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Telmisartan is a medication that is used to lower blood pressure. It is a medication that works by blocking the action of a hormone called angiotensin II. This hormone is involved in the regulation of blood pressure and the body’s fluid balance. Cilindipine is a medication that is used to lower blood pressure. It works by relaxing the muscles in the blood vessels, which makes them wider and reduces blood pressure.

The combination of Telmisartan and Cilindipine is effective in treating hypertension. It is used when one medication alone is not enough to control blood pressure. The combination of these two medications can be an effective treatment for hypertension, and it is often used as an alternative to surgery or other invasive treatment methods.

In conclusion, the combination of Telmasartan and Cilindipine is a safe and effective treatment for hypertension. It can help to lower blood pressure and reduce the risk of heart disease and stroke. The side effects of the combination are usually mild and manageable.

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Salt Restriction in Heart Failure: The Great Debate!!

Chandrashekhar K Ponde1*, Akshay Pawar2

“Let there be work, bread, water, and salt for all.”
—Nelson Mandela

Salt is an essential nutrient used in dietary practices across the globe and without which food, especially Indian, can be tasteless. Edible salt consists of 40% sodium and 60% chloride by weight. Physiologically approximately 0.5 gm/day of sodium is sufficient for human cells to meet their vital functions.

The average Indian adult consumes around 11 gm of salt/day which is double the amount of salt recommended (5 gm/day) and is way greater than the physiological requirement for the human body.

High sodium is associated with an increased risk of cardiovascular comorbidities, especially hypertension and heart failure (HF). HF prevalence is increasing globally and in India, it is 1.2/1,000 population as per India UK-India Education and Research Initiative study. HF is classified into two major groups, HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFrEF).

Treatment of HFrEF involves both pharmacologic and nonpharmacologic strategies. Neurohormonal imbalance involving the renin–angiotensin–aldosterone (RAAS) system is the key component of HF pathophysiology which causes sodium and water retention. An increase of 5 gm of salt a day leads to increase of extracellular volume of approximately 1.5 L and this in turn leads to worsening of HF. Dietary sodium restriction has been historically a mainstay of the management of HF patients to prevent fluid overload and subsequent clinical outcomes. Potential beneficial mechanisms of a low sodium diet with advanced HF are decreased pulmonary artery and capillary wedge pressures, decrease in extracellular fluid, decreased arterial stiffness and systemic vascular resistance, suppression of oxidative stress, and decrease in aldosterone synthesis.

Sodium restriction is frequently recommended in most standard guidelines, but the optimal restriction range (from <1.5 to <3 gm daily) and its effect on patients with HFrEF is not clear as they have often been excluded from most of the relevant studies. In addition, adherence to following a low sodium diet is challenging for most patients. Previous HF clinical trials that enrolled predominantly HFrEF patients provided mixed results, with epidemiological data and clinical trials of varying designs highlighting the beneficial, neutral, or harmful effects of sodium restriction. HF guidelines have evolved over the period and recent guidelines have downgraded the strength and grade of recommendations regarding dietary sodium restriction over time.

Therefore, before we vigorously start educating HF patients to restrict sodium intake in their diet, we need to reexamine the scientific evidence behind such recommendations.

Initially, let us look at the studies favouring sodium restriction in ambulatory HF patients

The Study of Dietary Intervention Under 100 mmol in HF (SODIUM-HF)—a pilot trial, was a randomized controlled trial (RCT) that compared a low sodium (1.5 gm/day) to a moderate (2.3 gm/day) sodium diet in HF patients. It concluded dietary restriction of sodium intake was feasible, and achievement of this low sodium goal was associated with lower brain natriuretic peptide (BNP) levels and improved quality of life in patients with HF. The Prevent Adverse Outcomes in HF by Limiting Sodium, another pilot trial, concluded that the quality of life improved among patients in the 1500 mg group but remained unchanged in the 3000 mg group, and there was no difference in the change in N-terminal-pro BNP levels. Another trial concluded that sodium restriction below 2 gm/day is not warranted in mild HF patients, whereas excessive sodium intake above 3 gm/day may be harmful in moderate to severe HF patients.

Colin Ramirez et al. in 2004 showed that in HF patients (both HFrEF or HFrEF), 2.0–2.4 gm/day of sodium restriction was associated with an improvement in New York Heart Association (NYHA) class and fewer reported signs of HF on 6-month follow-up. There were other clinical trials supporting the same notion of dietary sodium restriction in patients with HF.

Evidences favoring low sodium intake demonstrate higher sodium intake was associated with an increased risk of cardiovascular events and death compared with moderate sodium intake in HF populations. Sodium restriction is appropriate in patients with stage I (at risk for HF) and II (asymptomatic HF) due to its effect on lowering blood pressure, the incidence of hypertension, left ventricular hypertrophy, cardiovascular disease, and even the incidence of HF. However, there is insufficient evidence for such a recommendation for stages III (with prior or current symptoms) and stage IV (refractory) HF.

Now let us focus on studies indicating the negative impact of sodium restriction in ambulatory HF patients

Alvelos et al. reported that in patients with chronic HFrEF, with ejection fraction <40%, sodium restriction was not associated with improvement in functional class during 15-day follow-up. In 2015 Colin-Ramirez et al. showed no significant difference in NYHA class between the intervention group with sodium restriction of 1.5 gm/day compared to group of moderate sodium intake of 2.4 gm/day in patients with HF (both HFrEF and HFrEF) who are Optimal Medical Treatment during 6-months follow-up. In a recently published international, open-label, randomized controlled SODIUM-HFrE trial, 806 patients with HF (preserved or reduced left ventricular systolic function) were randomly assigned to a low sodium diet (<1500 mg/day) vs usual care. It concluded that, among ambulatory patients with HF, a low sodium diet was not associated with a reduction in adverse cardiovascular events. A low sodium diet was associated with a modest improvement in quality of life; however, the 6-minute walk test was not different between treatment groups. Unfortunately, the trial was terminated early.

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due to the coronavirus disease 2019 pandemic, limiting the interpretation of the findings. An earlier study by Doukky et al.6 in 2016 (adherence and retention trial) found that sodium restriction is not only disadvantageous but also has a rather detrimental impact on outcomes in symptomatic patients with chronic HF. They studied 902 chronic HF patients (both preserved or reduced left ventricular ejection fraction), which found no demonstrable evidence that dietary sodium restriction is associated with lower rate of death or HF hospitalization. They showed that sodium restriction to <2.5 gm/day in NYHA class II/III HF patients is associated with a 72% higher risk of death or HF hospitalization compared to a higher sodium intake of >2.5 gm/day, especially in patients not receiving therapy with RAAS blockers with a hazard ratio of 5.23.

Now we Discuss Role of Sodium Restriction in Acute Decompensated HF (ADHF)

Aliti et al.10 studied the role of sodium restriction, which showed no effect on weight loss or clinical stability at 3 days and they concluded that sodium restriction in patients admitted for ADHF is unnecessary. In a large Italian study of patients admitted with HF, patients assigned to low sodium intake (1.84 gm/day) compared to moderate sodium intake (2.76 gm/day), had reduced diuresis, more HF readmissions, and a trend towards increased mortality. Unfortunately, patients in this study did not receive optimal neurohormonal blockade and received strict fluid restriction of 1 L/day and high dose diuretic (up to 100–1000 mg of furosemide) without adjustment of clinical status.11 In a meta-analysis of 17 RCTs, sodium restriction was not associated reduction in CV or all cause mortality or hospitalizations in patients with HF.12

Role of Sodium Restriction in HFrEF

Prevalence of HF is increasing globally, and HF with HFrEF has gradually accounted for almost half of the HF population with near similar mortality rates. Although some observational studies and RCTs have focused on sodium intake in patients with HF, patients with HFrEF were frequently excluded from these studies. Moreover, patients with HFrEF have a different response to treatment and volume status than those with HFrEF. As salt intake could significantly affect volume status and neurohormonal status, it might play a role in response to treatment in HFrEF. However, contrary to the theoretical expectation, a recent study done13 in patients with HFrEF revealed that an overt strict dietary salt intake restriction could harm patients with HFrEF and is associated with a worse prognosis. A study done by Machado et al.14 showed that aggressive salt/water restriction does not provide clinical benefits in patients with HFrEF. Also, sodium restriction does not seem to have a neurohormonal effect in patients with HFrEF.

There are many potential reasons for conflicting evidence regarding the benefit/harm of sodium restriction. These include heterogeneity of the HF patient population studied, lack of uniformity in limiting the amount of sodium restriction per day, unclear data on the associated use of fluid restriction, and simultaneous usage of diuretics and neurohormonal blockade agents.

What should we do?

Given there is clear evidence of the benefit of limiting sodium intake to prevent various comorbidities leading to HF, it is recommended to limit sodium intake in those who are at risk (American College of Cardiology stages A and B) to prevent the onset of HF. In patients with HF, salt restriction is a double-edged sword, and the benefits and harm have to be balanced cautiously. Current data suggest a moderate salt restriction in ambulatory patients with HFrEF. Stringent salt restriction (I < 1.5 gm a day) is associated with worse outcomes in both ambulatory and decompensated patients with HFrEF. However, HFrEF data suggest that salt restriction does not confer any significant benefits. As the degree of dietary sodium reduction that would lead to a reduction in clinical events has not yet been defined, clinicians and patients should consider this dietary intervention similar to other medical therapies and balance the potential benefits on an individual basis.

References


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Abstract

Aim: Accumulation of advanced glycation end products (AGEs) occurs with aging and in various disease states. There are no reliable screening techniques to measure AGEs in clinical settings. In this study, a point-of-care (POC) device was used to validate skin AGE measurements with serum AGE levels and to assess its usefulness to identify individuals with abnormal glucose tolerance (AGT).

Materials and methods: The study group comprised individuals with normal glucose tolerance (NGT; n = 47) and with AGT, that is, either diabetes or prediabetes (n = 68). Intrinsic AGE fluorescence was measured spectrofluorometrically using a multimode plate reader in the serum by exciting the samples at 370 nm and emission readouts at 440 nm. Skin AGEs were acquired using a CE-marked Scout DS commercial device. Serum levels of biomarkers carboxymethyl lysine (CML), carboxyethyl lysine (CEL), and pentosidine were analyzed by enzyme-linked immunosorbent assay (ELISA).

Results: In subjects with AGT, the skin AGEs (61.3 ± 53.7 arbitrary units [AU], p < 0.0001) and serum AGEs (3.5 vs 2.8 AU, p < 0.0001) were significantly higher than in individuals with NGT. The levels of CML, CEL, and pentosidine were also significantly higher in the subjects with AGT when compared with NGT (138 vs 89 pg/mL; 2.4 vs 1.4 mmol/mL, and 64 vs 48 mmol/mL, p < 0.0001), respectively. Pearson correlation analysis showed a significant positive association of skin AGEs with serum AGEs (r = 0.344) (p < 0.001), CML (r = 0.323) (p < 0.001), CEL (r = 0.308) (p < 0.001), and pentosidine (r = 0.251) (p < 0.001). In addition, it also showed a positive correlation with fasting plasma glucose (FGP) (p < 0.001), 2-hour post-glucose (p < 0.001), glycated hemoglobin (HbA1c) (p < 0.001), and body mass index (BMI) (p < 0.005). Multiple logistic regression analysis using AGT as a dependent variable showed that skin AGE scores were significantly (p < 0.001) associated with AGT (odds ratio: 1.133, confidence intervals: 1.067–1.203).

Conclusions: This study shows that the measurement of skin AGEs using a POC device may be suitable for mass screening of AGT even in low-resource settings.

Introduction

Hyperglycemia and impaired insulin secretion or action are key characteristics of type 2 diabetes. Based on the 2021 Atlas of International Diabetes Federation, 10th edition, India is second in the prevalence of diabetes globally, next to China, with 74.2 million people being affected and it is projected to increase to 124.9 million in the year 2045.1,2

Screening of high-risk individuals is an imperative step in the primary prevention of diabetes. Conventional diabetes screening program of random capillary glucose needs pricking of skin to obtain blood samples. A noninvasive method of diabetes mass screening has been proposed as a substitute to invasive screening, based on skin intrinsic fluorescence.3–5 The POC device—Scout DS (VeraLight Inc., Albuquerque, NM) measures diabetes biomarkers in the skin, including AGEs and collagen cross-links as well as fluorescent mediators of cellular metabolism and oxidative stress, such as nicotinamide adenine dinucleotide and flavin adenine dinucleotide based on the principle of fluorescence spectroscopy.6,7 This can potentially be used as a first step in the noninvasive mass screening of individuals at risk, especially subjects with prediabetes. The device measures skin fluorescence to assess the absorption of light by melanocytes and hemoglobin in the subject’s skin and integrates this with the measurement algorithm to generate a diabetes risk score.

Advanced glycation end products are nonenzymatically glycated and oxidized modifications of proteins, lipids, or nucleic acids that may contribute to micro- and macrovascular disease development.8 The link between the pathogenesis of diabetes and products of AGE is very well established.9,10 In most clinical settings, AGE measurements are not possible because they require high-pressure liquid chromatography or gas or liquid chromatography-mass spectrometry analysis.11,12 In this scenario, our team had already developed an assay to calculate AGEs in serum expressed as advanced glycation index (AGI).13 In this paper, we have validated the skin AGE measurement by Scout DS by comparing it with systemic levels of AGEs in individuals with NGT and AGT.

Materials and Methods

Study Participants

Individuals with NGT (n = 47) and AGT (n = 68) were recruited from Dr Mohan’s Diabetes Specialities Centre, screening from community and referrals from study participants which have been described in detail earlier.14 Institutional Ethics Committee approval was obtained from Madras Diabetes Research Foundation. All participants provided written informed consent for the study. NGT and AGT were defined based on World Health Organization criteria as follows: after 75-gm glucose load during an oral glucose tolerance test, individuals with 2-hour post-plasma glucose value <7.8 mmol/L (140 mg/dL) were characterized as NGT and those with 2-hour post-plasma glucose value ≥7.8 mmol/L (≥140 mg/dL) were characterized as AGT.
post glucose value ≥7.8 mmol/L (140 mg/dL) were diagnosed to have AGT. AGT included those with either diabetes (n = 37) and prediabetes (n = 31). For the rest of the paper, AGT is considered as one group. Of the diabetic patients, 90% were on oral hypoglycemic agents (OHA) and 10% on OHA plus insulin for control of hyperglycemia. Among the diabetic patients, 90% took OHA and 10% used OHA plus insulin. The inclusion criterion was age ≥20 years of either sex. The exclusion criteria were detailed earlier.14

**Anthropometry and Biochemical Parameters Estimation**

Anthropometric measurements were obtained using standardized techniques. Weight (kg)/height (m²) was the formula used to calculate BMI. Venipuncture was performed to collect FPG, HbA1c, hemogram, lipid profile, and liver function tests. Automated analyzer (Beckman Coulter, Brea, CA, USA) and testing system analyzers (VARIANT II TURBO; Bio-Rad, Hercules, CA, USA) were used to perform FPG (hexokinase) and A1c assays. The A1c values were Diabetes Control and Complications Trial-aligned, and the laboratory is certified by the College of American Pathologists and the National Accreditation Board for Testing and Calibration. Beckman Coulter automated analyzer was used to perform lipid profile. The intra- and interassay coefficients of variation (CVs) for the plasma glucose assays were <2.2 and 2.5% and for A1c assay were <0.6 and 1.5%, respectively.

**SCOUT DS Measurement**

The study participants were measured twice using the SCOUT DS machine, with each measurement consisting of two consecutive positions of the forearm on the SCOUT device (Fig. 1).

SCOUT data were collected using a commercial SCOUT device marked with CE (software revision 1.2). Individuals who did not receive a SCOUT score after two attempts were classified as screen failures and did not proceed with blood testing at the first visit. A follow-up phase recalled screen failures for SCOUT remeasurement and reacquisition of blood work. This facilitated the performance evaluation of the new SCOUT algorithm, which is more robust for dealing with dark skin and skin contamination. M/S VeraLight provided scores from their proprietary SCOUT algorithm.

**ELISA Measurement**

**Estimation of Serum CML**

Fasting blood samples were collected into serum separator tubes (SST) and allowed to clot for 30 minutes at room temperature. Samples were then centrifuged at 3000 rpm for 15 minutes to separate the serum portion and used for the assay. Human CML ELISA kit was purchased from Cusabio Biotech Co., Ltd (CSB-E12798h) and assay was performed according to the manufacturer’s protocol. In brief, 100 μL of standards, control, and samples were added to the wells and incubated for 2 hours at 37°C. Solution was aspirated from each well and 100 μL of conjugate solution was added and incubated for 1 hour at 37°C. Unbound antibodies were removed by washing three times using 200 μL of wash buffer and 100 μL of enzyme conjugate solution was added. Incubated for 1 hour at 37°C and later washed five times before the substrate solution (90 μL) was added. The plate was incubated in the dark at 37°C for 30 minutes. Read the plate at 450 nm after adding 50 μL of stop solution. CML levels were represented as pg/mL.

**Estimation of Pentosidine**

Fasting blood samples were collected into SST and allowed to clot for 30 minutes at room temperature. Samples were then centrifuged at 3000 rpm for 15 minutes to separate the serum portion and used for the assay. Human N (epsilon) (carboxyethyl) lysine ELISA kit was purchased from Cusabio Biotech Co., Ltd (CSB-E009415h) and assay was performed according to the manufacturer’s protocol. In brief, 100 μL of standards, control, and samples were added to the respective wells and incubated at 37°C for 2 hours. Solution was aspirated from each well and 100 μL of conjugate solution was added and incubated for 1 hour at 37°C. After that wash the unbound antibodies three times using 200 μL of wash buffer. Then add 100 μL of enzyme conjugate solution. Incubated for 1 hour at 37°C. Repeat washing procedure five times. Then add 90 μL of the substrate solution. The plate was incubated for 30 minutes in the dark at 37°C. Stop the reaction by adding 50 μL of stop solution. Read the plate at 450 nm. Pentosidine levels are represented as pmol/mL.

**Serum AGE Measurement**

Serum AGE measurement was determined as previously described by Sampathkumar et al. with minor modifications. Intrinsic AGE-specific fluorescence was measured spectrophotometrically (multimode plate reader—PerkinElmer) by exciting the samples at 370 nm and emission readouts at 440 nm (Black Opaque 96-well Microplate, PerkinElmer). The concentrations of the AGE products were directly proportional to the fluorescence intensity, with each addition of serum sample the fluorescence intensity increased and fitted to a linear regression line. The slope of the regression line is called the AGI and is expressed in AU (100 units = 1 unit AGI). AGI values (representing serum AGE levels) are five-point linear regression estimates rather than the one-point derivation of fluorescent AGE levels reported in previous studies.

**Statistical Analysis**

Based on the primary outcome variable (skin AGEs) of our pilot study, the required minimum sample size was calculated as n = 40 in each group, considering the significance level set at 0.05 and statistical power of 0.80. Therefore, a higher number of samples (n ≥ 40) were considered for the study to ensure appropriate statistical power. One-way analysis of variance was used for the comparison between groups with p < 0.05 as the criterion for significance. Pearson correlation analysis was performed to determine the relationship between skin AGE and risk factors. All statistical analyses were performed using the Windows-based statistical package, SPSS (version 20.0, Chicago, IL, USA).
### Results

The clinical and biochemical characteristics are shown in Table 1. Waist circumference, FPG, 2-hour post-plasma glucose, HbA1c, systolic and diastolic blood pressure, and serum triglycerides were significantly higher in individuals with AGT when compared with NGT.

Figure 2 shows the levels of serum AGEs and skin AGEs in the two study groups. Skin AGEs were significantly higher in the subjects with AGT when compared with NGT (61.3 vs 53.7 AU; \( p < 0.0001 \) (Fig. 2A). The serum AGEs were also significantly higher in subjects with AGT when compared with NGT (3.5 vs 2.80 AU; \( p < 0.0001 \) (Fig. 2B).

Figure 3 shows the levels of CML (138 vs 89 pg/mL) (Fig. 3A), CEL (2.4 vs 1.4 nmol/mL) (Fig. 3B), and pentosidine (64 vs 48 pmol/mL, \( p < 0.0001 \) (Fig. 3C) were significantly higher (\( p < 0.001 \) for all three) in the subjects with AGT when compared with NGT.

Table 2 shows the Pearson correlation analysis of the skin AGEs with serum AGEs and other risk factors. Skin AGEs showed a positive association with serum AGEs (\( r = 0.344 \)) (\( p < 0.001 \), CML (\( r = 0.323 \)) (\( p < 0.001 \), CEL (\( r = 0.308 \)) (\( p < 0.001 \), and pentosidine (\( r = 0.251 \)) (\( p < 0.001 \). They also showed a positive correlation with FPG (\( p < 0.001 \), 2-hour post-glucose (\( p < 0.001 \), HbA1c (\( p < 0.001 \), and BMI (\( p < 0.05 \). Multiple logistic regression analysis using AGT as dependent variable showed that skin AGE scores were significantly (\( p < 0.001 \)) associated with AGT (odds ratio: 1.133, confidence intervals: 1.067–1.203) and this association persisted (\( p < 0.038 \)) even after adjusting for age, waist circumference, BMI, FPG, and HbA1c.

Figure 4 illustrates the scatter plot showing the correlation of skin AGEs with serum AGEs (Fig. 4A), HbA1c (Fig. 4B), FPG (Fig. 4C) and 2-hour post-plasma glucose (Fig. 4D).

### Discussion

Many studies have confirmed the accumulation of AGEs and its role in the pathogenesis of diabetes and its complications.
of diabetes and its complications.\textsuperscript{15} AGES induce tissue dysfunction through receptor for advanced glycation end products (RAGE) that has been reported to be enhanced in diabetes mellitus.\textsuperscript{16,17} Conventional methods for advanced glycation end products (RAGE) of diabetes and its complications.\textsuperscript{15} AGES with serum AGES and other risk factors.

Table 2: Pearson correlation analysis of skin AGES with serum AGES and other risk factors

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Skin AGES</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference</td>
<td>0.195</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>BMI</td>
<td>0.212</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>FPG</td>
<td>0.352</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2h-PPG</td>
<td>0.496</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c</td>
<td>0.390</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TC</td>
<td>0.181</td>
<td>0.073</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.114</td>
<td>0.251</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.007</td>
<td>0.937</td>
</tr>
<tr>
<td>TG</td>
<td>0.18</td>
<td>0.851</td>
</tr>
<tr>
<td>Serum AGES</td>
<td>0.344</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CML</td>
<td>0.323</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CEL</td>
<td>0.308</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pentosidine</td>
<td>0.251</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

\(2h\text{-}PPG, 2\text{-}hour\text{-}post\text{-}plasma\text{ glucose}; AGE, \text{Advanced glycation end product}; BMI, \text{Body mass index}; CEL, \text{Carboxymethyl lysine}; CML, \text{Carboxyethyl lysine}; FPG, \text{Fasting plasma glucose}; HbA1c, \text{Glycated hemoglobin}; HDL-C, \text{High\text{-}density lipoprotein\text{-}cholesterol}; LDL-C, \text{Low\text{-}density lipoprotein\text{-}cholesterol}; TC, \text{Total cholesterol}; TG, \text{TGlycated}.

In our previous study, we reported the usefulness of the noninvasive POC device, SCOUT DS for assessment of skin fluorescence in type 2 diabetes where the sensitivity of SCOUT DS and HbA1c to detect AGT were 87 and 86%, respectively.\textsuperscript{14} The main advantages of the SCOUT machine over the FPG or HbA1c are that it does not need a blood draw; there is no need of any reagents or disposables, and the test result is available within minutes. In this study, we have validated the sensitivity further by showing its association with the levels of serum AGES as well as other AGE\text{-}specific biomarkers viz., CML, CEL, and pentosidine. The study also shows a good correlation of skin AGES fluorescence with HbA1C and blood glucose levels which, in turn, substantiates the use of the instrument for mass screening.

AGEs formed after the molecular rearrangements of glycosylated proteins or lipids accumulate in the vessel wall where they may alter the cell structure and function thereby leading to micro- and macrovascular complications of diabetes.\textsuperscript{21} Hofmann et al.\textsuperscript{22} reported that skin autofluorescence (SAF) was correlated to the AGES in the cardiac tissue in CAD patients thus positive to the correlation between arterial tissue AGES and skin AGES. Due to their low concentration in tissue proteins, specific detection of AGES is cumbersome and requires preanalytical methods that may alter the sensitivity of the measurements.

A number of studies have shown the association of skin AGES with HbA1c.\textsuperscript{23,24} In our study also we observed that skin AGES had a significant correlation with HbA1c in diabetic subjects. Moreover, due to the short lifespan of red blood cells, skin fluorescence appears to be a good marker of past long-term tissue damage compared to the traditional HbA1c measure. In this study, we have demonstrated the association of skin AGES with serum levels of AGES.

Carboxymethyl lysine, CEL, and pentosidine represent the most prevalent AGES in vivo and these are frequently used as AGE markers.\textsuperscript{25,26} Temma et al.\textsuperscript{27} and Yuan et al.\textsuperscript{28} have shown that the levels of skin AGES in different patient groups and control subjects, measured by an AGE reader, are significantly correlated to levels of both nonfluorescent AGES (e.g., CML and CEL) and fluorescent (e.g., pentosidine) products assessed in skin biopsies. Meerwaldt et al.\textsuperscript{29} first reported the validity of the AGE reader as a tool to measure AGES. A study by Kida et al.\textsuperscript{30} showed that SAF correlated significantly with skin pentosidine but not with bone pentosidine content. Another study by Hu et al.\textsuperscript{31} reported that among diabetic and nondiabetic Chinese subjects with lower-limb amputation, the SAF was independently associated with different AGES such as CML in skin and pentosidine in artery and nerve. In our study also the level of AGES measured as both skin fluorescence and serum CML, CEL, and pentosidine were both consistently and significantly elevated in individuals with AGT when compared to those with NGT. Some studies have also confirmed that serum levels of non-CML AGES are significantly associated with the severity of micro- and macrovascular complications of diabetes.\textsuperscript{32}

In conclusion, our study shows that skin AGES measurement using a POC device may be useful in mass screening of diabetes in epidemiological surveys even in low-resource
settings, as there are literally no consumable costs. The correlation with serum AGEs and with biomarkers like CML, CEL, and pentosidine further support these findings.

