severity with an insignificant p-value of 0.0603.

Figure 4 depicts, CT scores among non-survivors: The mean CT severity score (CTSS) of cases was noted to be 16.33 with an SD of 4.90 and for controls, the CT score was 12.08 with an SD of 4.46 (significant p-value of 0.0329). The mortality outcomes were noted at a higher CTSS in the treatment group, in comparison to the control group.

On reviewing the mortality outcomes, there were 12 deaths out of 31 cases and 13 deaths out of 31 controls noted. Overall mortality in both groups was noted to be almost similar with an insignificant p-value of 0.0795.

There was a significant gender-wise difference among both the groups in terms of mortality (p-value of 0.016) that is, death among females was higher in both groups.

A single case of infusion-related reaction was reported with chills and rigors. The patient received symptomatic treatment with chlorpheniramine 20 mg IV, as he is already on steroids, but it was abated by extending the period of infusion. Repeat doses were not given to any patients.

**Discussion**

COVID-19 may remain mild in most cases but, turns severe and fatal in some patients. The disease advancement of COVID-19 is categorized into three different phases: the early infection phase, the pulmonary phase, and the hyper inflammation phase. As new cases of COVID-19 continue to grow worldwide in addition to developing antiviral treatments, there is also been a focus on how to combat a cytokine syndrome as systemic inflammation has been reported as a predictor for COVID-19 outcomes. Several monoclonal antibodies are under investigation in clinical trials targeting various cytokines IL-6, vascular endothelial growth factor (VEGF), and Jak-2 pathways. If untreated, this cytokine release syndrome may lead to increased endothelial permeability, hypercoagulation, multiorgan dysfunction, and eventually death.

![Fig. 1: Pre and posttreatment IL-6 levels in both groups](image1)

![Fig. 2: Pre and posttreatment D-dimer levels in both groups](image2)

![Fig. 3: CTSS of cases and controls](image3)

![Fig. 4: CTSS among expired cases and controls](image4)
A significant decrease in proinflammatory biochemical parameters such as IL-6 and D-dimer was observed after treatment with itolizumab. Our findings are in agreement with recent trials held in Cuba, where a reduction in IL6 levels was seen in COVID-19 patients treated with itolizumab.7,8 Saavedra et al. have reported that one dose of itolizumab reduced the baseline serum levels of IL-6 in 24 critically and severely ill COVID-19 patients as well as stabilized the baseline low levels in moderately ill elderly COVID-19 patients.7 A recent report by Vishal Gore et al. states that a single dose of itolizumab accelerated recovery in 25 adult patients with COVID-19 by controlling immune hyperactivation and clinical improvement was demonstrated by a reduction in inflammatory markers, getting weaned-off given standard care including steroids, hence, posttreatment results were not significantly impacted by the confounding variables.

Out of 62 patients recruited, 37 patients were survivors and 25 patients were non-survivors (deceased). Among non-survivors, 12 patients (12/31) belong to the treatment group and 13 patients (13/31) belong to the control group. No major difference was detected in the mortality rate among cases and controls (38% vs 41%) with an insignificant p-value of 0.795. Both groups demonstrated almost similar mortality outcomes at the end of 14 days as the majority of the patients were critically ill and needed ventilator support in both groups. Posttreatment inflammatory markers reveal a mean IL-6 value decline of 67.12% and a mean D-dimer decline of 76.96% with a significant p-value of 0.003 and 0.003, respectively in comparison to the control group. The mean duration of hospital stay was 10 days with an SD of 5.4 among cases while it was 10 days with an SD of five among controls. There was no significant difference in the length of hospital stay as there was a higher incidence of deaths in both groups.

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The optimal approach to the treatment of COVID-19 is evolving. CD6 is a glycoprotein expressed on the surface of mature T-cells, subsets of innate lymphoid and natural killer cells, but not on T-regulatory cells, CD6 is very important for the immunological synapse between the antigen-presenting cells and the activated T lymphocytes.5 The binding of CD6 to the activated leukocyte cell adhesion molecule, expressed in both the antigen-presenting cells and endothelial/epithelial tissue, including the blood-brain barrier, skin, gut, lung, and kidney, can modulate T-cell activity and trafficking.6

Itolizumab works early in the inflammatory cascade and regulates upstream signaling, in contrast to biologics like tocilizumab which block only the specific cytokine (IL-6) released downstream.1

Among the 62 patients recruited, the majority of the patients in both groups have comorbidities and also needed mechanical ventilation. Both the groups were comparable in terms of comorbidities and mechanical ventilation requirements with an insignificant p value of 0.792 and 0.788, respectively as shown in Table 2. Also, both the groups were given standard care including steroids, hence, posttreatment results were not significantly impacted by the confounding variables.

A significant decrease in proinflammatory biochemical parameters such as IL-6 and D-dimer was observed after treatment with itolizumab. Our findings are in agreement with recent trials held in Cuba, where a reduction in IL6 levels was seen in COVID-19 patients treated with itolizumab.7,8 Saavedra et al. have reported that one dose of itolizumab reduced the baseline serum levels of IL-6 in 24 critically and severely ill COVID-19 patients as well as stabilized the baseline low levels in moderately ill elderly COVID-19 patients.7 A recent report by Vishal Gore et al. states that a single dose of itolizumab accelerated recovery in 25 adult patients with COVID-19 by controlling immune hyperactivation and clinical improvement was demonstrated by a reduction in inflammatory markers, getting weaned-off given standard care including steroids, hence, posttreatment results were not significantly impacted by the confounding variables.

Table 2: Mechanical ventilation requirement among cases and controls

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Table 1: Inflammatory markers and their significance among both the groups

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Table 2: Mechanical ventilation requirement among cases and controls
Our study results are comparable to their results in terms of inflammatory markers reduction and weaning of oxygen. However, our study results did not demonstrate any mortality benefit.

Another recent piece of evidence by Thacker et al. shows treatment of moderate-to-severe COVID-19 disease with itolizumab reduced inflammatory markers and improved oxygen saturation levels in 27 ARDS patients with no mortality. Our study also depicted a similar reduction in inflammatory markers, but mortality outcomes are not similar to their study. A high threshold for CT severity score-related mortality in the treatment group is a significant finding in our study which is worth highlighting. Mortality was predicted at lower CT severity scores in the control group, with a significant p value of 0.0329, which can be regarded as a mortality benefit. The present study demonstrates that itolizumab does not seem to halt the cytokine storm once it is established, but possibly prevents/reduces it if given early in the pulmonary phase of COVID-19.

Limitations
It is a retrospective study and the results obtained were restricted to patients admitted to a tertiary hospital hence, a small sample size is a limiting factor for generalizing the results. Additional studies with larger sample sizes will be required to fully understand the time kinetics of its mechanism of action and also its role in reducing COVID-19 mortality.

Conclusion
The present retrospective study shows a significant reduction in inflammatory markers, in the treatment group. The study reveals no proven benefit in mortality outcomes, but this could be partly attributed to the delayed administration due to the nonavailability of itolizumab and also the criticality of illness as evidenced by ARDS and ventilatory needs. However, mortality was predicted at a lower CT score in the control group when compared to the treatment group with a significant p value of 0.0329, which may be regarded as a mortality benefit. Therefore, itolizumab should be considered early in the course of COVID-19 infection at the pulmonary phase of the disease when patients start experiencing labored breathing or needing supplemental oxygen. We propose that elevated inflammatory markers like IL-6 and D-dimer along with high CT severity scores may help identify patients at high risk for deterioration. Identifying asymptomatic patients at high-risk aids in the triage and escalation process. In conclusion, treating patients for cytokine storms before they require intubation/mechanical ventilation is crucial in preventing deaths. Timely initiation of itolizumab therapy may serve as a key therapeutic option in preventing mortality and morbidity outcomes in moderate-severe COVID-19 patients.

Funding: No financial assistance was required for this study.

Conflict of interest: There were no conflicts of interest to declare.

Ethics clearance: Obtained from institutional ethical committee.

Authors’ contributions: All the authors have substantially contributed to the conception, and drafting of the work, and revising it critically for important intellectual content and final approval of the version to be published.

References
Clinicopathological Study of Chronic Kidney Disease of Unknown Etiology in Odisha

Swati Parida1, Sidharth Das2, Asaranti Kar3, Rakesh Kumar Routray4

Received: 05 September 2021; Revised: 5 September 2021; Accepted: 20 July 2022

ABSTRACT

Introduction: Chronic kidney disease (CKD) is emerging as a serious health problem in Odisha, India. A new form of severe CKD affecting adults, not due to traditional risk factors like diabetes, hypertension, glomerulonephritis, has been reported in Sri Lanka, Central America, and Egypt in the last two decades. This has been named CKD of unknown origin (CKDu), and it is fatal due to late recognition and rapid disease progression. The aim of the study was to elucidate the association between different sociodemographic, and biochemical parameters with renal morphology in CKD of unknown origin patients.

Methods: A cross-sectional study was conducted on 124 consecutive patients with CKD from the period January 2018 to December 2018. Patients in the age group 18–60 years who met clinical criteria for CKD were included. Participants answered a questionnaire. After the necessary history, clinical evaluation, and blood and urine analyses, a kidney biopsy was undertaken. Kidney biopsy was feasible in 51 patients as the rest 61 patients had shrunken kidneys and 12 patients did not give consent. Patients with diabetes mellitus (DM), hypertension, glomerulonephritis, polycystic kidney disease, obstructive kidney disease or any other congenital diseases, snakebite, pregnancy, malignancy, gout, primary hyperparathyroidism, infectious diseases like human immunodeficiency virus (HIV), TB, Hepatitis B and C, malaria, syphilis, leprosy and coagulopathies were excluded. Among the 51 patients, 23 had CKDu, 25 had chronic glomerulonephritis and three biopsies were inconclusive.

Results: The mean age of CKDu patients was 36.78 ± 9.85 years. Males (73.9%) were predominantly affected. A family history of CKD was seen in 82.6% of CKDu cases. Hyponatremia and hypokalemia were predominant biochemical abnormalities in our CKDu cases. Binary logistic regression showed rural residence, family history of CKD, exposure to smoke from burning coal, charcoal, or biomass fuels, low socioeconomic status, and low body mass index were strongly associated with CKDu. There was an increased risk of developing CKDu in persons with a family history of CKD (p = 0.003, odds ratio (OR)—17.58), persons exposed to smoke from burning coal, charcoal or biomass fuels (p = 0.003, OR—32.4), and patients with low socio-economic status (p = 0.001, OR—15.87). Interstitial fibrosis (IF), interstitial inflammation with mononuclear infiltration, tubular atrophy (TA), and global glomerulosclerosis (GS) were pertinent histopathological findings in our study.

Conclusion: There is no strong evidence for a single cause for CKDu, and multiple environmental, occupational and social factors are probably involved. We need to design consistent and comparative multisite studies to identify etiologies of CKDu, across high-risk populations that may help elucidate the importance of region-specific vs global risk factors.

INTRODUCTION

Chronic kidney disease (CKD) encompasses a spectrum of different pathophysiological processes associated with abnormal kidney function and a progressive decline in the glomerular filtration rate (GFR). It is well established that DM, hypertension, and glomerulonephritis are the major causes of CKD. In the past few decades a new form of CKD, not associated with hitherto established causes has been observed whose etiology and pathogenesis are still uncertain. This form of CKD has been termed CKDu. CKD is considered to be of unknown origin in the absence of recognized conditions which cause renal disease, such as DM, hypertension, polycystic kidney disease, glomerular diseases, and obstructive uropathies together with normal hemoglobin A1c (HbA1c) < 6.5%, blood pressure < 160/100 mm Hg untreated or < 140/90 mm Hg with up to two antihypertensive medications.1

The endemic nature of CKDu was first observed in 1990 and over the last two decades, there is a remarkable rise in the prevalence of CKDu within certain geographical locations, mainly in Asia (Sri Lanka and India) and Central America (Nicaragua, El Salvador, Costa Rica).2,3 In most of the instances CKDu has been named according to the region where it appeared like Uddanam endemic nephropathy (in Andhra Pradesh), Sri Lankan agricultural nephropathy, Salvadoran agricultural nephropathy, Mesoamerican nephropathy (MeN).4 In India, Odisha, Andhra Pradesh, and Goa have been considered hot spot endemic zones for CKDu.5 High incidence of CKDu in Odisha is reported in several districts—Cuttack, Koraput, Malkangiri, Bolangir, Nayagarh, Boudh, and Nuapada. Narasinghpur and Badamba blocks in the Cuttack district are regarded by the local press as hotspots.6

Chronic kidney disease of unknown origin (CKDu) in Odisha contributes significantly to the national burden of CKD in India. Most of the affected persons are from the productive age group. There is no universally accepted case definition for CKDu but its common characteristics as observed in different studies are: long asymptomatic phase, progressive, non-nephrotic proteinuria, absence of hematuria, men are more affected than females, and most of the endemic zones for CKDu have hot and humid climate.7 CKDu is reported from most regions in India; however, is interpreted differently from the phenotype described in Central America and Sri Lanka. The differences include lack of a clear demographic or occupation group, older age of affected participants, and presence of mild hypertension and low-grade proteinuria.2 Different etiologies which have been proposed for causing CKDu are heavy metals, pesticides, infections, local brand alcohol consumption, genetic factors, heat exposure, and nephrotoxic drugs. MeN was mostly seen in the poor young male sugarcane cultivators who used to work in the hot and humid climate for long hours.8,9 Sri Lankan agricultural nephropathy has been attributed to prolonged exposure to agrochemicals,
Clinicopathological Study of CKDu in Odisha

Ochratoxin A, fluoride, and heavy metals like cadmium and arsenic. In the 1990s, endemic nephropathy was reported from Uddanam region of Andhra Pradesh which is a low-altitude terrain with coconut and cashew plantations. Studies done in Northern India showed increased levels of organochlorines in the urine of patients with CKD.

The predominant histopathological finding in patients with CKDu is chronic tubulointerstitial nephritis. This study aims to observe the association between different sociodemographic, and biochemical parameters with renal morphology in CKDu patients as the data regarding their association is limited.

**Materials and Methods**

A cross-sectional study was conducted on 124 consecutive patients with CKD attending the Department of Medicine and Nephrology, SCB Medical College, Cuttack, Odisha from the period January 2018 to December 2018. Patients of the age group 18–60 years with CKD who met clinical criteria for CKD: kidney damage for ≥3 months, as defined by structural or functional abnormalities of the kidney, with decreased GFR (GFR < 60 mL/min/1.73 m²), markers of kidney damage, including abnormalities in the composition of the blood or urine or abnormalities in imaging tests, were included. Participants answered a questionnaire.

Patients with DM, hypertension (>140/90 mm Hg), glomerulonephritis, polycystic kidney disease, obstructive kidney disease or any other congenital diseases, snakebite, pregnancy, malignancy, gout, primary hyperparathyroidism, infectious diseases like HIV, TB, Hepatitis B and C virus (HBV, HCV), malaria, syphilis, leprosy, and coagulopathies were excluded. Those patients in whom the cause of glomerular pathology could be established from history, clinical examination, and blood tests (e.g., collagen vascular diseases) were not biopsied.

Baseline evaluations included detailed history, general and systemic examinations, complete blood count, erythrocyte sedimentation rate (ESR), C-Reactive protein, renal function tests, liver function tests, random blood sugar, lipid profile, urine routine microscopy, 24 hours urinary protein, serum protein and albumin, serum uric acid, viral markers like HIV, HBV, HCV serology, HbA1c, antinuclear antibody, complements C3 and C4 (C3, C4), anti-neutrophil cytoplasmic antibody (ANCA), rheumatoid factor, a sickling test, thin and thick blood smear for malarial parasites, venereal disease research laboratory test (VDRL), bleeding and clotting time, prothrombin time and activated partial thromboplastin time, chest X-ray, electrocardiogram, echocardiogram, ultrasound of abdomen and pelvis, X-ray kidney, ureter and bladder (KUB) region and kidney biopsy. A kidney biopsy was done in all the patients with normal or near normal kidney size and a light microscopic and immunofluorescence study was done.

Ultrasonography-guided renal biopsy was done in all our cases using an 18G automated spring-loaded renal biopsy gun after taking informed written consent. Two-needle core specimens of renal tissues were obtained after renal biopsy, one core of tissue in 10% formal saline and the other piece in phosphate buffer saline (PBS). Further, the specimens were sent to the laboratory for light microscopy and immunofluorescence study. The second tissue core was cut into thin micro-sections of 5–8 micron thickness in the Cryostat (LEICA CM1510S) and the unstained sections were under the light microscope after staining with haematoxylin and eosin, periodic acid Schiff, Masson’s trichrome, and silver methenamine.

Chronic kidney disease (CKD) is graded into five stages based on GFR (mL/min/1.73 m²) namely, G1: ≥ 90, G2: 60–89, G3a: 45–59, G3b: 30–44, G4: 15–29, G5: < 15 and albuminuria (mg/g) A1: < 30, A2: 30–300, A3: > 300 by kidney disease improving global outcome.

Family history of CKD was defined as the presence of a first-degree relative with CKD. Socioeconomic status was calculated using Modified BG Prasad socioeconomic classification 2018.

**Results**

A description of the sociodemographic data of CKDu cases is presented in Table 2. More than half (60.9%) of the patients were in the age group of 31–45 years. The mean age of CKDu patients was 36.78 ± 9.85 years. The male to female ratio was 2.8:1. Mean duration of illness was 2.99 ± 1.52 years. About 95.7% of CKDu cases belonged to the rural areas, 82.65% had a family history of CKD and 87% belonged to lower socioeconomic class. Nearly 95.7% of patients were exposed to smoke from burning coal, charcoal, or biomass fuels. Around 13% of patients had a history of analgesic intake on and off, 13% used to take homeopathic medication and 21.7% took herbs and ayurvedic medications for many years. About 73.9% CKDu patients presented with nausea and vomiting, 65.2% presented with nausea and vomiting, 65.2% presented with nausea and vomiting, 65.2% presented with nausea and vomiting.

**Table 1: Scoring of the chronic lesions in individual tissue compartments**

<table>
<thead>
<tr>
<th>Tissue compartment</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerulosclerosis</td>
<td></td>
</tr>
<tr>
<td>Interstitial fibrosis</td>
<td></td>
</tr>
<tr>
<td>Tubular atrophy</td>
<td></td>
</tr>
<tr>
<td>Arteriosclerosis</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade</th>
<th>Total renal chronicity score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal chronic changes</td>
<td>0–1</td>
</tr>
<tr>
<td>Mild chronic changes</td>
<td>2–4</td>
</tr>
<tr>
<td>Moderate chronic changes</td>
<td>5–7</td>
</tr>
<tr>
<td>Severe chronic changes</td>
<td>≥8</td>
</tr>
</tbody>
</table>
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Fig. 1: Schematic representation of the methodology adopted in our study

with fatigue, lassitude, and weakness, 34.8% had a loss of appetite, 8.7% had back pain and 8.7% presented with altered sensorium. Around 95.6% of CKDu cases had hyponatremia (serum sodium < 135 mEq/L), 47.8% of patients had hypokalemia (serum potassium < 3.5 mEq/L) whereas in the chronic glomerulonephritis (CGN) group 12% of patients had hyponatremia and none had hypokalemia.