**Ethical Standard**
The study was approved by the Ethical Committee of Madras Diabetes Research Foundation.

**Acknowledgment**
We thank Department of Biotechnology (DBT) for supporting this study.

**References**

Hematological and other Laboratory Parameter Changes in COVID-19 Patients

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ABSTRACT

Background: World Health Organization (WHO) declared Coronavirus disease of 2019 (COVID-19) as a pandemic in March 2020. The disease showed a wide range of severity ranging from being asymptomatic to causing high mortality. Various laboratory parameters were investigated, which could be used as biomarkers to determine the severity of the disease. The objective of the present study was to analyze hematological, coagulation, and immunological markers in mild, moderate, severe, and critical cases of COVID-19 patients and their relation to the outcome.

Materials and methods: A retrospective observational study of 1,000 COVID-19-positive hospitalized patients was conducted. Cases were classified into mild, moderate, severe, and critical groups using WHO guidelines. Along with demographic data, hematological, coagulation, and inflammatory parameters were analyzed and correlated with severity and survival.

Result: Out of the total 1,000 cases, there were 510 cases in mild, 232 in moderate, 201 in severe, and 57 in the critical category. Increase in total white blood cell count, absolute neutrophil count (ANC), neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), and inflammatory parameters like C-reactive protein (CRP), serum ferritin, lactate dehydrogenase (LDH), interleukin-6 (IL-6), and decrease in absolute lymphocyte count (ALC) showed significant difference with disease severity and survival.

Conclusion: These are important biomarkers to predict the prognosis and outcome of COVID-19 patients. As these markers are easily available, they could be used to categorize the patients at an early stage for optimum management.

Original Article

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INTRODUCTION

Coronavirus disease of 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 is a highly infectious disease and spread across the globe within a short time, prompting the WHO to declare it a pandemic in March 2020. COVID-19 has varied clinical manifestations ranging from asymptomatic phase to life-threatening acute respiratory distress syndrome, and organ failure that may lead to death. Along with the clinical symptoms and computerized tomography findings, COVID-19 patients showed laboratory fluctuations in hematological, biochemical, coagulation, and inflammatory markers, which were proportional to the severity of the disease. Numerous studies carried out in parallel have also suggested that hematological parameters, including lymphocyte, platelet, neutrophil, and monocyte counts, appear to correlate with the severity and mortality of COVID-19 infection cases. Coagulation abnormalities, ranging from disseminated intravascular coagulation to COVID-19 related coagulopathy, are typically encountered in severe and critical COVID-19 patients. D-dimer is being used as a marker to identify these coagulation defects in COVID-19. As there is an exaggerated immune response in some patients leading to cytokine storm markers of inflammation like CRP, LDH, IL-6 levels, and ferritin levels, increased. Hence, these markers provide a simple, cost-effective method of triaging the patients to appropriate treatment and are crucial in limited respiratory support and when a large population is infected. However, studies have been done on individual parameters with limited sample sizes; the present study comprised a large sample size with the study of all the parameters, which has been done only in limited studies.

The main objective of this study was to compare levels of hematological, coagulation, and immunological markers in mild, moderate, severe, and critical cases of COVID-19 patients and their relation to the outcome. The relationship between disease severity, mortality, and laboratory parameters was investigated.

MATERIALS AND METHODS

This was a retrospective, observational study conducted in a tertiary care center on 1,000 COVID-19 positive patients of all age groups who were hospitalized in isolation wards and intensive care unit (ICU) between July 2020 and April 2021. Rapid antigen test and/or reverse transcription polymerase chain reaction tests were used to diagnose COVID-19 infection. Outpatient department patients and home quarantine were not included in this study. Approval from the Institutional Ethics Committee was taken prior to the onset of the study.

The hospital medical records of 1,000 consecutive COVID-19-positive patients hospitalized from July 2020 to April 2021 were retrieved to collect the details of the patients. All relevant clinical details, including the patient’s age, gender, and clinical parameters, were noted. Patients were categorized into four groups based on the severity of the disease using the WHO criteria. Mild cases were symptomatic patients with no evidence of hypoxia or pneumonia; moderate cases showed evidence of pneumonia with peripheral oxygen saturation (SpO2) of ≥90% on room air; severe cases showed severe pneumonia with SpO2 of <90% on room air or respiratory rate >30/minute and critical cases showed features of acute respiratory distress symptom. Values of laboratory parameters were analyzed with the degree of severity and survival. Data analysis was done using Statistical Package for the Social Sciences IBM software version 21.0. Proportions were calculated for qualitative variables, while mean with standard deviation (SD) was calculated for quantitative variables. One-way analysis of variance (ANOVA) test and post hoc Bonferroni test were done.

RESULT

This was a study of 1,000 COVID-19-positive patients, of which 682 were males and
318 were females. The mean age of the patients was 47.8 years, and the age ranged from 11 to 90 years. Maximum patients were in the age group of 4–60 years, followed by 26–40 years. There were 510 cases (51%) in the mild category, 232 cases (23.2%) in the moderate category, 201 cases (20.1%) in the severe category, and only 57 cases (5.7%) in the critical category. There were 771 survivors and 229 nonsurvivors in this study (Table 1).

Relation of Age And Gender With Severity and Survival
The severity and mortality of COVID-19 increased with age, and the difference was statistically significant; however, there was no significant relation of gender to severity and mortality in our study. The individuals who survived had a statistically significant lower age [mean SD = 42.8 (14.3)] than those who died [Mean (SD) = 64.8 (12.7)] (p < 0.0005, unpaired t-test). Significant mortality was noted with the severity of the disease (p-value of <0.0005) (Fig. 1 and Table 1).

Relation of Hematological Parameters with Severity and Survival
Increased total leukocyte count (TLC), ANC, NLR, PLR, and decreased ALC showed a correlation with an increase in the severity of the disease. One-way ANOVA test for these parameters showed a statistically significant difference between categories of severity as well as mortality. The mean plot also showed the same findings (Tables 2 and 3 and Figs 2 and 3). The post hoc Bonferroni test showed a significant difference between all pairs of severity for these parameters (Table 4). Hemoglobin (Hb) and platelet count did not show a statistically significant difference between the different categories.

Table 1: General characteristics of the study participants with outcome

<table>
<thead>
<tr>
<th>Factors</th>
<th>Survival No. of cases (%)</th>
<th>Death No. of cases (%)</th>
<th>Total No. of cases (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (in years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18</td>
<td>71 (97.3)</td>
<td>2 (2.7)</td>
<td>73 (7.3)</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td>18–25</td>
<td>319 (95.8)</td>
<td>14 (4.2)</td>
<td>333 (33.3)</td>
<td></td>
</tr>
<tr>
<td>26–40</td>
<td>288 (86)</td>
<td>47 (14)</td>
<td>335 (33.5)</td>
<td></td>
</tr>
<tr>
<td>41–60</td>
<td>91 (36.8)</td>
<td>156 (63.2)</td>
<td>247 (24.7)</td>
<td></td>
</tr>
<tr>
<td>61–80</td>
<td>1 (100)</td>
<td>0 (0)</td>
<td>1 (0.1)</td>
<td></td>
</tr>
<tr>
<td>&gt;80</td>
<td>1 (9.1)</td>
<td>10 (90.9)</td>
<td>11 (1.1)</td>
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<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>0.056</td>
</tr>
<tr>
<td>Male</td>
<td>514 (75.4)</td>
<td>168 (24.6)</td>
<td>682 (68.2)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>257 (80.8)</td>
<td>61 (19.2)</td>
<td>318 (31.8)</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1: Severity of COVID-19 in each age group

Table 2: Mean value of Hb, TLC, ANC, ALC and platelet count in different severities

<table>
<thead>
<tr>
<th>Hematological parameters</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Critical</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>11.8 (2.5)</td>
<td>12.1 (2.5)</td>
<td>11.9 (2.7)</td>
<td>11.5 (2.8)</td>
<td>11.9 (2.6)</td>
<td>0.344</td>
</tr>
<tr>
<td>TLC</td>
<td>9396.3 (8017.9)</td>
<td>13990.2 (20344.7)</td>
<td>14790.5 (14579.1)</td>
<td>20477.7 (11841.5)</td>
<td>12178 (13743.8)</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td>ANC</td>
<td>6207.9 (3464.5)</td>
<td>10127.8 (5203)</td>
<td>21345 (64093)</td>
<td>28666.2 (46582.3)</td>
<td>11440 (31740.6)</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td>ALC</td>
<td>1837.6 (992.7)</td>
<td>1236.1 (983.7)</td>
<td>826.7 (729.8)</td>
<td>637.5 (821.2)</td>
<td>1426.4 (1035.8)</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td>Platelet count</td>
<td>250829.4 (128186.4)</td>
<td>259490.9 (136285.7)</td>
<td>244781.2 (144466.7)</td>
<td>212054.4 (135653.5)</td>
<td>249413 (134109.6)</td>
<td>0.110</td>
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<tr>
<td>NLR</td>
<td>4.0 (2.6)</td>
<td>9.5 (4.5)</td>
<td>39.7 (0.002)</td>
<td>52.5 (0.5)</td>
<td>14.9 (0.01)</td>
<td>0.0005*</td>
</tr>
<tr>
<td>PLR</td>
<td>0.02 (0.01)</td>
<td>0.03 (0.02)</td>
<td>0.05 (0.002)</td>
<td>0.05 (0.04)</td>
<td>0.03 (0.1)</td>
<td>0.0005*</td>
</tr>
</tbody>
</table>

*mark indicated significant as p value
Hematological, Immunological, and Coagulation Parameters

A retrospective observational study was conducted in a tertiary care center on a population of 1,000 COVID-19-positive patients admitted to our hospital. Based on the WHO criteria of the severity of infection, they were classified into mild, moderate, severe, and critical groups. Age and gender along with inflammatory and coagulation parameters were studied and compared in the different groups.

The age distribution of COVID-19 patients in our study showed a wide range (11–90 years) affecting all age groups. Maximum patients were in the age group of 26–60 years. The proportion of males (68.2%) was more than females (31.8%), probably due to their higher exposure to infection. Limited evidence suggests that angiotensin-converting enzyme 2 expression is attenuated in females compared with males, which could justify the higher number of COVID-19 cases in men.7,8 The age group and gender distribution found in a metanalysis of 6,320 COVID-19 are similar to our study.3

Post hoc Bonferroni test showed a significant difference between all pairs of severity for these parameters (Table 7).

### Table 3: Showing difference in mean of hematological parameter between survival and nonsurvival

<table>
<thead>
<tr>
<th>Haematological parameters</th>
<th>Outcome</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Survival</td>
<td>Death</td>
</tr>
<tr>
<td>Hb</td>
<td>11.9 (2.5)</td>
<td>11.8 (2.7)</td>
</tr>
<tr>
<td>TLC</td>
<td>11068.7 (12133.5)</td>
<td>15912.6 (17671.4)</td>
</tr>
<tr>
<td>ANC</td>
<td>8141.8 (6793.5)</td>
<td>22544.3 (64014)</td>
</tr>
<tr>
<td>ALC</td>
<td>1631.3 (1043.5)</td>
<td>736.6 (635.2)</td>
</tr>
<tr>
<td>Platelet count</td>
<td>252271.1 (133559.2)</td>
<td>239790.5 (135798.4)</td>
</tr>
<tr>
<td>NLR</td>
<td>6.7 (7.8)</td>
<td>42.6 (209.6)</td>
</tr>
<tr>
<td>PLR</td>
<td>197.2 (140.6)</td>
<td>555 (1965.3)</td>
</tr>
</tbody>
</table>

*mark indicated significant as p value

### Table 4: Post hoc Bonferroni test for TLC, ANC, ALC, NLR, and PLR

<table>
<thead>
<tr>
<th>Differential counts</th>
<th>Pairs of severity</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC</td>
<td>Mild-moderate</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td></td>
<td>Mild-severe</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td></td>
<td>Mild-critical</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td></td>
<td>Moderate-severe</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>Moderate-critical</td>
<td>0.007*</td>
</tr>
<tr>
<td></td>
<td>Severe-critical</td>
<td>0.029*</td>
</tr>
<tr>
<td>ANC</td>
<td>Mild-moderate</td>
<td>0.662</td>
</tr>
<tr>
<td></td>
<td>Mild-severe</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td></td>
<td>Mild-critical</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td></td>
<td>Moderate-severe</td>
<td>0.001*</td>
</tr>
<tr>
<td></td>
<td>Moderate-critical</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td></td>
<td>Severe-critical</td>
<td>0.693</td>
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<tr>
<td>ALC</td>
<td>Mild-moderate</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td></td>
<td>Mild-severe</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td></td>
<td>Mild-critical</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td></td>
<td>Moderate-severe</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td></td>
<td>Moderate-critical</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td></td>
<td>Severe-critical</td>
<td>1.000</td>
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<td>NLR</td>
<td>Mild-moderate</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>Mild-severe</td>
<td>&lt;0.0005*</td>
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<tr>
<td></td>
<td>Mild-critical</td>
<td>0.003*</td>
</tr>
<tr>
<td></td>
<td>Moderate-severe</td>
<td>0.021*</td>
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<tr>
<td></td>
<td>Moderate-critical</td>
<td>0.023*</td>
</tr>
<tr>
<td></td>
<td>Severe-critical</td>
<td>1.000</td>
</tr>
<tr>
<td>PLR</td>
<td>Mild-moderate</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>Mild-severe</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td></td>
<td>Mild-critical</td>
<td>0.049*</td>
</tr>
<tr>
<td></td>
<td>Moderate-severe</td>
<td>0.025*</td>
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<td></td>
<td>Moderate-critical</td>
<td>0.422</td>
</tr>
<tr>
<td></td>
<td>Severe-critical</td>
<td>1.000</td>
</tr>
</tbody>
</table>

*mark indicated significant as p value

### Coagulation and Immunological Markers with Severity and Survival

Increased levels of the inflammatory markers CRP, serum ferritin, LDH, and IL-6 showed a correlation with an increase in the severity of the disease. One-way ANOVA test for these parameters showed a statistically significant difference between categories of severity as well as mortality. The mean plot showed higher values with increased severity (Tables 5 and 6 and Fig. 4). Post hoc Bonferroni test showed a significant difference between all pairs of severity for these parameters (Table 7). D-dimer value was raised in severe cases but did not show a statistically significant difference between different categories.

### Discussion

A retrospective observational study was conducted in a tertiary care center on a population of 1,000 COVID-19-positive patients admitted to our hospital. Based on the WHO criteria of the severity of infection, they were classified into mild, moderate, severe, and critical groups. Age and gender along with inflammatory and coagulation parameters were studied and compared in the different groups.

The age distribution of COVID-19 patients in our study showed a wide range (11–90 years) affecting all age groups. Maximum patients were in the age group of 26–60 years. The proportion of males (68.2%) was more than females (31.8%), probably due to their higher exposure to infection. Limited evidence suggests that angiotensin-converting enzyme 2 expression is attenuated in females compared with males, which could justify the higher number of COVID-19 cases in men.7,8 The age group and gender distribution found in a metanalysis of 6,320 COVID-19 are similar to our study.3
The majority of cases in the present study were in the mild category (51%), similar to other studies.9,10 We observed a significant correlation of mortality with severity similar to other studies. A meta-analysis of 15,680 COVID-19 patients done by Chidambaram et al.11 found higher mortality in cases with severe disease. They also demonstrated that age, male gender, diabetes, hypertension, and congestive heart failure are risk factors for increased severity among COVID-19 patients.

Similar to other studies, we also noted that age and severity showed a correlation with age, and the difference was statistically significant.10,12 A probable explanation of the increase in severity with age could be due to the presence of other risk factors and comorbidities in elderly patients. Similar to previous studies,13 we also noted increased mortality with an increase in age; the individuals who survived had a statistically significant lower mean age of 42.8 than those who died 64.8 (p < 0.0005, unpaired t-test).

**Hematological, Immunological, and Coagulation Parameters**

**Table 5:** Comparison of serum CRP, ferritin, LDH, D-dimer and Interluekin-6 in different severities of COVID-19 mean (SD)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Critical</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum CRP (mg/L)</td>
<td>30.4 (7.2)</td>
<td>45.3 (9.4)</td>
<td>89.6 (29.1)</td>
<td>158.3 (46.5)</td>
<td>53.1 (39.0)</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td>Serum ferritin (mcg/mL)</td>
<td>106.3 (51.6)</td>
<td>305.6 (49.0)</td>
<td>521.3 (158.3)</td>
<td>1084.6 (250.7)</td>
<td>291.7 (273.7)</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td>Serum LDH (IU/L)</td>
<td>264.6 (42.0)</td>
<td>380.6 (34.4)</td>
<td>483.3 (96.2)</td>
<td>697.2 (211.6)</td>
<td>360.0 (141.1)</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td>D-dimer (mcg/mL)</td>
<td>1.1 (0.1)</td>
<td>1.2 (0.2)</td>
<td>2.1 (1.5)</td>
<td>2.7 (0.4)</td>
<td>1.4 (10.7)</td>
<td>0.548</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>8.5 (5.0)</td>
<td>12.4 (3.0)</td>
<td>37.7 (16.2)</td>
<td>207.7 (0.01)</td>
<td>26.7 (55.7)</td>
<td>&lt;0.0005*</td>
</tr>
</tbody>
</table>

One-way ANOVA test was used; *significant as p-value of <0.05

**Table 6:** Showing difference in mean of biochemical, immunological parameter between survival and nonsurvival groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Outcome</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum CRP (mg/L)</td>
<td>Survival</td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td>39.3 (20.5)</td>
<td>99.1 (49.5)</td>
</tr>
<tr>
<td>Serum ferritin (mcg/mL)</td>
<td>Survival</td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td>192.5 (145)</td>
<td>625.4 (332.2)</td>
</tr>
<tr>
<td>Serum LDH (IU/L)</td>
<td>Survival</td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td>314.6 (92.8)</td>
<td>513.1 (165.3)</td>
</tr>
<tr>
<td>D-dimer (mcg/mL)</td>
<td>Survival</td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td>1.2 (12.1)</td>
<td>2.1 (1.5)</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>Survival</td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td>12 (10.9)</td>
<td>76.2 (99.8)</td>
</tr>
</tbody>
</table>

*mark indicated significant as p value

**Table 7:** Post hoc Bonferroni test for serum CRP, ferritin, LDH, and IL-6

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pairs of severity</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum CRP (mg/L)</td>
<td>Mild - Moderate</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td></td>
<td>Mild - Severe</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td></td>
<td>Mild - Critical</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td></td>
<td>Moderate - Severe</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td></td>
<td>Moderate - Critical</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td></td>
<td>Severe - Critical</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td>Serum ferritin (mcg/mL)</td>
<td>Mild - Moderate</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td></td>
<td>Mild - Severe</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td></td>
<td>Mild - Critical</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td></td>
<td>Moderate - Severe</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td></td>
<td>Moderate - Critical</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td></td>
<td>Severe - Critical</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td>Serum LDH (IU/L)</td>
<td>Mild - Moderate</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td></td>
<td>Mild - Severe</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td></td>
<td>Mild - Critical</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td></td>
<td>Moderate - Severe</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td></td>
<td>Moderate - Critical</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td></td>
<td>Severe - Critical</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td>Interluekin-6 (pg/ml)</td>
<td>Mild - Moderate</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td></td>
<td>Mild - Severe</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td></td>
<td>Mild - Critical</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td></td>
<td>Moderate - Severe</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td></td>
<td>Moderate - Critical</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td></td>
<td>Severe - Critical</td>
<td>&lt;0.0005*</td>
</tr>
</tbody>
</table>

*Significant as p-value of <0.05

The increase in TLC was predominantly due to neutrophilia. TLC and ANC showed an increase in the severity of the disease. A higher TLC and ANC were found in nonsurvivors as compared to survivors, and this difference was statistically significant, which was in concordance with other studies.9,10,11 In a study by Nair et al.,12 TLC was found to be higher in patients who were on mechanical ventilation than those who were not and was associated with a poorer prognosis. Lymphocyte count retains a specific clinical and biological significance in COVID-19, and lymphopenia is a significant hematological abnormality that negatively affects prognosis.19 There are some mechanisms that are postulated to cause lymphopenia in COVID-19 patients: Direct infections of lymphatic organs bone marrow, cytokine storm, and negative effects of some metabolic products, epigenetic alterations (age, gender, some gene expressions, and methylation pattern of
Hematological, Immunological, and Coagulation Parameters

In our study, we observed a significant relation between decreased ALC and severity and outcome. There are many studies that support the fact that lymphopenia is associated with increased severity and associated with poor survival. In a study by Mohamed et al., the difference between lymphopenia in survivor and nonsurvivor categories was statistically significant, and none of those patients over 60 years and having ALC < 0.6 ×103 cell/µL survived after being infected with COVID-19.

Neutrophil lymphocyte ratio (NLR) is the ratio of ANC to ALC and is normally <3.0. A higher NLR has been reported as a biomarker in different categories of COVID-19 with prognostic significance. In the present study, NLR was found to be an important prognostic indicator. It had a direct correlation with severity and outcome, which is also supported by many other studies and may be used for early prediction of the need for mechanical ventilation. In our study, the value of NLR was higher probably because of the higher incidence of secondary bacterial infection and sepsis in our patients. The present study showed an increased value of PLR when compared with a severity which was similar to the findings of Waris et al. Value of PLR showed a significant difference between survivors and nonsurvivors with p-value of <0.05. In a study by Tiwari et al., there was a significant difference in the value of PLR in patients who were mild symptomatic to those who were in ICU. In a study by Ozbalak et al., PLR value of >350 is predictive of progressive pneumonia.

In our study, 656 (65.6%) patients had anemia, and 208 (20.8%) had thrombocytopenia. Although decreased platelet count was noted in severe cases, we did not find a statistically significant difference in Hb, and platelet count between different categories of severity as well as mortality which was similar to the study by Waris et al. Decrease in platelet count in severe COVID-19 may be linked to thrombin generation, immunological destruction of platelet, and depression of megalakaryopoiesis.

Coagulation and Inflammatory Markers

In the present study, CRP, serum ferritin, LDH, and IL-6 showed a significant increase in severity as well as in the outcome. Because CRP is an inflammatory marker, its level is frequently linked to the severity of illness. In this study, levels of CRP increased with the severity of COVID-19 and the difference was statistically significant, which was also reported in other studies. We also observed a statistically significant difference in the value of CRP between survivor and nonsurvivor groups, which has also been reported in the study by Bairwa et al.

Ferritin is an acute phase reactant that has been associated with inflammation. High ferritin levels have been found to be a good predictor of disease severity and mortality in COVID-19 infection. Similar findings were noticed in our study.

Lactate dehydrogenase (LDH) is an enzyme used in glucose metabolism and is released due to cell membrane damage due to cell necrosis. COVID-19 patients have a higher level of LDH due to lung damage and pneumonia. Higher LDH level in severe infection was a predictor of poor prognosis. In our study, a statistically significant difference was found in the LDH level in different categories of COVID-19 as well as in survivors and nonsurvivor groups, which was similar to other studies.

In an animal study, the activity of urokinase was found to be enhanced in COVID-19 infection, which resulted in hyperfibrinolysis due to the conversion of plasminogen to plasmin and the development of ARDS. In the present study, levels of D-dimer were raised to some extent in all categories of COVID-19; however, in mild cases, the rise in D-dimer level was less as compared to moderate and severe cases where there was a marked increase in D-dimer levels. However, the difference was not statistically significant. An increase in D-dimer levels has also been reported in studies done by Minping et al., Ahmed et al., and Bozkurt et al. This is a significant biomarker indicating the hypercoagulable state in COVID-19, which needs prompt therapy to prevent complications.

Some COVID-19 patients develop cytokine storm, which is characterized by the production of a large number of cytokines that damage the lungs, indicating that these pro-inflammatory cytokines play an important role in the pathogenesis of COVID-19. IL-6 is one of the pro-inflammatory cytokines whose level is used as a useful prognostic biomarker to distinguish mild from severe disease. IL-6 levels were higher in our study in severe disease compared to mild disease. Levels of IL-6 were higher in the nonsurvivor group compared to the survivor group, indicating that the level of IL-6 is associated with poor prognosis and survival. Our observations correlated with other studies.

Limitations of the Study

This was a retrospective study. Stratification analysis of the data of associated conditions like diabetes, hypertension, and other comorbidities of COVID-19 was not done.

Conclusion

Maximum patients were in the mild category. Age and severity showed a linear correlation. Higher age was associated with more severe and critical disease and mortality. TLC, ALC, ANC, NLR, PLR, CRP, ferritin, LDH, and IL-6 levels were associated with more severe disease and mortality and thus can be used as important biomarkers to predict the prognosis and outcome of COVID-19 patients. As these markers are easily available, they should be used to categorize the patients at an early stage for optimum treatment.

Guarantor
Dr Yasmeen Kathib.

Acknowledgment
Dr Vikram Londhe, Professor, Department of Medicine, HBT Medical College and Dr R N Cooper Hospital, Mumbai.

References


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An Open-label, Prospective, Multicentric, Cohort Study of Nimesulide/Paracetamol Fixed Drug Combination for Acute Pain Management: Sub-group Analysis

Mangesh Tiwaskar1, A Muruganathan2, Ajitkumar Gondane3*, Dattatray Pawar4
Received: 11 November 2022; Accepted: 15 February 2023

Abstract
Objective: Nimesulide has been evaluated in numerous clinical studies in the management of a variety of acute painful conditions. However, there is limited Indian data available on the nimesulide/paracetamol fixed drug combination (FDC). Hence, an open-label prospective multicentric study was conducted to evaluate the safety and efficacy of this FDC in the management of acute painful conditions in real-world settings.

Materials and methods: A prospective, open-label, and multicenter study conducted at 24 centers across Indian patients with acute painful conditions due to trauma, tendinitis, myalgia, low backache, sprains, pulled muscle, soft tissue injury, dental pain, and dental procedure/surgery. Nimesulide/paracetamol FDC was prescribed by clinicians as a part of routine practice. The effectiveness was evaluated on the numerical rating scale (NRS), that is, pain intensity at rest and movement; and the physician/patient global assessment scale (GAS) among the subgroups of acute painful conditions like myalgia, dental pain, low backache, etc. Hepatic safety was also evaluated among the subgroups at the end of treatment.

Result: A total of 464 patients were included in the study. The reduction in NRS score at rest and movement during treatment duration across different types of pain was statistically significant (p < 0.001). Pain reduction was evident as per patient and physician GAS at the end of treatment in all indications. No clinically significant difference was found in liver parameters at the end of the study. Nimesulide/paracetamol (FDC) was well tolerated across all the subgroups.

Conclusion: Nimesulide/paracetamol FDC was found to be well-tolerated and effective in pain management across all acute painful conditions in a real-world setting without any hepatic safety concerns.

Introduction
Pain remains the chief complaint for medical consultation and a major reason for self-medication too. Unrelieved or untreated acute pain, however, can result in chronic pain.1 Use of multiple analgesics simultaneously can be considered a strategy that can improve pain control owing to posited additive or synergistic effects. The doses of the individual drugs have been shown to be reduced when used as a FDC, thereby minimizing the incidence and severity of potential side effects.2

Nonsteroidal antiinflammatory drugs (NSAIDs) are among the most often used analgesic agents for pain relief.1 Nimesulide is a unique NSAID that inhibits the enzyme cyclo-oxgenase (COX), thereby blocking the formation of prostaglandins that are important in pain and inflammatory pathways. COX-2 activity is most closely related to pain pathways as opposed to COX-1, which has major effects on gastric mucosa and platelet function. Nimesulide has a greater affinity for selective inhibition of COX-2, which corresponds to higher analgesic, antiinflammatory, and antipyretic activity.3

The effects of nimesulide are unique and not shared with other selective COX-2 inhibitors. The drug has a wide spectrum of actions due to the combination of effects on immune and nonimmune cells, resident cells, and extracellular matrix with a biochemical mechanism that has not been elucidated at all.3

The toxicological profile of nimesulide is different from other NSAIDs; its most relevant adverse effect is hepatotoxicity. Epidemiological studies quoting the data on the incidence of liver injury show that it is a rare adverse event. The mechanism is unknown, it might be of idiosyncratic nature, and this injury is related to the duration of the therapy.4

Studies have reported that up to 15% of patients taking NSAIDs experience at least transient serum aminotransferase elevations; however, a lower rate has been reported with nimesulide. These elevations are generally transient, mild, and asymptomatic and resolve even when a drug is continued.1,5

After 30 years of extensive clinical usage, nimesulide has demonstrated a favorable safety profile, including a decreased propensity to have negative gastrointestinal effects and rapid and persistent management of pain and inflammation.2

Current indications vary by country, but in India, it is approved for chronic as well as acute pain conditions such as rheumatoid arthritis, posttraumatic pain, fever, and acute pain in orthopedic, ear, nose, and throat, and dental conditions.3,6

However, there is limited published data on the safety and efficacy of a nimesulide/paracetamol FDC in the Indian population. The study was conducted to evaluate the safety and efficacy of nimesulide/paracetamol (100 + 325 mg) in the management of acute pain due to trauma, myalgia, low backache, soft tissue injuries, dental pain, dental procedure/surgery, and others, including sprains, pulled a muscle in Indian population.

Materials and Methods
Study Design and Patient Selection
The study was a prospective, open-label, multicenter study conducted at 24 centers across India. The safety and efficacy of nimesulide + paracetamol (100 + 325 mg) in an FDC was evaluated by the International Conference on Harmonization for good clinical practice and the applicable Indian regulatory guidelines after taking approval from the Independent Ethics Committee. Informed

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An Open-label, Prospective, Multicentric, Cohort Study

Patients aged >18 years with the acute painful condition due to trauma, tendinitis, myalgia, low backache, sprains, pulled muscle, soft tissue injury, dental pain, or dental procedure/surgery who were willing to visit the clinic as per the predefined schedule and sign informed consent were included in the study. The patients were excluded if they had clinically significant abnormal values of laboratory parameters, were pregnant or lactating females, had hepatic, renal, or cardiac diseases, had hypersensitivity to nimesulide or paracetamol, used hormonal contraceptives either oral or implants in females), had a history of blood donation 4 weeks before the study, were pregnant or lactating females, had hepatic, renal, or cardiac diseases, had hypersensitivity to nimesulide or paracetamol, used hormonal contraceptives either oral or implants in females, had a history of any medical disorder, and not willing to sign informed consent.

Efficacy and Safety Variables
The study assessed the clinical effectiveness of nimesulide plus paracetamol by using NRS scores, pain intensity at rest and on passive movement, and physician/patient GAS at baseline and after 2 weeks of treatment. The safety was assessed by the change in liver function tests parameters, including serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), serum bilirubin, and alkaline phosphatase after 2 weeks from baseline based on various indications.

Data on NRS scores were collected during the baseline visit (visit 1) and 2-week visits (visit 2). Clinical efficacy evaluation by the investigator and patient was performed by:

- NRS assessment of pain intensity at rest at baseline and then after 2 weeks of treatment.
- NRS assessment of pain intensity on movement was done at baseline and then after 2 weeks of treatment.
- Overall clinical response based on relief in signs and symptoms was evaluated by physician and patient through the GAS (graded from 1 (complete relief of symptoms) to 6 (worsening of symptoms)) after 2 weeks of treatment (visit 2).
- All qualitative parameters were summarized by frequency and percentage, and quantitative variables by descriptive statics such as mean.

Statistical Method
Paired t-test for pre and postcomparison was applied individually for each indication. The changes in NRS pain intensity between two visits and overall clinical response across indications were compared by analysis of variance (ANOVA). A p-value of <0.05 was considered statistically significant. The data were analyzed by statistical software R version 4.1.0 (R Core Team, 2021, Vienna, Austria).

RESULTS
Patient Population and Demographic
A total of 464 patients were included in the study. Table 1 gives the bifurcation of patients as per indications included in the study. All these patients with prescribed nimesulide/paracetamol FDC (100 + 325 mg) for the duration as per the clinician’s decision.

Efficacy Assessment
Pain Reduction
The reduction in the NRS score at baseline and during treatment duration across different types of pain was statistically significant ([p < 0.001] Fig. 1). Patients having soft tissue injuries and other painful conditions (3.8 with 95% confidence interval (CI) 3.4–4.2) demonstrated a maximum reduction in pain. This was followed by a reduction in patients with low back pain, myalgia, and dental pain. However, there were no significant differences within the group.

The changes in NRS pain intensity between the groups other painful conditions, low back pain, myalgia, and dental pain. The least significant reduction was for dental pain (3.1 with 95% CI 2.5–3.8), but no significant difference was found between the groups.

Table 1: Patient population as per clinical indication

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Number of patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dental pain</td>
<td>80</td>
</tr>
<tr>
<td>Low back-ache</td>
<td>108</td>
</tr>
<tr>
<td>Myalgia</td>
<td>149</td>
</tr>
<tr>
<td>Soft tissue injuries (Pulled muscle, sprains, tendinitis, traumatic pain)</td>
<td>70</td>
</tr>
<tr>
<td>Other painful conditions (miscellaneous)</td>
<td>56</td>
</tr>
</tbody>
</table>

Table 1: Patient population as per clinical indication

The reduction in the NRS score at movement during treatment duration across different types of pain was statistically significant ([p < 0.001] Fig. 2). Patients with soft tissue injuries (4.4 with 95% CI 4.0–4.8) demonstrated a maximum reduction followed by patients in the groups’ other painful conditions, low back pain, myalgia, and dental pain. The least significant reduction was for dental pain (3.1 with 95% CI 2.5–3.8), but no significant difference was found between the groups.

The patient and physician GAS demonstrated improvement in symptoms throughout the indications (p = 0.001 and p < 0.001, respectively). However, no significant differences were found between the groups. At the end of treatment, complete to moderate improvement of symptoms in the patient GAS was seen in 100% of patients with soft tissue injuries; 97.22% of patients with low back-ache; 98.32% of patients with other painful conditions, 95.3% in patients with myalgia and 93.75% of patients with dental pain, (Table 2). Similarly, at the end of treatment, complete to moderate improvement of symptoms on the physician GAS; 100% of patients were pain-free in the soft tissue injuries group, 98.32% of patients were pain-free in other painful condition groups, while this was followed in descending order—96.30% in low back-pain group, 97.99% in the group with myalgia, and least in patients with dental pain (93.75%) (Table 3).

![Fig. 1: Mean NRS at rest at baseline and at end of treatment across types of pain (p-value corresponds to paired t-test)](image-url)
Safety Assessment

The safety assessment was done through measurements of liver enzymes in all the patients. The mean values of aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum bilirubin, and alkaline phosphatase levels at the baseline and at the end of the treatment were evaluated separately with a one-way ANOVA test represented in Figures 3 to 6, respectively. The mean change in all the parameters across different indications was not significant. The mean change in AST level for patients with dental pain was 1.07 \( (p = 0.335) \); low back-ache was 0.79 \( (p = 0.493) \); myalgia was 1.03 \( (p = 0.074) \); other painful conditions were −1.71 \( (p = 0.335) \); low back pain was −1.61 \( (p = 0.641) \); myalgia was −1.25 \( (p = 0.528) \); other painful conditions were 0.01 \( (p = 0.996) \), and soft tissue injuries were 1.93 \( (p = 0.106) \). The mean change in ALT levels for patients with dental pain was −1.02 \( (p = 0.561) \); low back-ache was −1.08 \( (p = 0.323) \); myalgia was −2.2 \( (p \leq 0.001) \); other painful conditions was 1.7 \( (p = 0.229) \) and with soft tissue injuries was −1.87 \( (p = 0.335) \). The mean change in serum bilirubin level for patients with dental pain was 0.030 \( (p = 0.049) \); low back-ache was 0.02 \( (p = 0.446) \); myalgia was 0.03 \( (p = 0.064) \); other painful conditions were 0.02 \( (p = 0.615) \), and soft tissue injuries were 0.03 \( (p = 0.146) \). The mean change in alkaline phosphatase levels for patients with dental pain was 11.93 \( (p = 0.246) \); low back pain was −1.61 \( (p = 0.641) \); myalgia was −1.25 \( (p = 0.528) \); other painful conditions were 0.01 \( (p = 0.996) \), and soft tissue injuries were 4.04 \( (p = 0.229) \). No clinically significant increase in the liver enzymes, AST/SGOT, ALT/SGPT, serum bilirubin, and alkaline phosphatase levels were seen after treatment with nimesulide/paracetamol FDC at the end of the study. Only ALT levels in patients with dental pain were significantly increased at the end of treatment.

**Discussion**

Literature studies have proven that the combination of paracetamol and NSAID was found to be more effective with greater pain relief than either agent alone in 85 and 64%, respectively. In our study, too, the nimesulide/paracetamol FDC was observed to be safe and effective in patients with acute pain due to various indications. The majority of the patients showed a reduction in pain intensity and improvement in symptoms during the 2-week treatment period assessed using the NRS and GAS scores, while no significant difference was found amongst the group.

No clinically significant increase in the liver enzymes, AST/SGOT, ALT/SGPT, serum bilirubin, and alkaline phosphatase levels were seen after treatment with nimesulide/paracetamol FDC at the end of the study, which proves the safety of this combination.

Levini et al. performed an observational, multicenter, prospective survey to evaluate the prescription pattern of NSAIDs. Nimesulide was the most used drug (68%), followed by diclofenac, ketoprofen, and ibuprofen in 616 patients undergoing dental procedures. It was more effective than other NSAIDs in reducing the intensity of pain, delaying the time to maximum pain intensity, and providing complete pain relief on the day of the procedure. On day 1, 72.6% of patients who had taken nimesulide experienced complete pain relief versus 54.7% of those treated with other drugs. The results confirmed that nimesulide is an effective NSAID for the treatment of acute postoperative pain induced by dental procedures. Similar results were seen in our study, where significant improvements were seen in the dental pain group on the patient and physician GAS.

Another similar study conducted by Cornaro et al. compared the effects of nimesulide and placebo in 49 patients who had undergone oral surgery for various conditions. Overall, pain relief judged as “excellent” or “good” was found in 64% of patients treated with nimesulide compared with 25%.

---

**Fig. 2:** Mean NRS at passive movement at baseline and at end of treatment across types of pain (p-value corresponds to paired t-test)

**Table 2:** Patient GAS for improvement in symptoms

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Dental pain</th>
<th>Low backache</th>
<th>Myalgia</th>
<th>Soft tissue injuries</th>
<th>Other</th>
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<tbody>
<tr>
<td>Percentage of patient with</td>
<td></td>
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<tr>
<td>Complete relief to moderate</td>
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<td>97.22</td>
<td>95.30</td>
<td>100</td>
<td>98.32</td>
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<tr>
<td>Slight improvement to no change in</td>
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<td>2.78</td>
<td>4.70</td>
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<td>1.68</td>
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</table>

**Table 3:** Physician GAS for improvement in symptoms

<table>
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<th>Low backache</th>
<th>Myalgia</th>
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<td>93.75</td>
<td>96.30</td>
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<td>improvement of symptoms</td>
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<tr>
<td>Slight improvement to no change in</td>
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</tbody>
</table>
either to treatment with oral nimesulide (100 mg twice daily for 10 days) or oral ibuprofen (600 mg three times daily for 10 days). On day 3 of the treatment, a definite improvement in all measured parameters for pain and functioning was observed with the two study drugs. The patient’s ability to perform daily tasks showed improvement in both groups ($p < 0.001$), but after 10 days, a statistically significant difference was found between the two groups in favor of nimesulide ($p < 0.05$), and more gastrointestinal adverse events were reported with ibuprofen.¹⁰

No clinically significant increase in the liver enzymes, AST/SGOT, ALT/SGPT, serum bilirubin, and alkaline phosphatase levels were seen after treatment with nimesulide/paracetamol FDC at the end of the study, which proves the safety of this combination. Comparable results were reported by Chandanwale et al. in a postmarketing study amongst the Indian population regarding the adverse effects of nimesulide. There was no statistical difference in liver enzymes pre and posttreatment with nimesulide (Table 4).¹¹

Studies have noted marked amino transferase elevations (>3-fold elevated) occur in <1% of patients with the use of nimesulide. Duration of therapy <15 days may be associated with fewer chances of developing a liver injury.¹² The European Medicines Agency (EMA) and several publications have not discovered any risk of severe hepatotoxicity higher than different NSAIDs.¹,⁵ Compared to other NSAIDs, nimesulide has a comparatively low propensity to cause serious gastrointestinal (GI) problems. The risk/benefit profile for hepatic side effects is comparable with other drugs of its class.¹ Compared to other NSAIDs, nimesulide has a comparatively low propensity to cause serious GI problems.

**Conclusion**

The results of the present study conclude that a nimesulide/paracetamol FDC is safe and effective in the management of various painful conditions, including myalgia, low backache, soft tissue injuries, dental pain, dental procedure/surgery, sprains, pulled muscle, and soft tissue injury in Indian population without any intergroup difference. It showed a significant reduction in pain intensity at rest and movement during the 2-week treatment duration. There was no significant difference in the liver enzymes pre and posttreatment with this FDC elucidating the hepatic safety when used over a short duration of 2 weeks. The impact of long-term therapy needs further investigation. The benefits of systemic nimesulide-containing medicines continue to outweigh their risks in the treatment of patients with acute pain.
Manuscript and editorial support by Insignia Communication Pvt Ltd, Mumbai.

REFERENCES


Table 4: Laboratory investigations in study group by Chandanwale et al.

<table>
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<th>Parameters</th>
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<td>Poststudy</td>
</tr>
<tr>
<td>S bilirubin</td>
<td>0.69 ± 0.21</td>
<td>0.81 ± 0.47</td>
</tr>
<tr>
<td>SGPT</td>
<td>23.15 ± 9.17</td>
<td>25.45 ± 10.71</td>
</tr>
<tr>
<td>SGOT</td>
<td>21.82 ± 8.72</td>
<td>24.59 ± 11.60</td>
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</tbody>
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(By student t-test) p > 0.05 not significant

COMPLIANCE WITH ETHICAL STANDARDS

This article has a related publication—Tiwaskar M, Muruganathan A, Pawar DA. Safety and efficacy of nimesulide/paracetamol fixed-dose combination in acute pain (SAFE study). Indian Journal of Clinical Practice. 2022 Jul; 33(2).

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We would like to acknowledge all the study investigators for conducting this study.
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---

**Cure for Sure**

**In Mixed Skin Infections**

**SURFAZ-SN**® Cream

- Chlorimazole 1% + Beclomethasone Dipropionate 0.025% + Neomycin Sulfate 5000 Units/gm

**In the Management of Superficial & Systemic Fungal Infections**

**SURFAZ-O**®

**For Various Types of Fungal Infections**

**SURFAZ**®

- (1% Chlorimazole)

**In Fungal Infections with Inflammation**

**SURFAZ-B**®

- Chlorimazole 1% + Beclomethasone Dipropionate 0.025% + Cream

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Franco-Indian Pharmaceuticals Pvt. Ltd.
20, Dr. E. Moses Road, Mumbai 400 011.
A Questionnaire-based Study on Perceptions, Attitudes, and need Assessment regarding Geriatric Healthcare among Geriatric Outpatients at a Tertiary Care Hospital in India

Santosh Salagre1*, Amey Kundawar2, Abhishek Ukarde3, Ameya Dandekar4, Ameya Machave5, Nikita Chandak6, Prarthna Srivastava7, Shruti Deshpande8, Shubhaangi Dhanjit9, Vaibhav Karandekar10

Background: The lack of specialized geriatric healthcare in India, coupled with an aging population, has resulted in longer wait times, communication barriers, and a potential increase in unmet needs in a demographic that is already financially and socially vulnerable. This raises the need for exploring the perspectives and needs of the geriatric patient population to improve the quality and accessibility of the healthcare they receive.

Objective(s): This study was conducted to assess the perceptions and perceived needs of geriatric patients regarding current healthcare and their attitudes toward specialized geriatric healthcare.

Materials and methods: Following the Institutional Ethics Committee (IEC), a cross-sectional study was carried out among 262 geriatric patients (age >60) from seven outpatient departments (OPD). A structured 10-item questionnaire was administered to assess the perceptions and perceived needs of the study population.

Results: A total of 165 (63%) patients were not satisfied with the healthcare being provided to them. Around 96.1% of patients felt the need for a separate geriatric OPD/department. A total of 98% of patients had optimistic attitudes toward the possibility of specialized geriatric healthcare. A total of >80% of the patients were willing to spend more time for checkups and follow-ups regularly if that would improve their quality of life.

Conclusion: This study showed a low satisfaction rate of geriatric patients with the current healthcare and a high felt need for specialized geriatric facilities. There was an overall positive attitude of patients toward the implementation of various facilities of specialized geriatric healthcare.

Introduction

The geriatric population in India was estimated to be around 8.6% in 2011 and is likely to increase to as much as 19% by the year 2050.1 Thus, India has been titled “an aging nation.”

Increased life span and improved quality of life are not necessarily mutually inclusive. On the contrary, it has been theorized that a decline is seen in terms of physical/psychological well-being as well as an increase in disability over the age of 75 years.3 Changes in the composition of the body, mismatch in energy production/utilization, dysregulation in homeostasis, and neurodegeneration lead to infirmity, which in turn, results in conditions typically seen in geriatric patients such as malnutrition, gait disorders, disease susceptibility, urinary incontinence, sleep disorders, delirium, cognitive impairment, etc.6

With the anticipated increase in the number of older persons in the future, the likely shift in disease patterns from communicable diseases to Non Communicable Diseases (NCDs) is a predicament the current healthcare system needs to prepare itself for to be able to cater to the growing health needs of the elderly. Special emphasis needs to be placed on improving quality of life alongside increasing lifespans. Help must be sought to address the rise in disease and disability. Education regarding healthy aging needs to be promoted amongst the elderly, including not just curative but preventive and palliative aspects of health as well.5

All of this calls for the development of specialized healthcare for the elderly, which is well-established in many developed countries. Specialized geriatric healthcare is practiced in specialized departments which are equipped with adequate bedded wards and multidisciplinary OPDs.

In India, however, minimal effort has been made to formulate a model of health and community-based care that could keep up with the changing need and time.6 The current geriatric healthcare facilities in India are grossly deficient in meeting the needs of the population. The critique against the administration and private hospitals is that facilities to provide comprehensive geriatric care to the elderly are yet to be set up.5 A handful of hospitals in the country have geriatric OPDs, and even these hospitals lack geriatric inpatient facilities. Moreover, daycare centers assisted living facilities and mobile clinics are very few and concentrated in urban areas.7 The services provided are not affordable to the general population as they are more focused on tertiary care than on primary care, leaving many elderly patients without accessible healthcare.8 Barriers like lack of time, inaccessibility, and communication gaps add to this problem, the result of which is a highly unsatisfied geriatric patient population. Healthcare services should be based on the “felt needs” of the elderly population.3 This study aimed to investigate the perceptions and perceived needs of geriatric patients regarding current healthcare and their attitudes toward specialized geriatric healthcare.

Materials and Methods

Study Design and Participants

We carried out a cross-sectional study in medicine, surgery, orthopedic surgery, ophthalmology, ENT, gynecology, and general OPDs of Seth Gordhandas Sunderdas Medical College (GSMC) and the King Edward Memorial Hospital (KEMH), Mumbai, Maharashtra, India.

A total of 262 patients were equally recruited from each of the seven OPDs.
Criteria for eligibility were—age greater than 60 years and a minimum of one assessment/visit to the pertaining OPD prior to being enrolled. Patients with terminal conditions/critical illnesses and those with known diagnoses of severe psychiatric disorders were excluded.

**Study Procedure**

The study was sanctioned by the IEC. Written informed consent was taken from all the participants prior to being assigned to the study. It was carried out between the months of April and October 2019.

**Study Tool**

A total of 10 participants underwent unstructured interviews to gather data regarding the perceptions, attitudes, and perceived needs with respect to geriatric healthcare. A structured 10-item questionnaire was drafted after analyzing their responses. The questionnaire items comprised multiple-choice questions and yes/no type questions. The questionnaire was then validated by experts and a pilot study. This final structured questionnaire was then used as a study tool for this study.

**Data Analysis**

Statistical analysis was done by using descriptive statistics. Data were collected in a predesigned Microsoft Excel sheet and analyzed in Statistical Package for the Social Sciences 24.0. Continuous variables were presented as mean values ± standard deviation (SD), and categorical variables were presented as percentages.

**RESULTS**

**Demographic Data**

Table 1 shows the demographic information of the patients who participated in the study.

**Perceptions regarding Current Healthcare**

Only 37% of patients were satisfied with the healthcare being provided to them when required, whereas 74% were satisfied with the care provided at home. Around >80% of the patients avoided medical treatment because of various reasons like distance, inconvenient timing, long queues, and ineffective communication (Table 2).

**Perceived needs regarding Healthcare**

Nearly 90% of patients felt the need for various facilities with respect to healthcare. Out of these, the highest (96.1%) need was for geriatric healthcare. The majority (>80%) of the patients felt unsatisfied due to the “distance” to healthcare service. Around 90.4% of patients felt the need for mobile healthcare facilities and geriatric health camps. The provision of mobile healthcare vans and elderly-specific community healthcare workers like Accredited Social Health Activists and auxiliary nursing midwives by the government would reduce the burden of inaccessibility, especially in rural areas where a majority of elderly residents.

**DISCUSSION**

**Perceptions regarding Current Healthcare**

This study showed a high dissatisfaction rate of 63% among geriatric patients. In comparison to other countries, this is relatively low. This reaffirms the need for the development of geriatric healthcare in India. Nearly >75% of patients felt unsatisfied due to the “distance” to healthcare service. Around 90.4% of patients felt the need for mobile healthcare facilities and geriatric health camps. The provision of mobile healthcare vans and elderly-specific community healthcare workers like Accredited Social Health Activists and auxiliary nursing midwives by the government would reduce the burden of inaccessibility, especially in rural areas where a majority of elderly residents.