Clinical and biochemical parameters of CKDu cases are shown in Table 3. Around 51/23 (78.3%) patients had 2+ proteinuria in the urine dipstick test and the remaining 5 (21.7%) patients had 1+ proteinuria. Nearly 4.3% of patients were in stage 2 CKD. About 30.4% of patients were in stage 3a, 52.2% patients were in stage 3b. The remaining 13.1% of patients were in CKD stage 4.

A summary of the light microscopic findings is presented in Table 4. A total of 51 selected CKD patients underwent kidney biopsy. Twenty-three patients had chronic tubulointerstitial nephritis, 25 had CGN and the remaining three biopsies were inconclusive.

Among the 25 patients with CGN, 13 had membranous glomerulonephritis, five had IgA nephropathy, three had amyloidosis, and four had focal segmental GS. Therefore, 23 cases constituted our study sample of CKDu. In our study, we compared the differences between both groups (CKDu and CGN).

About 4.3% of patients had grade 0 global GS. Around 34.8% of patients had grade 2 GS and 60.9% of patients had grade 3 GS (Figs 2 and 3). The majority of the patients had >50% GS. About 34.8% of patients had periglomerular fibrosis. Around 17.4% patients had grade 1 TA, 56.5% patients had grade 2 TA and 26.1% patients had grade 3 TA (Figs 4 and 5).

1. Nearly 17.4% patients had grade 1 IF, 65.2% patients had grade 2 IF and 17.4% patients had grade 3 IF (Figs 6 and 7).

None of the CKDu patients had glomerulomegaly and tubular fibrosis. About 91.3% of patients had hyaline casts. Interstitial infiltrates were present in all 23 cases which mainly comprised lymphocytes and plasma cells. Around 21.7% of patients had arterolar hyalinosis. Nearly 21.7% of patients had tubular media thickening and 17.4% of patients had tubular media vacuolation. (Immunoglobulin deposits like Immunoglobulin M, G, and A (IgM, IgG, IgA), complement component 1q (C1q), C3, kappa and lambda light chains, and fibrinogen were absent in the glomeruli, interstitium, or tubules in all the CKDu cases. Based on the total renal chronicity score: 13% (3/23) cases had mild chronic changes, 56.6% (13/23) had moderate chronic changes and 30.4% (7/23) had severe chronic changes.

We observed as the stage of CKD in CKDu patients progresses, renal damage is increasing as shown by increased total renal chronicity score from mild changes in CKD stage 2 to severe chronic changes in CKD stages 3b and 4. There was statistically significant association between stages of CKD and GS (\( p = 0.001 \)), TA (\( p = 0.011 \)), and IF (\( p = 0.001 \)) in CKDu cases.

• About 5.9% of male patients had grade 0 GS. About 47% of males had grade 2 GS, 100% of the females and 47% of males had grade 3 GS. Nearly 17.6% of male and 16.7% of female patients had grade 1 TA. Around 64.8% of males and 33.3% of females had grade 2 TA. About 17.6% of males and 50% of females had grade 3 TA. Nearly 23.5% of males had grade 1 IF. About 64.7% of males and 66.7% of females had grade 2 IF. Around 11.8% of males and 33.3% of females had grade 3 IF. There was no statistically significant difference of GS (\( p = 0.072 \)), TA (\( p = 0.279 \)), and IF (\( p = 0.272 \)) with gender in CKDu cases.
Table 3: Clinical and biochemical characteristics of CKDu and CGN cases

<table>
<thead>
<tr>
<th>Variables</th>
<th>CKDu cases (n = 23)</th>
<th>Percentage</th>
<th>CGN cases (n = 25)</th>
<th>Percentage</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical and biochemical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of disease (in years)</td>
<td>2.99 ± 1.52</td>
<td>25.7 ± 1.28</td>
<td>0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>**BMI (kg/m²)</td>
<td>19.81 ± 2.2</td>
<td>25.03 ± 2.4</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>123.2 ± 8.45</td>
<td>139.2 ± 5.62</td>
<td>0.006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>75.3 ± 4.57</td>
<td>74.8 ± 3.7</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (gm/dL)</td>
<td>11.16 ± 0.7</td>
<td>10.88 ± 0.5</td>
<td>0.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum urea (mg/dL)</td>
<td>54.6 ± 7.6</td>
<td>60.64 ± 10.9</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.9 ± 0.63</td>
<td>1.92 ± 0.62</td>
<td>0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>e-GFR(ml/mnt/1.73m²)</td>
<td>39.1 ± 11.38</td>
<td>35.52 ± 7.6</td>
<td>0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum sodium (mEq/L)</td>
<td>129.5 ± 2.3</td>
<td>137.7 ± 4.13</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum potassium (mEq/L)</td>
<td>3.6 ± 0.44</td>
<td>4.2 ± 0.47</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum ionized calcium (mmol/L)</td>
<td>1.2 ± 0.1</td>
<td>1.23 ± 0.11</td>
<td>0.57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum uric acid (mg/dL)</td>
<td>5.89 ± 0.67</td>
<td>6.08 ± 0.74</td>
<td>0.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum total cholesterol (mg/dL)</td>
<td>141.3 ± 14.6</td>
<td>182.36 ± 40.6</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-hour urine protein (grams/24 hours)</td>
<td>1.17 ± 0.24</td>
<td>3.32 ± 0.25</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

There was statistically significant difference in the occurrence of GS (p = 0.001), TA (p = 0.001) and IF (p = 0.001) among the two groups. Significant difference was observed among both the groups considering different independent variables like gender (p = 0.018), family history (p = 0.001) and rural residence (p = 0.001). There was no significant difference between the groups considering alcohol or smoking history (Table 5).

We used binary logistic regression to look for the association between independent variables and dependent variables. We compared the two groups, that is, patients with CKDu and those with CGN. Our dependent variable was CKD of unknown etiology. Different independent variables were gender, residence, family history of CKD, exposure to smoke from burning coal, charcoal or biomass fuels, exposure to pesticides and insecticides, socioeconomic status, tube well water users, and body mass index. It showed rural residence (p = 0.016), family history of CKD (p = 0.003), exposure to smoke from burning coal, charcoal or biomass fuels (p = 0.003), low socioeconomic status (p = 0.001) and low BMI (p = 0.001) were strongly associated with CKDu.

There was significant risk of developing CKDu in persons having a family history of CKD (p = 0.003, OR- 17.58, 95% CI = 2.63–117.47), persons exposed to smoke from burning coal, charcoal or biomass fuels (p = 0.003, OR- 32.4, 95% CI = 3.277–320.36) and patients with low socioeconomic status (p = 0.001, OR- 15.87, 95% CI = 2.95–85.15) (Table 6). The Nagelkerke R² for the model was 0.71.

Discussion

The mean age of CKDu patients was 36.78 ± 9.85 years. Most of the patients (60.9%) were in the age group of 31–45 years. About 95.7% of CKDu patients belonged to a rural area in our study. The mean age of the CKDu patients in Sri Lanka was 46.2 ± 11.63 years in one study. About 30.4% CKDu patients were farmers (paddy cultivators) in our study. In CKDu in Sri...
patients from Sri Lanka, Central America and Uddanam had lower socioeconomic status. Studies by Oommen John et al. showed more than 70% CKDu patients in Odisha belonged to lower socioeconomic groups, and 48% were engaged in agricultural activities. The prevalence of CKD was equal in the two sexes. The prevalence was ≥20% in one-third of the sampled villages, suggesting geographic clustering. This could mean either an environmental or genetic basis to the disease, with potential for higher exposure to either environmental (contaminated food, water, or air), behavioral (use of nonsteroidal anti-inflammatory drugs, occupational activities, how foods are stored) or genetic (genes in families) factors. Most of our patients were exposed to smoke from burning coal, charcoal or biomass fuels. This high percentage of exposure could be attributed to the higher proportion of patients from rural areas. More studies are needed to assess the fine particulate matter composition. Around 56.5% patients were exposed to pesticides and insecticides. We need longitudinal studies to assess life-time pesticide exposure assessments. In our study, 82.6% patients used tube well as source of water. Estimation of levels of heavy metals like arsenic, cadmium, lead, mercury in water need to be done.

Nausea and vomiting were the most common presentation (73.9%). CKDu patients in Sri Lanka presented with back pain and dysuria and those from Nicaragua presented with chistata (dysuria and back pain). Around 34.8% CKDu cases were underweight. It could be due to the poor socioeconomic status observed in these cases. Mean 24 hours of urinary protein was non-nephrotic proteinuria. About 95.6% of patients had hyponatremia and 47.8% of patients had hypokalemia. In MeN studies from Central America, hyponatremia, hypokalemia, and hypomagnesemia were common features. In hypokalemic nephropathy, the morphological features in the kidney include swelling and vacuolization of the proximal tubular epithelium, tubular dilatation and atrophy, and progressive capillary loss but the glomerular structures are usually normal. Chronic hypokalemia induces renal vasoconstriction, renal ischemia, and progressive IF. We cannot say firmly whether chronic tubulointerstitial kidney damage leads to hypokalemia or vice versa but as the pathological findings did not match, we assume chronic tubulointerstitial kidney damage causes renal wasting which results in hyponatremia and hypokalemia. The glomerulus is not involved in the early stages

<table>
<thead>
<tr>
<th>Light microscopy</th>
<th>Cases (n = 23)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glomerular changes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global glomerulosclerosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10%</td>
<td>01</td>
<td>4.3%</td>
</tr>
<tr>
<td>10–25%</td>
<td>Nil</td>
<td>0%</td>
</tr>
<tr>
<td>26–50%</td>
<td>08</td>
<td>34.8%</td>
</tr>
<tr>
<td>&gt;50%</td>
<td>14</td>
<td>60.9%</td>
</tr>
<tr>
<td>Periglomerular fibrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>08</td>
<td>34.8%</td>
</tr>
<tr>
<td>Absent</td>
<td>15</td>
<td>65.2%</td>
</tr>
<tr>
<td>Glomerulomegaly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>Nil</td>
<td>0%</td>
</tr>
<tr>
<td>Absent</td>
<td>23</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Tubular changes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tubular atrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10%</td>
<td>Nil</td>
<td>0%</td>
</tr>
<tr>
<td>10–25%</td>
<td>04</td>
<td>17.4%</td>
</tr>
<tr>
<td>26–50%</td>
<td>13</td>
<td>56.5%</td>
</tr>
<tr>
<td>&gt;50%</td>
<td>06</td>
<td>26.1%</td>
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<td>Tubular fibrosis</td>
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<tr>
<td>Present</td>
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<td>0%</td>
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<tr>
<td>Absent</td>
<td>23</td>
<td>100%</td>
</tr>
<tr>
<td>Tubule casts</td>
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<td></td>
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<tr>
<td>Present (hyaline)</td>
<td>21</td>
<td>91.3%</td>
</tr>
<tr>
<td>Absent</td>
<td>02</td>
<td>8.7%</td>
</tr>
<tr>
<td><strong>Interstitial changes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interstitial fibrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10%</td>
<td>Nil</td>
<td>0%</td>
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<tr>
<td>10–25%</td>
<td>04</td>
<td>17.4%</td>
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<tr>
<td>26–50%</td>
<td>15</td>
<td>65.2%</td>
</tr>
<tr>
<td>&gt;50%</td>
<td>04</td>
<td>17.4%</td>
</tr>
<tr>
<td>Interstitial Infiltrates</td>
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<td></td>
</tr>
<tr>
<td>Present (lymphocytes, plasma cells)</td>
<td>23</td>
<td>100%</td>
</tr>
<tr>
<td>Absent</td>
<td>Nil</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Vascular changes</strong></td>
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<td></td>
</tr>
<tr>
<td>Arteriolar hyalinosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>05</td>
<td>21.7%</td>
</tr>
<tr>
<td>Absent</td>
<td>18</td>
<td>78.3%</td>
</tr>
<tr>
<td>Tunica media thickening</td>
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<td></td>
</tr>
<tr>
<td>Present</td>
<td>05</td>
<td>21.7%</td>
</tr>
<tr>
<td>Absent</td>
<td>18</td>
<td>78.3%</td>
</tr>
<tr>
<td>Tunica media vacuolation</td>
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<td></td>
</tr>
<tr>
<td>Present</td>
<td>04</td>
<td>17.4%</td>
</tr>
<tr>
<td>Absent</td>
<td>19</td>
<td>82.6%</td>
</tr>
<tr>
<td>Intima proliferation</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>Nil</td>
<td>0%</td>
</tr>
<tr>
<td>Absent</td>
<td>23</td>
<td>100%</td>
</tr>
</tbody>
</table>

Lanka most of the patients were chena (slash and burn) cultivators. In Central America nephropathy most of the CKDu patients were agricultural workers associated with sugarcane cultivation. Nearly 87% of our CKDu patients belonged to lower socioeconomic class.
Fig. 2: Globally sclerosed and solidified glomeruli with IF (Masson’s trichome×100X)

Fig. 3: Global GS with marked IF and TA (Silver methenamine×200X)

Fig. 4: Dilated tubules containing hyaline casts (PAS×200X)

Fig. 5: Chronic IF and TA with collapsed glomeruli (PAS×100X)

Fig. 6: Marked stripped fibrosis of interstitium (Masson’s trichome×100X).

Fig. 7: Marked IF and TA with dilated tubules containing hyaline casts (PAS×100X)
had intimal thickening and 10/11 patients had arteriolar hyalinosis. 28 Renal histopathology of Salvadoran agricultural communities revealed >25% GS was present in 58.7% of patients and 41.3% of patients had <25% GS. 17

Limitations of our Study are

• Small sample size: Most of the CKD patients presented with an end-stage renal disease with shrunken kidneys, so a very less number of patients were fit to undergo biopsy due to which sample size was less. Probably CKDu in Odisha has also a long asymptomatic period like CKDu in Sri Lanka and Central America due to which most of the patients present with end-stage renal disease. Therefore, we need to do epidemiological studies in CKDu endemic zones where we can get more patients in the early stages of CKD.

• It was a hospital-based study where we included all CKD patients who presented to us in the outpatient department and satisfied our eligibility criteria. No sampling methods could be adopted.

• Estimation of levels of heavy metals like arsenic, cadmium, lead, and mercury in water needs to be done. 4 We need to speculate further whether hyponatremia and hypokalemia are due to renal wasting caused by tubulointerstitial damage or if there is some form of hyponatremic or hypokalemic nephropathy. We need to estimate the urinary levels of sodium, potassium, phosphate, uric acid, and magnesium along with arterial blood gas analysis.

Strengths of our Study

There are limited studies on histopathology of CKDu from Odisha as well as India. Most of the studies in India have considered CKDu based on the case definition without conducting a biopsy to rule out other causes. Though it is a cross-sectional study, we found certain factors like family history, exposure to biomass fuel smoke, and low socioeconomic status were associated with an increased risk of CKDu.

Conclusion

The major histopathological pattern observed in our CKDu cases was IF and TA. Global GS, 63% patients had moderate GS and 37% had severe GS. 26 In another study done on CKDu patients of Sri Lanka global GS, glomerular hypertrophy, IF, and TA were present in all 11 patients. About 7/11 patients had periglomerular fibrosis. Around 5/11 patients had intimal thickening and 10/11 patients had arteriolar hyalinosis. 28 Renal histopathology of Salvadoran agricultural communities revealed >25% GS was present in 58.7% of patients and 41.3% of patients had <25% GS. 17

Table 5: Correlations of gender, residence, family history, alcohol history, and smoking history in patients with CKDu and CGN

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<td>Males</td>
<td>17</td>
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<td>5.59</td>
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<tr>
<td>CKD(GN)</td>
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<td>Males</td>
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<td></td>
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<td>Females</td>
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<td>Residence</td>
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<td>Rural</td>
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<td>CKD(GN)</td>
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<tr>
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<td></td>
<td>Urban</td>
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<td>35.4%</td>
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<tr>
<td>Family history</td>
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<td>24.05</td>
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<td>03</td>
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<td>Alcoholic</td>
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<td>Smoker</td>
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<td>06</td>
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<td></td>
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<td>39.5%</td>
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Table 6: Possible risk factors associated with CKDu

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<th>OR*</th>
<th>CI Lower</th>
<th>CI Upper</th>
<th>p-value</th>
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<td>Males</td>
<td>27</td>
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<td>1.94</td>
<td>0.293</td>
<td>12.83</td>
<td>0.49</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residence</td>
<td>Rural</td>
<td>30</td>
<td>62.5%</td>
<td>0.05</td>
<td>0.005</td>
<td>0.57</td>
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<td></td>
<td>Urban</td>
<td>18</td>
<td>37.5%</td>
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<td></td>
<td></td>
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<tr>
<td>Family history of CKD</td>
<td>Present</td>
<td>26</td>
<td>54.2%</td>
<td>17.58</td>
<td>2.63</td>
<td>117.47</td>
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<tr>
<td></td>
<td>Absent</td>
<td>22</td>
<td>45.8%</td>
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<td></td>
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<tr>
<td>Exposure to smoke from</td>
<td>Exposed</td>
<td>29</td>
<td>60.4%</td>
<td>32.4</td>
<td>3.277</td>
<td>320.36</td>
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<td>burning coal, charcoal, or</td>
<td>Not exposed</td>
<td>19</td>
<td>39.6%</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>biomass fuels</td>
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<td>Exposure to</td>
<td>Exposed</td>
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<td>3.611</td>
<td>0.57</td>
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<td>insecticides, pesticides</td>
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<td>Socioeconomic status</td>
<td>Low (class IV, V)</td>
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<td>2.95</td>
<td>85.15</td>
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<td></td>
<td>High (class II, III)</td>
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<td>52.1%</td>
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<td>Tube well water users</td>
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<td>0.64</td>
<td>0.071</td>
<td>5.93</td>
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<tr>
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<td>43.7%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>BMI</td>
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<td>23</td>
<td>47.9%</td>
<td></td>
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<td>25–29.9</td>
<td>16</td>
<td>33.4%</td>
<td></td>
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</tr>
</tbody>
</table>

*OR- Odds ratio calculated by logistic regression using SPSS
Clinicopathological Study of CKDu in Odisha

has a long asymptomatic period like CKDu in other parts of the world due to which most of the patients present late with renal failure. As the etiology of CKDu is not known we need to report all renal histopathological findings as they may be important in understanding the pathogenesis of the disease. We need to do a biopsy in the early stages of CKDu and conduct large multicentric studies to understand the pathogenesis better.

Conflicts of interest: The authors declare that they have no conflicts of interest.

Funding statement: No organization or institution has contributed fund for this work.

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We are very much thankful to Dr Chittaranjan Kar, Professor and Head Department of Nephrology, SCB Medical College & Hospital, Cuttack for his guidance and immense support in carrying out this study. It is very unfortunate for us that when we are communicating this article he passed away due to the ongoing COVID-19 pandemic in November 2020. We sincerely pay our homage to him.

REFERENCES

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Start with

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Across Comorbidities

Hypertension | CAD / PAD | ASCVD & CHF

Across BMI

Underweight | Normal | Overweight | Obese

Across Ages

Young | Elderly | >90 Years

Across Stages

Newly Diagnosed | Early Stage | Long Duration

Across Complications

Nephropathy | Neuropathy / Diabetic Foot | Retinopathy

Prescribing information

Information: Metformin hydrochloride (as prolonged release) and glibenclamide tablets. Glycomet-GP 1/2 Tablets: Glycomet-GP 1/2 Tablets (500 mg + 1 mg) each. Each tablet contains metformin hydrochloride 500 mg and glibenclamide 1 mg.

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- 10/1000 XR

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*English, Hindi, Bengali, Gujarati, Marathi, Punjabi, Tamil, Assamese, Kannada, Malayalam, Oriya and Telugu.
Transcranial Doppler Screening for Patent Foramen Ovale Closure in Cryptogenic Strokes in Young: A Single Center Experience from South India

Deepthi Bal1, Atif Iqbal Ahmed Shaikh2, Murali Rayani3, Sanjith Aaron4*, Viji Samuel Thompson5, John Jose6, Jesu Krupa7, Rohit Ninan Benjamin8, Joanne Lydia Rajkumar9, Appaswamy Thirumal Prabhakar10

Received: 06 May 2022; Accepted: 07 July 2022

ABSTRACT

Background: Cryptogenic strokes are common in young adults. Patent foramen ovale (PFO) is an important cause of cryptogenic ischemic strokes. Transcranial Doppler (TCD) with bubble contrast is a noninvasive bedside tool in screening for PFO and other right to left shunt (R-L shunt). Percutaneous PFO closure in selected patients with a high risk for paradoxical emboli is beneficial. Data on PFO in young cryptogenic strokes from India are limited.

Aims: To determine the utility of screening for R-L shunt using TCD in young patients with cryptogenic strokes and to identify clinical predictors of an R-L shunt.

Materials and methods: This was a hospital-based prospective study conducted between January 2013 and December 2019 in a tertiary hospital in South India. All consecutive patients with ischemic stroke and ages between 18 and 45 years were included. TCD with bubble contrast study was performed on all patients. Those who were TCD bubble contrast study positive and had features of an embolic stroke of undetermined source (ESUS) underwent transesophageal echocardiography (TEE) to confirm a PFO and to look for its high-risk features. Selected ESUS patients with PFO and associated high-risk features as identified on TEE underwent percutaneous PFO device closure. All patients were followed up in the stroke and cardiology clinics.

Results: During the study period, 6,197 patients with ischemic strokes were screened for eligibility of which 304 (4.9%) were between the age of 18 and 45 years. Of these, 300 patients with ischemic stroke in young underwent the TCD bubble contrast study. R-L shunt was found in 121 (40.3%) patients. Based on an extensive etiological evaluation, 72 patients were identified to have an ESUS and underwent TEE for confirming PFO. Of these, 65 patients had PFO, four were negative, and three were found to have extracardiac shunts. Based on clinical findings, imaging features, and high-risk features on TEE, 29 patients underwent PFO device closure. The patients who had a higher modified anatomical-functional risk of paradoxical embolism (AF-RoPE) score, a high-grade shunt on the TCD bubble contrast study had a longer length of the funnel and had the presence of an interatrial septal aneurysm (p = 0.012) were referred for PFO device closure.

Conclusions: R-L shunt is common in cryptogenic ischemic strokes in young. TCD with bubble contrast study is a noninvasive and feasible bedside tool to detect them. Applying the ESUS criteria in these cryptogenic strokes with a positive TCD bubble contrast study can be then used for selecting patients for more invasive tests like TEE. High-risk PFOs picked up with TEE can be then considered for PFO closure for secondary stroke prevention. The history of Valsalva maneuver-like activity (such as lifting heavy weights or straining) at the time of stroke onset can be a clinical predictor for the presence of an R-L shunt. In addition to isolated cortical infarction, the presence of posterior circulation infarct in ESUS can predict the presence of an R-L shunt.

INTRODUCTION

Ischemic stroke continues to remain as one of the major causes of disability and death in the Indian setting. Despite extensive vascular, cardiac, and serological evaluations, the etiology remains unknown in 20–40% of patients. These are classified as cryptogenic strokes. Cryptogenic strokes are especially important in young adults. Cryptogenic strokes can be further classified as non-embolic and ESUS. ESUS can be due to paroxysmal atrial fibrillation (AF), atheroembolism, cancer-associated, and paradoxical embolism. The term paradoxical embolism is used to describe an embolus of venous origin entering the systemic circulation through a PFO, atrial septal defect, ventricular septal defect, or extracardiac communication such as pulmonary arteriovenous malformation. PFO is present in about 25% of the adult population. PFO is seen more commonly in patients with ESUS compared to the general population and is known to contribute to recurrent strokes. In patients with ESUS, PFO remains an important cause. PFO can cause ischemic strokes due to multiple mechanisms. The most common mechanism described is paradoxical embolism. Rarely, in situ thrombus formation can be seen. Also, patients with PFO have more susceptibility to arrhythmias.

The RoPE score combines some of the clinical and imaging details to help identify cryptogenic strokes more likely to have a pathogenic PFO. In younger patients without vascular risk factors and cortically placed infarcts if a PFO is identified, it is likely that the PFO is the cause of the stroke. Whereas, if a PFO is picked up in an older patient with a subcortical cryptogenic stroke who has vascular risk factors, it is likely that the PFO is an incidental finding and not the cause of the stroke. There are few features of a PFO and certain associated features which can make it a high risk for an ischemic stroke. The combination of atrial septal aneurysm (ASA) and PFO has the strongest association with a higher risk of cryptogenic strokes. Other features which increase the possibility of the PFO to be the cause of the stroke are large-size PFO (≥2 mm in height), long-tunnel PFO (≥10 mm in length), ASA, hypomobile interatrial septum large R-L shunt during Valsalva maneuvers, low-angle PFO (≤τ0° of PFO angle from inferior vena cava), and the presence of a prominent Eustachian valve or Chiari’s network. The AF-RoPE score has incorporated these high-risk features of PFO into the existing RoPE score trying to identify...
patients at high risk for recurrence who may benefit with PFO closure. Recent studies have shown the importance of identifying high-risk PFOs and the benefits of PFO closure for secondary stroke prevention. These observations are supported by findings of the CLOSE and DEFENSE-PFO trials which included only high-risk PFO patients. Thus, screening for PFO in patients with cryptogenic stroke is essential for stroke prevention. The routine transthoracic echocardiography (TTE) is of limited diagnostic power in detecting PFO while TEE is considered the reference standard. However, TEE is a semi-invasive test requiring patient cooperation and often mild sedation. Also, it is difficult to perform a Valsalva maneuver during this procedure. TCD bubble contrast study is a noninvasive, simple, and easy-to-perform test. It has been shown previously that TCD is superior to TEE for the detection of R-L shunt in stroke patients. Thus, the aim of our study was to determine the utility of screening for an R-L shunt using the TCD bubble contrast study in young patients with cryptogenic strokes and to identify clinical predictors of an R-L shunt.

**Materials and Methods**

This was a prospective observational study between January 2013 and December 2019, conducted in the Department of Neurological Sciences of a tertiary-level teaching hospital in South India. All ischemic stroke patients between the ages of 18–45 years were included. The study was approved by the Institutional Review Board (Mi. No. 13438). All included patients underwent a detailed history and physical examination to look at any clues towards a possible etiology. All patients had imaging including vascular imaging with computed tomography angiogram or magnetic resonance angiogram and 4-vessel carotid Doppler, TTE, and hematological evaluation including vasculitis, retroviral, and venereal disease research laboratory screening. Full thrombophilia workup was done which included genetic markers and protein assays. Fabry’s screening was done on selected patients. Magnetic resonance imaging (MRI) scans were performed on a 1.5T (Magnetom Avanto, Siemens) or a 3T (Intera Achieva, Philips Medical Systems) scanner. Computed tomography (CT) scan was performed on a 64-section scanner (Discovery 750HD, GE Healthcare). Radiological images were reviewed from Picture Archiving and Communication System (PACS, GE) and lesion location with the vessel involvement was noted. All included patients underwent a TCD bubble contrast study that was performed by a trained stroke neurologist. The TCD head frame was fixed with a 2MHz Probe (Nicolet® SONARA®, TCD System). The middle cerebral artery (MCA) was identified through the temporal window. Continuous monitoring was done to look for any microembolic signals (MES). Agitated saline (9 mL of saline and 1 mL air with a few drops of patient’s blood mixed 20 times using a three-way stopcock) was injected through an 18-gauge needle inserted into the antecubital vein. Each patient underwent a total of four injections. The injections were done in the supine and sitting (45° incline) positions, with and without the Valsalva maneuver. Any MES noted was graded according to Spencer’s logarithmic scale (grade 0: no MES, grade I: MES count 1–10, grade II: MES count 11–30, grade III: MES count 31–100, grade IV: MES count 101–300, and grade V: MES count more than 300). After extensive evaluation the stroke neurologist categorized the patients as those with established etiology of stroke in the young, cryptogenic stroke, and ESUS.

Embolic stroke of the undetermined source was defined as a non-lacunar infarct (subcortical infarct ≤1.5 cm on CT or ≤2.0 cm on MRI) in the absence of the following: extracranial or intracranial atherosclerosis causing >50% luminal stenosis in the artery supplying the ischemic region, major cardioembolic sources (permanent or paroxysmal AF, sustained atrial flutter, intracardiac thrombus, prosthetic cardiac valve, atrial myxoma or other cardiac tumors, mitral stenosis, myocardial infarction within the past 4 weeks, left ventricular ejection fraction <30%, valvular vegetation’s or infective endocarditis), and no other specific cause of stroke (e.g., dissection, arteritis, migraine/vasospasm, and drug misuse). Those patients who were diagnosed to have ESUS and TCD bubble contrast study positive underwent TEE. The TEE was performed by a trained cardiologist who was part of the cardiology-neurology team. The patients who were diagnosed to have a PFO were seen by the stroke neurology team and the interventional cardiologist. The RoPE and AF-RoPE scores were calculated for those who had a PFO. The decision of PFO closure was made after discussing with the patient/relatives about the risks and benefits of the procedure taking into consideration the negative workup for stroke etiology, risk of recurrent strokes, high-risk TEE parameters like ASA, PFO size, and length, and also presence or absence of spontaneous shunting. PFO closure was done under conscious sedation with fentanyl and midazolam. All patients received intravenous

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**Fig. 1: Study flow diagram**
heparin 5000 units prior to the procedure. The access was through the femoral vein and intracardiac echocardiography/TEE guidance was used. MP 1 (5 or 6F) and straight tip glide wire (260 cm) were used for crossing the defect. Amplatzer PFO Occluder (Abbott, Illinois, United States) was used for PFO closure. \(^{21}\) Patients were followed up in the stroke clinic and in the cardiology clinic (for those who underwent PFO closure). Any further events noted.

Statistical analysis was done using a statistical package STATA (Stata Corp). Variables were compared using univariate analysis. All factors reaching significance were analyzed using a logistic regression model to perform a multivariate analysis. Two-tailed Fisher’s exact test was used to look for significant associations.

### Results

During the study period, a total of 7,179 patients were admitted in the neurology unit of Christian Medical College, Vellore. Of these, 6,197 (86.32\%) were ischemic strokes and 972 (13.68\%) were hemorrhagic strokes. The number of patients with ischemic strokes with an age at the time of stroke onset between 18 and 45 years was 304. A total of 304 patients were screened for possible paradoxical emboli with the TCD bubble contrast study. However, four were excluded due to technical difficulty. Thus, 300 patients underwent the TCD bubble contrast study. The mean age at presentation was 32 (7.2) years and 225 (75\%) patients were males. Of the included patients 283 (94.3\%) had infarcts and 17 (5.7\%) had transient ischemic attacks (TIAs). Among the 300 patients who were evaluated, 121 (40.3\%) patients were found to have a positive TCD bubble study. The flow of patients recruited for the study is given in Figure 1. The baseline characteristics of the patients with and without a positive TCD bubble study are given in Table 1.

The activity at the time of stroke was documented in 105 (35\%) patients. Patients who lifted heavy weights (\(p = 0.02\)), strained to perform mechanically challenging work, or did an activity that was equivalent to a Valsalva maneuver (\(p \leq 0.01\)) were likely to have a positive bubble study. The list of activities at the time of stroke onset is given in Table 2.

A total of 72 (59.5\%) patients were identified to have an ESUS and based on clinical discretion of the stroke neurologist and RoPE score, underwent TEE for PFO confirmation. Of these, 65 patients had PFO, four were negative and three were found to have extracardiac shunts. All three extracardiac shunts were pulmonary arteriovenous malformation, of which two of them had additional fistulas over the liver, and two of them fulfilled the criteria for Osler–Weber–Rendu syndrome.

Finally, based on clinical indication and affordability, 29 patients underwent PFO closure. The patients with PFO who did not undergo PFO closure were managed with dual antiplatelet therapy. The mean RoPE score was 6.8 in the patients who underwent PFO closure and in those who were medically managed (\(p = 0.906\)). The patients who were referred for a PFO device closure had a higher AF-RoPE score, a high-grade shunt on the TCD bubble contrast study, a longer length of the tunnel, and the presence of an interatrial septal aneurysm (\(p = 0.012\)). Eighteen (27.7\%) patients were managed with anticoagulation and the rest were on antiplatelet therapy. The outcomes of the patients who underwent PFO closure in our center have been described by Thomson et al. \(^{25}\)

### Discussion

Transcranial Doppler bubble contrast study is known to be superior to direct imaging of the left atrium and can easily be done in an office setting, hence, it is a simple and reliable tool

---

**Table 1: Baseline characteristics of the patients who underwent TCD bubble contrast study**

<table>
<thead>
<tr>
<th></th>
<th>Transcranial Doppler bubble contrast study</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>N = 121</td>
<td>N = 179</td>
</tr>
<tr>
<td>Age (years)</td>
<td>33.0 ± 7.4</td>
<td>31.7 ± 7.2</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>85</td>
<td>70.2</td>
</tr>
<tr>
<td>Female</td>
<td>36</td>
<td>29.8</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systematic hypertension</td>
<td>33</td>
<td>27.3</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>15</td>
<td>12.4</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>14</td>
<td>11.6</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>2</td>
<td>1.7</td>
</tr>
<tr>
<td>Smoking</td>
<td>22</td>
<td>18.2</td>
</tr>
<tr>
<td>Alcohol</td>
<td>22</td>
<td>18.2</td>
</tr>
<tr>
<td>Obesity</td>
<td>8</td>
<td>6.6</td>
</tr>
<tr>
<td>Elevated homocysteine</td>
<td>24</td>
<td>19.8</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>Carotid disease</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>Recurrent stroke</td>
<td>15</td>
<td>19</td>
</tr>
<tr>
<td>Type of stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>118</td>
<td>97.5</td>
</tr>
<tr>
<td>Oxfordshire classification</td>
<td>3</td>
<td>2.5</td>
</tr>
<tr>
<td>Total anterior circulation stroke</td>
<td>4</td>
<td>3.3</td>
</tr>
<tr>
<td>Partial anterior circulation stroke</td>
<td>76</td>
<td>62.8</td>
</tr>
<tr>
<td>Posterior circulation stroke</td>
<td>38</td>
<td>31.4</td>
</tr>
<tr>
<td>Lacunar stroke</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Large vessel occlusion</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ICA</td>
<td>4</td>
<td>3.3</td>
</tr>
<tr>
<td>MCA</td>
<td>4</td>
<td>3.3</td>
</tr>
<tr>
<td>PCA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cortically located infarcts</td>
<td>48</td>
<td>39.6</td>
</tr>
</tbody>
</table>

BA, basilar artery; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; TIA, transient ischemic attack
in the evaluation of cryptogenic strokes. This study demonstrates that 40% of cryptogenic strokes in young have positive TCD bubble contrast study indicating an R-L shunt. This is similar to the findings from North India and other parts of the world. When we looked at the subgroup of young patients with ischemic strokes fulfilling the ESUS criteria, the TCD bubble contrast study was positive in 54%. We found a history of Valsalva maneuver-like activity (such as lifting heavy weights or straining) at the time of stroke onset can be an important clinical predictor for the presence of an R-L shunt. In addition to isolated cortical infarction, the presence of posterior circulation infarct in ESUS can predict the presence of an R-L shunt.

### Table 2: Activity at the time of stroke onset in patients with stroke in the young who underwent TCD bubble study

<table>
<thead>
<tr>
<th>Activity</th>
<th>N = 300</th>
<th>Positive</th>
<th>Negative</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Push and pull activity</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>0.700</td>
</tr>
<tr>
<td>Pulling bike</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0.412</td>
</tr>
<tr>
<td>Pushing a heavy chair</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0.222</td>
</tr>
<tr>
<td>Ironing</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0.412</td>
</tr>
<tr>
<td>Seizures at onset</td>
<td>26</td>
<td>7</td>
<td>19</td>
<td>0.143</td>
</tr>
<tr>
<td>Neck pain</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0.242</td>
</tr>
<tr>
<td>Prolong hours of sitting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At work-1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0.222</td>
</tr>
<tr>
<td>Travel in bus</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0.222</td>
</tr>
<tr>
<td>Driving long hours</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0.780</td>
</tr>
<tr>
<td>Postflight travel</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0.412</td>
</tr>
<tr>
<td>Sitting for a written examination</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0.412</td>
</tr>
<tr>
<td>History of lower limb DVT</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0.597</td>
</tr>
<tr>
<td>Valsalva maneuver before stroke</td>
<td>24</td>
<td>18</td>
<td>6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Lifting heavy weights</td>
<td>9</td>
<td>7</td>
<td>2</td>
<td>0.02</td>
</tr>
<tr>
<td>Straining activity</td>
<td>13</td>
<td>10</td>
<td>3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Squatting/toileting</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0.780</td>
</tr>
<tr>
<td>Aerobic activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swimming</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0.222</td>
</tr>
<tr>
<td>Jogging</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Riding cycle/bike</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>0.412</td>
</tr>
<tr>
<td>Road traffic accident/fall</td>
<td></td>
<td></td>
<td></td>
<td>0.167</td>
</tr>
<tr>
<td>Head injury</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>RTA</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0.412</td>
</tr>
<tr>
<td>Wake up stroke</td>
<td>11</td>
<td>1</td>
<td>10</td>
<td>0.031</td>
</tr>
<tr>
<td>During sleep</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>0.390</td>
</tr>
<tr>
<td>In-hospital stroke</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Migraine</td>
<td>15</td>
<td>9</td>
<td>6</td>
<td>0.111</td>
</tr>
<tr>
<td>History of lower limb DVT</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0.597</td>
</tr>
<tr>
<td>Immediate postpartum</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0.222</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0.175</td>
</tr>
</tbody>
</table>

DVT, deep vein thrombosis; RTA, road traffic accident

Conclusions

Right to left shunt is common in cryptogenic ischemic strokes in young. TCD with bubble contrast study is a noninvasive and feasible bedside tool to identify them. Applying the ESUS criteria in these cryptogenic strokes with a positive TCD bubble contrast study can be then used for selecting patients for more invasive tests like TEE. High-risk PFOs detected on TEE can be then considered for PFO closure for secondary stroke prevention. The history of Valsalva maneuver-like activity (such as lifting heavy weights or straining) at the time of stroke onset can be an important clinical predictor for the presence of an R-L shunt. In addition to isolated cortical infarction, the presence of posterior circulation infarct in ESUS can predict the presence of an R-L shunt.