**Table 1: Patients demographic data (n = 262)**

<table>
<thead>
<tr>
<th>Age years (mean, SD)</th>
<th>68.13 ± 5.29</th>
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</thead>
<tbody>
<tr>
<td>Sex (%)</td>
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</tr>
<tr>
<td>Female</td>
<td>150 (57.2)</td>
</tr>
<tr>
<td>Male</td>
<td>112 (42.7)</td>
</tr>
<tr>
<td>Region (%)</td>
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<tr>
<td>Urban</td>
<td>231 (88.1)</td>
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<tr>
<td>Rural</td>
<td>31 (11.9)</td>
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<tr>
<td>Religion</td>
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<tr>
<td>Hindu</td>
<td>228 (87.0)</td>
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<tr>
<td>Muslim</td>
<td>30 (11.4)</td>
</tr>
<tr>
<td>Christian</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Buddhist</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Education (%)</td>
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<tr>
<td>Illiterate</td>
<td>45 (17.2)</td>
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<tr>
<td>Primary</td>
<td>119 (45.4)</td>
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<tr>
<td>Secondary</td>
<td>79 (30.2)</td>
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<tr>
<td>Higher secondary</td>
<td>7 (2.6)</td>
</tr>
<tr>
<td>Diploma</td>
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</tr>
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<td>Graduate</td>
<td>9 (3.4)</td>
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<td>1 (0.4)</td>
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<tr>
<td>Marital status (%)</td>
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<tr>
<td>Married</td>
<td>240 (91.6)</td>
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<tr>
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<td>17 (6.5)</td>
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<td>1–3</td>
<td>160 (61.0)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>88 (33.7)</td>
</tr>
</tbody>
</table>

**Table 2: Perceptions regarding current healthcare**

| Satisfied with healthcare when required (%) | 97 (37.0) | 165 (63.0) |
| Reasons for no satisfaction (n = 165) |          |            |
| Distance                          | 125 (75.7) | 40 (24.3)  |
| Inconvenient timing                | 104 (63.0) | 61 (37.0)  |
| Long queues                        | 140 (84.8) | 25 (15.2)  |
| Ineffective communication           | 102 (61.8) | 63 (38.2)  |
| Satisfied with care at home         | 194 (74.0) | 68 (26.0)  |
| Presence of inconvenience in multiple referral systems | 204 (77.8) | 58 (22.2)  |
| Avoidance of medical treatment      | 210 (80.1) | 52 (19.9)  |
| Reasons for avoiding medical treatment (n = 210) | | |
| Lack of money                      | 134 (51.1) | 128 (48.9) |
| Think that diseased condition is a normal part of aging | 156 (59.5) | 106 (40.5) |
| Fear of going to hospitals/doctors  | 102 (38.9) | 160 (61.1) |
| Inconvenience in visiting healthcare facilities | 148 (56.4) | 114 (43.5) |

**Table 3: Perceived needs with respect to healthcare**

| Need for a separate geriatric OPD/department (%) | 252 (96.1) |
| Need for geriatric health camps (%)             | 237 (90.4) |
| Need for the availability of mobile Healthcare (%) | 237 (90.4) |
| Need for the establishment of elderly day care centers (%) | 235 (89.7) |
A total of 84.8% of patients faced the problem of “long queues” for which simple yet effective solutions like separate queues with the help of specific cards or papers can be followed. Around >80% of patients avoided medical treatment when needed due to various reasons like lack of money (51%), fear of going to hospitals/doctors (39%), and inconvenience in visiting healthcare facilities (56%). Many geriatric patients have a negative perception of health and healthcare. This was also reflected in our study findings. Nearly 60% of patients reported that the reason for them avoiding medical treatment was their perception that “diseased condition is a normal part of aging.” This can be tackled by counseling the elderly and their caregivers with information, education, and communication in the community.

**Perceived needs regarding Healthcare**

Studies have shown that a separate specialized OPD and department for geriatric healthcare are beneficial for the proper practice of comprehensive geriatrics and comprehensive geriatric assessment (CGA). Our study showed that 96% of patients felt the need for a separate geriatric OPD or department. This one-stop center will reduce excessive traveling due to referrals since 78% of patients were inconvenienced by the multiple referral systems. Additionally, the problems of inconvenient timings, long queues, and ineffective communication can also be successfully solved by a separate OPD/department.

**Attitudes toward specialized Geriatric Healthcare**

Around 98% of geriatric patients had an affirmative attitude toward the possible benefits of specialized geriatric healthcare, like aiding accessibility, providing a friendly atmosphere, and facilitating efficient treatment. This reinforces that the introduction of specialized healthcare would be well accepted, supported, and utilized by the masses. Moreover, a significant proportion of patients were ready to spend more time for a checkup (80.5%), undergo additional tests (62.5%), and follow-up regularly (89.3%) if these would improve their quality of life and prevent comorbidities. These factors can be attributed to the acceptance and willingness toward an instrumental model of CGA, which involves a series of tests and regular follow-ups for early detection and treatment by providing specialized healthcare to geriatric patients. However, a comparatively higher number (50.8%) had a negative attitude toward spending more money on healthcare, even if it improved their quality of life. This clearly reflects the substandard level of financial security of the elderly, which has a substantial role to play in healthcare. Hence, the policymakers need to improve the health schemes and strengthen pensions for the elderly in order to adequately dispense specialized geriatric healthcare in India.

**Future Research**

Research exploring the perceptions, attitudes, and perceived needs of admitted inpatients also needs to be conducted. Our study was conducted only in seven OPDs. However, perceptions, attitudes, and needs of geriatric patients from other OPDs should also be explored. The healthcare perceptions and needs should also be investigated among the community-dwelling elderly and their caregivers for a comprehensive understanding. To prepare for the increasing demands of geriatric healthcare with the increasing population, nationwide assessments need to be conducted. This can be promoted by inclusion in surveys like the National Family Health Survey, Annual Health Survey, and District Level Health Survey, which mainly focus on maternal and child healthcare. These population surveys, when conducted among households in large samples, unlike this study, would help to better gauge the current scenario of India’s geriatric population and healthcare.

**CONCLUSION**

This study found the low satisfaction rates of the elderly with the current healthcare and a high felt need for specialized geriatric facilities. The highly affirmative attitudes of patients toward the implementation of some aspects of specialized geriatric healthcare indicate the need for these establishments.

**ACKNOWLEDGMENTS**

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References

Dyspepsia includes a spectrum of symptoms, including epigastric burning or pain, early satiety, and postprandial fullness.1 OD, where a specific structural or organic cause can be established for dyspepsia, is less common than FD, where a specific cause is not found.2 The worldwide prevalence of dyspepsia is around 20–30%,3 and is slightly higher in the Western population and occurs more frequently among women.4 While precise prevalence data of dyspepsia in India is not available, different studies estimate that it affects 7.6–49% of the Indian population.4 In the Indian context, patients with dyspepsia usually do not seek medical help due to the belief that it is a natural part of the aging process and that medication is not effective.5 Dyspepsia includes a spectrum of symptoms ranging from epigastric pain and early satiety to postprandial fullness.2 Several studies have estimated the prevalence of dyspepsia to be around 7.6–49% of the Indian population.3 Dyspepsia is more prevalent in males and in the 31–50 age group.4 Dyspepsia in India is more prevalent in males and in the 31–50 age group.4 Results: A total of 3,739 patients from across 29 states of India participated in the study. Most of the patients were male (70.8%) and were from urban areas (56.8%). The highest percentage of patients were aged 31–40 (33.8%), and most patients (60.2%) had dyspepsia for a duration of 6–12 months. Patients with functional dyspepsia (FD) (78.5%) were significantly higher compared to organic dyspepsia (OD) (21.5%) (\( p < 0.001 \)). The most frequent presenting symptoms were epigastric pain, nausea, vomiting, and heartburn. A quarter (25.6%) of the dyspepsia patients were associated with various comorbid conditions, of which diabetes mellitus, hypertension, and irritable bowel syndrome are the most common ones. A total of 619 patients in the study were on concomitant medications, of which the most common were antidiabetic drugs (271/619, 43.8%). Rabeprazole was the most frequently used PPI (2467/3739, 66.0%) among the study participants. The patient satisfaction analysis showed that, overall, patients were satisfied with PPIs, as most patients (~80%) agreed to almost all questions. The analysis for individual PPIs showed the highest “agree” responses in the rabeprazole group for almost all questions (12 of 13). Around 86.4% of patients on rabeprazole agreed with “immediate relief from acidity,” 84.9% for “gives me complete relief,” and 85.9% for “relief from nighttime acidity symptoms.” Conclusion: Our study involving over 3,700 Indian patients with dyspepsia adds to the growing knowledge of dyspepsia in India. Dyspepsia is more prevalent in males and in the 31–50 age group. FD is the most common form. Overall, patients were satisfied with PPIs in dyspepsia management in India. Patients on rabeprazole showed higher levels of medication adherence, satisfaction with symptom relief, convenience of therapy, and safety compared to patients on other PPIs. Against the backdrop of a paucity of reliable data about dyspepsia in India, our study results provide valuable insights into Dyspepsia and its management in an Indian setting.

Studies across the world suggest that dyspepsia is associated with a reduction in overall quality of life. It also causes considerable distress to the patient in terms of pain, anxiety, depression, and impairment of usual activity.6 FD is also associated with a substantial economic impact, absenteeism, and impaired work productivity,7 more in the urban regions than rural regions.8 Even though the humanistic and economic burden of dyspepsia in India has not been adequately reported, considering the high clinical burden of dyspepsia in India, we can expect dyspepsia to be associated with a similar loss in quality of life and economic burden as the rest of the world.

The present study was conducted with the objective of understanding the demographics, diagnosis, clinical presentation, and management of patients with dyspepsia in India. We also planned to evaluate the pattern of different PPI usage, the extent of medication adherence, and levels of patient satisfaction with different PPIs among Indian patients with dyspepsia.

**Materials and Methods**

**Study Setting and Participants**

This pan-India multi-centric, cross-sectional, questionnaire-based, noninterventional, observational study was conducted in February–October 2021. Consecutive patients of either gender aged 18 years or more were included in the study. Patients with dyspepsia were selected through a random sampling method. Patients were excluded if they had any contraindications to using PPIs or had a history of peptic ulcer disease. A total of 3,739 patients from across 29 states of India participated in the study. Most of the patients were male (70.8%) and were from urban areas (56.8%). The highest percentage of patients were aged 31–40 (33.8%), and most patients (60.2%) had dyspepsia for a duration of 6–12 months. Patients with functional dyspepsia (FD) (78.5%) were significantly higher compared to organic dyspepsia (OD) (21.5%) (\( p < 0.001 \)). The most frequent presenting symptoms were epigastric pain, nausea, vomiting, and heartburn. A quarter (25.6%) of the dyspepsia patients were associated with various comorbid conditions, of which diabetes mellitus, hypertension, and irritable bowel syndrome are the most common ones. A total of 619 patients in the study were on concomitant medications, of which the most common were antidiabetic drugs (271/619, 43.8%). Rabeprazole was the most frequently used PPI (2467/3739, 66.0%) among the study participants. The patient satisfaction analysis showed that, overall, patients were satisfied with PPIs, as most patients (~80%) agreed to almost all questions.

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and above, visiting the participating centers with a clinical diagnosis of any form of dyspepsia, and on treatment for the same were informed about the study, and patients were recruited after taking their consent. Non-consenting patients, patients without a clinical diagnosis of dyspepsia (either FD or OD), and patients aged <18 years were excluded from the study. All study data were collected during a single patient visit to the site, and the study did not involve a follow-up evaluation of the patients. The study was registered in the CTRI portal with registration number CTRI/2021/02/031271, dated 12th February 2021.

Data Collection and Analysis
A comprehensive case record form (CRF) was developed and adopted into an electric-CRF (e-CRF). All participating centers received training in the usage of e-CRF, and the individual study centers collected the data through e-CRF. The paper CRF used to develop e-CRF in this study is available as supplementary Table S1.

Data collected included demographic data (age, gender, and location), clinical data (presenting symptoms, type of dyspepsia (FD or OD), comorbidities, and concomitant medications), and pattern of PPI usage. For recording patient experiences with PPI usage, a questionnaire containing 13 questions with a 4-point Likert scale was used (Table 1).

A unique patient identifier was generated at the time of patient recruitment, and anonymized patient data collected in each participating center were instantaneously submitted to a coordinating center via the internet through a secure web portal. The study was conducted with the help of a contract research organization (CRO)—Innovate Research, which was also involved in the drafting of the study protocol, generation of the CRF and informed consent forms, study site visits, training, ethical committee approvals, study monitoring, data collection and storage, and data analysis. The integrity of data collection and data entry quality was monitored through regular quality checks of the data, during which adherence to subject eligibility criteria and study protocol, appropriateness of the processes followed for recruitment, obtaining informed consent, and data collection was verified.

All data were entered electronically and analyzed using R software version 4.1.2. Descriptive statistics were used for categorical variables, and between-group comparisons were made using Fisher’s exact test, with p < 0.05 denoting statistical significance.

Ethical Considerations and Data Availability
The study was approved by the Independent Ethics Committee at all participating sites prior to study initiation. All investigators, sponsor representatives, CRO staff, and study personnel were well-versed in the study protocol. Ethical principles enshrined in the Helsinki declaration, ICMR guidelines, and all other applicable ethical guidelines were followed during the conduct of the study, and patient anonymity was maintained at all stages of data collection and analysis. Patient data were collected only after the patients provided written informed consent to participate in the study. All datasets leading to the results of the study are available with the corresponding author upon reasonable request.

Table 1: Questions included in the patient satisfaction component of the survey. The patients were asked to select one of the four responses to each question—completely agree, slightly agree, slightly disagree, completely disagree.

<table>
<thead>
<tr>
<th>No</th>
<th>Question</th>
<th>Facet</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I take my medication only when I have symptoms</td>
<td>Convenience</td>
</tr>
<tr>
<td>2</td>
<td>I always complete the medication course</td>
<td>Adherence</td>
</tr>
<tr>
<td>3</td>
<td>I usually take the medication 30 minutes prior to food</td>
<td>Convenience</td>
</tr>
<tr>
<td>4</td>
<td>I find once daily dosing advantageous</td>
<td>Convenience</td>
</tr>
<tr>
<td>5</td>
<td>Medication gives me complete relief from acidity</td>
<td>Symptom relief</td>
</tr>
<tr>
<td>6</td>
<td>Acidity symptoms are completely under control</td>
<td>Symptom relief</td>
</tr>
<tr>
<td>7</td>
<td>Medication provides immediate relief from acidity</td>
<td>Symptom relief</td>
</tr>
<tr>
<td>8</td>
<td>Medication gives me relief from nighttime acidity symptoms</td>
<td>Symptom relief</td>
</tr>
<tr>
<td>9</td>
<td>Medication allows me to do my daily activities normally</td>
<td>Symptom relief</td>
</tr>
<tr>
<td>10</td>
<td>Medication allows me to eat or drink anything I want</td>
<td>Satisfaction</td>
</tr>
<tr>
<td>11</td>
<td>Medication is cost-effective</td>
<td>Cost-effectiveness</td>
</tr>
<tr>
<td>12</td>
<td>I am satisfied with the lack of side effects with this medication</td>
<td>Safety</td>
</tr>
<tr>
<td>13</td>
<td>I have not found side effects or safety issues over long-term usage</td>
<td>Safety</td>
</tr>
</tbody>
</table>

**RESULTS**

**Study Overview and Demographic Details**
Over the course of 9 months, a total of 3,739 patients (mean age 42.71 ± 11.60 years) from across 29 states of India participated in the study. Most participants were from Maharashtra, Andhra Pradesh, and Uttar Pradesh (N = 547, 328, and 320, respectively). Region-wise, most patients were from the Southern region of India (N = 1212, 32.4%) (Table S2).

The demographic details are provided in Table 2. There were more male patients and patients from urban areas compared to female and rural patients, respectively. Most patients were from 31 to 40 years age group, and most patients suffered from dyspepsia for 6–12 months. The proportion of patients with FD was significantly more than the proportion of patients with OD (p < 0.001). History of alcohol and tobacco usage was given by 1802/3739 (48.2%) and 1556/3739 (41.6%) patients, respectively, with more male patients and patients in the age group 31–40 years reporting this. The highest proportion of patients with a history of alcohol and tobacco usage was found in the urban male population in the age group 31–40 years (alcohol: 316 patients, 17.5%; tobacco—258 patients, 16.6%) (Table S3).

The most frequent presenting symptoms were epigastric pain, nausea, vomiting, and heartburn. A total of 959 patients gave a history of comorbid illnesses, of which the three most common were diabetes (311/959, 32.4%), hypertension (218/959, 22.7%), and irritable bowel syndrome (53/959, 5.5%). A total of 619 patients reported taking concomitant medications, of which the most frequent were anti-diabetic (271/619, 43.8%) and anti-hypertensive (171/619, 27.6%) drugs.

A comparison of different patient characteristics between patients with FD and OD is presented in Table 3. FD was more common in patients aged <40 years and among patients with a history of smoking and alcohol, whereas OD was more common in patients aged >40 years and among obese patients.

**Pattern of PPI Usage**
The pattern of PPI usage in different subgroups of patients is summarised in Table 2. Rabeprazole was the most frequently used PPI (2467/3739, 66.0%), followed by pantoprazole (720/3739, 19.3%) and esomeprazole (329/3739, 8.8%) in our study. The usage of rabeprazole was higher within every patient subgroup considered in the study, namely both genders, all age groups, either location,
Patient Satisfaction with PPI Usage

Results of the patient satisfaction survey are shown in Figures 1A to D and 2. The proportion of patients answering “completely agree” for 12 out of 13 questions was highest with rabeprazole (only for the first question, the proportion of “completely agree” responses was highest with Pantoprazole). This indicates that more patients on rabeprazole have a higher degree of medication adherence, symptom relief, convenience of therapy, cost-effectiveness of therapy, safety, and overall satisfaction with the therapy (Tables 1 and S4).

The proportion of patients who answered agree (“completely agree” and “slightly agree”) was considerably higher in the rabeprazole group for all 13 questions. In fact, >80% of patients agreed to 12/13 questions, and this proportion was 73.2% for the first question, which asked if the patients took the medications only when symptomatic. This suggested that patients on rabeprazole perceive a high degree of satisfaction with therapy (Table S5).

Table 3: Comparison of different patient characteristics between patients with FD and OD

<table>
<thead>
<tr>
<th></th>
<th>FD (N = 2936)</th>
<th>OD (N = 803)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2088 (71.11%)</td>
<td>560 (69.75%)</td>
</tr>
<tr>
<td>Female</td>
<td>848 (28.88%)</td>
<td>243 (30.26%)</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>1645 (56.02%)</td>
<td>478 (59.52%)</td>
</tr>
<tr>
<td>Rural</td>
<td>1291 (43.97%)</td>
<td>325 (40.97%)</td>
</tr>
<tr>
<td>Age group (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–30</td>
<td>386 (13.1%)</td>
<td>97 (12.1%)</td>
</tr>
<tr>
<td>31–40</td>
<td>1037 (35.3%)</td>
<td>227 (28.3%)</td>
</tr>
<tr>
<td>41–50</td>
<td>817 (27.8%)</td>
<td>229 (28.5%)</td>
</tr>
<tr>
<td>51–60</td>
<td>470 (16.0%)</td>
<td>174 (21.7%)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>226 (7.7%)</td>
<td>76 (9.5%)</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight (&lt;18.5 kg/m²)</td>
<td>66 (2.2%)</td>
<td>17 (2.1%)</td>
</tr>
<tr>
<td>Normal (18.5–22.9 kg/m²)</td>
<td>612 (20.8%)</td>
<td>142 (17.7%)</td>
</tr>
<tr>
<td>Overweight (23–24.9 kg/m²)</td>
<td>636 (21.7%)</td>
<td>170 (21.2%)</td>
</tr>
<tr>
<td>Obese (≥25 kg/m²)</td>
<td>1622 (55.2%)</td>
<td>474 (59.0%)</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>1266 (43.1%)</td>
<td>290 (36.1%)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>1472 (50.1%)</td>
<td>330 (41.1%)</td>
</tr>
</tbody>
</table>

Table 2: Demographic details and pattern of proton pump inhibitor usage in different patient groups

<table>
<thead>
<tr>
<th>Group</th>
<th>N (%)</th>
<th>Dexlansoprazole</th>
<th>Esomeprazole</th>
<th>Omeprazole</th>
<th>Pantoprazole</th>
<th>Rabeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>3739 (100%)</td>
<td>2 (0.1%)</td>
<td>329 (8.8%)</td>
<td>221 (5.9%)</td>
<td>720 (19.3%)</td>
<td>2467 (66.0%)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1091 (29.2%)</td>
<td>1 (0.1%)</td>
<td>98 (9.0%)</td>
<td>65 (6.0%)</td>
<td>188 (17.2%)</td>
<td>739 (67.7%)</td>
</tr>
<tr>
<td>Male</td>
<td>2648 (70.8%)</td>
<td>1 (0.04%)</td>
<td>231 (8.7%)</td>
<td>156 (5.9%)</td>
<td>532 (20.1%)</td>
<td>1728 (65.3%)</td>
</tr>
<tr>
<td>Age group (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–30</td>
<td>483 (12.9%)</td>
<td>0 (0.0%)</td>
<td>55 (11.4%)</td>
<td>43 (8.9%)</td>
<td>108 (22.4%)</td>
<td>277 (57.3%)</td>
</tr>
<tr>
<td>31–40</td>
<td>1264 (33.8%)</td>
<td>2 (0.2%)</td>
<td>138 (10.9%)</td>
<td>77 (6.1%)</td>
<td>241 (19.1%)</td>
<td>806 (63.8%)</td>
</tr>
<tr>
<td>41–50</td>
<td>1046 (28.0%)</td>
<td>0 (0.0%)</td>
<td>83 (7.9%)</td>
<td>62 (5.9%)</td>
<td>202 (19.3%)</td>
<td>699 (66.8%)</td>
</tr>
<tr>
<td>51–60</td>
<td>644 (17.2%)</td>
<td>0 (0.0%)</td>
<td>33 (5.1%)</td>
<td>22 (3.4%)</td>
<td>119 (18.5%)</td>
<td>470 (73.0%)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>302 (8.1%)</td>
<td>0 (0.0%)</td>
<td>20 (6.6%)</td>
<td>17 (5.6%)</td>
<td>50 (16.6%)</td>
<td>215 (71.2%)</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>1616 (43.2%)</td>
<td>0 (0.0%)</td>
<td>138 (8.5%)</td>
<td>124 (7.7%)</td>
<td>296 (18.3%)</td>
<td>1058 (65.5%)</td>
</tr>
<tr>
<td>Urban</td>
<td>2123 (56.8%)</td>
<td>2 (0.1%)</td>
<td>191 (9.0%)</td>
<td>97 (4.6%)</td>
<td>424 (20.0%)</td>
<td>1409 (66.4%)</td>
</tr>
<tr>
<td>Dyspepsia duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 months</td>
<td>2 (0.1%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (100.0%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>3–6 months</td>
<td>520 (13.9%)</td>
<td>0 (0)</td>
<td>51 (9.8%)</td>
<td>40 (7.7%)</td>
<td>86 (16.5%)</td>
<td>343 (65.9%)</td>
</tr>
<tr>
<td>6–12 months</td>
<td>2254 (60.2%)</td>
<td>2 (0.1%)</td>
<td>193 (8.6%)</td>
<td>117 (5.2%)</td>
<td>437 (19.4%)</td>
<td>1505 (66.8%)</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>963 (25.8%)</td>
<td>0 (0)</td>
<td>85 (8.8%)</td>
<td>64 (6.6%)</td>
<td>195 (20.2%)</td>
<td>619 (64.3%)</td>
</tr>
<tr>
<td>Dyspepsia type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Functional</td>
<td>2936 (78.5%)</td>
<td>0 (0.0%)</td>
<td>259 (8.8%)</td>
<td>192 (6.5%)</td>
<td>554 (18.9%)</td>
<td>1931 (65.8%)</td>
</tr>
<tr>
<td>Organic</td>
<td>803 (21.5%)</td>
<td>2 (0.2%)</td>
<td>70 (8.7%)</td>
<td>29 (3.6%)</td>
<td>166 (20.7%)</td>
<td>536 (66.7%)</td>
</tr>
<tr>
<td>Personal history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>1802 (48.2%)</td>
<td>1 (0.1%)</td>
<td>126 (7.0%)</td>
<td>111 (6.2%)</td>
<td>374 (20.8%)</td>
<td>1190 (66.0%)</td>
</tr>
<tr>
<td>Tobacco*</td>
<td>1556 (41.6%)</td>
<td>1 (0.1%)</td>
<td>123 (7.9%)</td>
<td>94 (6.0%)</td>
<td>299 (19.2%)</td>
<td>1039 (66.8%)</td>
</tr>
</tbody>
</table>

*Includes both tobacco smoking and tobacco chewing

Discussion

The major findings of our study are that dyspepsia is more common among males, duration, and type of dyspepsia (p < 0.05 in each comparison). Rabeprazale was also the most frequently used PPI among patients with a history of alcohol and tobacco consumption and among patients with different comorbid illnesses and taking concomitant medications.
in urban populations, and in the age group 31–40 years; FD is more frequent than OD; rabeprazole is the most frequently prescribed PPI for this indication among all subgroups. Another important finding is that patient satisfaction, and convenience of therapy are higher with rabeprazole compared to other PPIs. Against the backdrop of a paucity of reliable data about dyspepsia from India, our study results provide valuable insights into the disease burden and treatment patterns in an Indian setting.

It is known that FD is more prevalent than OD. The Rome IV criteria define FD as having no evidence of the structural or organic cause of dyspepsia symptoms; and having either postprandial fullness, early satiation, epigastric pain, or epigastric burning. In addition, FD is classified into two subgroups based on the predominant symptom—postprandial distress syndrome and epigastric pain syndrome. Previous epidemiological studies have suggested that FD is more common amongst females; however, some studies do not report any significant gender difference in FD. By contrast, our study had more male patients with dyspepsia. FD appears to be more common among younger age groups in previous Asian epidemiological studies, a finding replicated in our study as well. We also observed that while FD was more common in patients aged <40 years, OD was more frequent in patients aged >40. This finding needs to be confirmed in a larger population. While our study observed that most patients had dyspepsia for 6–12 months, a previous study from Mumbai reported a longer median duration of symptoms of 24 months. In our study, more patients were from urban than rural settings. While the study by Chowdry et al. also concluded...
Dyspepsia the Indian Perspective

that the prevalence of dyspepsia was more in urban regions, the study by Mahadeva et al. had findings contrasting to ours. Thus, there is a considerable amount of variation with respect to the epidemiology of dyspepsia. This highlights the need for a population-based study with a large sample size to bring about more clarity on this topic.

There is varied literature on risk factors for dyspepsia. Studies by Kim et al., Nwokediuko et al., and Jaber et al. have suggested that smoking, inadequate sleep, female gender, education below college level, presence of irritable bowel syndrome, alcohol consumption, and use of nonsteroidal anti-inflammatory drugs to be associated with dyspepsia. However, none of these associations has been consistently found in another Chinese study. However, with respect to patient satisfaction, our study indicates that rabeprazole has better patient-reported outcomes among different PPIs. Rabeprazole was associated with the best rates of medication adherence, symptom relief, the convenience of therapy, cost-effectiveness, and overall patient satisfaction compared to other PPIs.