Authors’ Contribution

Study design—Sanjith Aaron, Appaswamy Thirumal Prabhakar.
Data collection—Deepti Bal, Joanne Roopkumar, Murali Rayani, Appaswamy Thirumal Prabhakar.
Data Analysis—Appaswamy Thirumal Prabhakar.
Preparation of manuscript—Deepti Bal, Atif Shaikh.
Review, intellectual inputs, and critical revision of manuscript and supervision—Sanjith Aaron, Appaswamy Thirumal Prabhakar, Viji Samuel Thompson, John Jose, Atif Shaikh, Jesu Krupa, Rohit Benjamin.

References

ANNOUNCEMENT
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¹ J. Am Coll Cardiol 2021 Mar; 77 (10) 1300-1301  
CV Cardiovascular, * Real World Evidence, Data on file
The Hindi Version of International Consensus Criteria: A Cross-cultural Adaptation and Validation Study for Myalgic Encephalomyelitis in Post-COVID Patients

Mansi Shah¹, Atul Kakar²*, Atul Gogia³

Received: 04 April 2022; Accepted: 21 June 2022

ABSTRACT

Context: Fatigue is the most prominent feature of long COVID. With the increasing burden of long COVID cases post-acute phase of illness after recurrent waves of the pandemic, understanding its pathophysiology is of paramount importance. Such fatigue and post-viral illness could be associated with features of neuroimmune exhaustion and thus be a part of a larger syndrome such as myalgic encephalomyelitis (ME). Identifying the proportion of patients having ME from those experiencing fatigue would bring us one step closer to understanding the pathophysiology. International consensus criteria (ICC) originally published in English (ICC-E) is a valid and reliable tool for identifying cases of ME. However, a validated Hindi version of ICC-E is not available.

Aims: To develop and validate an equivalent version of ICC-E in the native Hindi language (ICC-H) to suit Indian patients and health care workers even at peripheries and to make conducting large scales surveys more feasible.

Subjects and methods: Once permission from the ethics board was granted, guidelines given by MAPI Research Trust were followed and ICC-H was developed from ICC-E, in the following steps: (a) translation to Hindi, (b) back translation, (c) comparison between the translated and back-translated version performed by experts, and (d) pre-pilot test in the intended population. The ICC-H was applied to 53 bilingual individuals knowing both Hindi and English.

Statistical analysis used: The distribution of Hindi and English questionnaires was analyzed using the Chi-square test and Spearman's correlation coefficient was used for correlation between answers of each question.

Results: The score of individual items and its global score was highly correlated with each other (p < 0.001). The scores of individual components and global scores of ICC-H at baseline and original ICC-E after 4 weeks did not differ significantly.

Conclusion: This study shows that the ICC-H is a valid and reliable instrument for the assessment of ME. ICC-H can be used for Hindi speaking population for identifying cases of ME.

KEY MESSAGES

- There is a significant overlap in symptoms of long COVID and ME, with fatigue being a major component in both.
- Understanding the prevalence of ME in the post-acute phase of COVID illness can bring us a step closer to understanding its pathophysiology.
- In a multilingual country like ours, regionally translated criteria are a must for conducting large-scale surveys.

INTRODUCTION

Long COVID has become a new challenge for the treating physicians. It is becoming more and more evident that there is a wide spectrum of possible post-acute sequelae in COVID-19 cases even in patients with a mild or asymptomatic illness. Unsurprisingly, the most commonly listed post-acute sequelae is fatigue, ranging from a simple feeling of lack of stamina to patients being bedridden and unable to carry out daily activities without support.¹ While many symptoms can be explained on the basis of pathophysiology of COVID-19 per se and could be considered as a direct extension of the primary viral illness, there is a considerable number of symptoms that seem to be borne out of alterations in immunopathology left behind by the virus presenting as a part of a larger syndrome such as ME.

The interesting overlap of symptoms in the post-acute phase of COVID-19 and ME could be explained by the similar underlying pathophysiology of cytokine storm implicated in both post-infectious ME and COVID-19.²-⁴ Furthermore, fatigue accompanied with neuroimmune exhaustion post-viral illness is well established in the literature, especially with relation to severe acute respiratory syndrome (SARS) which belongs to the same family as the novel coronavirus.⁵ A study conducted in Hong Kong followed up post-SARS patients for a 4-year period and inferred that 40.3% reported chronic fatigue of which 27.1% qualified for the diagnosis of ME.⁶ We can therefore expect a similar pattern in patients post-COVID-19.

To estimate the prevalence of this entity, especially in a multilingual country like India, it is of paramount importance that ICC-E, originally published in English language, is translated and culturally adapted into a common vernacular language to expand its application to larger populations.

SUBJECTS AND METHODS

Type of Study

This was a longitudinal prospective study conducted at a tertiary care hospital in New Delhi.

Study Participants

A total of 53 bilingual individuals knowing both Hindi and English, participated in this study. Study participants were patients experiencing long COVID symptoms of age 18–60 years. Individuals with confounding medical conditions such as psychiatric illness, current or past history of drug abuse along with the illness part of the exclusion criteria of original ICC-E were excluded. Participants were briefed on the purposes of the research and written informed consent was obtained. The study was commenced after obtaining approval from the research ethics committee.

Research Tools

International consensus criteria originally published in English consist of a total of
18 items combined to form four components of ME: namely post-exertional neuroimmune exhaustion, neurological, immune or gastrointestinal or genitourinary symptoms, and energy and transport. Each component is answered as yes or no and the criteria are met if a required number of symptoms are present from each category (Fig. 1). Participants were dichotomized into two categories: ME and do not have ME.

**Translation**

After securing permission from the corresponding author of the original English ICC-E, translation into Hindi was done by following linguistic validation guidelines given by MAPI which comprises the following steps. The ICC-E was forward translated into Hindi by two independent bilingual translators. A third unbiased expert formed a common version after resolving discrepancies between the two. A final version was created with the consensus of all three. After discussion among the experts, translators, and researchers, Hindi-translated ICC criteria was obtained. Back translation of the final Hindi version into English was carried out by two other independent translators blind to the original English version. The comparison of the ICC-E with back translation was made by the research committee members who were fluent in Hindi and English. After a detailed analysis of each item, a prefinal version of ICC in Hindi was obtained in an expert committee review by health care professionals and translators where the original English version and translated versions were reviewed. The goal was to achieve semantic, idiomatic, conceptual, and experiential equivalence between the source language (English) and target language (Hindi). A pre-pilot test was done to assess the linguistic interchangeability of the prefinal version of the translated ICC questionnaire and then the original ICC-E after a 4-week interval. After completing the translated questionnaire, the respondent was asked to elaborate on what they thought each questionnaire item and their corresponding response meant. The scores of each version were correlated with each other and it was well understood by the subjects. After incorporating inputs from study participants, a final version of ICC-H (Appendix 1) was made.

**Procedure**

The ICC-H was applied to 53 participants at a tertiary care hospital in New Delhi between November 2021 and January 2022 after obtaining informed consent. To be eligible to participate in the study, the patients were required to read, speak, and write in Hindi and be diagnosed to have long COVID, between the age of 18 and 60 years. After 4 weeks of administration of ICC-H, 53 participants were administered original ICC-E. All volunteers were given general instructions for answering the questions by simple demonstration. For this pilot study, we enrolled 53 patients (minimum of 50 patients as required by the guidelines issued by the quality criteria for health status questionnaire) for appropriate analysis of construct, criterion validity, and reproducibility.

**Statistical Analysis**

Statistical analysis was performed by the SPSS version 17.0 program for Windows. Continuous variables are presented as mean ± SD, and categorical variables are presented as absolute numbers and percentages. The distribution of Hindi and English questionnaires was analyzed using the Chi-square test. Spearman’s correlation coefficient was used for correlations between scores. For all statistical tests, a p-value less than 0.05 was taken to indicate a significant difference.

**Results**

The sample consisted of 53 participants. The correlations between each individual question were statistically significant (p < 0.001). The correlation ranged from 0.656 to 1. The lowest correlation was noted for two questions (Category B, Question 2, Subquestion b–0.656 and Category C, Question 1–0.671) where translation was most challenging. However, as evident from Table 1, the difference was not statistically significant. The final outcome was highly correlated between both the questionnaires (ICC-E and ICC-H) (100%, p < 0.001) (Table 2).

**Discussion**

International consensus criteria is among the most accepted methods to identify a case of ME at present, while a definitive way to diagnose ME does not exist. 1 Presently in the global literature not much is known about ME as sequelae from the pandemic. Chronic fatigue has an overall prevalence of 30% in adults among the general population; while ME has a prevalence of about 1%. As there is considerable overlap in symptoms of long COVID and those required to diagnose ME, ICC can be applied to estimate the proportion of patients having ME among those experiencing long COVID. However, the paucity of the suitable regionally translated questionnaire is a major hindrance to assess true prevalence. In this study, we translated the original ICC-E into Hindi (ICC-H) and validated it. The present study shows that the ICC-H is a reliable instrument for measuring the subjective perception of symptoms in Hindi speaking population. The use of the questionnaire in a group of bilingual individuals shows good linguistic interchangeability between ICC-H and ICC-E. The items in the Hindi version were easily understood and completed in 20–30 minutes. The global score and the individual components of ICC-H were strongly correlated with each other at a 4-week interval. The advantage of this study is that it was applied to patients having at least one or more long COVID symptoms. Identifying patients qualifying for the ICC for ME would lead to a better understanding of the post-acute phase of COVID-19 and perhaps offer better management to this progressively increasing subset of the population. There were multiple challenges during the translation. The exact terms for multiple medical conditions and symptoms do not exist in Hindi. To retain its core meaning, the nearest words or phrases were used. For example, ME = मायलिगिक एंट्रोपाई, बीजिका, निरुच. विज्ञानिका किंव मेडिकल प्रश्नीय कोरिका; orthostatic intolerance = ओरथोस्टॅटिक इनटॉलेंट; irritable bowel syndrome = वायबरल सिंडरम, etc. It was noted that in Hindi textbooks and posters for health care awareness, certain terms for symptoms and ailments were retained in English but written in Hindi (e.g., मायलिगिक एंट्रोपाई). They were used as a reference to identify commonly used medical terms that were understood by the general population. Thus, to further ensure standardization of conveyed meaning, especially for complex syndromes where a complete expansion of exact meaning/mechanism into phrases was not feasible, the original English terms are retained in parenthesis to assist health care workers of different levels while applying. To further assist health care workers such as ASHA workers in peripheries, we translated the notes and pointers given along with the criteria to increase its efficacy and ease the application. This will enable researchers to conduct large-scale surveys.
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The Hindi Version of ICC showed good internal consistency and validity and it can be used for the assessment of ME in a predominantly Hindi-speaking population.

APPENDIX 1: HINDI VERSION OF ICC FOR ME

The Hindi version of ICC showed good internal consistency and validity and it can be used for the assessment of ME in a predominantly Hindi-speaking population.

Table 2: Statistical validation of Hindi criteria

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The Hindi version of ICC showed good internal consistency and validity and it can be used for the assessment of ME in a predominantly Hindi-speaking population.
1. हृदय-वात्हक संबंधी (कात्मक योग्य रूप) लक्न: उदाहरण–एक प्रजताक (इम्यून)/िठरांजत्क (रैसट-इंसेिाइनल)/िनन-मयूरीय (िेजनिों-ययूररनररी) संबंधी जिकार:

- विषम स्थिति को सहन करने में असमथ्घता—दीर्घ-काल तक खडे रहने पर चककर आने (ऑथथो-सिैत्िक)
- बहुत जयादा या कम तापमान के लाए असहनशीलता।

2. ऊष्म-त्सथरता की कमी: उदाहरण–असामानय (त्नमन-सतर) शारीरर के समस्याओं में से दोंक, मायोफ ेत्शयल दद्घ त्संड्ोम, इरर्घि ेबल बॉवेल त्संड्ोम, इंरसिीत्शयल त्सत्सित्िस, रेनॉि की त्क्रया, प्रोलैपसि माइट्ल वाल व, माइग्रेन, एल जजी,

3. जनन-मूरिीय संबंधी लक्न: उदाहरण–मूरि संबंधी तातकात्लकता या क्रमबद्ध चाल (िैनिम गैि) और रोमबग्घ परीक्ण पॉत्जत्िव देखा जा सकता है। असहजता महसूस हो सकती है।

4. बहुत जयादा या कम तापमान के लाए असहनशीलता।

5. विषम स्थिति की उंगत्लयों का नीला पडना) का प्रदश्घ न कर सकते हैं। नाखूनों पे चाँद के समय की उंगत्लयों का नीला पडना) का प्रदश्घ न कर सकते हैं।

6. सीिी-मुद्ा त्सथत्त को सहन करने में असमथ्घता—दीर्घ-काल तक खडे रहने पर चककर आने (ऑथथो-सिैत्िक)

(४) जड़े चापापए (मेटाबोलिम) (ऑथरेफिलग्राफ) (आयु) परिफाउ दितात: बम से कम एक लाख

1. बम-आयुक्त संबंधी (हाइड्रोकोक्सुटा) स्थान: उदाहरण–एक सोीसीय गैस या रसायन को सहन करने में आसामी-तीर्थ黑夜 एक खडे दक्षता एक व्यक्ति के लाभ में बदल जाता है, वह वहीं एक जड़े चापापए (मेटाबोलिम) (ऑथरेफिलग्राफ) (आयु) परिफाउ दितात: बम से कम एक लाख हो सकती है, लेकिन ईयर पानी में आसामी-तीर्थ黑夜 एक बम का दक्षता (टेंड्र रैट) और (आयु) परिफाउ कोहिन जा जाता है।

2. बम प्रभावित लक्न: जड़े चापापए—पूर्व पूर्व, बम से लाने में तकरीक, छानी और वृद्धि की दोस्तों की मायोफ ेत्शयल में पहचान।

3. उम्र-विचार की बंप: जड़े चापापए (हाइड्रोकोक्सुटा) शारीर तापमान, वैज्ञानिक तापमान में बीनी उम्र-दक्षता, वृद्धि परीक्ण अत्यधिक आमतौर पर गरीब को पहचानते हैं, जिसमें उम्र के साथ वृद्धि के लाए प्रभावी है।

4. ब्यटु उपयोग या बुद्ध तापमान के लाए असहनशीलता।

5. विषम स्थिति की उंगत्लयों का नीला पडना) का प्रदश्घ न कर सकते हैं। नाखूनों पे चाँद के समय की उंगत्लयों का नीला पडना) का प्रदश्घ न कर सकते हैं।

6. सीिी-मुद्ा त्सथत्त को सहन करने में असमथ्घता—दीर्घ-काल तक खडे रहने पर चककर आने (ऑथथो-सिैत्िक)

7. ब्यटु उपयोग या बुद्ध तापमान के लाए असहनशीलता।

8. ब्यटु उपयोग या बुद्ध तापमान के लाए असहनशीलता।
A Systematic Review on Prevalence and Assessment of Sexual Dysfunction in Vitiligo

Prodduturu Saikarthik1, Vesam Harinath Reddy2, Shaik Mahammed Rafi3, Valluru Wazeed Basha4, Somanaboina Padmakar5*

Received: 29 May 2022; Accepted: 08 July 2022

ABSTRACT

Objective: Vitiligo is a common depigmenting disorder with significant psychosocial consequences. Vitiligo has been associated with psychological disorders such as depression, low self-esteem, anxiety, and sexual dysfunction (SD). In recent years, there is an increase in the number of studies looking into the impact of vitiligo on sexual functions. This systematic review investigates the assessment and prevalence of SD in vitiligo patients.

Materials and methods: We carried out a systematic search for observational studies on the prevalence of SD in vitiligo patients. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to prepare this systematic review. We searched PubMed, Scopus, Google Scholar, and the Cochrane Library databases.

Results: We observed 308 studies for screening. Finally, 12 studies that meet the eligibility criteria were included in this study. The prevalence of SD ranged from 2.7 to 82.0%. Most of the studies used the dermatology life quality index (DLQI) to assess SD. Our findings also show that vitiligo patients were more likely to experience symptoms of depression and anxiety, one of the risk factors for SD.

Conclusion: Psychological comorbidities are related to a high risk of SD in vitiligo patients. Further prospective longitudinal studies are required to investigate the causal factors for SD in vitiligo patients.

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INTRODUCTION

Vitiligo is a common depigmented dermatological condition characterized by hypomelanosis or complete loss of melanocytes in the skin and hair. This impacts on the skin, mucous membranes, and retina. The disease affects about 1.0% of people in the United States and Europe, but it affects anywhere from less than 0.1% to over 8.0% of the world’s population. Vitiligo affects both men and women equally, though women experience it earlier and more frequently. It can occur at any age, but it is most common before the age of 30.

Vitiligo has a significant and broad impact on psychosocial wellbeing, an aspect of quality of life (QoL) that currently available QoL instruments may not accurately or entirely capture. Those who place a high value on appearance, men and singles, are significantly more likely to report that vitiligo has affected their sexual relationships. Self-esteem is by far the most powerful of these factors. Age, disease visibility and severity, race, and socioeconomic class are all factors to consider for these people. Casual contact with strangers is the most stressful situation. This stress can make it difficult to form sexual relationships, especially for a single person.

Females who develop vitiligo after marriage may experience marital difficulties and, in some cases, divorce. Young women with vitiligo may be regarded as unclean and unfit for marriage, and thus have a low probability of marrying. Between the ages of 40 and 70, the prevalence of moderate-to-severe erectile dysfunction (ED) increases by about two to threefold. The etiology of ED has been linked to many medical, psychological, and lifestyle factors, all of which harm self-esteem, QoL, and interpersonal relationships. In various cross-sectional surveys, vitiligo patients have been reported to have a wide range of psychological characteristics, including high depression/anxiety scores, obsessionality, social stigmatization, and other psychosocial comorbidities. There has been no systematic review of SD in vitiligo to our knowledge. As a result, the goal of this review was to compile all of the available data from observational studies.

MATERIALS AND METHODS

Literature and Search Methods

We used the PRISMA guidelines to systematically review observational studies on the prevalence and assessment of SD in vitiligo. We searched for peer-reviewed published English-language literature in the PubMed, Scopus, Google Scholar, and Cochrane Library databases. We combined the terms increase the sensitivity of the search strategy like vitiligo AND (“Sexual Dysfunction” OR “Erectile Dysfunction” OR “Genital Dialogues” OR “Depressive Symptoms” OR “Depression” OR “Sexual difficulties” OR “Prevalence”). Because there have been few studies on our concept, the review concentrated on all previous research articles on vitiligo and SD. The abstracts of all identified papers were then screened to check if they met the inclusion criteria. Finally, we checked through the reference lists of all eligible studies to determine additional relevant articles.