The reasons behind this favorable patient response towards rabeprazole remain to be uncovered. Available evidence suggests that all the approved PPIs may have a similar range of efficacy by virtue of similar mechanisms of action for most of the indications concerned. However, there are differences between the PPIs with respect to binding affinities and pharmacokinetics. These may confer differences in response rates, treatment outcomes, drug interactions, and adverse effect profiles. For example, rabeprazole is reported to have greater selectivity for the cysteine 813/822 sites in the gastric proton pump; it converts to its active form rapidly; it dissociates quickly from the proton pump. Probably because of these factors, rabeprazole was observed to have a faster onset of action and a greater degree of acid suppression compared to other PPIs.

Rabeprazole is also unique among PPIs in that a large proportion of administered rabeprazole is metabolized non-enzymatically. It has a lower dependence on enzymatic metabolic pathways (involving CYP2C19 and CYP3A4) compared to the other PPIs. This lower dependence on an enzymatic metabolic pathway may be the probable reason why there is a lack of interperson variability in response rates to rabeprazole. This also may be the reason for fewer drug-drug interactions when rabeprazole was co-prescribed with many other drugs, which gets metabolized through the CYP2C19 pathway. Multiple studies have discussed the CYP2C19 genetic polymorphism and the different genotypes which can make individuals respond to the PPIs differently. The CYP2C19 genotypes are classified into rapid, extensive metabolizer (RM), intermediate metabolizer (IM), and poor metabolizer based on how quickly the CYP2C19 metabolizes a substrate. The same PPI in a particular dose behaves differently in individuals with different genotypes. The plasma levels of the drug do not sustain long enough in RM individuals, resulting in insufficient acid suppression. Whereas an IM individual gets an adequate response with the same dose of PPI, as the plasma levels of the drug sustain long enough. These genotype variations result in uncertainty in patient response to various PPIs. But unlike other PPIs, rabeprazole is different in that its metabolism is not dependent on the CYP2C19 pathway. Any type of CYP2C19 metabolizer would respond similarly to rabeprazole treatment. There won’t be any uncertainty in patient response to rabeprazole.

In addition to this, the lack of dependency on an enzymatic metabolic pathway may also be the reason for rabeprazole to have less drug-drug interactions with other drugs like clopidogrel which gets metabolized through the CYP2C19 pathway. There is no reduction in the antiplatelet effect of clopidogrel when rabeprazole is coadministered, as rabeprazole does not compete with clopidogrel for the CYP2C19 enzymes for metabolism. This unique pharmacokinetic feature can be of significance among patients who require co-administration of these two classes of drugs. Rabeprazole has an advantage over other PPIs in this aspect. In fact, Niu et al. reported in their 2018 meta-analysis that the combination of clopidogrel with certain types of PPIs, including omeprazole, lansoprazole, esomeprazole, and pantoprazole, but not rabeprazole, was associated with a higher incidence of major adverse cardiovascular events among patients with coronary artery disease. As a result of these observations, the United States Food and Drug Administration recommends avoiding omeprazole and esomeprazole in patients who are on clopidogrel since drug-drug interactions between clopidogrel and omeprazole or esomeprazole can lead to adverse clinical outcomes. Not just the safety related to drug-drug interactions, rabeprazole has also shown a better safety profile in terms of having lower rates of acute and chronic kidney injury compared to other PPIs. Thus, while efficacy-wise, there seems to be little difference between the PPIs, there are important differences in the safety profile and variability in response rates. These factors may have been responsible for patients having a higher extent of satisfaction with rabeprazole compared to other PPIs in our study. So, it is important to consider all these factors, especially the drug-to-drug interactions, and overall safety, while choosing a PPI for the management of dyspepsia.

The findings of our study must be interpreted against the backdrop of some limitations. This was a cross-sectional clinic-based study, and hence it is difficult to draw conclusions on the epidemiology of dyspepsia, especially relating to prevalence. We did not evaluate the impact of different dosing regimens on the PPIs. We did not evaluate the economic aspect of PPI usage. Though we did evaluate patient satisfaction with different PPIs, we did not use standardized quality of life (QoL) instruments for measuring QoL in our study.
Nevertheless, because of the large sample size, and the pan-India representation of participants in the study, the study results provide an overview of the current treatment patterns in India. They also indicate the need for large-scale epidemiological studies to further understand the burden and treatment patterns of dyspepsia in India.

CONCLUSION

To conclude, our study involving over 3700 Indian patients with dyspepsia adds to the growing knowledge of epidemiology and risk factors of dyspepsia. Rabeprazole appears to be the most frequently prescribed PPI for the management of dyspepsia in India. This observation was true irrespective of gender, age, geographic location, type of dyspepsia, presence of comorbidities, and concomitant medications. Rabeprazole appears to be associated with the best rates of medication adherence, symptom relief, convenience of therapy, cost-effectiveness, and overall patient satisfaction among PPIs in Indian patients.

ETHICS COMMITTEE APPROVAL

All participating centers obtained regional independent ethics committee approvals prior to study initiation.

ACKNOWLEDGMENTS

We thank Dr Bharadwaja Pendurthi, ex-medical advisor at Dr Reddy’s Laboratories, for his contribution to the study. We also acknowledge and thank CRO-Innovate Research, who have contributed significantly to the methodology, project administration, resources, software, supervision, validation, visualization, and analysis of the trial.

REFERENCES

## Supplementary Tables

### Table S1: Case record form (CRF) used in the study

<table>
<thead>
<tr>
<th>Survey visit</th>
<th>Date of Visit: [<strong>I</strong>]-[<strong>I</strong>]-[<strong>I</strong>]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed consent</td>
<td>Yes☐ No☐</td>
</tr>
</tbody>
</table>

If “No,” then obtain informed consent before proceeding further or do not include the subject in this study.

If “Yes,” please enter the date of obtaining informed consent: [__I__]-[__I__]-[__I__] (DD-MM-YY)

<table>
<thead>
<tr>
<th>Subject enrolment</th>
<th>Is the subject eligible to participate in the study as per the study inclusion criteria? Yes☐ No☐</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patients of either sex aged 18 years and above</td>
<td>Yes☐ No☐</td>
</tr>
<tr>
<td>2. Willing and able to give an informed consent form</td>
<td>Yes☐ No☐</td>
</tr>
<tr>
<td>3. Patient with a confirmed diagnosis of Dyspepsia</td>
<td>Yes☐ No☐</td>
</tr>
</tbody>
</table>

*If No, exclude the subject from the study.

### Disease history and severity

<table>
<thead>
<tr>
<th>Year of initial diagnosis of dyspepsia</th>
<th>[<strong>I__I__I</strong>] (YYYY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of dyspepsia</td>
<td>Functional ☐ Organic ☐ (If organic, please tick from the type of OD)</td>
</tr>
<tr>
<td>Cause of OD</td>
<td>Peptic ulcer ☐ GERD ☐ Gastric or esophageal cancer, ☐ Pancreatic or biliary disorders ☐ Intolerance of food or drugs ☐ Other infectious or systemic diseases</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease symptom</th>
<th>☐ Epigastric pain ☐ Nausea ☐ Vomiting ☐ Dyspepsia ☐ Heartburn ☐ Chest discomfort ☐ Anorexia ☐ Weight Loss ☐ Hematemesis/Malena ☐ Others*</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Please specify: _____________________________________________</td>
<td></td>
</tr>
</tbody>
</table>

### Demographic data

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male ☐ Female ☐</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of Birth (DD-MM-YY)</td>
<td>[<strong>I</strong>]-[<strong>I</strong>]-[<strong>I</strong>]</td>
</tr>
<tr>
<td>Current Age (Yrs.)</td>
<td>[<strong>I</strong>] yrs.</td>
</tr>
<tr>
<td>Height</td>
<td>[<strong>I</strong>] cm</td>
</tr>
<tr>
<td>Weight</td>
<td>[<strong>I</strong>] Kgs</td>
</tr>
<tr>
<td>BMI</td>
<td>[<strong>I</strong>]. [<strong>I</strong>]. [<strong>I</strong>]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>State/UT</th>
<th>Residential location of patient Rural ☐ Urban ☐</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did the subject have a smoking/tobacco chewing habit</td>
<td>Yes ☐ No ☐ Occasionally (not every day) ☐</td>
</tr>
<tr>
<td>Did the subject have a history of or currently consuming alcohol</td>
<td>Yes ☐ No ☐ Occasionally (not every day) ☐</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical history</th>
<th>Does the subject suffer from any disease other than dyspepsia? If yes, please fill in the details below Yes ☐ No ☐</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sl. No. Disease</td>
<td>Start Date ☐ End Date ☐ Ongoing Yes ☐ No ☐</td>
</tr>
<tr>
<td>1</td>
<td>[<strong>I</strong>]-[<strong>I</strong>]-[<strong>I</strong>] [<strong>I</strong>]-[<strong>I</strong>]-[<strong>I</strong>] Yes ☐ No ☐</td>
</tr>
<tr>
<td>2</td>
<td>[<strong>I</strong>]-[<strong>I</strong>]-[<strong>I</strong>] [<strong>I</strong>]-[<strong>I</strong>]-[<strong>I</strong>] Yes ☐ No ☐</td>
</tr>
</tbody>
</table>

Contd...
Dyspepsia the Indian Perspective

Contd...

Medication record (For current PPIs, past PPIs, and other medications)
Has the subject taken medications that were completed 3 months prior or are ongoing at the time of the survey? Yes□ No□
If "Yes," please complete as applicable:

<table>
<thead>
<tr>
<th>S No.</th>
<th>Medication</th>
<th>Indication</th>
<th>Start date(DD-MM-YY)</th>
<th>End date(DD-MM-YY)</th>
<th>Ongoing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>□</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>□</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>□</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>□</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>□</td>
</tr>
</tbody>
</table>

Diagnostic test results (If available)
Type of diagnostic test (please specify): _______________________________________________
Date of assessment: [____-____-____] (DD-MM-YYYY)
Overall Interpretation
(Please check one):
□ 1. Normal
□ 2. Abnormal, not clinically significant
□ 3. Abnormal, clinically significant (specify)

Satisfaction of subjects with PPIs in dyspepsia

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Questions</th>
<th>Completely disagree (1)</th>
<th>Slightly disagree(2)</th>
<th>Slightly agree(3)</th>
<th>Completely agree(4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I take my medications only when I have symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>I always complete the medication course Rxed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>I usually take the medication 30 minutes prior to food</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>I find once daily dosing advantageous</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Acidity medication gives me complete relief</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Acidity symptoms are completely under control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Medicine provides immediate relief from acidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Medication gives me Relief from nighttime acidity symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>The prescribed medicine allows me to do my daily activities normally</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Medication allows me to eat or drink anything I want</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>I find treatment cost-effective</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>I am satisfied with the lack of side effects with this anti-acidity medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>I have not found side effects or safety issues over long-term usage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table S2: Number of participants from each state and region

<table>
<thead>
<tr>
<th>No</th>
<th>Region</th>
<th>State/union territory</th>
<th>Study participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>North (N = 470)</td>
<td>Delhi</td>
<td>166</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Haryana</td>
<td>143</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Rajasthan</td>
<td>119</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>Punjab</td>
<td>21</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>Chandigarh</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>Himachal Pradesh</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>Jammu and Kashmir</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>Central (N = 587)</td>
<td>Uttar Pradesh</td>
<td>320</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>Madhya Pradesh</td>
<td>170</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>Chhattisgarh</td>
<td>55</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>Uttararakhand</td>
<td>42</td>
</tr>
<tr>
<td>12</td>
<td>East (N = 675)</td>
<td>Odisha</td>
<td>301</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td>West Bengal</td>
<td>230</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>Jharkhand</td>
<td>95</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td>Bihar</td>
<td>49</td>
</tr>
<tr>
<td>16</td>
<td>North-East (N = 148)</td>
<td>Assam</td>
<td>83</td>
</tr>
<tr>
<td>17</td>
<td></td>
<td>Tripura</td>
<td>31</td>
</tr>
<tr>
<td>18</td>
<td></td>
<td>Arunachal Pradesh</td>
<td>14</td>
</tr>
<tr>
<td>19</td>
<td></td>
<td>Meghalaya</td>
<td>9</td>
</tr>
<tr>
<td>20</td>
<td></td>
<td>Manipur</td>
<td>8</td>
</tr>
<tr>
<td>21</td>
<td></td>
<td>Sikkim</td>
<td>2</td>
</tr>
<tr>
<td>22</td>
<td></td>
<td>Mizoram</td>
<td>1</td>
</tr>
<tr>
<td>23</td>
<td>West (N = 647)</td>
<td>Maharashtra</td>
<td>547</td>
</tr>
<tr>
<td>24</td>
<td></td>
<td>Gujarat</td>
<td>100</td>
</tr>
<tr>
<td>25</td>
<td>South (N = 1212)</td>
<td>Andhra Pradesh</td>
<td>328</td>
</tr>
<tr>
<td>26</td>
<td></td>
<td>Telangana</td>
<td>260</td>
</tr>
<tr>
<td>27</td>
<td></td>
<td>Karnataka</td>
<td>255</td>
</tr>
<tr>
<td>28</td>
<td></td>
<td>Kerala</td>
<td>189</td>
</tr>
<tr>
<td>29</td>
<td></td>
<td>Tamil Nadu</td>
<td>180</td>
</tr>
</tbody>
</table>

Total 3739
Dyspepsia the Indian Perspective

### Table S3: Pattern of Alcohol and tobacco usage among Indian patients with dyspepsia

<table>
<thead>
<tr>
<th>Age group</th>
<th>Gender</th>
<th>Location</th>
<th>Alcohol N (%)</th>
<th>Tobacco* (N, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–30</td>
<td>Male</td>
<td>Urban</td>
<td>91 (5.0%)</td>
<td>71 (4.6%)</td>
</tr>
<tr>
<td></td>
<td>Rural</td>
<td></td>
<td>85 (4.7%)</td>
<td>80 (5.1%)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>Urban</td>
<td>16 (0.9%)</td>
<td>8 (0.5%)</td>
</tr>
<tr>
<td></td>
<td>Rural</td>
<td></td>
<td>6 (0.3%)</td>
<td>6 (0.4%)</td>
</tr>
<tr>
<td>31–40</td>
<td>Male</td>
<td>Urban</td>
<td>316 (17.5%)</td>
<td>258 (16.6%)</td>
</tr>
<tr>
<td></td>
<td>Rural</td>
<td></td>
<td>247 (13.7%)</td>
<td>223 (14.3%)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>Urban</td>
<td>36 (2.0%)</td>
<td>18 (1.2%)</td>
</tr>
<tr>
<td></td>
<td>Rural</td>
<td></td>
<td>22 (1.2%)</td>
<td>20 (1.3%)</td>
</tr>
<tr>
<td>41–50</td>
<td>Male</td>
<td>Urban</td>
<td>265 (14.7%)</td>
<td>219 (14.1%)</td>
</tr>
<tr>
<td></td>
<td>Rural</td>
<td></td>
<td>250 (13.9%)</td>
<td>231 (14.8%)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>Urban</td>
<td>18 (1.0%)</td>
<td>12 (0.8%)</td>
</tr>
<tr>
<td></td>
<td>Rural</td>
<td></td>
<td>17 (0.9%)</td>
<td>17 (1.1%)</td>
</tr>
<tr>
<td>51–60</td>
<td>Male</td>
<td>Urban</td>
<td>152 (8.4%)</td>
<td>125 (8.0%)</td>
</tr>
<tr>
<td></td>
<td>Rural</td>
<td></td>
<td>140 (7.8%)</td>
<td>138 (8.9%)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>Rural</td>
<td>22 (1.2%)</td>
<td>25 (1.6%)</td>
</tr>
<tr>
<td></td>
<td>Urban</td>
<td></td>
<td>4 (0.2%)</td>
<td>5 (0.3%)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>Male</td>
<td>Rural</td>
<td>57 (3.2%)</td>
<td>51 (3.3%)</td>
</tr>
<tr>
<td></td>
<td>Urban</td>
<td></td>
<td>53 (2.9%)</td>
<td>40 (2.6%)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>Rural</td>
<td>3 (0.2%)</td>
<td>6 (0.4%)</td>
</tr>
<tr>
<td></td>
<td>Urban</td>
<td></td>
<td>2 (0.1%)</td>
<td>3 (0.2%)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>1802 (100%)</td>
<td>1556 (100%)</td>
</tr>
</tbody>
</table>

*Tobacco includes both smoking and tobacco chewing

### Table S4: Proportion of patients answering “completely agree” for the questions in the patient satisfaction questionnaire, stratified by PPIs

<table>
<thead>
<tr>
<th>No</th>
<th>Question</th>
<th>Overall (N = 3739)</th>
<th>Rabeprazole (N = 2467)</th>
<th>Pantoprazole (N = 720)</th>
<th>Esomeprazole (N = 329)</th>
<th>Omeprazole (N = 221)</th>
<th>Dexlansoprazole (N = 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I take my medication only when I have symptoms</td>
<td>1526 (40.8%)</td>
<td>1020 (41.3%)</td>
<td>298 (41.4%)</td>
<td>116 (41.0%)</td>
<td>91 (41.2%)</td>
<td>1 (50.0%)</td>
</tr>
<tr>
<td>2</td>
<td>I always complete the medication course</td>
<td>1707 (45.7%)</td>
<td>1160 (47.0%)</td>
<td>311 (43.2%)</td>
<td>135 (41.0%)</td>
<td>99 (44.8%)</td>
<td>2 (100.0%)</td>
</tr>
<tr>
<td>3</td>
<td>I usually take the medication 30 minutes prior to food</td>
<td>1575 (42.1%)</td>
<td>1076 (43.6%)</td>
<td>293 (40.7%)</td>
<td>112 (34.0%)</td>
<td>92 (41.6%)</td>
<td>2 (100.0%)</td>
</tr>
<tr>
<td>4</td>
<td>I find once daily dosing advantageous</td>
<td>1884 (50.4%)</td>
<td>1278 (51.8%)</td>
<td>349 (48.5%)</td>
<td>144 (43.8%)</td>
<td>111 (50.2%)</td>
<td>2 (100.0%)</td>
</tr>
<tr>
<td>5</td>
<td>Medication gives me complete relief from acidity</td>
<td>1694 (45.3%)</td>
<td>1170 (47.4%)</td>
<td>299 (41.5%)</td>
<td>130 (39.5%)</td>
<td>94 (42.5%)</td>
<td>1 (50.0%)</td>
</tr>
<tr>
<td>6</td>
<td>Acidity symptoms are completely under control</td>
<td>1631 (43.6%)</td>
<td>1120 (45.4%)</td>
<td>299 (41.5%)</td>
<td>124 (37.7%)</td>
<td>87 (39.4%)</td>
<td>1 (50.0%)</td>
</tr>
<tr>
<td>7</td>
<td>Medication provides immediate relief from acidity</td>
<td>1779 (47.6%)</td>
<td>1250 (50.7%)</td>
<td>303 (42.1%)</td>
<td>130 (39.5%)</td>
<td>96 (43.4%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>8</td>
<td>Medication gives me relief from nighttime acidity symptoms</td>
<td>1745 (46.7%)</td>
<td>1183 (48.0%)</td>
<td>327 (45.4%)</td>
<td>135 (41.0%)</td>
<td>100 (45.2%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>9</td>
<td>Medication allows me to do my daily activities normally</td>
<td>1820 (48.7%)</td>
<td>1278 (51.8%)</td>
<td>314 (43.6%)</td>
<td>140 (42.6%)</td>
<td>86 (38.9%)</td>
<td>2 (100.0%)</td>
</tr>
<tr>
<td>10</td>
<td>Medication allows me to eat or drink anything I want</td>
<td>1477 (39.5%)</td>
<td>1038 (42.1%)</td>
<td>249 (34.6%)</td>
<td>119 (36.2%)</td>
<td>69 (31.2%)</td>
<td>2 (100.0%)</td>
</tr>
<tr>
<td>11</td>
<td>Medication is cost-effective</td>
<td>1549 (41.4%)</td>
<td>1088 (44.1%)</td>
<td>266 (36.9%)</td>
<td>121 (36.8%)</td>
<td>72 (32.6%)</td>
<td>2 (100.0%)</td>
</tr>
<tr>
<td>12</td>
<td>I am satisfied with the lack of side effects with this medication</td>
<td>1836 (49.1%)</td>
<td>1272 (51.6%)</td>
<td>331 (46.0%)</td>
<td>137 (41.6%)</td>
<td>93 (42.1%)</td>
<td>2 (100.0%)</td>
</tr>
<tr>
<td>13</td>
<td>I have not found side effects or safety issues over long-term usage</td>
<td>2009 (53.7%)</td>
<td>1384 (56.1%)</td>
<td>363 (50.4%)</td>
<td>158 (48.0%)</td>
<td>102 (46.2%)</td>
<td>2 (100.0%)</td>
</tr>
</tbody>
</table>
### Table S5: Proportion of patients answering “completely agree” and “slightly agree” for the questions in the patient satisfaction questionnaire, stratified by PPIs

<table>
<thead>
<tr>
<th>No</th>
<th>Question</th>
<th>Overall (N = 3739)</th>
<th>Rabeprazole (N = 2467)</th>
<th>Pantoprazole (N = 720)</th>
<th>Esomeprazole (N = 329)</th>
<th>Omeprazole (N = 221)</th>
<th>Dextlansoprazole (N = 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I take my medication only when I have symptoms</td>
<td>2784 (74.5%)</td>
<td>1806 (73.2%)</td>
<td>549 (76.3%)</td>
<td>252 (76.6%)</td>
<td>176 (79.6%)</td>
<td>1 (50.0%)</td>
</tr>
<tr>
<td>2</td>
<td>I always complete the medication course</td>
<td>3147 (84.2%)</td>
<td>2085 (84.5%)</td>
<td>610 (84.7%)</td>
<td>278 (84.5%)</td>
<td>172 (77.8%)</td>
<td>2 (100.0%)</td>
</tr>
<tr>
<td>3</td>
<td>I usually take the medication 30 minutes prior to food</td>
<td>3124 (83.6%)</td>
<td>2071 (83.9%)</td>
<td>603 (83.8%)</td>
<td>272 (82.7%)</td>
<td>176 (79.6%)</td>
<td>2 (100.0%)</td>
</tr>
<tr>
<td>4</td>
<td>I find once daily dosing advantageous</td>
<td>3227 (86.3%)</td>
<td>2139 (86.7%)</td>
<td>627 (87.1%)</td>
<td>283 (86.0%)</td>
<td>176 (79.6%)</td>
<td>2 (100.0%)</td>
</tr>
<tr>
<td>5</td>
<td>Medication gives me complete relief from acidity</td>
<td>3160 (84.5%)</td>
<td>2096 (85.0%)</td>
<td>610 (84.7%)</td>
<td>278 (84.5%)</td>
<td>174 (78.7%)</td>
<td>2 (100.0%)</td>
</tr>
<tr>
<td>6</td>
<td>Acidity symptoms are completely under control</td>
<td>3044 (81.4%)</td>
<td>2023 (82.0%)</td>
<td>570 (79.2%)</td>
<td>278 (84.5%)</td>
<td>171 (77.4%)</td>
<td>2 (100.0%)</td>
</tr>
<tr>
<td>7</td>
<td>Medication provides immediate relief from acidity</td>
<td>3168 (84.7%)</td>
<td>2131 (86.4%)</td>
<td>604 (83.9%)</td>
<td>261 (79.3%)</td>
<td>170 (76.9%)</td>
<td>2 (100.0%)</td>
</tr>
<tr>
<td>8</td>
<td>Medication gives me relief from nighttime acidity symptoms</td>
<td>3155 (84.4%)</td>
<td>2119 (85.9%)</td>
<td>598 (83.1%)</td>
<td>267 (81.2%)</td>
<td>169 (76.5%)</td>
<td>2 (100.0%)</td>
</tr>
<tr>
<td>9</td>
<td>Medication allows me to do my daily activities normally</td>
<td>3180 (85.0%)</td>
<td>2129 (86.3%)</td>
<td>603 (83.8%)</td>
<td>272 (82.7%)</td>
<td>174 (78.7%)</td>
<td>2 (100.0%)</td>
</tr>
<tr>
<td>10</td>
<td>Medication allows me to eat or drink anything I want</td>
<td>2919 (78.1%)</td>
<td>1987 (80.5%)</td>
<td>513 (71.3%)</td>
<td>258 (78.4%)</td>
<td>159 (71.9%)</td>
<td>2 (100.0%)</td>
</tr>
<tr>
<td>11</td>
<td>Medication is cost-effective</td>
<td>2990 (80.0%)</td>
<td>2018 (81.8%)</td>
<td>559 (77.6%)</td>
<td>256 (77.8%)</td>
<td>155 (70.1%)</td>
<td>2 (100.0%)</td>
</tr>
<tr>
<td>12</td>
<td>I am satisfied with the lack of side effects with this medication</td>
<td>3250 (86.9%)</td>
<td>2175 (88.2%)</td>
<td>612 (85.0%)</td>
<td>283 (86.0%)</td>
<td>177 (80.1%)</td>
<td>2 (100.0%)</td>
</tr>
<tr>
<td>13</td>
<td>I have not found side effects or safety issues over long-term usage</td>
<td>3294 (88.1%)</td>
<td>2189 (88.7%)</td>
<td>628 (87.2%)</td>
<td>293 (89.1%)</td>
<td>182 (82.4%)</td>
<td>2 (100.0%)</td>
</tr>
</tbody>
</table>
Abridged Prescribing Information

Active Ingredients: Metformin hydrochloride (as sustained release) and glimepiride tablets

Indication: For the management of patients with type 2 diabetes mellitus when diet, exercise and single agent (glimepiride or metformin alone) do not result in adequate glycemic control.

Dosage and Administration: The recommended dose is one tablet daily during breakfast or the first main meal. Each tablet contains a fixed dose of glimepiride and Metformin Hydrochloride. The highest recommended dose per day should be 8 mg of glimepiride and 2000 mg of metformin. Due to prolonged release formulation, the tablet must be swallowed whole and not crushed or chewed.

Adverse Reactions:

For Glimepiride: hypoglycaemia may occur, which may sometimes be prolonged. Occasionally, gastrointestinal symptoms such as nausea, vomiting, sensations of pressure or fullness in the epigastrium, abdominal pain and diarrhoea may occur. Hepatotoxicity, elevation of liver enzymes, cholestasis and jaundice may occur. Allergic reactions or pseudo-allergic reactions may occur occasionally. For Metformin: GI symptoms such as nausea, vomiting, diarrhoea, abdominal pain, and loss of appetite are common during initiation of therapy and may resolve spontaneously in most cases. Metallic taste, mild erythema, decrease in B12 absorption, very rarely lactic acidosis. Haemolytic anaemia, Reduction of thyrotropin level in patients with hypothyroidism, Hypomagnesemia in the context of diarrhea, Encephalopathy, Photosensitivity, hepatobiliary disorders.

Warnings and Precautions:

For Glimepiride: Patient should be advised to report promptly exceptional stress situations (e.g., trauma, surgery, febrile infections, etc.) where blood glucose regulation may deteriorate, and a temporary change to insulin may be necessary to maintain good metabolic control. Metformin Hydrochloride may lead to Lactic acidosis; in such cases metformin should be temporarily discontinued and contact with a healthcare professional is recommended. Sulfonylureas have an increased risk of hypoglycaemia. Long-term treatment with metformin may lead to peripheral neuropathy because of decrease in vitamin B12 serum levels. Monitoring of the vitamin B12 level is recommended. Overweight patients should continue their energy-restricted diet, usual laboratory tests for diabetes monitoring should be performed regularly.

Contraindications: Hypersensitivity to the active substance of glimepiride & Metformin or to any of the excipients listed. Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis, diabetic precoma). Severe renal failure (GFR < 30 ml/min). In pregnant women. In lactating women. Acute conditions with the potential to alter renal function (dehydration, severe infection, shock, intravascular administration of iodinated contrast agents, acute or chronic disease which may cause tissue hypoxia, recent myocardial infarction, shock; hepatic insufficiency; acute alcohol intoxication; alcoholism). Use in a special population: Pregnant Women: Due to a lack of human data, drugs should not be used during pregnancy. Lactating Women: It should not be used during breastfeeding. Pediatric Patients: The safety and efficacy of drugs has not yet been established. Renal Impairment: A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

Contraindicated for use in dialysis patients.

Additional information is available on request.

Last updated: March 13, 2023

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Manufacturing
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Quality Check
U 10 Quality Assurance

Packaging
Automated Packaging

Patient
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- Widely Available
- Real World Evidence

*Data on file.

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IN21DI00078
Study of Efficacy of Injection Remdesivir in Patients of COVID-19

Bharat R Chaudhary¹, Prafful J Dudhrejia², Rahul M Gambhir³, Mahesh M Rathod⁴

Received: 14 February 2022; Revised: 21 November 2022; Accepted: 10 December 2022

ABSTRACT

Introduction: The coronavirus disease of 2019 (COVID-19) is a highly contagious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). World Health Organization (WHO) declared it a pandemic on 11th March 2020. Injectable remdesivir (RDV), a repurposed antiviral, was first accorded approval by the United States of America (USA) Food and Drug Administration (FDA) on 1st May 2020, for emergency use to treat suspected or laboratory-confirmed COVID-19 patients. Interim analysis of the Solidarity trial revealed no benefits in patients treated with RDV in any group of patients with COVID-19. Here, we have attempted to place our data on the efficacy of RDV in patients of COVID-19 with moderate to severe categories.

Materials and methods: A retrospective review and data analysis of 100 COVID-19 patients with reverse transcriptase polymerase chain reaction (RT-PCR)/rapid antigen test positive was performed. Among them, 50 received RDV in addition to the standard treatment protocol (STP), while the remaining 50 received only the STP. STP is an injectable steroid and heparin, along with other supportive management. Prevalent government guidelines were followed as per usual for the classification of the patients and treatment protocol. Every day of hospitalization, the status of respiratory support was checked, and every 3rd-day inflammatory markers [C-reactive protein (CRP) and D-dimer] were measured until the patient was discharged or died. Statistical analysis of the data was done using online software.

Results: Age and comorbidity distribution in both groups ensures adequate matching between the two groups. A statistically significant difference in hospitalization days was obtained in RDV-treated patients (15 vs 19 days, p-value −0.003). Statistically significant differences were not found in mortality (6 vs 10 deaths, p-value −0.27) and reduction in oxygen (O₂)/ventilatory support requirements (p-value −0.75) in the RDV group as compared to other groups. The difference in the value of CRP (p-value 0.001) and D-dimer (p-value 0.049) on day 5 is statistically significant in the RDV group as compared to the other groups.

Discussion: The finding of a reduction in days of hospitalization was similar to the Adaptive COVID-19 Treatment Trial (ACTT) 1 study conducted by Beigel et al. The mortality data were also comparable to those from WHO’s Solidarity trial. No similarity was found in data on the reduction in ordinal scale from higher to lower scale for O₂/ventilatory support on day 10 from 0. Similarity regarding the reduction in values of inflammatory markers on day 5 was found in studies conducted by Kannan et al. and Stoeckle et al.

Conclusion: We found mortality benefit and reduction in O₂ requirements/ventilatory support in RDV plus STP-administered cases as compared to STP only. But statistically, this difference is not significant, which suggests that mortality benefit in the RDV group in our study is merely by chance. Here, we can definitely conclude that days of hospital stay and inflammatory markers are reduced in the RDV plus STP-administered group, and the difference between the two groups is statistically significant, which suggests that early use of RDV could shorten the time to clinical improvement.

ORIGINAL ARTICLE

INTRODUCTION

Coronavirus disease of 2019 (COVID-19) is a highly contagious disease caused by SARS-CoV-2. The first known case was identified in Wuhan, China, in December 2019. Since then, the disease has spread very rapidly worldwide. WHO declared it a pandemic on 11th March 2020.¹ The first case in India was reported in Kerala on 27th January 2020. To date, many mutational variants have been detected from various parts of the world. Alpha, delta, and omicron are variants of concern among them.

There is currently no specific or effective antiviral medicine available for the SARS-CoV-2 virus. Several experimental treatments are being actively studied in clinical trials. Injectable RDV, a repurposed antiviral, was first accorded approval by the USA FDA on 1st May 2020 for emergency use to treat suspected or laboratory-confirmed COVID-19 in hospitalized adult and paediatric patients with severe disease.² In India, the Central Drugs Standard Control Organization (CDSCO) approved its use for the treatment of severe COVID-19 patients on 20th June 2020.³ CDSCO’s approval was restricted to the hospitalized setting along with informed consent of the patient or his/her legally acceptable representative. On 16th October 2020, the Indian Council of Medical Research issued a press release stating that the interim analysis of the Solidarity trial reveals no benefits in patients treated with RDV in any group of patients (asymptomatic/mild/moderate/severe/critical).² This immediately led to debates in social media and the lay press about the utility of the drug. Against this backdrop and the continuing debate on the utility of this drug in the ongoing pandemic, we attempted to place our small-scale data on the efficacy of injectable RDV in moderate to severe categories of COVID-19 patients.

MATERIALS AND METHODS

This is a retrospective review and data analysis of 100 RT-PCR/rapid antigen test positive COVID-19 patients hospitalized from September 2020 to August 2021 in a tertiary care hospital attached to Government Medical College, Rajkot, Gujarat, India. The study was approved by the institutional ethical committee. The need for consent was waived off due to the nature of the study (retrospectiveobservational). We started treatment of COVID-19 patients in March 2020, before the recommendation or availability of RDV. Though there were minor interconsultant variations, a uniform STP was followed, which was based on the categorization of patients into mild, moderate, and severe categories, as defined by the Health Ministry of India.³ Mild category is defined by symptoms of upper respiratory tract involvement and fever with oxygen saturation >94% on room air at rest. The moderate category is defined by symptoms and signs of lower respiratory tract involvement and fever with a respiratory rate >24/minute and
O₂ saturation between 90 and 94% on room air at rest. The severe category is defined the same as moderate but with respiratory rate >30/minute and O₂ saturation below 90% on room air. Patients of the severe category mostly require high-flow O₂ and/or mechanical ventilation (MV) (invasive or noninvasive).

Here, the STP is injectable steroids and heparin, along with other supportive care. STP was prescribed only in the moderate and severe categories of COVID-19 patients, not in the mild category. After the recommendation severe categories of COVID-19 patients, not in STP was prescribed only in the moderate and severe categories of patients. To assess our institute along with STP in the moderate and severe categories of patients. To assess RDV’s efficacy, we collected and analyzed case reports from patients we treated prior to the availability of injection RDV in our institute. A total of 50 such cases were analyzed in which only the STP was followed as defined earlier. Similarly, 50 cases were chosen from records in which injection RDV was administered in addition to the STP. The group was termed the non-RDV group (received only STP), and the second group was termed the RDV group (received RDV with STP). The selection of cases for both these groups was done in such a way that it ensured adequate matching between the groups. RDV was started on the 1st day of admission to the patients of the second group at a dose of 200 mg loading on day 1, followed by a 100 mg daily for 5 days, though the duration could be extended up to 10 days at the discretion of the treating doctor. The selection of the patients was done after fulfilling the below-mentioned criteria.

**Inclusion Criteria**

- Age of >18 years at the time of admission to the hospital.
- Positive COVID-19 RT-PCR or a rapid antigen test.
- In the hospital with persistently <94% O₂ saturation on room air at rest.
- Patients receiving standard care (steroids, anticoagulants, and other forms of support).

**Exclusion Criteria**

- Patients having a severe liver disease (e.g., cirrhosis) or having alanine transaminase or aspartate aminotransferase >5 times the upper normal limit.
- Patients with severe renal impairment (glomerular filtration rate <30 mL/minute/1.73 m² or on hemodialysis).
- Patients who were pregnant, nursing, or had a positive pregnancy test.
- Patients receiving treatment with other agents that have direct antiviral activity against SARS-COV-2.

Routine blood investigations, inflammatory markers (CRP, D-dimer), chest X-rays, and electrocardiograms of all study patients were analyzed. D-dimer was measured using an automated machine analyzer. D-dimer’s normal range is 500 ng/mL. The CRP value was measured by the latex agglutination test. CRP’s normal value is 0.5 mg/dL. Inflammatory markers CRP and D-dimer levels were measured every third day until day 15 of the hospitalization. The status of respiratory support was recorded on each day during hospitalization. The clinical status of the patients was recorded on a six-category ordinal scale as below:

- Admitted to the hospital with a fever and no O₂ support (on room air).
- Hospitalized with nasal prongs (NP) for O₂ support.
- Hospitalized with O₂ support using a venti mask (VM).
- Hospitalized with O₂ support using a non-rebreathing mask (NRBM).
- Admitted to the hospital with a high flow nasal cannula (bilevel positive airway pressure (BiPAP).
- Hospitalized with MV.

The initial three ordinal scales were termed “lower ordinal scales,” while the remaining three ordinal scales were termed “higher ordinal scales.” For 2–3 L/minute O₂ requirements, NP was used, while for 3–6 L/minute O₂ requirements, VMs were used. An NRBM was used for O₂ requirements ranging from 6 to 15 L/minute. BiPAP ventilation or MV was used for patients with higher work of NRBM breathing and O₂ requirements. Details of the patients were filled in the prefixed pro forma. The patients’ collected data were entered into a Microsoft Excel sheet for further evaluation and analysis. For statistical analysis of data, online software was used (www.socscistatistics.com).

### Results

To evaluate the efficacy of intravenous RDV combined with standard care as compared to only standard care in adult patients of COVID-19 having moderate and severe disease categories, we analyzed the data of 100 patients, and the below-mentioned results were obtained.

Age and comorbidity distribution in both groups are shown in Tables 1 and 2. This distribution ensures adequate matching between these two defined groups. As per age distribution, COVID-19 most commonly affects 41–60-year-old, and it occurs in association with any comorbidity, but most commonly occurs in patients with hypertension, diabetes mellitus, and ischemic heart disease.

Table 3 shows a decrease in morbidity in the form of a reduction in hospitalization days in patients who received RDV plus standard treatment (15 days) as compared to those who had received only standard treatment (19 days). In our study, the measurement of the “t-test p-value” was 0.003, and the

<table>
<thead>
<tr>
<th>Table 1: Age distribution among both groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age group (years)</strong></td>
</tr>
<tr>
<td><strong>Age group (years)</strong></td>
</tr>
<tr>
<td>21–40</td>
</tr>
<tr>
<td>41–60</td>
</tr>
<tr>
<td>61–80</td>
</tr>
<tr>
<td>81–100</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2: Distribution of comorbidities among both groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Distribution of comorbidities</strong></td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
</tr>
<tr>
<td>DM type II</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>DM + hypertension</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
</tr>
<tr>
<td>Cerebrovascular accidents</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Thyroid diseases</td>
</tr>
</tbody>
</table>
The study results revealed a mortality of 12% in the RDV group and 20% in the non-RDV group. The calculated p-value of our study is 0.27, which is not significant at a cut-off p-value of 0.05. Thus, in spite of the reduction in days of hospital stay, the difference in mortality between the two groups is not statistically significant. Reduction in mortality was also studied by Beigel et al. (ACTT-1 study), which demonstrated that RDV was superior to placebo in shortening the time to recovery in hospitalized COVID-19 patients, but the mortality rate was 11% in the RDV group compared to 15% in non-RDV group patients, which was also not significant statistically.

An open-label study sponsored by WHO (Solidarity trial) done in 2020, which was the biggest trial conducted across 30 countries, didn’t show a significant reduction in mortality. It shows 12.7% mortality in the non-RDV group vs 12.5% mortality in the RDV group patients. Results of the Solidarity trial indicated that RDV might have an important role in reducing the duration and severity of illness (both important outcomes when hospitals are overwhelmed with patients having COVID-19), but it didn’t give any mortality benefit to COVID-19 patients with moderate to severe categories. In a study conducted by Grein et al. in 2020 for the compassionate use of RDV also shows a mortality rate of 13% in patients to whom RDV was administered.9

In our study, it is observed that the addition of RDV to the STP leads to faster recovery in the form of an early reduction in O₂ requirement.

**Table 3: Comparison between two groups with respect to their duration of hospital stay**

<table>
<thead>
<tr>
<th>Duration of hospital stay</th>
<th>RDV group</th>
<th>Non-RDV group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>15 days</td>
<td>19 days</td>
</tr>
<tr>
<td>Variance</td>
<td>55</td>
<td>41</td>
</tr>
</tbody>
</table>

r-test value (two tail)–1.98, p-value = 0.003 (i.e., significant)

**Table 4: Mortality distribution in both groups**

<table>
<thead>
<tr>
<th></th>
<th>Survived</th>
<th>Not survived</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDV group</td>
<td>44</td>
<td>6</td>
<td>50</td>
</tr>
<tr>
<td>Non-RDV group</td>
<td>40</td>
<td>10</td>
<td>50</td>
</tr>
</tbody>
</table>

The Chi-square statistic is 1.1905. The p-value is 0.27, Not significant at p < 0.05

**Table 5: Oxygen (O₂) requirements/ventilatory support in both groups**

<table>
<thead>
<tr>
<th>Ordinal scale</th>
<th>O₂/ventilator category</th>
<th>Non-RDV group—day 0</th>
<th>Non-RDV group—day 10</th>
<th>RDV group—day 0</th>
<th>RDV group—day 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Room air</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>NP</td>
<td>1</td>
<td>12</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>VM</td>
<td>1</td>
<td>9</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>NRBMR</td>
<td>23</td>
<td>11</td>
<td>29</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>BIPAP</td>
<td>21</td>
<td>7</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>Invasive MV</td>
<td>4</td>
<td>5</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>
and/or ventilator support compared to those on the STP only. Improvement in ordinal scale from higher scale to lower scale occurred more in the RDV group as compared to the non-RDV group. In a study conducted by Madan et al., progression to higher ordinal scales (suggestive of deteriorating respiratory condition), as well as mortality across all the ordinal scales, occurred less in the RDV group (Table 10). This study suggested that treatment with RDV might have prevented the progression to a more severe disease and that the role of RDV may exist even in the inflammatory phase of the illness. The drawback of this study is that it did not have any statistical analysis to determine the significance of the said difference/benefit. Our study results show that RDV reduces the inflammatory markers more rapidly compared to the patients on the STP. The statistical p-value of mean CRP at day 5 is 0.001, which suggests that the difference between these two treatment groups regarding CRP is statistically significant. Similarly, we also found a statistically significant difference between these two treatment groups for D-dimer. The calculated p-value of the D-dimer on day 5 is 0.04. Thus, RDV rapidly reduces the inflammatory/thrombosis markers, which may lead to early recovery compared to non-RDV patients. The Randomised Evaluation of COVID-19 Therapy trial\(^{11}\) was designed to evaluate the effects of dexamethasone in patients hospitalized with COVID-19 at 176 national health service organizations in the United Kingdom. Study results show that dexamethasone leads to an early reduction in inflammatory markers, decreases hospital stay, as well as reduces the need for MV compared to the placebo group. Mortality, morbidity, and inflammatory markers may reduce further if other drugs like RDV are given along with dexamethasone.

In a study conducted by Kannan et al.\(^{12}\) in 2021 to see the reduction in inflammatory markers in patients with COVID-19 treated with only RDV and combination therapy of RDV plus dexamethasone. Out of the 49 patients, 26 were treated with only RDV and 23 with the RDV plus dexamethasone combination. After treatment, levels of CRP (31 mg/dL vs 10 mg/dL; \(p = 0.01\)) and D-dimer (172.3 ng/mL vs 118 ng/mL; \(p = 0.0005\)) were significantly lower in the combination group. More studies are required to compare the efficacy of RDV as well as corticosteroids in the reduction of inflammatory markers, as only a limited number of patients were included in the study.

An observational study conducted by Stoeckle et al.\(^{13}\) in 2020 at New York-Presbyterian Hospital/Weill Cornell Medical Centre describes changes in inflammatory markers in patients hospitalized with COVID-19 and treated with RDV plus corticosteroid. Of the 55 patients included, nine were progressors (died), and 46 were nonprogressors (survivors). The study shows that median CRP, D-dimer, and lactate dehydrogenase levels were higher in patients who progressed to intubation or death by day 14 compared to those who did not progress. CRP and D-dimer levels in nonprogressors (survivors) decreased significantly after RDV plus corticosteroid administration compared to patients on the STP only. Improvement in ordinal scale from higher scale to lower scale occurred more in the RDV group as compared to the non-RDV group.

### Table 6: Statistical analysis of Table 5

<table>
<thead>
<tr>
<th></th>
<th>Non-RDV group</th>
<th>RDV group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with a higher ordinal scale on day 0</td>
<td>48</td>
<td>47</td>
</tr>
<tr>
<td>Number of patients with a lower ordinal scale on day 10</td>
<td>27</td>
<td>31</td>
</tr>
</tbody>
</table>

The Chi-square statistic with Yates correction is 0.0964. The \(p\)-value is 0.756211. Not significant at \(p < 0.05\).

### Table 7: Mean value of CRP in two groups

<table>
<thead>
<tr>
<th>Day of hospitalization</th>
<th>RDV group (in mg/dL)</th>
<th>Non-RDV group (in mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Day 5</td>
<td>6.5</td>
<td>9.5</td>
</tr>
<tr>
<td>Day 10</td>
<td>4.5</td>
<td>7</td>
</tr>
<tr>
<td>Day 15</td>
<td>3.5</td>
<td>6</td>
</tr>
</tbody>
</table>

### Table 8: Mean value of D-dimer in two groups

<table>
<thead>
<tr>
<th>Day of hospitalization</th>
<th>RDV group (in ng/mL)</th>
<th>Non-RDV group (in ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0</td>
<td>2920</td>
<td>2920</td>
</tr>
<tr>
<td>Day 5</td>
<td>1870</td>
<td>2520</td>
</tr>
<tr>
<td>Day 10</td>
<td>1410</td>
<td>1720</td>
</tr>
<tr>
<td>Day 15</td>
<td>1000</td>
<td>1110</td>
</tr>
</tbody>
</table>

### Table 9: Comparison of mortality in various studies

<table>
<thead>
<tr>
<th></th>
<th>Beigel et al. (ACTT-1 trial)</th>
<th>Pan et al. (Solidarity trial)</th>
<th>Our study</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDV group(^*)</td>
<td>11.4%</td>
<td>12.5%</td>
<td>12%</td>
</tr>
<tr>
<td>Non-RDV group(^*)</td>
<td>15.2%</td>
<td>12.7%</td>
<td>20%</td>
</tr>
</tbody>
</table>

### Table 10: Comparison in RDV group regarding the change in O2/ventilatory support from day 0–10 of hospitalization

<table>
<thead>
<tr>
<th>Percentage of patients</th>
<th>Madan et al. RDV group day 0</th>
<th>Madan et al. RDV group day 10</th>
<th>Our study RDV group day 0</th>
<th>Our study RDV group day 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Room air</td>
<td>65.1%</td>
<td>86%</td>
<td>0%</td>
<td>26%</td>
</tr>
<tr>
<td>(ordinal scale 1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NP</td>
<td>15.6%</td>
<td>3.8%</td>
<td>2%</td>
<td>28%</td>
</tr>
<tr>
<td>(ordinal scale 2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VM</td>
<td>5%</td>
<td>0.8%</td>
<td>4%</td>
<td>8%</td>
</tr>
<tr>
<td>(ordinal scale 3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRBM</td>
<td>6%</td>
<td>1%</td>
<td>58%</td>
<td>16%</td>
</tr>
<tr>
<td>(ordinal scale 4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIPAP</td>
<td>6.5%</td>
<td>3%</td>
<td>34%</td>
<td>16%</td>
</tr>
<tr>
<td>(ordinal scale 5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MV</td>
<td>1.8%</td>
<td>2%</td>
<td>2%</td>
<td>6%</td>
</tr>
<tr>
<td>(ordinal scale 6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
compared to progressors (died). Further studies are needed to understand the link between antiviral activity and subsequent inflammatory response. Because this study didn’t have a control group, it is unclear whether the differences seen between progressors and nonprogressors were due to RDV, the natural course of the disease, or another factor such as corticosteroids.

**Conclusions**

In our comparative retrospective study, we found mortality benefit and reduction in $O_2$ requirements/ventilatory support in RDV-administered cases as compared to STP only, but statistically, this difference is not significant, which suggests that mortality benefit in the RDV group in our study is merely by chance. Here, we can definitely conclude that days of hospital stay and inflammatory markers are reduced in the RDV-administered group, and the difference between the two groups is statistically significant, which suggests that early RDV use may shorten the time to clinical improvement. The present study included a much higher percentage of patients from underrepresented minority groups than in previous RDV clinical trials. Approximately >90% of patients in the present study were non-white individuals, compared with 30–47% in clinical trials in western countries. Because underrepresented minority groups had shouldered a disproportionate burden during the COVID-19 pandemic but had not been widely represented in clinical trials, our study results may provide important evidence about RDV’s role in a reduction in time to clinical improvement in these populations.

**References**

Predictors of Poor Outcome in Patients with COVID-19 associated Respiratory Failure: A Retrospective Observational Study

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Received: 22 September 2022; Revised: 01 December 2022; Accepted: 07 December 2022

ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) is majorly known to cause mild to moderate disease, but a small fraction of patients may develop respiratory failure due to diffuse lung injury, requiring management in the intensive care unit (ICU). This study attempts to identify factors that can predict unfavorable outcomes in moderate to severe COVID-19 patients.

Methods: Hospital records of 120 COVID-19 patients admitted to the ICU were retrospectively analyzed and data pertaining to demographic, clinical, and laboratory parameters were obtained. These data were then compared with outcome parameters like survival, duration of hospital stay, and various adverse events.

Results: Out of 120 patients, 70% were male, with a mean age of 54.44 years (standard deviation (SD) ± 14.24 years). Presenting symptoms included breathlessness (100%), cough (94.17%), fever (82.5%), and sore throat (10.83%). Diabetes, hypertension, and chronic obstructive pulmonary disease (COPD) were the common comorbidities associated. Increased serum D-dimer, ferritin, interleukin-6 (IL-6) levels, and unvaccinated status were associated with higher mortality. Overall, 25.83% of patients survived, 24.41% of patients developed septic shock, and 10.6% of patients were discharged on oxygen. World Health Organization (WHO) clinical progression scale score ≥ 6 had 57 and 82% sensitivity and 83 and 77% specificity on days 7 and 14 after admission, respectively, for predicting mortality. A baseline National Early Warning Score 2 (NEWS 2) ≥ 9 had 48% sensitivity and 88% specificity for predicting mortality.

Conclusion: Advanced age and associated comorbidities are linked to adverse outcomes in moderate to severe COVID-19. Persistently high D-dimer levels, despite standard treatment, may also contribute to increased mortality. WHO clinical progression scale and NEWS 2 have high specificity for predicting mortality.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which belongs to the family of Coronaviridae, was first recorded in Wuhan, the capital of Hubei province of China, in December 2019.1 This disease spread worldwide and was declared a global pandemic by the WHO in January 2020. While SARS-CoV-2 is primarily a respiratory virus, it can affect other organ systems, including gastrointestinal, hepatic, cardiac, neurological, and renal systems.2,3 Epidemiological studies have shown that most patients develop mild to moderate disease, while a small fraction, about 6–10% of patients, develops a more severe form of COVID-19 requiring hospitalization in the ICU due to acute hypoxemic respiratory failure.4 Most of the patients admitted to the ICU require mechanical ventilation due to diffuse lung injury and acute respiratory distress syndrome (ARDS). Studies from western countries and China showed that severe COVID-19 ARDS is associated with prolonged mechanical ventilation and mortality rates of up to 97%.4 Such high mortality rates and poor ICU outcomes observed in these patients have raised concerns about the standard protocols of COVID-19 management.