Selection of Studies and Data Extraction

The titles and abstracts of potential studies were reviewed, followed by an independent full-text review by the author, and any study that didn’t meet the inclusion criteria were excluded. Using a standardized reporting form, the following information was extracted: The first author, the year of publication, the country of origin of the study, and the sample size, gender, research objectives, study design, prevalence, and assessment tools for SD. The information was extracted and stored in an electronic database. To summarize the data, descriptive methods were used (percentage, ranges).

Eligibility Criteria

We looked at observational studies (cohort, case-control, cross-sectional, and case series) that evaluated the prevalence of vitiligo, depressive symptoms, and SD assessment. Eligible studies: (1) Previously diagnosed with vitiligo. (2) SD is stated as a major problem. (3) Studies that were published in the PubMed, Scopus, Google Scholar, and Cochrane Library databases.
Prevalence and Assessment of Sexual Dysfunction in Vitiligo

Prevalence and Assessment of Sexual Dysfunction in Vitiligo

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Fig. 1: PRISMA flow diagram

Results

We identified 12 articles that met the study inclusion criteria (Fig. 1). Articles were evenly distributed from China (n = 1), USA (n = 1), Korea (n = 1), India (n = 2), Turkey (n = 2), and Egypt (n = 3). The majority of studies were from Egypt and recruited patients from dermatology settings reported as case-control and cross-sectional.

Prevalence of SD

Prevalence of SD varied among studies because of heterogeneity of population and assessment methods. Prevalence of SD ranged from as low as 2.7% in a sample of adults three Patients²⁹ who were already diagnosed with vitiligo attending the dermatology department to as high as 82% using the Female Genital Self-Image Scale (FGSIS) and Female Sexual Function Index (FSFI).³⁰ Complete prevalence data are presented in Table 1.

Measurement of SD

Measurement of SD varied across studies. Most of the studies relied on 10-item DLQI (n=3),¹¹-¹³ and 5 items Arizona Sexual Experience Scale (ASEX) (n=2),¹⁴,¹⁵ followed by other items included 19 items FSFI (n=2),¹⁶-¹⁰ and 12 items General Health Questionnaire (GHQ-12) (n = 2).⁹,¹⁷ The remaining studies relied on 5-item International Index of Erectile Function (IIED) (n = 1),¹⁸ 7-items FGSIS (n = 1),¹⁰ 43-item Social Readjustment Rating Scale (SRRS) (n = 1),¹⁹ and 42 items Schedule of Recent Experience (SRE) (n = 1).²⁰

Psychological Symptoms

The findings showed many cases had difficulty in initiation of depression and anxiety and these are the most common symptoms stress, sleeping habits, eating habits sexual difficulties, and low mood are some of the experiences in patients with vitiligo. Reported vitiligo was strongly associated with a high incidence of depression and anxiety, which correlates to SD and a high incidence of social phobia and lower self-esteem. According to our study, many of the patients are experiencing anxiety and depression with vitiligo with SD.⁹,¹¹,¹⁴,¹⁵,¹⁷,¹⁹,²⁰

Discussion

Skin diseases have long harmed the sex life of those affected.²¹ Skin diseases can lead to low self-esteem, anxiety, depression, work problems, social phobia, thoughts of suicide, and other psychological problems. Skin diseases can have psychosocial effects on the QoL of patients and the relatives and partners of patients with skin diseases.²² Certain aspects of sexual response, like sexual interest, are predominantly psychological and can be influenced by anxiety and depression, whereas others, like erection and orgasm, can be influenced by both psychological and physical factors.²³ According to Thakurta et al.²⁴ and Kendurkar and Kaur,²⁵ depressed men have reduced libido, ED, and problems with ejaculation and orgasm in 33.0% and 45.0% of cases, respectively.

The relationship between psoriasis and SD is the best studied in various dermatological diseases. Several studies have shown that psoriasis has a significant impact on sexual function, which leads to significant changes in QoL.²⁶ Chen et al. conducted a large-scale statewide claims-based study that found male psoriasis patients were more likely to develop SD.²⁷ According to Egeberg et al. psoriasis was associated with a significantly higher prevalence and a significantly higher risk of new ED.²⁸ Cuenca-Barrales et al. concluded that patients with hidradenitis suppurativa have a high prevalence of SD and ED.²⁹ Neill and Ridley found that anogenital lichen sclerosus is a common cause of SD.³⁰ Mercan et al. compared the sexual function of 31 patients with neurodermatitis, 24 patients with psoriasis, and 33 control cases using the ASEX scale. They discovered that those with eczema had more sexual problems than those with psoriasis and other control groups.³¹

The main purpose of this systematic review was to investigate the current state of SD in vitiligo patients based on previous reviews that looked at ED and SD in this population. This review focused on articles published within the previous years, providing a significant update to the literature. Besides investigating the prevalence of SD, this review also focused on the assessment tools for SD in vitiligo patients.
Prevalence and Assessment of Sexual Dysfunction in Vitiligo

Table 1: Articles included in this review

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Country</th>
<th>Sample size</th>
<th>Male/ Female</th>
<th>Study aims</th>
<th>Study design</th>
<th>Prevalence of SD</th>
<th>Additional psychological symptoms</th>
<th>Measurement tools</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alhetheli GI et al.</td>
<td>2021</td>
<td>Saudi Arabia</td>
<td>173</td>
<td>96/77</td>
<td>To assess the effect of vitiligo on psychological condition, and sexual function</td>
<td>Cross-sectional study</td>
<td>53.2%</td>
<td>Depression</td>
<td>ASEX</td>
</tr>
<tr>
<td>Khaled HN et al.</td>
<td>2021</td>
<td>Egypt</td>
<td>50</td>
<td>0/50</td>
<td>To observe the effect of psoriasis and vitiligo on female sexual function</td>
<td>Case-control study</td>
<td>62.0%</td>
<td>N/A</td>
<td>FSFI</td>
</tr>
<tr>
<td>Nikam B et al.</td>
<td>2020</td>
<td>India</td>
<td>92</td>
<td>34/58</td>
<td>To assess the risk of psychiatric disorders in patients with vitiligo</td>
<td>Prospective study</td>
<td>5.5%</td>
<td>Anxiety and depression</td>
<td>GHQ-12</td>
</tr>
<tr>
<td>Abdel-Motaleb A et al.</td>
<td>2017</td>
<td>Egypt</td>
<td>100</td>
<td>100/0</td>
<td>To evaluate the impact of chronic skin disease on male sexual function</td>
<td>Case-control study</td>
<td>60.0%</td>
<td>N/A</td>
<td>IIEF</td>
</tr>
<tr>
<td>Sarhan D et al.</td>
<td>2015</td>
<td>Egypt</td>
<td>75</td>
<td>0/75</td>
<td>To assess the impact of vitiligo on genital self-image, sexual function, and QoL in female patients.</td>
<td>Cross-sectional study</td>
<td>82.0%</td>
<td>N/A</td>
<td>FGSIS &amp; FSFI</td>
</tr>
<tr>
<td>Almomani N et al.</td>
<td>2015</td>
<td>Saudi Arabia</td>
<td>234</td>
<td>123/111</td>
<td>To observe the QoL and psychological impact of vitiligo</td>
<td>Cross-sectional study</td>
<td>23.9%</td>
<td>Depression and anxiety</td>
<td>DLQI</td>
</tr>
<tr>
<td>Kim DY et al.</td>
<td>2013</td>
<td>Korea</td>
<td>167</td>
<td>54/113</td>
<td>To assess the effect of genital involvement on the sexual lives in vitiligo patients</td>
<td>Prospective study</td>
<td>21.6%</td>
<td>N/A</td>
<td>DLQI</td>
</tr>
<tr>
<td>Silverberg JI et al.</td>
<td>2012</td>
<td>United States of America</td>
<td>1541</td>
<td>433/1080</td>
<td>To evaluate the relation between vitiligo extent and distribution, and QoL impairment</td>
<td>Prospective questionnaire based study</td>
<td>18.0%</td>
<td>N/A</td>
<td>DLQI</td>
</tr>
<tr>
<td>Ahmed I et al.</td>
<td>2007</td>
<td>Pakistan</td>
<td>100</td>
<td>38/62</td>
<td>To assess the frequency and pattern of psychiatric disorders in patients with vitiligo</td>
<td>Cross-sectional study</td>
<td>2.0%</td>
<td>Depression, anxiety, social phobia, and agoraphobia</td>
<td>GHQ-12</td>
</tr>
<tr>
<td>Sukan M et al.</td>
<td>2006</td>
<td>Turkey</td>
<td>175</td>
<td>26/24</td>
<td>To observe the problems in sexual functions of vitiligo</td>
<td>Case-control study</td>
<td>36%</td>
<td>Dysthymic disorder and generalized anxiety</td>
<td>ASEX</td>
</tr>
<tr>
<td>Manolache L et al.</td>
<td>2006</td>
<td>Romania</td>
<td>32</td>
<td>10/22</td>
<td>To evaluate the involvement of stress before the onset/development of alopecia areata and vitiligo</td>
<td>Case-control study</td>
<td>3.1%</td>
<td>Stress</td>
<td>SRRS</td>
</tr>
<tr>
<td>Papadopoulos L et al.</td>
<td>1998</td>
<td>London</td>
<td>88</td>
<td>35/38</td>
<td>To assess the impact of life events on the onset of vitiligo in adults</td>
<td>Cross-sectional study</td>
<td>16.0%</td>
<td>Depression, change in sleeping and eating habits, and low mood</td>
<td>SRE</td>
</tr>
</tbody>
</table>

N/A, not available; ASEX, arizona sexual experience; FSFI, female sexual function index; GHQ-12, general health questionnaire; QoL, quality of life; IIEF, International Index of Erectile Function; FGSIS, female genital self-image scale; FSFI, female sexual function index; SRRS, social readjustment rating scale; SRE, schedule of recent experience.

The prevalence of SD in vitiligo patients ranged from 2.0 to 82.0% in the studies included in this systematic review. The DLQI was utilized in 25.0% of the studies, which is a simple, self-administered, and validated questionnaire designed to measure the health-related QoL of adult patients suffering with a skin disease. The DLQI is a tool for assessing the physical, psychological, and social burden of dermatological diseases. The DLQI is a 10-question survey that asks patients about the impact of skin diseases on various aspects of their health-related QoL in the previous week. ASEX is a 5-item rating scale that quantifies sex drive, arousal, vaginal...
lubrication/penile erection, ability to reach orgasm, and satisfaction from orgasm and was designed to be self- or clinician-administered. The total score ranges from 5 to 30, with higher scores indicating greater SD.33

Female Sexual Function Index and GHQ-12 versions were other popular methods for the measurement of SD which was used in two studies included in this systematic review. Also, the selected studies utilized other tools for measurement of SD such as IIEF, FSFI, SRRS, and SRE. A 19-item version of FSFI, a popular tool for measuring SD. It is a multidimensional self-report instrument for assessing female sexual functions. The 19-item scale assesses sexual function over the last 4 weeks and provides domain scores in six areas as follows: sexual desire, arousal, lubrication, orgasm, satisfaction, and pain.34

The GHQ-12 is designed to screen for general psychiatric morbidity. It is widely validated and is reliable. GHQ-12 is a one-dimensional scale with no response bias.35 The score was used to generate a total score between 0 and 36. Positive items were corrected from 0 (always) to 3 (never), while negative items were corrected from 3 (always) to 0 (never). A high value indicates poor health.36 The remaining studies relied on IIEF which is a multidimensional self-reporting tool for assessing male sexual function. It has been suggested as the primary endpoint for clinical ED studies and the diagnostic evaluation of ED severity. The IIEF meets the test reliability and validity criteria and have a high degree of sensitivity and specificity and correlate well with other measures of the treatment outcome.37

Item 7 of the FGSIS uses a 4-point response scale to assess women’s feelings and beliefs about their genitals. In a convenience sample, the scale demonstrated reliability and validity.38 Another tool used in the study was SRRS consists of 43 stressful life events, and identified from clinical psychological experiences. Event-related items address family constellation, marriage, occupation, economics, residence, group and peer relationships, education, religion, recreation, and health.39 The SRE scale is a self-administered tool to examine the relationship between social stress adjustment and the onset of ill health. The SRE includes a list of 34 stressful life events that were intended to represent the majority of the situations faced by the patient populations and which required varying degrees of readjustment.40

The limitation of this review was the low number of research with relevant information as well as the heterogeneity of the study design and sample size. Because the studies used different screening tools, the prevalence of SD in vitiligo will vary.

**Conclusion**

Psychological comorbidities are related to a high risk of SD in vitiligo patients. Further prospective longitudinal studies are needed to investigate the causal factors and management strategies for SD in vitiligo patients. Clinicians should focus on vitiligo patients for psychiatric symptoms to improve disease and treatment outcomes.

**Acknowledgement**

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**References**

SGLT2 Inhibitors in the Management of Chronic Kidney Disease: An Expert Consensus

Vivekanand Jha1*, Alan Almeida2, Arpita R Choudhury3, Arup R Dutta4, Dinesh Khullar5, Gokulnath6, Urmila Anandh7, Umesh Khanna8, Vijay Kher9

ABSTRACT

Despite the availability of multiple therapies for chronic kidney disease (CKD), there still exists an unmet need for better options to slow down disease progression and prevent complications. The Dapagliflozin and Prevention of Adverse Outcomes in CKD (DAPA-CKD) trial, which demonstrated the renoprotective effects of the sodium-glucose cotransporter-2 inhibitor (SGLT2i) dapagliflozin, independent of diabetes, with improved survival, even in patients with CKD with estimated glomerular filtration rate (eGFR) as low as 25 mL/min/1.73 m², has highlighted the potential beneficial role of SGLT2i in patients with CKD. These benefits were also achieved in patients who were already receiving optimal therapies for slowing the progression of CKD. The potential candidature of SGLT2i for CKD therapy is now being widely discussed in the nephrology community. Therefore, a consensus meeting was held in September 2020 with a group of expert nephrologists from India, to discuss the need to improve CKD management and assess the position of SGLT2i, based on compelling evidence from recent studies. This document summarizes the expert opinions and views on the position of SGLT2i in CKD management and aims to enhance the current understanding of the applicability of SGLT2i in patients with CKD. This will aid nephrologists and physicians across the country in decision-making on the management of patients with CKD using SGLT2i.

Keywords: Chronic kidney disease, Dapagliflozin, Estimated glomerular filtration rate, SGLT2i inhibitors, Type 2 diabetes mellitus.

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INTRODUCTION

Chronic kidney disease (CKD) is a growing cause of morbidity and mortality worldwide.1,2 In 2017, the estimated global prevalence of CKD was pegged at 9.1%, with the number of cases of CKD worldwide being 697.5 million.3 The population prevalence of CKD in India varies between 7 and 13%.4 Recent community-based studies have shown an even higher (18–21%) prevalence of CKD in certain rural populations.5,6

Diabetes is the leading cause of kidney failure worldwide and in India.7 According to the report of the Indian CKD registry, 31% of all CKD cases were attributed to diabetes.10 Other causes of CKD are also gaining importance, especially in rural communities where a significant proportion of patients develop CKD in the absence of traditional risk factors.5

Current Options for CKD Management and their Limitations

The current options to prevent the development or reduce the progression of CKD and the development of cardiovascular (CV) complications include lifestyle interventions (healthy diet, physical exercise, weight optimization, and cessation of smoking), control of hypertension and blood glucose, and lipid-lowering therapies.11 Agents that block the renin-angiotensin-aldosterone system (RAAS)—angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs)—have long been the preferred agents for managing hypertension and proteinuria.11,12 These benefits were first reported in pivotal studies, such as the reduction of endpoints in NIDDM with the angiotensin II antagonist losartan and the Irbesartan Diabetic Nephropathy Trial.13

Despite the salutary effect of these agents, a significant residual risk of kidney function deterioration and/or development of CV complications remains.13,14 Lipid-lowering therapies provide CV benefits in patients with CKD, but do not have renoprotective effects.11 Endothelin receptor antagonists, can lower proteinuria, arterial stiffness, and blood pressure (BP) in patients with CKD, but at the cost of unacceptably high side effects risk is high.18

The bardoxolone methyl evaluation in patients with chronic kidney disease and type 2 diabetes (BEACON) trial evaluated the effects of bardoxolone methyl, a synthetic triterpenoid with antioxidant and anti-inflammatory properties, on the risk of kidney failure or death from CV causes among 2,185 patients with type 2 diabetes (T2DM) and stage 4 CKD. The intervention was associated with a higher rate of CV events compared to placebo, which led to the termination of the trial.19

Other approaches like correction of anemia and acidosis and lowering uric acid have not been shown to be unequivocally effective.20

Therefore, the absolute risk of CV and renal morbidity and mortality remains high in patients with CKD. Thus, novel therapies for mitigating renal complications are highly desirable.11

SGLT2 Inhibitors for CKD Management: Lessons Learned in the Past Years

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) directly block SGLT2, present in proximal tubules, which inhibits renal glucose reabsorption, causing enhanced urinary glucose excretion. SGLT2i are postulated to have pleiotropic benefits, such as lowering BP, serum urate levels, and body weight, all of which contribute to their attractive clinical profile. Clinical trials of SGLT2i in patients with T2DM and high CV risk have indicated that SGLT2i may have cardioprotective and renoprotective effects.21 The SGLT2i currently

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available in the global market include dapagliflozin, canagliflozin, empagliflozin, and ertugliflozin. Other SGLT2i launched/ approved in specific countries include satogliflozin, tofogliflozin, luseogliflozin (Japan), and remogliflozin (India).  

**Cardiovascular Outcome Trials of SGLT2i in Patients with T2DM**

Since 2008, regulatory agencies have been requiring that all new antidiabetic agents must be tested for CV safety. As a result, all SGLT2i underwent phase 3 trials of CV safety. Large CV outcome trials (CVOTs), such as dapagliflozin effect on cardiovascular events (DECLARE-TIMI 58), Canagliflozin Cardiovascular Assessment Study (CANVAS), empagliflozin cardiovascular outcome trial in type 2 diabetes mellitus patients (EMPA-REG), evaluation of ertugliflozin efficacy and safety cardiovascular outcomes trial (VERTIS-CV), and the effect of sitagliptin on cardiovascular and renal events in patients with type 2 diabetes and moderate renal impairment who are at cardiovascular risk (SCORED), reported a reduced risk of CV events with dapagliflozin, canagliflozin, empagliflozin, ertugliflozin, and sitagliptin, respectively, in patients with established atherosclerotic cardiovascular disease (ASCVD) or at high risk of CV events.

These trials also reported a significant reduction in the hazards of progression of kidney disease. In the EMPA-REG study, the hazard ratio (HR) for the prespecified renal outcomes (doubling of serum creatinine level accompanied by eGFR ≤ 45 mL/min·1.73 m², initiation of renal replacement therapy, or death from renal disease) was 0.54 (95% confidence interval [CI]: 0.40–0.75, p = 0.001) for the empagliflozin group, and the HR for incident or worsening nephropathy was 0.61 (0.53–0.70, p = 0.001). For the composite outcomes of sustained 40% reduction in eGFR, need for kidney replacement therapy, or death from renal causes in the CANVAS-R study, the HR was 0.60 (0.47–0.77). In the DECLARE-TIMI 58 trial, the HR for the renal composite of ≥ 40% reduction in eGFR to 0 mL/min·1.73 m², new-end stage kidney disease (ESKD), or death from CV or renal causes was 0.76 (0.67–0.87). In the VERTIS-CV trial, the HR for the secondary renal composite endpoint comprising a doubling of serum creatinine level, renal replacement therapy, or death from renal causes with ertugliflozin compared with placebo was 0.81 (0.63–1.04). For the exploratory renal composite outcome of the VERTIS-CV trial, comprising sustained 40% reduction from baseline in eGFR, renal replacement therapy, or renal death, the HR for ertugliflozin was 0.86 (0.50–0.88), as compared to placebo. For satogliflozin in the SCORED trial, the HR for the renal composite endpoint, comprising a sustained decrease of ≥ 50% in eGFR for ≥ 30 days, renal replacement therapy, or sustained eGFR of < 5 mL/min·1.73 m² for ≥ 30 days, was 0.71 (0.46–1.08).

A recent meta-analysis of the three CVOTs, EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58, reported that empagliflozin, canagliflozin, and dapagliflozin exert a consistent effect in lowering the risk of hospitalization due to heart failure (31%) and in reducing the risk of progression of kidney disease (45%), as measured by a composite of worsening of renal function, ESKD, or renal death.

A meta-analysis of two other trials, namely the DAPE in heart failure (DAPE-HF) and the empagliflozin outcome trial in patients with chronic heart failure and a reduced ejection fraction (EMPEROR-Reduced) showed that reduced risk of composite renal endpoints (HR: 0.62, 95% CI: 0.43–0.90, p = 0.013), comprising a composite of 50% or higher sustained decrease in eGFR, ESKD, or renal death. Similar cardioprotective effects have been reported in patients with heart failure and preserved ejection fraction in the EMPEROR with preserved ejection fraction (EMPEROR-Preserved). The details of the CVOTs of SGLT2i are presented in Table 1.

**Randomized Controlled Trial of SGLT2i in Patients with T2DM and CKD**

The CVOTs included only a small proportion of participants with CKD, especially those with eGFR < 45 mL/min·1.73 m². The effect of dapagliflozin on blood glucose level and renal safety in patients with T2DM trial assessed the efficacy and safety of dapagliflozin in 321 patients with T2DM and moderate renal impairment (CKD stage 3A: eGFR: 45–59 mL/min·1.73 m²). As compared to placebo, the decline in eGFR was greater with dapagliflozin at 24 weeks. However, eGFR returned to baseline levels with dapagliflozin at week 27. Also, dapagliflozin decreased in urine albumin-to-creatinine ratio (UACR) at week 24, for those with baseline UACR ≥ 30 mg/gm.

The albuminuria-lowering effect of dapagliflozin alone and in combination with saxagliptin and effect of dapagliflozin and saxagliptin on glycemic control in patients with T2DM and CKD trial assessed the efficacy of dapagliflozin (alone or in combination with the dipeptidyl peptidase-4 inhibitor saxagliptin) in patients with T2DM and moderate-to-severe CKD (eGFR: 25–75 mL/min·1.73 m²) and albuminuria (UACR: 30–3500 mg/gm), despite being on ACEi/ARB therapy. Throughout the study period of 24 weeks, dapagliflozin reduced UACR as compared to placebo, both alone and in combination with saxagliptin.

The canagliflozin and renal events in diabetes with established nephropathy clinical evaluation (CREDENCE) trial was designed to specifically evaluate the effects of canagliflozin on primary renal outcomes in patients with established diabetic kidney disease (DKD) on top of renin-angiotensin system blockade. The risk of both CV events and kidney failure was lower with canagliflozin than with placebo, at a median follow-up of 2.62 years. The CREDENCE was the first trial that had major renal endpoints as the primary outcome; hence, its results could be used to inform clinical practice, rather than being hypothesis-generating.

**DAPA-CKD Trial: Confirmation of the Benefits of SGLT2i for Patients with CKD**

The DAPA-CKD trial examined the long-term efficacy and safety of the SGLT2i dapagliflozin in patients with CKD, with or without type 2 diabetes. Over 4,300 participants with an eGFR of 25–75 mL/min·1.73 m² and a UACR of 200–5000 mg/g were randomized to receive dapagliflozin 10 mg once daily or a matched placebo. Over a median of 2.4 years, dapagliflozin reduced the eGFR decline by 25% (2.86 mL/min·1.73 m²/year) and 3.79 mL/min·1.73 m²/year in the dapagliflozin and placebo groups, respectively, reduced heart failure by 29% and all-cause mortality by 31%. Furthermore, the trial showed that the kidney benefits of SGLT2i were cumulative with RAAS blockade in patients with CKD and without diabetes.

Different eGFR categories involved in the key SGLT2i trials, along with the median UACR values, are presented in Figure 1.
Potential Mechanisms of Renal Effects of SGLT2i

The potential mechanism of the beneficial effects of SGLT2i is an area of active research (Fig. 3). Diabetes is associated with increased proximal tubular glucose and sodium reabsorption, which possibly results from upregulation of SGLT2 mRNA and/or an increase in transporter function. Consequently, lowered sodium delivery to the macula densa suppresses the tubuloglomerular feedback, resulting in afferent arteriolar vasodilation, hyperfiltration, and hyperperfusion, which lowers the eGFR. SGLT2i also impedes proximal glucose and sodium reabsorption, which leads to natriuresis. Increased sodium excretion is associated with contraction of plasma volume and acute reductions in BP and body weight. SGLT2i lower arterial stiffness, which is a marker of both renal and CV risk. Anti-inflammatory and antifibrotic pathways are also promoted by SGLT2i, which potentiates the beneficial effects of reduced glomerular hypertension and hyperfiltration and renal oxygenation. SGLT2i have also been associated with lowered histologic evidence of nephropathy. SGLT2i-mediated reduction in glomerular hypertension also reduces albuminuria. Newer studies are throwing further light on the mechanism of the beneficial action of SGLT2i and there are reviews elsewhere.48–50

How has this Evidence Been Incorporated into Clinical Practice Guidelines?

The accumulating evidence on the cardiorenal benefits of SGLT2i prompted updates in clinical practice guidelines for the management of T2DM worldwide.51 An important pivot is to choose antiglycemic therapy based on underlying CV and CKD risks, instead of only glycemic parameters, with a focus on comorbidities and end-organ protection.52 This represents a paradigm shift in the current glucocentric approach for the management of this condition.53 The American Diabetes Association (ADA) guidelines recommend the use of SGLT2i as primary therapy in patients with T2DM and established kidney disease, heart failure, ASCVD, or indicators of high ASCVD risk.54 The ADA 2021 guidelines recommend the use of SGLT2i in patients with T2DM and DKD with eGFR ≥30 mL/min/1.73 m² and UACR >300 mg/g for CV risk reduction.55 The European Society of Cardiology and the European Association for the Study of Diabetes (ESC/EASD) 2019 guidelines recommend the use of SGLT2i in patients with T2DM with ASCVD,

Table 1: Major clinical trials on SGLT2i with renal endpoints 24–26,34,41–43,59,78

<table>
<thead>
<tr>
<th>Study name</th>
<th>EMPA-REG outcome</th>
<th>CANVAS/ CANVAS-R</th>
<th>CREDENCE</th>
<th>DECLARE-TIMI 58</th>
<th>DAPA-HF</th>
<th>EMPEROR-Reduced</th>
<th>DAPA-CKD</th>
<th>EMPA-Kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Empagliflozin vs placebo</td>
<td>T2DM, high CV risk, N = 7020</td>
<td>Canagliflozin vs placebo</td>
<td>T2DM, albuminuric CKD, N = 4401</td>
<td>Dapagliflozin vs placebo</td>
<td>Patients with T2DM and nonpatients with diabetes, heart failure, and reduced ejection fraction, N = 4744</td>
<td>Empagliflozin vs placebo</td>
<td>Patients with T2DM and nonpatients with diabetes, high CV risk, N = 4304</td>
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<tr>
<td>Patient population and No. (N)</td>
<td>eGFR ≥30–&lt;60 mL/min/1.73 m²</td>
<td>eGFR ≥30 mL/min/1.73 m²</td>
<td>eGFR ≥30–&lt;90 mL/min/1.73 m²</td>
<td>eGFR ≥60 mL/min/1.73 m²</td>
<td>eGFR ≥30 mL/min/1.73 m²</td>
<td>eGFR greater than 60 mL/min/1.73 m²</td>
<td>eGFR ≤25–75 mL/min/1.73 m²</td>
<td>eGFR ≥20–&lt;90 mL/min/1.73 m²</td>
</tr>
<tr>
<td>Renal function inclusion criteria</td>
<td>74 mL/min/1.73 m²</td>
<td>77 mL/min/1.73 m²</td>
<td>56 mL/min/1.73 m²</td>
<td>85 mL/min/1.73 m²</td>
<td>~66 mL/min/1.73 m²</td>
<td>~62 mL/min/1.73 m²</td>
<td>44 mL/min/1.73 m²</td>
<td>TBA</td>
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<tr>
<td>Baseline mean eGFR</td>
<td>Incident or worsening nephropathy (doubling of the serum creatinine level, progression to macroalbuminuria, initiation of RRT, or death from renal disease), a composite of worsening or incident nephropathy, or death from CV causes; and incident albuminuria</td>
<td>44 mL/min/1.73 m²</td>
<td>Time to the first occurrence of any of the components of the composite: ≥50% sustained decline in eGFR or reaching eGFR ≤10 mL/min/1.73 m², renal death, or a sustained decline of ≥40% in eGFR from randomization) or (ii) cardiovascular death (time frame: median follow-up approx. 3.1 years)</td>
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### Study outcomes

<table>
<thead>
<tr>
<th>Study name</th>
<th>EMPA-REG</th>
<th>CANVAS/CANVAS R</th>
<th>CREDENCE</th>
<th>DECLARE-TIMI 58</th>
<th>DAPA-HF</th>
<th>EMPEROR-Reduced</th>
<th>DAPA-CKD</th>
<th>EMPA-Kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study outcomes</strong></td>
<td>A 55% relative risk reduction of initiation of RRT (0.3% vs 0.6%); 44% relative risk reduction of doubling of SCr (1.5% vs 2.6%); 38% relative risk reduction of progression to macroalbuminuria (11.2% vs 16.2%); incident of worsening nephropathy (12.7% vs 18.8%, p &lt; 0.001) slowing eGFR decline (adjusted annual decrease 0.19 ± 0.11 vs 1.67 ± 0.13 mL/ min /1.73 m², p &lt; 0.001)</td>
<td>Reduction in the progression of albuminuria (HR, 0.73; 95% CI: 0.67–0.79) and the composite outcome of a sustained 40% reduction in the eGFR, the need for RRT, or death from renal causes occurred less frequently in the canagliflozin group (HR, 0.60; 95% CI: 0.47–0.77)</td>
<td>The relative risk of a renal-specific composite of end-stage kidney disease, doubling of SCr, or death from renal causes was lower by 34% (HR, 0.66; 95% CI: 0.53–0.81; p &lt; 0.001), and the relative risk of ESKD was lower by 32% (HR, 0.68; 95% CI: 0.54–0.86; p = 0.002)</td>
<td>Incidence of the renal composite outcome was 4.3% in the dapagliflozin group and 5.6% in the placebo group (HR, 0.76; 95% CI: 0.67–0.87)</td>
<td>Serious renal adverse events were higher in the placebo group as compared to the dapagliflozin group (2.7% vs 1.6%, p = 0.009)</td>
<td>A composite renal outcome occurred in 1.6% in the empagliflozin group and 3.1% in the placebo group (HR, 0.50; 95% CI: 0.32–0.77)</td>
<td>The HR for the composite of death from CV causes or hospitalization for heart failure was 0.71 (95% CI: 0.55–0.92; p = 0.009), and the HR for the composite of a sustained decline in the eGFR of at least 50%, ESKD, or death from renal causes was 0.56 (95% CI: 0.45–0.68; p &lt; 0.001); mortality rates were 4.7% and 6.8% in the dapagliflozin and placebo groups, respectively (HR, 0.69; 95% CI: 0.53–0.88; p = 0.004); effects were similar for patients with and without T2DM</td>
<td>TBA</td>
</tr>
</tbody>
</table>

**CANVAS/CANVAS R**, canagliflozin cardiovascular assessment study; 95% CI, 95% confidence interval; CKD, chronic kidney disease; CV, cardiovascular; CREDENCE, evaluation of the effects of canagliflozin on renal and cardiovascular outcomes in participants with diabetic nephropathy; DAPA-CKD, dapagliflozin and prevention of adverse outcomes in chronic kidney disease; DAPA-HF, dapagliflozin and prevention of adverse outcomes in heart failure; DECLARE-TIMI 58, dapagliflozin effect on cardiovascular events; eGFR, estimated glomerular filtration rate; EMPA-Kidney, the study of Heart and kidney protection with empagliflozin; EMPA-REG OUTCOME, empagliflozin cardiovascular outcome event trial in type 2 diabetes mellitus patients; ESKD, end-stage kidney disease; HR, hazard ratio; RRT, renal replacement therapy; SCr, serum creatinine; TBA, to be announced; T2DM, type 2 diabetes mellitus.

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**Fig. 1**: Renal risk categories in key SGLT2i clinical trials (Adapted from Giorgino)⁴³
Fig. 2: Effects of SGLT2 inhibitors on renal outcomes from the EMPA-REG, CANVAS, DECLARE-TIMI 58, and CREDENCE trials. 

Explanation: The figures illustrate the effects of SGLT2 inhibitors on different outcomes such as dialysis, transplantation, renal death, substantial loss of kidney function, ESKD, or death due to renal diseases, and acute kidney injury. The data from the EMPA-REG OUTCOME, DECLARE-TIMI 58, CANVAS Program, and EMPA-REG OUTCOME trials are presented in terms of events, patients, and relative risks. The figures show the statistical significance of these effects with confidence intervals and p-values.

Adapted from: (Nuen BL, 2019).
or at a high risk of CV disease, irrespective of being treatment naïve or already receiving metformin therapy.56

The KDIGO 2020 guidelines recommend the use of metformin and SGLT2i combination as first-line therapy for patients with T2DM and CKD with eGFR ≥30 mL/min/1.73 m² and suggest the continuation of SGLT2i (if already initiated) even if eGFR falls below 30 mL/min/1.73 m², unless kidney replacement therapy is initiated, or it is not tolerated.30

The 2020 scientific statement from the American Heart Association endorses the use of SGLT2i in patients with T2DM with an established or high risk of CVD or CKD and suggests that SGLT2i may be used preferentially in earlier stages of CKD (eGFR > 30 mL/min/1.73 m²).37

The new BMJ Rapid Recommendations clinical practice guideline aimed at clinicians has provided newer insights into SGLT2i or glucagon-like peptide 1 receptor agonists (GLP1-RA) for the treatment of T2DM. The guideline focuses on the absolute reduction of renal and CV disease outcomes for determining the anticipated benefits of SGLT2i or GLP1-RA therapy and strongly recommends initiating SGLT2i in patients with established CV disease and CKD (Fig. 4).58

**Cost-effectiveness**

Several studies from high-income countries confirm the cost-effectiveness of this approach.50,61 For low-and middle-income countries, Basu et al. evaluated the effect of switching from sulfonylureas to alternative agents on disability-adjusted life-years and the costs of CV events, heart failure, ESKD, vision loss, pressure sensation loss, severe hypoglycemia, and drug-specific side effects. They found that to be cost-effective, the price of SGLT2i would need to come down by 17.4%.62

**Future Perspectives**

The awaited results of the EMPA-KIDNEY trial might further strengthen the evidence-based rationale for recommending the use of SGLT2i in patients with CKD with eGFR < 30 mL/min/1.73 m².63 Although SGLT2i should be considered for patients with T2DM and CKD and eGFR ≥30 mL/min/1.73 m² and UACR > 30 mg/gm, a real-world study64 showed that SGLT2i are largely underprescribed, with only 32.9% of eligible patients receiving treatment with SGLT2i.

This is largely driven by clinical inertia, which highlights the need for clinicians to move from a glucocentric approach toward reducing renal events in patients with T2DM. From the implementation point of view, an appropriate cost-benefit analysis needs to be undertaken to define the place for this agent in treatment algorithms. Given the complexity of reimbursement systems in low-and middle-income countries including India, this is crucial for policymakers and insurance companies.

Based on the above discussion and the consensus opinion of the experts, the group developed the following recommendations on the use of SGLT2i in patients with CKD with or without diabetes:

**Box: Summary of Consensus Statements**

- All subjects with T2DM should be assessed for the presence of CVD and/or CKD using standard diagnostic criteria.
- All subjects with T2DM and established CVD and/or CKD should be started on an SGLT2i.
- All subjects with three or more CVD risk factors without established CVD and/or CKD should be considered for SGLT2i.
- All subjects with CKD should be assessed for their risk of progression of kidney disease.
- Subjects with stage 3–5 CKD and high progression risk (UACR > 300 mg/g) should be considered for starting SGLT2i therapy.
- SGLT2i should not be started for the first time in those with eGFR below 25 mL/min/1.73 m² but can be continued if the patient is already on this agent.
- SGLT2i should be considered as part of nonspecific conservative antiproteinuric therapy in patients with glomerular diseases, such as IgA nephropathy.
- SGLT2i should be used with caution in those with a history of genital or urinary tract infections.
- Patients should be advised to withhold SGLT2i during an acute illness that can lead to dehydration.
- More research is needed to establish the role of SGLT2i therapy in specific populations with kidney diseases, such as kidney transplant recipients, those with lower grades of proteinuria (A2, e.g., those with chronic interstitial nephritis or CKD of unknown etiology), and those with lower eGFR values.
- Cost-benefit analyses need to be undertaken to define the place of SGLT2i in standard treatment algorithms.
Fig. 4: Summary of recommendations by the Rapid Recommendations clinical practice guideline on the initiations of SGLT2i or GLP1-RA in patients with T2DM.
10. Rajapurkar MM, John GT, Kirpalani AL, et al. What references...  
Disclosures

Vij has received research grant funding from GSK, Baxter Healthcare, and Biocon and honoraria from GlaxoSmithKlein, AstraZeneca, Boehringer Ingelheim, NephroPlus and Zydus Cadilla, under the policy of all fees being paid to the organization.

References


Adrenal Tuberculosis

Ankur Jindal1, Rakesh Kumar Jagdish2*, Prayas Vats3

Received: 28 November 2018; Accepted: 20 May 2022

Adrenal Tuberculosis

Ankur Jindal1, Rakesh Kumar Jagdish2*, Prayas Vats3

52-year-old male presented with progressive unintentional weight loss of 15 kg, postural dizziness, and patchy skin hyperpigmentation involving face and hands for 6 months, not associated with palpitation, cough, dyspnea, or altered bowel habits. Physical examination revealed orthostatic hypotension (20 mm Hg fall in systolic BP after 5 minutes of standing) and presence of Dupuytren’s contracture and brownish-brown pigmentation of palmar creases (Fig. 1A, arrow), tongue, and back of hand (Figs 1B and C). Systemic examination and routine labs were unremarkable. Contrast-enhanced computed tomography (CT) upper abdomen showed nodular bilateral adrenomegaly with necrotic center and heterogenous contrast enhancement (Fig. 1D, arrows), and high-resolution CT thorax showed centrilobular nodules in bilateral lungs apices (Fig. 1E). There were also necrotic precardinal, subcarinal, and right paratracheal lymph nodes. These findings go typically in favor of tuberculosis. The test for human immunodeficiency virus infection was negative. An early morning low serum cortisol concentration (40 nmol/L) and high plasma adrenocorticotropic hormone concentration (880 pmol/L) strongly suggested primary adrenal insufficiency likely due to disseminated tuberculosis. The patient was started on hydrocortisone and antitubercular regimen and has shown marked improvement in symptoms.