This study describes the demographics, baseline characteristics, medical management, and outcomes observed in patients with moderate to severe COVID-19 admitted to the ICU. We have tried to develop insights and formulate hypotheses as to what may be the important factors predicting poor outcomes for this group of patients.

METHODS

Ethical Approval

The study was approved by the Institutional Ethics Committee of the All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India, vide approval no. AIIMS/IEC/20/441 dated 18th July 2020. The need for written informed consent was deferred, considering the use of anonymous records and the retrospective nature of data collection.

Study Design, Setting, Dates, and Sampling

This retrospective observational study was conducted during the second wave of the COVID-19 pandemic at a tertiary care referral center in North India from April to July 2021. All patients who were admitted to our tertiary care ICU during the study period fulfilling our inclusion and exclusion criteria, were taken in the study. Thus, our sampling technique was total enumerative sampling/consecutive sampling. A total of 182 COVID-19 pneumonia patients were admitted to the dedicated COVID-19 ICU of our hospital during these 4 months. Records of these patients were retrospectively reviewed to include subjects if they (1) were >18 years of age, (2) were reverse transcription polymerase chain reaction/rapid antigen test positive for SARS-CoV-2, (3) presented within 10 days from symptom onset, and (4) had features suggestive of moderate or severe disease needing ICU admission.5 Those who presented later than 10 days from symptom onset or had an upfront requirement of invasive mechanical ventilation owing to ARDS, multiorgan failure, or septic shock, and pregnant/lactating women, were excluded from the study. After excluding 62 patients according to these criteria, 120 patients were finally included for analysis (Fig. 1).

Data Collection

Two authors (AR, AK) independently reviewed the electronic and file-based hospital records of included subjects. Demographic variables, clinical and...
laboratory parameters, COVID-19 vaccination details, and patient outcomes were extracted. NEWS 2 was analyzed at admission (D-0). Clinical/laboratory parameters and WHO clinical progression scale scores were analyzed on D-0 and on days 3 (D-3), 7 (D-7), and 14 (D-14).

The primary outcome studied in the subjects was their survival. Secondary outcomes that were studied included duration of hospital stay, adverse events like acute kidney injury (AKI), septic shock, myocardial infarction, pneumothorax, pulmonary embolism, and atrial fibrillation, and requirement of oxygen after discharge.

Statistical Analysis
Captured data were entered into an excel sheet master chart and analyzed using Statistical Package for the Social Sciences, version 26.0. Descriptive statistics for quantitative data was done using mean and standard deviation for continuous normal variables, and median and interquartile range (IQR) for skewed/nonnormal variables. Testing for the normality of data was done using the Shapiro–Wilk test. Categorical data were described using frequency tabulation and percentages.

Inferential statistics were done using an independent (unpaired) sample t-test for comparing means between outcome groups and Chi-squared or Fisher’s exact test as appropriate for comparison between proportions. Time-series data for various continuous variables were represented as line plots. Mixed effect modeling methods were used to draw inferences from repeated measures data. Primary and secondary outcome parameters and their predictors were analyzed using survival plots.

Finally, the receiver operating characteristics (ROC) curve and area under curve (AUC) analysis was done to test the diagnostic accuracy of the WHO clinical progression scale and NEWS 2 scores in predicting primary and secondary outcome parameters and to find the optimum cutoff for the same.

The level of statistical significance was set at 5% \((p < 0.05)\). However, since this is a study where multiple hypotheses have been tested on a post hoc basis, we have adjusted our \(p\)-value for statistical significance as per the Bonferroni correction method.

Results
A total of 120 eligible patients were enroled in the study, among which 84 (70%) were male, and 36 (30%) were female. The mean age of enroled participants was 54.44 years (SD ± 14.27 years), with a range of 18–84 years. The mean duration of presenting symptoms was 6.32 days (SD ± 2.16 days) with a range of 2–10 days and the median duration of hospital stay was 13 days (IQR 11 days) with a range of 2–56 days. The most common risk factor was age > 60 years (43.33%, \(n = 52\)). Other major risk factors were diabetes mellitus (39.16%, \(n = 47\)), hypertension (31.66%, \(n = 38\)), and COPD (20.83%, \(n = 25\)). Minor risk factors were cerebrovascular disease, coronary artery disease, chronic liver disease, chronic kidney disease (CKD), obesity, hypothyroidism, and immunocompromised status. Patients presented with various complaints at hospitalization, but the most common complaint was breathlessness which was present in all cases, followed by cough (113, 94.17%), fever (99, 82.5%), and sore throat (13, 10.83%) (Table 1).

Comparing the above findings in both primary and secondary outcome groups, we found that increased age was a predictor of mortality (57.40 years in the deceased group (SD ± 13.54) vs 45.94 years in the alive group (SD ± 12.89), \((p = 0.0001)\)) and age of >60 years was also associated with poor survival (90.38% deaths (age of >60 years) vs 61.76% deaths (age <60 years), \((p < 0.001)\)). Kaplan Meier plot for log survival between age >60 years and younger age showed significant differences in survival, with more advanced age associated with more chances of mortality (log-rank test, \(p\)-value of 0.019) (Fig. 2).

Increased age was also associated with risk of developing AKI in these patients (65.90 years in AKI group (SD ± 7.56) vs 53.40 years in the non-AKI group (SD ± 14.27), \((p < 0.0001)\)). There were other notable clinically meaningful findings that were not statistically significant. Patients with any one of the comorbidities had a high proportion of deaths overall (81.18%), and so was the case for patients with diabetes mellitus (85.10%), hypertension (84.21%), and COPD (88%) (Table 1).

Complete blood counts, renal and liver function tests along with serum inflammatory biomarkers were performed on days 0, 3, 7, and 14 from the day of admission. Marked differences were seen in D-dimer values at days 3, 7, and 14 between the “deceased” and “alive” groups (D-3—6.43 vs 3.88 μg/mL, D-7—6.10 vs 1.91 μg/mL, D-14—7.28 vs 1.24 μg/mL, Fig. 3). Serum ferritin and IL-6 levels were also higher in the “deceased” group than in the “alive” group at all times (D-0—1702.02 vs 942.22 ng/mL, D-3—1210.77 vs 832.31 ng/mL, D-7—1607.56 vs 823.21 ng/mL, D-14—1892.78 vs 1547.99 ng/mL for serum ferritin, Fig. 4; D-0—116.88 vs 14.65 pg/mL, D-3—77.35 vs 12.70 pg/mL, D-7—596.45 vs 14.41 pg/mL, D-14—216.58 vs 90.70 pg/mL for serum IL-6, Fig. 5). Serum ferritin values were the highest at day 14 and serum IL-6 values at day 7 for the “deceased” group. Notably, upon analysis via mixed methods modeling, there was a statistically significant difference overall between the serum D-dimer and ferritin values of “deceased” and “alive” groups \((p = 0.004\) (D-dimer) and 0.007 (Ferritin)), the “alive” group having lower values. Our study did not show similar patterns for any of the secondary outcome parameters.

The mean baseline NEWS 2 score at admission was 8.58 (SD ± 1.08) and 9.39...
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from the hospital. Among the adverse events, the most common was septic shock 24.4% (n = 30), AKI 8.1% (n = 10), pulmonary thromboembolism 2.4% (n = 3), myocardial infarction 1.6% (n = 2), & pneumothorax and atrial fibrillation 0.8% each (n = 1 each). Oxygen therapy had to be prescribed on discharge to 10.6% (n = 13) of patients. Only 23 (19.17%) patients were vaccinated (3 fully vaccinated and 20 partially vaccinated), either with the Covishield or Covaxin coronavirus vaccine. Mortality was higher in unvaccinated patients (75.3%) (Table 2).

Out of total 120 patients, only 25.83% (n = 31) patients survived and were discharged (SD ± 1.08) in the “alive” and “deceased” groups, respectively (p-value of 0.001). Similarly, the WHO clinical progression scale score was also higher in the “deceased” group and progressed along days 0, 3, 7, and 14 (p-values < 0.001 for days 0, 3, 7, and 14). Both scores were significantly higher in the “deceased” group of patients, which indicates poorer outcomes with higher values of these scores (Table 2). We also did a ROC analysis to check for sensitivity, specificity, and optimum cutoffs to predict both primary and secondary outcome parameters. No significant results were obtained for secondary outcome parameters; however, for the primary outcome parameter (survival), we found that a WHO clinical progression scale score of 6 or more had an 82% sensitivity and 77% specificity on day 14 (AUC = 0.880) and 57 and 83% sensitivity and specificity respectively on day 7 (AUC = 0.738), for predicting mortality (Fig. 6).

Out of total 120 patients, only 25.83% (n = 31) patients survived and were discharged to 10.6% (n = 13) of patients. Only 23 (19.17%) patients were vaccinated (3 fully vaccinated and 20 partially vaccinated), either with the Covishield or Covaxin coronavirus vaccine. Mortality was higher in unvaccinated patients (75.3%) (Table 2).

Table 1: Baseline characteristics of patients on admission to the ICU

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total patients</th>
<th>Alive</th>
<th>Deceased</th>
<th>p-value (adjusted p-value for significance = 0.0008)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>120</td>
<td>31 (25.83%)</td>
<td>89 (74.17%)</td>
<td>--</td>
</tr>
<tr>
<td>Age in years mean (SD)</td>
<td>54.44 (14.24)</td>
<td>45.94 (12.89)</td>
<td>57.40 (13.54)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Male sex</td>
<td>84 (70%)</td>
<td>26 (30.95%)</td>
<td>58 (69.05%)</td>
<td>0.068</td>
</tr>
<tr>
<td>Duration of symptoms (days)</td>
<td>6.33 (2.16)</td>
<td>5.68 (1.81)</td>
<td>6.55 (2.24)</td>
<td>0.034</td>
</tr>
<tr>
<td>Any risk factor</td>
<td>85</td>
<td>16 (18.82%)</td>
<td>69 (81.18%)</td>
<td>0.011</td>
</tr>
<tr>
<td>Age of ≥60 years</td>
<td>52</td>
<td>05 (9.62%)</td>
<td>47 (90.38%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>47</td>
<td>07 (14.89%)</td>
<td>40 (85.11%)</td>
<td>0.033</td>
</tr>
<tr>
<td>Hypertension</td>
<td>38</td>
<td>06 (15.79%)</td>
<td>32 (84.21%)</td>
<td>0.117</td>
</tr>
<tr>
<td>COPD</td>
<td>25</td>
<td>03 (12.00%)</td>
<td>22 (88.00%)</td>
<td>0.121</td>
</tr>
<tr>
<td>CAD</td>
<td>05</td>
<td>02 (40.00%)</td>
<td>03 (60.00%)</td>
<td>0.603</td>
</tr>
<tr>
<td>CVA</td>
<td>05</td>
<td>00 (0.00%)</td>
<td>05 (100.00%)</td>
<td>0.326</td>
</tr>
<tr>
<td>CKD</td>
<td>04</td>
<td>00 (0.00%)</td>
<td>04 (100.00%)</td>
<td>0.571</td>
</tr>
<tr>
<td>Obesity</td>
<td>04</td>
<td>03 (75.00%)</td>
<td>01 (25.00%)</td>
<td>0.053</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>03</td>
<td>00 (0.00%)</td>
<td>03 (100.00%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>01</td>
<td>00 (0.00%)</td>
<td>01 (100.00%)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Initial symptoms

Breathlessness 120 31 (25.83%) 89 (74.17%) --
Cough 113 29 (25.66%) 84 (74.34%) 1.000
Fever 99 26 (26.26%) 73 (73.74%) 1.000
Sore throat 13 07 (53.85%) 06 (46.15%) 0.038

CAD, Coronary artery disease; CVA, Cerebro-vascular accident

Fig. 2: Kaplan–Meier plot for the age of >60 years vs survival

Fig. 3: Comparison of serum D-dimer levels from day 0 to day 14 with primary outcome status of patients (adjusted p-value = 0.004)

Fig. 4: Comparison of serum Ferritin levels from day 0 to day 14 with primary outcome status of patients (adjusted p-value = 0.007)
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Discussions

This study comprised 120 COVID-19 patients with hypoxemic respiratory failure admitted to the ICU of a tertiary care hospital in North India. The most important risk factor in these patients for poor outcomes was increased age (age of >60 years). Similar findings have been reported in a study by Saluja et al.,7 where they have presented a series of 406 patients with COVID-19 admitted to the hospital. We also observed that the frequency of comorbidities, symptoms, and outcomes in our study was similar to another Indian study.8 In our study, we found that the presence of various comorbidities like diabetes mellitus, hypertension, COPD, CKD, and older age, especially >60 years, etc., was associated with poorer outcomes. These findings are consistent with previous studies.9—11

Persistently high levels of serum D-dimer, even after therapeutic anticoagulation, were associated with higher inhospital mortality as compared to those who responded to anticoagulation therapy. These findings are consistent with the study done by Bhadade et al.11 Our study showed that persistently elevated levels of serum ferritin were associated with higher inhospital mortality despite standard therapy for severe SARS-CoV-2 pneumonia. These findings are consistent with the study of Raman et al., which showed that a higher level of serum ferritin was an independent predictor of mortality.12 A transient fall in serum ferritin levels noticed in the “deceased” group on day 3 might be in response to the initiation of anti-inflammatory therapy with corticosteroids after hospitalization. On days 7 and 14, an upsurge of serum ferritin levels presented in both “alive” and “deceased” groups, but it was significantly higher in the “deceased” group. This upsurge in ferritin level on day 7 might be due to a cytokine storm in patients of both groups, which was brisker in the “deceased” group, and is commonly seen in the second week of COVID-19.13 Again, a rise in ferritin levels is noticed on day 14 in both the groups. This might be contributed to by the ongoing cytokine storm and withholding of steroid therapy after 10 days as per standard treatment protocol for COVID-19.14

Multiple line means of IL-6, as shown in Figure 5, shows a rapid incline in IL-6 levels on day 7 in “deceased” group, which might be due to a stronger cytokine storm in 2nd week of disease in nonsurvivors as compared to survivors. Previous systematic review and meta-analysis done by various authors also showed similar kind of results that higher levels of IL-6 and stronger cytokine storm were associated with poor outcomes and higher mortality.15 These findings support the clinical studies and the role of immunomodulatory

Table 2: Vaccination status, NEWS 2, and WHO clinical progression scale scores compared with primary outcome status of patients

<table>
<thead>
<tr>
<th>Feature</th>
<th>Number</th>
<th>Deceased (n, %)</th>
<th>Alive (n, %)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>COVID-19 vaccination</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccinated [n, (%)]</td>
<td>23</td>
<td>16 (69.6%)</td>
<td>07 (30.4%)</td>
<td>0.371</td>
</tr>
<tr>
<td>Unvaccinated [n, (%)]</td>
<td>97</td>
<td>73 (75.3%)</td>
<td>24 (24.7%)</td>
<td>0.371</td>
</tr>
<tr>
<td>NEWS 2° day 0 (mean ± SD)</td>
<td>--</td>
<td>9.39 ± 1.08</td>
<td>8.58 ± 1.08</td>
<td>0.001</td>
</tr>
<tr>
<td>WHO—scale° day 0 (mean ± SD)</td>
<td>--</td>
<td>5.69 ± 0.59</td>
<td>5.16 ± 0.37</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>WHO—scale day 3 (mean ± SD)</td>
<td>--</td>
<td>6.50 ± 0.93</td>
<td>5.68 ± 0.65</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>WHO—scale day 7 (mean ± SD)</td>
<td>--</td>
<td>7.32 ± 1.22</td>
<td>5.62 ± 0.82</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>WHO—scale day 14 (mean ± SD)</td>
<td>--</td>
<td>8.34 ± 1.28</td>
<td>5.78 ± 1.52</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

aNEWS 2, national early warning score 2; bWHO-scale, WHO clinical progression scale

Fig. 5: Comparison of serum IL-6 levels from day 0 to day 14 with primary outcome status of patients (results not statistically significant)

Fig. 6: ROC curve analysis to assess the performance of the NEWS 2 score on day 0 and WHO clinical progression scale score on days 0, 3, 7, and 14 in predicting survival. NEWS 2, national early warning score 2; WHO-scale, WHO clinical progression scale
therapy in severe COVID-19 via IL-6 inhibition to prevent cytokine storm-induced organ damage. However, our findings with respect to IL-6 levels, even though clinically relevant, were not statistically significant.

Mortality was higher in unvaccinated (75.3%) as compared to vaccinated patients (69.56%); however, this difference was statistically nonsignificant. This might be due to a small sample size, a number of partially vaccinated patients, and a potential selection bias as only ICU-admitted patients were taken. These results, however, are concordant with previous studies. Moreover, our findings in partially vaccinated patients are consistent with the observational study done by Papagoras et al. This might be due to the development of some degree of immunity against COVID-19 following vaccination.

Our findings showed that higher values of the NEWS 2 score are associated with poor outcomes in COVID-19, like a prolonged hospital stay, adverse events like septic shock and AKI, or higher in-hospital mortality. This is consistent with the findings of another Indian study done by CR et al., which showed that a score of ≥ 2 on NEWS 2 is associated with worse outcomes. The WHO clinical progression scale showed the patient’s clinical trajectory and use of resources over time with the disease course. However, to the best of our knowledge, we did not find any study using this scale in COVID-19 as a predictor of poor outcomes, so more studies are required to confirm the validation of the WHO clinical progression scale in this context.

In our study, the mortality rate was 74.17% in severe COVID-19, which is higher than the findings of two other western studies that showed approximate mortality rates between 25 to 40% at a follow-up period of 30 days. This disparity in mortality rates between our study and these western studies might be due to the difference in the maximum duration of hospital stay, which was longer (56 days) in our study. However, various studies carried out by other authors showed similar mortality rates—77, 88.3, and 78%, respectively. These findings are similar to our study as they followed up with all the patients till the outcome.

Our study has several strengths. First, it analyzed the response of standard treatment care for COVID-19 by monitoring various inflammatory markers at regular intervals. This is the first study to assess the severity of disease so enthusiastically at different intervals of Day 0, 3, 7, and 14 by using the WHO clinical progression scale. Second, we analyzed several risk factors and comorbidities simultaneously along with the inflammatory markers and tried to gain insights about their effects not just on overall survival but also on the increased duration of hospital stay and adverse events like septic shock, AKI, and the need for oxygen at discharge. Third, we have tried to find cutoff points for NEWS 2 and WHO clinical progression scale scores to obtain an optimum sensitivity and specificity for predicting mortality.

Limitations of our study include its retrospective nature and relatively small sample size. Most of the data were collected from patient records and hence may have been subjected to any bias introduced by the data collector. All patients were treated as per the prevalent COVID-19 treatment guidelines at the time and received largely similar supportive therapy and dose, duration, and timing of corticosteroid therapy; however, some dissimilarity could not be avoided due to the use of experimental therapies like remdesivir and tocilizumab which might have affected the results. Lastly, this was a single-center study and may not be representative of the larger population as a whole. Hence, further studies should be done to test the numerous hypotheses which have been put forward in this observational study.

CONCLUSION

In this study of COVID-19-associated respiratory failure patients admitted to the ICU, advanced age and the presence of comorbidities seem to be important risk factors for unfavorable outcomes. It is, therefore, advisable for such a high-risk group population to take extra precautions to prevent COVID-19 infection. Our findings also suggest that persistently higher levels of D-dimer, despite standard treatment, are associated with increased mortality. The patients whose inflammatory markers decline with standard treatment have better outcomes. WHO clinical progression scale and NEWS 2 score system can also guide us in predicting poor patient outcomes and help triage patient care. Finally, vaccination may be associated with better outcomes and lower mortality, so its role must be considered.

PATIENT CONSENT

The need for written informed consent was deferred, considering the use of anonymous records and the retrospective nature of data collection.

ACKNOWLEDGMENT

We wish to thank the entire COVID-19 care task force of our hospital, comprising of residents, fellows, physicians, nursing staff, paramedics, physiotherapists, and all other support staff, for providing dedicated care to all afflicted COVID-19 patients at our hospital during the deadly second wave of the pandemic.

REFERENCES


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Three-dimensional Bioprinting in Gastroenterology: A Literature Review

Pravin Rathi¹, Ashwin Prabhughate²*

Received: 09 February 2022; Accepted: 02 November 2022

ABSTRACT

Three-dimensional (3D) bioprinting is one of the most upcoming research areas which apply 3D printing technology in medical and surgical applications. The basic concept of 3D bioprinting is to design tissue scaffolds to replace diseased or injured tissues. Gastroenterology is one of the medical fields in which 3D bioprinting is being rigorously researched. Although attempts are made to design 3D-geometrical constructs, the overall performance is currently hindered by limitations, including material viability and toxicity affecting the clinical outcome. However, further research at the current pace should overcome these limitations, helping open a new horizon in gastroenterology. In this review, we cover all the aspects of 3D bioprinting in gastroenterology with a holistic perspective on its current limitations and future perspectives in clinical applications.

INTRODUCTION

Gastroenterology is a field that provides primary care to patients suffering from diseases in the gastrointestinal (GI) tract. Some of the main organs in the GI tract include the stomach, small intestine (SI), large intestine, liver, and pancreas.¹ Since it is a diversified field, continuous updates in knowledge and practice are needed to cope with GI diseases. One of the major potential ways to level up the diagnosis and treatment efficiencies is 3D bioprinting. 3D bioprinting is a modern approach enabling the fabrication of tissue scaffolds and organs with the assistance of 3D-computed stimulation.² This was first elaborated at a conference at the University of Manchester, Manchester, United Kingdom.³ Since then, 3D bioprinting has been used in varied medical fields as an alternative to current medical treatments, with an aim to improve patients’ lives. Some of the target factors in this initiative were low cost, higher accuracy, and precision in replication of structure and function, accessibility, and endurance.⁴ 3D bioprinting covers major niche research areas in subjects like regenerative medicine and nanotechnology. Tissue engineering (TE) has also shown great promise in acting as an alternative to a few of the current medical treatments.⁵ TE usually finds itself dependent on bioactive cues, matrices, and bulk materials.⁶ However, Malda et al. also elaborated on the ability of 3D bioprinting to control the critical architecture of 3D components like polymers, living cells, and biochemicals.⁶,⁷

One of the major limitations in 3D bioprinting remains the accuracy of full-size organ printing by maintaining factors like structural integrity and mechanical performance.⁶ As a result, combining 3D bioprinting in gastroenterology is one of the major medical challenges, which shows the opportunity of wonders if achieved. An article by Abraham et al., posted on auntninnie.com, elaborates this point very effectively by reporting a case study of a 65-year-old female having multiple GI complications, including Barrett’s esophagus and ineffective peristalsis. The patient was required to undergo antireflux surgery based on chest computed tomography (CT) scan results showing a compressed esophagus between the left atrium and thoracic aorta. However, surgeons decided to apply 3D bioprinting due to the lack of accuracy in traditional imaging, denying access to preoperative planning. As a result, a team of surgeons and computed engineers accurately determined a 3D bioprinted model of the esophagus. This model allowed surgeons to accurately plan and maneuver various treatment approaches, giving them clarity to operate beforehand. The application of 3D bioprinting varies depending on the GI disease and individual patient requirements. This review elaborates on the application of 3D bioprinting in gastroenterology with an emphasis on comparison with its current treatments, limitations, and future perspectives.

THREE-DIMENSIONAL (3D) BIOPRINTING IN ESOPHAGEAL AILMENTS

Esophagus is a long tube connecting the pharynx to the stomach and is also known as the GI tract. It is further divided into three sections, namely the thoracic, cervical, and abdomen.⁸ Esophagus is also known to be one of the least regenerative organs making it novel to explore 3D bioprinting in esophageal diseases like Barrett’s esophagus and achalasia. Tissue-engineered 3D printed scaffolds have shown better potential than esophageal repair by traditional stents. A study by Spurrier et al. reported the successful implantation of a 3D-printed esophagus made of poly-lactic acid (PLA)/poly-glycolic acid in mice (Table 1).¹⁰ Some reports have shown the application of 3D-printed scaffolds made of poly-glyco lactic acid (PGLA) embedded with the autologous cells helped the esophagus increase its regeneration capacity. A porcine-derived extracellular matrix (ECM) derived from SI submucosa (SIS) was placed in female dogs to observe the regeneration of ECM (Table 1).¹¹ However, some limitations recorded included stenosis (narrowing of the passage) and leakage of cells. In order to overcome this, epithelial cells were captured from a pig and placed on poly ε-caprolactone (PCL) and PGLA (nanofibers).¹² The aim of this study was to regenerate the esophageus gap and analyze whether normal functioning is retained. Results reported full matrix regeneration of the esophagus due to the malleability presented by the nanofibers, and successful implantation was witnessed for the next month.