Addison’s disease (AD) with adrenal tuberculosis was first highlighted by Thomas Addison. Approximately 20–30% of cases of AD are due to tuberculosis in developing countries. AD manifests frequently with generalized weakness, anorexia, nausea, fatigue, weight loss, vomiting, skin hyperpigmentation (60–100%), dyselectrolytemia, and refractory hypotension. In an autopsy series, 6% of patients of active tuberculosis have adrenal involvement. Other secondary causes of adrenal insufficiency include fungal or viral infection, infiltration by primary or metastatic neoplasms, hemorrhage or adrenal thrombosis, amyloidosis, sarcoidosis, hemochromatosis, or related to the use of drugs that interfere with adrenal steroidogenesis. The typical CT features of adrenal tuberculosis include bilateral enlargement of the adrenal gland mimicking mass with calcification and peripheral rim-like enhancement. The final diagnosis of AD is established on the bases of clinical symptoms, biochemistry results, imaging, and pathological findings. Early treatment with antitubercular therapy, laboratory monitoring of adrenal tests, and timely adequate steroid therapy are the cornerstone of the treatment of adrenal tuberculosis.

Figs 1A to E: (A) Dupuytren’s contracture (arrow) and brownish-brown pigmentation of palmar creases; (B) Hyperpigmentation of tongue; (C) Hyperpigmentation of back of the hand; (D) Nodular bilateral adrenomegaly (arrows) with necrotic center and heterogenous contrast enhancement; (E) Centrilobular nodules in bilateral lungs apices

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An 8-year-old female presented to us with a history of palpitation since childhood. At the age of around 4 years, her mother noticed increased precordial activity. The child felt palpitation at rest, but more so during walking. There was no history of breathlessness or angina. There was no past history of recurrent chest infections in childhood.

On examination, her blood pressure was 120/50 mm Hg, heart rate was 76/min. There was no cyanosis, clubbing, or anemia. Jugular venous pressure was not elevated. The apex beat was palpated in the 5th intercostal space, in the mid-clavicular line. There was a grade II continuous murmur, best heard in the 3rd and 4th intercostal space. Echocardiography showed dilatation of coronary sinus (CS), dilated right atrium (RA), and right ventricle (RV) (Figs 1 and 2). On Doppler examination, there were continuous color flow signals in the CS, with high flow signals on continuous wave Doppler (Figs 3 and 4), suggestive of coronary artery (CA) fistula opening into the CS.

Her coronary angiography was done from the femoral route. It showed dilatation of the left main and left circumflex (LCx) CAs with a fistula between LCx and CS. The left anterior descending (LAD) artery is small in size (Fig. 5). Right coronary artery (RCA) was normal.

Coronary artery (CA)/coronary cameral fistula (CF) is a rare abnormality that is characterized by an abnormal connection found incidentally in between the CAs and cardiac structures or some nearby vessel. The majority of coronary artery fistulas (CAF) are small and are of no consequence. The incidence of these fistulas is only 0.1% of adult patients who are undergoing routine coronary angiography, and the majority of these do not need any treatment. The majority of the CAFs are congenital in origin. The most common artery which is involved in studies is LAD, which is seen in around 49% of the cases, after that is the RCA which is seen in around 33%, and very less often seen is the LCx artery, which is seen in around 17% of cases. Congenital CA/CF mostly opens into the right side of the heart.
Left Circumflex Artery to Coronary Sinus Fistula

chambers or pulmonary circulation. CA/CF of LCx artery communicating with the CS is very rarely seen. Our patient had a large CA/CF, which was seen arising from the LCx and draining into the CS.

REFERENCES


Fig. 5: Left coronary angiography-showing dilated left main and LCx CAs, with CAF between LCx artery and CS, small LAD artery
A Rare Case of Blood & Sweat: Hematohidrosis

Abhijit Chatterjee1, Dip K Chowdhury2, Arnab Kundu3, Jayanta Datta4*

Received: 11 March 2022; Accepted: 07 August 2022

ABSTRACT
Hematohidrosis is an uncommon pathophysiological condition of sweating blood. A young lady with abrupt bleeding from the skin (since January 2017) was brought to the emergency. The bleeding was vanished after mopping with no site of injury, but it reappeared soon enough confirming its nature. Bleeding time (BT), clotting time (CT), and the prothrombin time (PT) was within normal limit. This patient is confirmed as a case of hematohidrosis by the method of exclusion and the presence of blood was finalized by benzidine test as well as biochemical and microscopic examination of it. Now, no treatment is available as per the latest pieces of evidence. Also, the cause of it is not known till date. Psychological anxiety is a predisposing cause for hematohidrosis.

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INTRODUCTION
Hematohidrosis is an extremely uncommon phenomenon of blood sweating. There are only a few reports in the literature. Leonardo Da Vinci to Physician Luke described that a common soldier to even Jesus Christ had also experienced a such event during critical moments. Hematohidrosis is a state where the capillary blood vessels that supply sweat glands explode, resulting in the perspiration of blood, occurring under excessive physical or emotional stress.

CASE DESCRIPTION
Presentation
A 19-year-old female presented in ED with complaints of occasional loss of consciousness at home with violent random movements of limbs and bending of the spine followed by spontaneous recovery along with bleeding from the nose and eyes (Figs 2A and B).

Present and Past History
She was hospitalized 4 years back (on 2017) as she was found unconscious at her home-stairway with bleeding from her nose and ears (Figs 2A and B). CBC, coagulation profile, and CT brain was normal as she was discharged after observation. A similar episode of bleeding from the nose and mouth occurred after a month and again she was hospitalized but once again the CBC, coagulation profile and other metabolic profile parameters were normal. ENT consultation revealed no source of bleeding even after fibreoptic laryngoscopy (FOL) and she was advised to take oral tranexamic acid at home in case of emergency (FOL) and she was advised to take oral tranexamic acid at home in case of emergency.

Course in the Hospital
Repeated LOCs and restlessness followed by complete recovery even after admission to ICU. IV levetiracetam has been started but non contrast CT (NCCT) Brain, MRI brain (Seizure Protocol), and electroencephalogram (EEG) brain showed no anomaly. One episode of jerky limb movements with opisthotonic posture in ICU was managed by IV phenytoin and IV lorazepam. The neurologist confirmed it as psychogenic non-epileptic seizure. A connective tissue disorder profile has been advised by the hematologist but revealed no abnormality. Psychological counseling by a psychiatrist revealed childhood sexual abuse multiple times by close relatives in the family with severe depressive spectrum. She was discharged with the advice of regular psychological counseling and oral amitriptyline, sertraline, and propranolol.

DISCUSSION
Manonukul et al. suggested the word “hematofolliculohidrosis” as it is visible with liquid like sweat and the blood is going out through follicular channels. Many reasons have been mentioned by Holoubek, such as a part of systemic disease, varicose menstruation, immense exhaustion, psychogenic purpura, etc. Sudden anxiety and psychogenic strain are the most common causative agents, as evidenced before. Here, the most possible cause of it was acute on chronic mental strain, as the other etiologies were nullified by comprehensive history taking and laboratory testing. Psychogenic purpura is caused by hypersensitivity to the patient’s blood or autoerythrocyte sensitization and is specified by recurring episodes of ecchymoses, gastrointestinal (GI) bleeding, and hematuria.

Psychogenic stigmata is another variety of bleeding that occurs through the skin—the term usually mention areas of scars, open wounds or oozing through the uninjured dermis. Patients of this group are mostly neurotic. The physiological characteristic is a mild elevation of skin following prolonged bleeding, a pea-sized blue-whish patch on palm, and lesions like erysipelas. Copeland had mentioned a woman who exhibited bleeding from old scars during episodes of mental stress. Manonukul et al. have observed some aberrations in the skin resulting in stromal fragility. Those flaws will interact with intervacular spaces within the skin and they will ultimately dilate and enlarge as bloody balloons when blood enters these pathological areas. Then it will release the bloody discharge out either through follicular channels or onto the dermis and it will happen when the positive pressure within is optimal. Lately, it will collapse without any scar just like a balloon resulting in waxing and waning. That’s why these oozing are mostly spontaneous. Urgent biopsy is a gold standard as a late one, after these spaces collapse, will be of no help. A dermal histopathological article by Zhang et al. described the idea of bleeding within the dermis and blocked capillaries. No anomaly was revealed in sweat and sebaceous glands as well as in hair follicles. They remarked that hematohidrosis might have a different vasculitic pathophysiology.

Our patient’s histopathology was done during the remission phase which didn’t show any blood-filled vascular pockets, the most possible cause of it was acute on chronic mental strain, as the other etiologies were nullified by comprehensive history taking and laboratory testing. Psychogenic purpura is caused by hypersensitivity to the patient’s blood or autoerythrocyte sensitization and is specified by recurring episodes of ecchymoses, gastrointestinal (GI) bleeding, and hematuria.

Psychogenic stigmata is another variety of bleeding that occurs through the skin—the term usually mention areas of scars, open wounds or oozing through the uninjured dermis. Patients of this group are mostly neurotic. The physiological characteristic is a mild elevation of skin following prolonged bleeding, a pea-sized blue-whish patch on palm, and lesions like erysipelas. Copeland had mentioned a woman who exhibited bleeding from old scars during episodes of mental stress. Manonukul et al. have observed some aberrations in the skin resulting in stromal fragility. Those flaws will interact with intervacular spaces within the skin and they will ultimately dilate and enlarge as bloody balloons when blood enters these pathological areas. Then it will release the bloody discharge out either through follicular channels or onto the dermis and it will happen when the positive pressure within is optimal. Lately, it will collapse without any scar just like a balloon resulting in waxing and waning. That’s why these oozing are mostly spontaneous. Urgent biopsy is a gold standard as a late one, after these spaces collapse, will be of no help. A dermal histopathological article by Zhang et al. described the idea of bleeding within the dermis and blocked capillaries. No anomaly was revealed in sweat and sebaceous glands as well as in hair follicles. They remarked that hematohidrosis might have a different vasculitic pathophysiology.

Our patient’s histopathology was done during the remission phase which didn’t show any blood-filled vascular pockets,
including localized collusio of abdomen, hitherto unreported till now. Significant response and recovery on psychological counseling sessions proves the connection between psychogenic factors and hematohidrosis.

**Conclusion**

To conclude, though it is a very rarely reported case in medical literature, we should keep a close watch on our daily patient interactions to register more cases of hematohidrosis to know further about it. We should also encourage skin biopsy to be done during acute episodes not later on.

**Consent**

Informed written consent was taken from the patient and her family for reporting the same.

**References**


See Figs 1, 2A and B: (A and B) Spontaneous bloody discharge from nose and mouth

echymoses, blocked capillaries, or anomaly in the follicle or glands. Confirmation of hematohidrosis is done by benzidine test where hemoglobin reacts with hydrogen peroxide resulting in oxygen production which transforms the organic reagent into a greenish blue compound. A Hemochromogen test also finalized that the blood is of human origin. Here pyridine results in the reduction of hemoglobin liberating typical salmon-pinkish crystals of pyridine-hemoglobin that is visible in the microscope. Keystones of the case
Drug-induced Capillary Leak Syndrome

Rikita R Mudhol1*, Rohan Bhise2
Received: 22 September 2018; Accepted: 26 May 2022

Abstract
Capillary leak syndrome is a disease with a high mortality rate. Its signs and symptoms are nonspecific. Generalized edema, hypotension, hypoproteinemia, and hemoconcentration are the characteristic features of capillary leak syndrome. Here we report three cases of capillary leak syndrome developed after being treated with gemcitabine and paclitaxel. Immediate treatment with corticosteroids may be life-saving.

Introduction
Rapid extravasation of plasma to the interstitial space due to sudden hyperpermeability causes capillary leak. The primary cause is endothelial damage and results in hypotension, edema, weight gain, and renal failure if not treated early. We present three cases of capillary leak syndrome triggered by chemotherapy drugs.

Case 1
A 56-year-old female who was diagnosed with adenocarcinoma pancreas underwent Whipple’s procedure followed by adjuvant chemotherapy with gemcitabine on days 1, 8, and 15 cycled every 28 days. A few days after day 1 of the fifth cycle, she presented to the emergency department with breathlessness, facial puffiness, abdominal distention, and bilateral lower limb edema. On detailed examination, the patient had anasarca, bilateral pleural effusion, ascites, bilateral pedal edema, and hypotension. Renal function test, liver function, and albumin levels were normal. Urine routine and microscopy were also normal. Chest X-ray showed pleural effusion on one side and the patient was put on an implantable cardioverter defibrillator. Echocardiogram (ECHO) revealed the presence of massive pericardial effusion. She underwent a therapeutic pericardial tap. There were no malignant cells in the pericardial fluid and workup for tuberculosis (TB) and other infections was negative. The patient was given methylprednisolone (1 mg/kg) and the patient responded within 24 hours. It was asymptomatic and is on regular follow-up in the oncology OPD.

Case 2
A 57-year-old lady was a diagnosed case of breast cancer—stage IV, she was on chemotherapy with gemcitabine on days 1 and 8 and on carboplatin on day 1 given three times weekly.

A few days after the fourth cycle, the patient presented with breathlessness and bilateral lower limb swelling.

Chest X-ray showed no pleural effusion, renal function test was normal, liver function test was normal, albumin levels and urine routine and microscopy were normal. ECHO revealed massive pericardial effusion and pericardial tapping was done. The pericardial fluid was tested for malignant cells and TB-PCR and was negative.

The patient was treated with steroids. The patient improved rapidly. Steroids were continued for 2 weeks and tapered. Repeat ECHO was done which showed mild pericardial effusion. She was asymptomatic for the next 1–2 months. She expired due to disease progression.

Case 3
A 48-year-old patient with stage II breast cancer was treated with chemotherapy with doxorubicin and cyclophosphamide for 4 weeks and paclitaxel weekly for 12 weeks.

After which the patient received was referred for radiotherapy. During the first week of radiotherapy, the patient presented with edema of both lower limbs. On examination, blood pressure and systemic examination were normal. Complete blood count was normal and renal and liver function tests were normal. Thyroid stimulating hormone levels were normal, albumin levels and urine routine and microscopy were normal. Chest X-ray and Doppler study of both the lower limbs were normal. ECHO turned out to be normal.

Since all the workup for bilateral pedal edema was normal, a diagnosis of capillary leak syndrome due to paclitaxel was made and the patient was started on prednisolone for 2 weeks (1 mg/kg). After 2 weeks the pedal edema was completely resolved and the steroids were tapered and stopped. The patient is asymptomatic and is on regular follow-up in the oncology OPD.

Discussion
Capillary leak syndrome is a rare adverse effect of gemcitabine. Initial diagnosis is missed due to nonspecific symptoms.

It is characterized by endothelial hyperpermeability. Rapid extravasation of plasma from the intravascular compartment to the extravascular compartment leads to the symptoms in the patient. The pathophysiology of the disease is not known. Decreased albumin can be a predictor of capillary leak. However it is not a sensitive test. Snakebite, sepsis, treatment with interleukin, and docetaxel chemotherapy have been known to cause capillary leak.

Dr Clarkson first described capillary leak syndrome in 1960. Hemococoncentration and hypoalbuminemia are described as characteristic features.

Vascular endothelial growth factor, complements, and various other cytokinesis are supposed to play important roles in pathogenesis.

Gemcitabine is a pyrimidine antimetabolite which impairs DNA synthesis. It is used in pancreatic cancer, biliary tract cancer, urothelial cancer, breast cancer, ovarian cancer, and lymphomas. Neutropenia and thrombocytopenia are dose-liming side effects. Capillary leak syndrome is described as a rare adverse effect.
Paclitaxel is a microtubule inhibitor. It is used in ovarian cancer, breast cancer, lung cancer, Kaposi sarcoma, cervical cancer, and pancreatic cancer. Neutropenia and neuropathy are common side effects. Capillary leak syndrome is rarely described.

There are cases reported on gemcitabine-induced capillary leak syndrome but only one case has been reported on capillary leak syndrome induced by nab-paclitaxel, documented by Andrea et al.

Gemcitabine-induced capillary leak syndrome is described along with gemcitabine pulmonary toxicity. Both are thought to occur due to endothelial dysfunction. Both typically respond to systemic steroids. Cessation of gemcitabine is mandatory.

**CONCLUSION**

Chemotherapeutic drugs are one of the most common causes of capillary leak syndrome. Immediate treatment with corticosteroids may save the life of the patient.

**REFERENCES**

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Rosalyn Yalow and Radioimmunoassay

Jayant Pai-Dhungat

Rosalyn Yalow (1921–2011) was an American medical physicist, with a special interest in nuclear physics and radioisotopes. She was the second US woman to receive a Nobel Prize in Medicine or Physiology in 1977 along with Roger Guillemin and Andrew Schally for the development of radioimmunoassay. Her coworker Solomon Berson (1918–1972) could not be awarded the prize since he was not alive.

Yalow received her Ph.D. in 1945 from the University of Illinois. She decided to devote her career to full-time research. In 1950, turning to nuclear medicine and began working with physician Solomon Berson from 1954, with whom she gained clinical expertise. Rosalyn became a senior medical investigator for the Bronx Veterans Administration Hospital working with Berson.

They theorized that foreign insulin stimulated the production of antibodies, which became bound to the body’s insulin and prevented the hormone from carrying out its function. In order to prove their hypothesis to a skeptical scientific community, the researchers combined techniques from immunology and radioisotope tracer to measure minute amounts of these antibodies. In the course of their investigation on insulin, Berson and Yalow had also come to a startling realization; the technique they had used to quantify antibodies to a hormone could be used reciprocally to measure concentrations of the antigen, in this case, the insulin itself. Their 1956 article was eventually accepted for publication and thus the method of radioimmunoassay was born.

Soon it was apparent that this method could be used to measure hundreds of other biologically active substances. This method can be used to measure tiny amounts of any substance for which antibodies can be made. It has been of immense value in locating the origin of hormones in the body and in clinical diagnosis and treatment of a variety of diseases.

Rosalyn faced opposition to her attempt as a Jewish female to enter her chosen career but it did not deter her. Experience as a physicist in VA hospital, which was dominated by medical men made her unpleasant. After Berson’s death, she saw that Berson had been assumed to be the creative member of their 22 years of highly productive professional partnership. Stung by this, she increased her research output in the 20 years before her retirement and became even more abrasive, unsoftened by her Nobel Prize (1977).
SIR,

COVID-19 has affected people across the world, especially individuals with comorbid conditions. A systematic review published during the initial phase of COVID-19 has suggested that the risk of poorer COVID-19 disease outcomes in HIV-infected individuals with well-controlled disease is similar to that in general population whereas another systematic review has reported HIV as a significant risk factor for acquiring SARS-CoV-2 and mortality from COVID-19. The data on short-term HIV virological outcome after COVID-19 among people living with HIV (PLWH) are scanty in India.

This analysis is a part of an observational prospective study that aimed to estimate the seroprevalence and persistence of anti-SARS-CoV-2 IgG antibodies among PLWH attending ART Centre in Pune, India. The Institutional Ethics Committee approved the study. Sociodemographic and clinical data were collected and entered into the database. The plasma samples were tested for IgG antibodies against SARS-CoV-2 by using a commercial COVID-19 IgG enzyme-linked immunosorbent assay (ELISA) kit. Change in HIV viral load before and after enrollment was calculated using McNemar’s test.

A total of 384 HIV-infected individuals were included in this study. Of these, 212 (55.2%) were females. Mean age of participants was 42 years (SD: 9.8) and 240 (62.5%) were more than 40 years of age. Mean duration of HIV disease and being on antiretroviral treatment (ART) was 10 years (SD: 4.9) and 9 years (SD: 4.2), respectively. Mean CD4 count of participants at study entry was 630 cells/mm³ (SD: 287) and 247 (64.3%) had CD4 count more than 500 cells/mm³. The median duration of performing HIV viral load assays before and after enrollment was 6 months (95% CI: 5.7–7) and 5 months (95% CI: 4–6), respectively.

Overall 95.3% (366/384) were virologically suppressed prior to study entry and 99.2% (363/384) of these remained suppressed at follow-up visit. No significant change was observed in viral load (p = 0.092).

The data among the IgG antibody positive and negative were analyzed groupwise. Among the IgG antibody positive individuals 202/211 (95.7%) were virologically suppressed prior to study entry and 99% of these (200/202) remained suppressed at follow-up (p-value = 0.289) whereas among IgG antibody negative individuals 164/173 (94.8%) were virologically suppressed prior to study entry and 163/164 (99.4%) of these remained suppressed at follow-up (p-value = 0.375).

Our results are similar to the report from Italy that has mentioned no significant effect of COVID-19 on immunological and virological parameters in patients with HIV infection. Our findings differ from a study from China which has reported that SARS-CoV-2 coinfection may put HIV-infected individuals at greater risk for HIV viral rebound, especially for severe COVID-19.

This is the first report on virological outcome among HIV-infected individuals with positive anti-SARS-CoV-2 antibodies in India as per our understanding. The results showed that there was no short-term effect of COVID-19 on HIV viral load. This is important as Indian National AIDS Control Programme is committed to an ambitious treatment target of UNAIDS 90-90-90 of which the third 90% of all those receiving ART to achieve viral suppression is crucial.

Our study has limitations of non-generalizability due to single-center data, short follow-up period, assumption of study entry point as COVID-19 positivity time, and approximate representation of the COVID-19 as confirmatory RT-PCR test was not done. Studies with a larger number and longer follow-ups will help in understanding the virological outcomes in PLWH with long COVID-19.

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Clinical Associations of Liver Injury in COVID-19

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Dear Sir,

We read with interest the article by Kaushik et al., published in your esteemed journal where in they demonstrated a prevalence rate of deranged liver function tests (LFTs) to be 59.04% in COVID-19 patients, who were seen between April and May 2020 (during the first wave of COVID-19 in India). Over the last 2 years, there have been a number of descriptions of liver injury associated with COVID-19 from all parts of the world. We also evaluated 303 patients admitted to Max Hospital, Saket between 1st April 2020 and 30th June 2020 for the presence of liver injury [defined as elevated aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) above 40 IU/L or >1.5 x the baseline] and factors associated with it. The study was cleared by EIC. The uniqueness of our cohort was that it was more like a community cohort, since according to the Indian Council of Medical Research (ICMR) guidelines, all patients who were positive for SARS-CoV-2 RT-PCR were to be admitted, irrespective of the severity of symptoms.

The mean age of the study population (n = 303) was 47.9 (15.9%) years and 214 (70.6%) were males. A total of 149 (49.2%) patients had evidence of liver injury. Among the 303 patients, mild, moderate-severe, and severe liver injuries were present in 95 (31.3%), 54 (17.8%), and 5 (1.6%) patients, respectively.
Liver injury was significantly associated with male sex (80.5 vs 57.7%; \( p < 0.001 \)), symptomatic disease (97.3 vs 90.3%; \( p = 0.012 \)), and with longer duration of symptoms before presentation [6 (3–8) vs 4 (3–7) days; \( p = 0.021 \)]. Liver injury was not significantly associated with the need of oxygen therapy, ICU stay, mechanical ventilation, or mortality but patients with a moderate-severe liver injury had a longer hospital stay than those without [12 (5.1) vs 10.2 (4.8) days; \( p = 0.042 \)].

Many previous studies, however, have demonstrated that COVID-19 patients who have liver injury have the worst outcomes including higher mortality. But unlike our cohort which resembled more of a community cohort, these other studies had included sick hospitalized patients who were more likely to have severe diseases.

Serum ferritin was found on multivariate analysis, to be the only factor, independently associated with liver injury \([322 (156–552) vs 151 (44.9–299.5) \text{ng/mL}; \ p = 0.021]\). Serum ferritin levels correlated positively with AST \((r = 0.416; \ p = 0.0001)\) and ALT \((r = 0.458; \ p = 0.001)\) also. Since serum ferritin is a marker of hyperinflammatory response in COVID-19, this positive correlation between liver enzymes and serum ferritin suggests that liver injury may be a by-product of COVID-19-mediated inflammatory response rather than direct cytopathic injury. Previous studies have also shown correlation between serum ferritin and liver enzymes.4 Since the data are based on the first LFT at the time of admission, drug-induced liver injury due to drugs started later is unlikely to be the cause of elevated AST and ALT in our cohort.

In conclusion, our study demonstrated that liver injury at presentation is frequent, usually mild, occurs around the end of the first week of illness, possibly associated with immune activation, mostly in those who are symptomatic, and is rarely associated with adverse outcomes like mortality and need for ICU admission. Correlation with serum ferritin levels suggests a significant association with immuno-inflammation.

References


Prevalence and Predictor of Hypogonadism in Newly Onset Type 2 Diabetes Mellitus: A Cross-sectional Study

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In conclusion, our study demonstrated...
Correspondence

84.69 and 85.15 mm Hg, 5.61 and 5.40 mg/dL, 108.43 and 108.02 mL/min, respectively. The prevalence of hypogonadism was 38.53%. Prevalence of central obesity based on WC (≥90 cm) and WC (≥102 cm) criteria was 82.25 and 35.49% in all, 81.15 and 43.82% in hypogonadal group, and 81.69 and 30.28% in eugonadal group, respectively.

It is clear from the present study that the prevalence of hypogonadism is high (38.53%) in newly diagnosed Indian diabetic patients. Zheng et al. (35.21%) and Al Hayek et al. (36.5%) have also reported a high prevalence rate of hypogonadism.5,6 In our study, age was not associated with hypogonadism and this was similar to Zheng et al.’s study. A1c, SBP, DBP, UA, eGFR, TC, LDL, and HDL levels were similar in the two groups. BMI, central obesity (WC: ≥102 prevalence, and TG level were significantly more in group A (hypogonadal) as compared to group B (eugonadal). Low T in obesity is due to bidirectional relationship between visceral fat (VF) and T. More VF leads to increased secretion of proinflammatory cytokines (TNF-α and IL-6), estradiol, and leptin, and all these impair the activity of hypothalamic-pituitary-gonadal axis at multiple levels. Low T promotes further accumulation of VF via preferential deposition of abdominal fat and thus leads to a vicious cycle of progressive hypogonadal state. In our study, WC (≥102 cm) and not the WC (≥90 cm) is associated with low T. This suggests that men have to become more central obese (WC: ≥102) to develop hypogonadism while DM develops at lower WC (≥90 cm). In Teka et al.’s study, average ± SD WC in hypogonadal group was 104.84 ± 8.7 cm.7 High TG is due to high BMI and central obesity (WC: ≥102). Teka et al. have also reported high TG in their study.

In conclusion, this study demonstrates that the prevalence of hypogonadism is high in newly diagnosed DM. BMI, central obesity (WC: ≥102 cm), and TG levels are significantly associated with low T. So obese and hyper-TG patients should be evaluated for T levels at the time of diagnosis. These patients should be treated with drugs that promote weight loss (GLP 1-RA), reduce IR (metformin), and raise T (glimepiride). Recent American Diabetes Association and the European Association for the Study of Diabetes (ADA-EASD) 2022 recommendation also endorses the individualization of therapy.

References


Intravenous Immunoglobulin-induced Hemolysis

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Sirs,

Intravenous immunoglobulin is an established treatment for many immune-mediated disorders and primary immune deficiency states. Hemolytic anemia (HA) is a known adverse effect in patients receiving IVIG for various therapeutic indications.1–3 The most speculated mechanism of hemolysis is a dose-dependent, passive transfer of anti-A/B hemagglutinins from IVIG product to non-O blood group individuals.4–6 There are many reports of HA occurring in patients of GBS and other neurological disorders after IVIG therapy.1–3,7–9 In this article, we report two cases of IVIG-induced hemolysis from the neurology department of our institute.

Case 1

A 67-year-old female, with no significant past medical history, presented with a 3-day history of acute onset progressive quadriaparesis without bladder-bowel involvement. Neurological examination revealed global areflexia and intact sensations. Motor demyelinating polyneuropathy in NCS and albuminocytological dissociation in CSF examination favored the diagnosis of GBS. Considering his BW of 70 kg, we infused a total IVIG dose of 140 gm over 5 days. He developed acute onset anemia with a rapid drop in hemoglobin level to 7.7 gm/dL on day 10 of initiating IVIG infusion, suggestive of intravascular hemolysis. Peripheral smear revealed 2–3 nucleated red blood cells (RBCs)/100 white blood cells and abundant polychromatophils. His blood group was AB type Rhesus positive, but antibody screening identified clinically significant anti-A and anti-B antibodies. Her direct antiglobulin test (DAT) was negative on two occasions. She was transfused with one unit of packed RBCs. Her hemoglobin improved to 11.2 gm/dL and her reticulocyte count dropped to 2% on day 24 after IVIG initiation.

Case 2

A 28-year-old male, with no significant past medical history, presented with a 4-day history of acute onset progressive motor quadriaparesis without bladder-bowel involvement. Neurological examination revealed global areflexia and intact sensations. Motor demyelinating polyneuropathy in NCS and albuminocytological dissociation in CSF examination favored the diagnosis of GBS. Considering his BW of 70 kg, we infused a total IVIG dose of 140 gm over 5 days. He developed acute onset anemia with a rapid drop in hemoglobin level to 7.7 gm/dL on day 10 of initiating IVIG (Fig. 1A). Rise in indirect bilirubin and serum LDH (Fig. 1C and 1D) along with peripheral smear showing nucleated RBCs and polychromasia, favored hemolysis. His blood group was AB type Rhesus positive, and antibodies screening revealed clinically significant levels of anti-A and anti-B antibodies. DAT test was negative. He was conservatively managed and transfused two units of packed red blood cells. His hemoglobin improved to 11.8 gm/dL on day 24 after IVIG initiation.

Intravenous immunoglobulin products used in both cases were of the same lot; the liquid preparation had 5 gm of human immunoglobulin G and maltose as a stabilizer in 100 ml vial. Analysis of the IVIG products revealed high titers of anti-A (1024 IgM) and...
Correspondence

512 (IgG) and anti-B antibodies [1024 (IgM) and 256 (IgG)], confirming the diagnosis of IVIG-induced hemolysis.

**DISCUSSION**

The incidence rate of IVIG-associated hemolysis ranges from 2.1 to 2.8 per 1000 IVIG administrations. Risk factors associated with IVIG-induced hemolysis include non-O blood group type, high individual (≥2 gm/kg BW) dose or cumulative dose (>120–200 gm), and the underlying immunological or inflammatory condition of the patient. Antibody-coated RBCs undergo complement-mediated enhanced erythrocyte sequestration leading to erythrophagocytosis. In patients with underlying inflammatory conditions, accelerated activity of immune system removes the sensitized RBCs at a speed up rate from circulation. One previous study on patients receiving high dose IVIG observed the highest risk for hemolysis in patients with AB blood group, those who were first time recipients, those who were not on immunosuppressants, and who had a positive (≥1+) DAT immediate postinfusion.

We observed clinically significant hemolysis in two patients who received IVIG for treatment of GBS. Both received IVIG for the first time, at a dose of 2 gm/kg BW and had AB type Rhesus positive blood group. The DAT in our patients may be false negative because of rapid removal of the sensitized RBCs. In severe hemolysis, RBCs are cleared so quickly, and in such great numbers, that there are few circulating sensitized RBCs left for detection. Most commercial antiglobulin tests screen for antibodies to IgG, complement C3, or both. Autoantibodies other than IgG, such as IgM or IgA can cause a false negative DAT. In our patients, high titer of IgM anti-A and anti-B antibodies compared to IgG in the IVIG product might have competitively inhibited the binding of IgG on the RBCs, bringing it below the detection threshold.

The current industry standard antibody titers are 1:64 for anti-A and 1:32 for anti-B; there should not be any agglutination beyond 1:64. Both cases reported here received the same liquid preparation of IVIG. The immunological analysis of IVIG product used in the patients with hemolysis revealed a higher anti-A and anti-B titer than the permissible limit. The adverse reactions were reported to the IVIG manufacturer, and the culprit batch was withdrawn from the market. None of the other patients who received IVIG during the same period had developed hemolysis. It is possible that the titers of anti-A and anti-B varied within the IVIG lot and patients with higher risks developed hemolysis. Individual susceptibility and certain unidentified patient factors might have also contributed to the occurrence of clinically significant hemolysis. Measures like immunoaffinity chromatography can

Figs 1A to D: Pattern of fluctuations in laboratory parameters including: (A) Hemoglobin levels (normal = 12–16 gm/dL); (B) Total bilirubin (normal value ≤ 1.2 mg/dL); (C) Indirect bilirubin (normal value ≤ 0.7 mg/dL); (D) Serum LDH (normal value ≤ 240 units/L), in patients with hemolysis.
Correspondence

considerably reduce the incidence rate of IVIG-associated HA by decreasing the amount of anti-A/B isoagglutinins in the IVIG product. However, hemolytic reactions continue to occur and at times severe enough, requiring transfusion. Physicians should monitor high-risk patients for 5–10 days after IVIG infusion. If the patient has a drop in hemoglobin level, testing for markers of hemolysis, including DAT, is recommended.

Our article highlights a potentially serious but under-recognized side effect of IVIG therapy. It is important that medical practitioners are aware of this adverse effect for early recognition and management. A package insert containing an antibody titer of IVIG preparation is highly recommended.

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PATIENT CONSENT

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

REFERENCES


Post-COVID Vaccine Thrombocytopenia

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Sir/Madam,

Vaccination is the most potent weapon against COVID-19 infection. This is highly safe and effective. Side effects are rarely reported after administration of the vaccine and include mild, nonspecific symptoms like self-limiting fever, local pain, myalgia, headache, or fatigue.1 Very rarely, grave adverse events are documented. We here describe one such extremely rare side effect of a COVID vaccine.

A 54-year-old male was admitted with fever following the first dose of COVID vaccination (Covishield: ChAdOx1 nCoV-19). He started running high temperature 3 days after receiving the vaccine and got admitted on day 7 after his blood reports showed certain abnormalities. On admission, his hemoglobin was 7.3 gm/dL, total leukocyte count 15,800/cmm, and platelet count was 20,000/cmm. There was no bleeding manifestation. Examination revealed no sternal tenderness or lymphadenopathy. Among other blood tests, C-reactive protein (CRP) was 19.5 mg/L, procalcinogen was 0.55 ng/mL, and liver and kidney function tests were normal. Serum lactate dehydrogenase was also normal. In view of the low platelet count, 5 units of random donor platelet were transfused but it did not help. Two days after transfusion, the platelet count again came down to 14,000/cmm. Blood for antinuclear factor and antineutrophil cytoplasmic antibodies were negative; C3 and C4 levels were normal. Screening for infections like malaria, dengue, scrub typhus, HIV, and viral hepatitis was all negative. There was no significant history of use of any drugs like heparin in the recent past. Thus, the thrombocytopenia was assumed to be immune-mediated. Since COVID vaccination was the only significant event before this episode, this thrombocytopenia was assumed to be triggered by the vaccination.

In view of the falling platelet count, i.v. pulse dose of methylprednisolone (1000 mg) was given for 3 days. This was followed by oral prednisolone (1 mg/kg/day). The CRP came down to 6.4 mg/L after 4 days. Slowly, the platelet count started rising. On day 7, it was 49,000/cmm. On day 12, it was 77,000/cmm. The patient was discharged with slowly tapering doses of oral steroids. No second immunosuppressant was needed.

Thrombocytopenia is a highly unusual complication of the COVID vaccine, ChAdOx1 nCoV-19 or otherwise. In a recent report from Norway, five cases of thrombocytopenia after administration of ChAdOx1 nCoV-19 vaccine have been documented.2 All were middle-aged adults with no comorbidity or drug history.2 Their nadir platelet counts varied from 10,000 to 70,000/cmm. In our patient, the nadir was 14,000/cmm. The events occurred around 7 days after vaccination in all these cases, which is the same as the timeline of our case.

However, in addition, all of these patients had venous thrombosis along with thrombocytopenia.2 In our patient, no such thrombotic event was documented. Serum assays in the Norwegian patients revealed high levels of IgG antibodies to PF4–polyanion complex. Thus, the authors opined that this vaccine-induced immune thrombotic thrombocytopenia (VITT) was a variant of spontaneous heparin-induced thrombocytopenia (HIT).3 Although this is not conclusive evidence, still, based on the molecular mechanism of VITT, it may be advisable to avoid the ChAdOx1 nCoV-19 vaccine in patients with a previous history of HIT.

Like our patient, the Norwegian patients also had improvement in platelet counts with steroids and/or IVIG.2 Thus, the immune basis for the syndrome is further established.

In another study from the USA, it was seen that 12% of chronic immune thrombocytopenic purpura patients had a significant drop in platelet count 2–5 days after COVID vaccination.3 All of them recovered quickly with steroids.3

The issue of vaccine-induced thrombocytopenia is an extremely rare but well-known entity.4 Similar thrombocytopenia has been reported earlier with the MMR vaccine.5 Usually, these are mild self-limiting events and administration of the second dose of the same vaccine usually does not lead to recurrence.4 But for COVID vaccines, our experience is still limited and there is no data on whether the second dose of the same
vaccine will be safe or not. Our patient refused the second dose of ChAdOx1 nCoV-19 and is still not fully vaccinated.

We present this case to highlight this extremely rare adverse event following COVID vaccination. Billions of doses of the vaccine have been administered in our country with minimal side effects. Still, clinicians should be on the lookout for such rare events.

Immunosuppression is usually effective in most cases. Completion of the vaccination course after this adverse event is still a matter of discussion.

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