Drug delivery using nanotubes is also researched in recent years. Surgical stents can be delivered to the affected esophageal site with the accuracy of nanotech-drug delivery systems making it one of the most effective ways to regenerate the esophagus. A study by Chung et al. elaborates on this point with detail in which a three-layered combination of PCL and silk fibroin (SF) nanofiber scaffold...
<table>
<thead>
<tr>
<th>Sr. no</th>
<th>Study</th>
<th>Sample type</th>
<th>GI organ</th>
<th>Description</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Spurrier et al.</td>
<td>C57BL/six mice</td>
<td>Esophagus</td>
<td>TE esophagus (TEE) was generated by basic progenitor; esophageal organoid units (EOUs) were isolated from human/murine esophagus; implanted on a poly-L-lactic acid collagen-coated scaffold in allogenic mice.</td>
<td>Epithelium and sub-adjacent muscularis of the esophagus were recapitulated by the TEE; mesenchyme of single TEE can be contributed to by multiple EUOs—lineage tracing.</td>
</tr>
<tr>
<td>2</td>
<td>Stephen et al.</td>
<td>Adult female dogs</td>
<td>Esophagus</td>
<td>Porcine-derived xenogenic ECM derived from urinary bladder submucosa or SIS; surgical implanted to repair defects in adult female dogs.</td>
<td>In a range of 30–60 days, xenogenic ECM was reabsorbed and replaced by skeletal tissue; no signs of clinical esophageal dysfunction were observed.</td>
</tr>
<tr>
<td>3</td>
<td>Kuppan et al.</td>
<td>In vitro testing</td>
<td>Esophagus</td>
<td>PCL and PCL-gelatin based nanofibers were generated using electrospinning (324 ± 50 nm for PCL and 242 ± 30 nm for PCL-gelatin); suture regeneration and <em>in vitro</em> degeneration were compared between PCL and PCL-gelatin nanofibers.</td>
<td>PCL nanofibers showed slower degradation, higher tensile strength, contact angle, and suture regeneration in comparison to PCL-gelatin fibers; epithelial cells proliferated well with PCL and PCL-gelatin; cell proliferation was observed to be higher in PCL-gelatin fibers than PCL fibers.</td>
</tr>
<tr>
<td>4</td>
<td>Chung et al.</td>
<td>Sprague Dawley rats</td>
<td>Esophagus</td>
<td>Application of three-layered esophagus made PCL SF scaffold in rat model electrospinning; inner and outer layer of PCL were created with the same procedure; middle layer of lyophilized SF was created after the scaffold insertion.</td>
<td>Rats were sacrificed after 1st and 2nd weeks; three rats died of wound infection and esophageal fistula; no perforation, fistula, soft tissue necrosis, or abscess formation was observed in other rats; complete healing was observed after three-layered artificial esophagus; this esophagus was also histologically confirmed to have inner and outer layers of SF and middle layer of SF.</td>
</tr>
<tr>
<td>5</td>
<td>Takeoka et al.</td>
<td>F344 male rats</td>
<td>Esophagus</td>
<td>A 3D bioprinted scaffold-free structure composing NHDFs, MSCs, HUVECs, and human ESMCs; inserted in F344 male rats; mechanical and histochemical assessment was performed using Gellex Machine vision system (Japan) and hematoxylin and eosin (H and E) stains, respectively.</td>
<td>Immunohistochemistry showed higher α-smooth muscle actin and VEGF for MSCs; mechanical testing showed greater agility and strength for MSCs; hence, MSCs dominant structure was selected for transplantation in F344 male rats; after transplantation, smooth muscle cells were maintained, and food was also normally passed through the esophagus.</td>
</tr>
<tr>
<td>6</td>
<td>Nam et al.</td>
<td>In vitro testing</td>
<td>Esophagus</td>
<td>Developed a 3D printing method called the dragging technique to improve the pore size in the single extrusion process; This technique was used to develop an esophageal structure and filled with biochemical cues identical to the esophagus due to usage of decellularized bioinks from muscular and mucosal layers of the esophagus.</td>
<td>The cross-sectional area of MFT—two-layered—9.21 ± 0.21 mm², three-layered: 11.05 ± 0.15 mm²; pore controlled multilayered tubular constructs of bioinks could successfully mimic the microlayers of the esophagus.</td>
</tr>
<tr>
<td>7</td>
<td>Kim et al.</td>
<td>Rat model</td>
<td>Esophagus</td>
<td>A MSC-based bioreactor and two-layered tubular scaffold were used in combination to regenerate esophageal mucosa; omentum cultured esophagus (scaffold) was used for comparison.</td>
<td>No regeneration was observed around the control's esophageal mucosa; histopathological examination showed improved regeneration of mucosa accounting for &gt;80%; major coverage was stratified squamous epithelium and some blood vessels.</td>
</tr>
</tbody>
</table>
of the artificial esophagus was placed in a test rat model. Results showed this combination to stay overall intact (Table 1).13 However, further research is still needed in 3D bioprinting and esophageal regeneration to cover the unexplored aspects like toxicity and biophysical accessibility. One main limitation is the peristaltic; the contraction and relaxation of the esophagus can be a challenge since regenerated esophagus by bioprinting may fail to replicate its mapping accurately.14 In an attempt to overcome this, Takeoka et al. used four different cell types, namely—esophageal smooth muscle cells (ESMCs), normal human dermal fibroblasts (NHDFs), umbilical-derived stem cells, and mesenchymal stem cells (MSCs) in 3D bioprinted scaffold-free structure using a 3D-bioprinter (Table 1).15 This structure was transplanted in vivo in 10–12 weeks-old M-344 male rats for its assessment.

Mechanical and histopathological assessment was performed to analyze the efficacy and toxicity. Maximum a-smooth muscle strength was observed in MSCs with increased vascular endothelial growth factor (VEGF). Food was passed through the esophageal structure, and no toxicity was observed. The research was also performed in the application of 3D bioprinting ink to design a multilayered esophageal structure and provide realistic training in endoscopic biopsy to the residents at their institution. Another joint research is performed by companies Merck and Organovo using 3D bioprinting to make a muscle tissue-based SI epithelium flat model.22 The aim of this joint project was to establish a basis for the successful dissection of toxicity and accessibility during drug delivery. Crossing the pond from teaching platforms to application, a project was dedicated to creating a microchip-installed endoscope to unfold unreachable areas of the human body (Table 2).23

Using this method, the gelatin-alginic hydrogel was used to mimic the structure, and gastric smooth muscle cells, along with gastric epithelial cells, were used to mimic the function of the stomach. In order to elaborate on the functioning, immunological analysis of gastric cells is required. A study by Barker et al. sheds light on this concept by analyzing the impression of Lgr5 positive in the stomach using in vivo lineage tracing (Table 2).24 In vivo 3D bioprinting is the focus of current clinical research since the necessary equipment used to treat stomach diseases is usually too large and requires surgery to be placed in the digestive tract. An article from Scientific American by Lee et al. covers the potential of a 3D bioprinted stomach, elaborating on a study by Tao Zu from Tsinghua University, Beijing, China, who started making mechanical bees with potential medical applications.25

**Application of 3D Bioprinting in SI**

Another area that could highly benefit from 3D bioprinting is the SI. Injuries to the SI can occur due to many reasons, including ischemic, traumatic, and other GI diseases like inflammatory bowel disease (IBD). Small intestinal 3D bioprinting can aid the current requirement for treating SI diseases. SI is known as metabolite and contains microbiota.27 One of the major paradigms in 3D bioprinting is a durable scaffold injected with target cells to replenish itself into tissue.28 Research is performed to inject intestinal epithelial cells into a 3D-printed tissue scaffold to mimic the SI (Table 3).29

However, physical geometry was observed to be a limitation for testing 3D bioprinting on in vitro models. In order to address this, a multicellular 3D printed biomodel was developed using a proprietary bioprinting platform (Table 3).30 The laminar architecture of a full-cell derived tissue had an intestinal epithelium (polarized) supported by an interstitial tissue layer. This approach was a combination of biophysical cues, microengineered scaffolds, and varied chemical gradients created ex vivo. This is a complex structure mimicking the small intestinal epithelium of the human body. One of the major limitations while designing complex 3D structures is the physiological and geometrical strength of the structure. The design of a tube-like structure will require synthetic prosthesis or donor tissues if transplantation is proposed.31 Donor tissue transplantation remains an ideal solution for many diseases; however, the gap between donor tissues and medical requirements is still wide.32 This is a second limitation that is potentially overcome by 3D bioprinting.33 With respect to the crypt-villus surface topology, it is crucial to achieve threshold accuracy in mimicking the small intestinal scaffold. In an attempt to solve this limitation, a doctoral thesis by Taebina covers the application of the polyethylene glycol diacrylate platform was used to fabricate the human biointestine models.34 Advanced microscopes were used in combination with this method to establish and mark the intestinal barrier. Two main ideas were seen incorporated; microfluidic platforms act as a baseline to provide nutrients and oxygen to the intestinal cells with the support of a culture medium, and diffusion is limited to the hydrogel due to the solid counterparts, giving a strong corner to study the intestinal barrier strength. These models may also play a strong role in developing drugs for intestinal diseases.30 3D TE replicates a mirror of the future in improving the small intestinal design and functionality with higher efficacy and potentially reduced toxicity.
Three-dimensional Bioprinting in Gastroenterology: A Literature Review


Just in a shout with the SI, the large intestine is responsible for absorbing any remaining water materials and waste products left over after digestion. Diseases related to the large intestine, including IBD and colorectal cancer (CRC), have been on the rise in recent years. As the saying goes—“In order to solve a problem, first we need to realize there is a problem.” Establishing a baseline with immunological and anatomical similarity is crucial before working on a particular treatment. An attempt was made by Kuriyama et al. to design a 3D-printed rat model to mimic IBD (Table 4). One of the major hurdles in tracking IBD is the consistency of ulcers in testing animals in vivo. Inconsistency can lead to a lack of accuracy in detecting IBD and hence, in treating it. Kuriyama et al. attempted to develop a novel device with a 10 × 10 mm window that can be rectally fitted to mimic ulcerative colitis (UC) in interstitial cells. The degree of inflammation and ulcer size were histologically assessed after drug delivery of prednisolone and mesalazine; results were compared with the delivery of adipose-derived MSCs (AD-MSCs). AD-MSCs are hypothesized to be immunologically safe and anti-inflammatory in treating UC. Induction of UC with 2,4,6-trinitrobenzene sulfonic acid showed an accurate depiction of repetitive ulcers in rat models.

Three-dimensional (3D) bioprinting has taken entry into CRC treatment in recent years. CRC is considered to be the second leading cancer in GI and has led to > 9,00,000 deaths in 2020. Drug development shows an acceptance rate of 3.4% passing all the clinical trials with significant evidence. The superiority of 3D bioprinting has been proved by organoid cell cultures and spheroids. No evidence of 3D printing had been developed for CRC. Hence, Sbirko et al. developed a 3D-printed workflow platform for CRC with an aim to personalize medical treatment as per patients’ individual needs (Table 4). CaC2 cells were assessed, revealing granular-like structures resembling tumors, and upregulation of gene expression was marked by epidermal growth factor receptor/Kirsten rat sarcoma viral oncogene homolog signaling. These models were validated in CRC patient samples with three common chemo-therapeutics, namely 5-fluourouracil, irinotecan, and oxaliplatin. Increased resistance was observed in comparison to two-dimensional (2D) culture models, and the platform also showed potential to be applied in primary CRC models for clinical trials (Table 4).


Fabrication of 3D-printed liver constructs is successfully achieved by scientists working on TE projects, possessing essential abilities like self-renewing ability and restoration focus. Studies used 3D-bioprint prototype printing technology was used to laminate 30 layers of gelatin mixture with traces of hepatocytes in a high spatial structure.

Table 2: Description of articles using 3D bioprinting in the stomach

<table>
<thead>
<tr>
<th>Sr. no</th>
<th>Study</th>
<th>Sample type</th>
<th>GI organ</th>
<th>Description</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lee et al.</td>
<td>26 subjects (including 10 residents with no colonoscopy)</td>
<td>Stomach</td>
<td>Silicone-based 3D printed stomach using 3D slicer version 4.5.0; first step—design upper GI tract (UGIT); second step—silicone molding of core of UGIT; third step—design the shell of UGIT; fourth step—E and B stimulator; UGI structure transferred to 3D printing editing program Netfabb professional.</td>
<td>Average completion times: residents—244.8 seconds, first year—107.9, second year—106.8, faculty members—103.8; times reduced from first trial (347.0) to fifth trial (169.6); simulator reflected the endoscopies making it appropriate endoscopic training: difficulty levels of 10 biopsy sites were similar to that of the actual stomach.</td>
</tr>
<tr>
<td>2</td>
<td>Zhao et al.</td>
<td>Kinematic model to a test tissue scaffold.</td>
<td>Stomach</td>
<td>Delta robot—capable of folding while entering the body and unfolding before treatment action; printed circuit microelectromechanical systems; mathematical equation for feasibility of 3D bioprinting; kinematic models for the input of trajectory; algic acid sodium salt powder and gelatin for bioink preparation.</td>
<td>Steady proliferation and high viability were observed; normal structure and function of cells in the scaffolds; day 10 proliferation showed 2.1, indicating great proliferation over 10-day period.</td>
</tr>
<tr>
<td>3</td>
<td>Nick et al.</td>
<td>Two Lgr5 mouse models with either EGFP or lacZ reporter gene.</td>
<td>Stomach</td>
<td>Lgr5 mice were injected with BrdU to trace the active cycling cells; Lgr5 mice crossed with lacZ reporter gene to assess if Lgr5 at the base of pyloric glands; serial stains for common epithelial cells present on pyloric epithelium; in situ hybridization performed with SP6-RNA polymerase EcoRI sequence; Immunoelectron microscopy to trace the development.</td>
<td>Mucin 5AC +ve muscle cells and G +ve gastrin enteroendocrine cells were readily visible in lacZ zones; cell proliferation was predominant in the isthmus region above the neck region; Lgr5 stem cells contributed to a significant self-renewal of the distal stomach region; Lgr5 expression acts as a signaling stem cell in the distal stomach.</td>
</tr>
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</table>
Three-dimensional Bioprinting in Gastroenterology: A Literature Review

The first comparison plot was initiated in 2013, comparing native liver with actual synthetic human liver during surgery. In brief, hepatic liver tissues possessed crucial components like endothelial cells (ECs), hepatocytes, and liver-cell stellates. These tissue models can be implanted into human patients to mimicking the liver construct. Results showed acceptable viability of structure and biological functions, with consistency witnessed over a period of 2 months. 3D liver tissues possessed crucial components like endothelial cells (ECs), hepatocytes, and liver-cell stellates. These tissue models can be implanted into human patients to potentially replace liver transplantation. The first comparison plot was initiated in 2013, comparing native liver with actual synthetic human liver during surgery.

Table 3: Application of 3D bioprinting in SI

<table>
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<tr>
<th>Sr.no</th>
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<th>Sample type</th>
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<tr>
<td>1</td>
<td>Madden et al.</td>
<td>In vitro</td>
<td>SI</td>
<td>Organovo 3D Gen-Novo bioprinter used to create a SI model in vitro; bilayered architecture consisting of intestinal myofibroblast and human intestinal epithelial cells (hIECs); metabolic enzymes and tissue markers analyzed using gene expression analysis; functional assays for evaluation of CYP3A4 and CYP2C9, two P450 metabolic enzymes; transepithelial electrical resistance (TEER) used to analyze the absorption of xenobiotics and nutrients; efflux transporters P-glycoprotein (P-Gp) and breast cancer resistance protein (BRCP) analyzed to assess the capabilities of 3D printed intestinal tissue; nonsteroidal anti-inflammatory drugs and prostaglandin E2 used to evaluate the GI toxicity of the model.</td>
<td>Periodic acid-schiff (PAS) staining for the presence of mucus excretion and goblet cells; hIECs with Caco2 cells showed thickened epithelial layer and cyst formation; gene expressions in 3D printed tissues were similar to the native tissues; CYP3A4’s consistency was similar to that of the native tissue gene expressions; low, intermediate and high permeability compounds were successfully distinguished by 3D intestinal tissue; P-gp and BRCP expressed correctly by the 3D printed tissue; gene expressions of several tumor necrosis factor α targets upregulated, suggesting inflammatory cascade activation in response to tissue injury.</td>
</tr>
<tr>
<td>2</td>
<td>Wang et al.</td>
<td>In vitro</td>
<td>SI</td>
<td>Expansion medium containing stem/progenitor cells prepared from a mixture of L-WRN medium and Dulbecco’s modified eagle medium (DMEM) medium supplemented with GlutaMax; surgical resected specimen of jejunum (SI) obtained by gastric bypass surgery; villi and crypts detached before incubation; crypts encapsulated in matrigel for EM basis; EM suspended in neutralized collagen hydrogel prior to two-step dissociation method; gel fragmented into small pieces; collagen cross-linked with 1-ethyl-3-carbodiimide hydrochloride for collagen integrity; Nikon Eclipse TE300 inverted microscope used for image analysis</td>
<td>The presence of stem cells with normal cells was consistent within the monolayer; In response to biochemical cues, human intestinal cells (hICs) supported by the collagen hydrogel; cross-linked collagen scaffold embraced the shape of human intestinal tissue; hICs form the outer layer of collagen hydrogel scaffold; proliferative cells migrate into the villi showing normal functioning; porosity observed in the collagen scaffold showed gradient development showing polarization of stem cells.</td>
</tr>
<tr>
<td>3</td>
<td>Yu et al.</td>
<td>In vitro</td>
<td>SI</td>
<td>Polymethylmethacrylate (PMMA) sheet used as a template; CO2 laser system Versa-laser with Corel Draw X5 software used for the design; collagen villi hydrogel scaffold created with PMMA mold; sterile tweezers to inject hydrogel in a six-well plate; human carcinoma cell line (Caco) maintained; TEER measured using EVOM2 volt ohmmeter with STX3 electrode to ensure scaffolds with no disintegration of monolayers were used; drug permeability was measured using high-performance liquid chromatography; Image J software to analyze villous parameter measurement.</td>
<td>The permeability coefficient of the Caco2 monlayer in the 3D scaffold showed better efficiency than that of the 2D scaffold; cells were less differentiated in the villous phase and more polarized in the top phase; 3D synthetic TEER values of 3D printed villi scaffolds depicted better efficacy than that of 2D printed scaffolds.</td>
</tr>
</tbody>
</table>
Three-dimensional Bioprinting in Gastroenterology: A Literature Review

Table 4: 3D bioprinting in the large intestine

<table>
<thead>
<tr>
<th>Sr. no</th>
<th>Study</th>
<th>Sample type</th>
<th>GI organ</th>
<th>Description</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kuriyama et al.</td>
<td>Male Sprague Dawley rats</td>
<td>Large Intestine</td>
<td>Sprague Dawley rats used as a model for UC; ObJet Eden 350 3D printer used for ultraviolet curing resin; 2,4,6-trinitrobenzene sulfonic acid for injecting colitis in each rat; prednisolone sodium or mesalazine administered rectally; adipose stem cells (ASCs) obtained from adipose tissues of rats; ASCs differentiated by their adipogenic, osteogenic and colony forming abilities; 1 million cells suspended using flow-cytometry assay; ulcer injected with ASCs or saline; histological analysis using JMP pro 12.0.0.</td>
<td>ASCs successfully delivered to the ulcer site; no significant difference between the histological score of the control and testing group depicting similar efficacy; elliptical, localized, or circular ulcers were produced by this novel method; ulcer area was significantly reduced by prednisolone/mesalazine.</td>
</tr>
<tr>
<td>2</td>
<td>Sbirkov et al.</td>
<td>In vitro testing</td>
<td>Large intestine (colon)</td>
<td>Caco2 and CRC cells grown in DMEM/F12 medium; tumor specimens collected from CRC patients; Tinkercad used to make CAD and BioX extrusion based bioprinter used to slice the 3D designed model composed of nanofiber cellulose and RGD with algin; Cacein M used for viability testing of 3D bioprinter; accutase to split Caco2 cells and seeded in 96 well plates with 5,000 cells/well; chemotherapeutics treated for 3 days in nine concentrations for drug testing viability; microscope for histological analysis; HistoStat2 software, Edge2 and DESeq2 software for statistical analysis.</td>
<td>The H and E and histopathological stains showed a resemblance between 3D printed cells and small glandular-like CRC cells; transcriptional programs of hypoxia and cell-cell adhesion by 3D bioprinted cells; significant differences between Caco2 3D printed cells and 2D CRC cells; similar growth rates of tumors observed between 2D CRC cells and 3D bioprinted cells.</td>
</tr>
</tbody>
</table>

and biliary structures of livers from three living donors, three respective recipients, and six patients were analyzed, and synthetic livers were printed replicating them. The inkjet printing technique was used to analyze the liver before surgery based on each patient’s magnetic resonance imaging and CT scans.

Three-dimensional (3D) bioprinted liver based on these findings can help reduce intraoperative complications and improve the drug delivery system. However, the size of the complete printed liver can be an issue due to mismatching and structure complexity. As a result, research is also performed on liver tissue development. In that attempt, a study was performed designing a 3D-printed liver tissue consisting of HSCs (hepatic stellate cells), hepatocytes, and human umbilical vein ECs (HUVEC) using an inkjet bioprinter. There are three main limitations of 3D-printed liver tissue maintenance of hepatocyte functionality, long-term cell culture, and cell proliferation in the procedure. This was further enlightened when liver functions were further analyzed by printing a liver scaffold using the inkjet bioprinter. Hierarchal sandwich structures were observed when the native liver structure was compared with the 3D-printed liver scaffold of hepatoma G2/HUVEC cells. In another study, hepatocytes were obtained from eight weeks old mice and were injected into a tissue scaffold using an extrusion-based bioprinting platform. Research has also enlightened the application of stem cells in 3D bioprinting of the liver. Human embryonic stem cells and induced pluripotent stem cells were used in combination for liver tissue scaffolding using a valve-based bioprinting system. Drug toxicity and metabolism rates are studied using organoid-developed 3D bioprinting platforms. These platforms often override the limitations faced by 2D cultures, like prolonged cell functionality and viability. Several different methods like 96 and 384 well plate culturing, rotating cultures, and spinner cultures are introduced to develop organoids. In comparison to static cell cultures, the native cellular environment is better mimicked by the microfluidic cell culture. One of the main features of liver cell culture is the perfusion of fluid. Evidence has suggested that liver function is enhanced significantly by microfluidic chips. A study was performed on the application of microfluidic culture involving a combination of 3T3-J2 embryonic fibroblasts and pluripotent stem cells derived for drug screening of liver diseases. Results showed great promise in mimicking liver diseases and their treatment modalities on a prolonged scale.

Application of 3D Bioprinting in Pancreas

The pancreas is transversely located between the spleen on the left and the duodenum on the right. Pancreas is responsible for performing two essential functions in the body—endocrine (blood sugar levels and glandular secretion levels are maintained by endocrine hormones) and exocrine (digestive gland function is maintained by exocrine hormones). However, a recent rise is observed in pancreatic diseases like chronic pancreatitis, pancreatic adenocarcinoma, and hyperinsulinemic hypoglycemia, which require surgery to remove the prostate (known as the prostatectomy) depending on the criticality of the patient.
there are many complications reported in prostatectomy by multiple retrospective patients. Overall, a complication rate is reported to be in the range of 2.3–18% for robotic radical prostatectomy/laparoscopic radical prostatectomy.\textsuperscript{60,61} Diabetes mellitus (DM) is one of the most commonly researched areas when it comes to 3D bioprinting. Usually, an established treatment for type 1 and type 3c DM is the transplantation of Langheran islets.\textsuperscript{62} There are two main limitations in this procedure: lack of donor material and loss of islets post transplantation.\textsuperscript{63} As a result, 3D bioprinted tissue scaffolds show great potential as an alternative to transplantation.\textsuperscript{54}

A study by Gabriel et al. used 3D printing to develop a scaffold functionalized caprolactone and hydrogel with the potential to treat immune secretion deficiency.\textsuperscript{65} An upregulation of B-cell cascades was observed via transcriptomics. A natural cellular niche was created with cocultured EC, increasing insulin production and glucose stimulation. Another study by Jaewook et al. focuses on the application of a 3D-printed TE ECM scaffold as an alternative for transplantation in type-1 DM patients.\textsuperscript{66} Several studies seeded pancreatic islets in degradable 3D-printed scaffolds, which has proven to provide a higher surface to volume ratio than the alternative hydrogel models.\textsuperscript{67} Animal studies were performed to report the efficacy of this procedure.\textsuperscript{68,69} The radar of 3D bioprinting was also focused on other diseases like pancreatic ductal adenocarcinoma (PDAC).\textsuperscript{70} Laser-assisted bioprinting was used to design 3D-pancreatic spheroid arrays to replicate the pancreatic tissue for PDAC. Made of both acinar and ductal cells, bioprinted spheroid arrays can mimic the early development stages of PDAC, allowing the treatment to be predetermined. However, there are certain limitations that still need to be addressed. Chief among these is the vascularization in a 3D bioprinted tissue scaffold.\textsuperscript{71} Mimicking blood vessels in a tissue scaffold can be challenging due to its complexity. Another limitation of 3D bioprinting, based on which method of printing is used for each application, is the low resolution.\textsuperscript{72} This is mainly for the extrusion-based bioprinting technique. This can also lead to another limitation of tissue cell accuracy; some tissue cells need small pores to function properly, and poor resolution (meaning bigger size) pores can lead to the proliferation of injected cells in the tissue scaffold.\textsuperscript{73} However, 3D bioprinting still shares its advantages with other 3D printing applications in gastroenterology, and hence, more focus needs to be given to emphasis and critical dissection of tissue/organ engineering approaches in pancreatic diseases.

**APPLICATION OF 3D BIOPRINTING IN GALLBLADDER**

Gallbladder is a pear-shaped small hollow organ and is a part of the biliary system.\textsuperscript{74} The biliary system or the biliary tree is a series of ducts in the gallbladder, pancreas, and liver which empty into the SI. The need for 3D bioprinting has been on the rise due to more than 5,000,000 gallbladder surgeries performed each year in the United States of America alone.\textsuperscript{75} Less attention is given to the gallbladder diseases like gallstones in Indonesia due to their asymptomatic nature, often leading to misdiagnosis.\textsuperscript{76} Many studies applied 3D bioprinting in combination with PLA for improvement in surgical procedures. One of these studies used 3D bioprinting with PLA in designing gallbladder for virtual surgical planning.\textsuperscript{77} Data were obtained from a radiologist who performed image processing of gallbladder in previous patients. This data was used to design a 3D-printed gallbladder using a U-Print Plus 3D printer (BioMed Tech Lab, University of Indonesia, Depak, Jakarta, Indonesia). The validation of the final model was highly efficient for surgeons to preplan gallbladder surgeries. However, that being said, there are several limitations that need to be addressed, including a selection of compatible materials and avoiding transmission of diseases postinsertion.\textsuperscript{78} 3D bioprinting heading in the right direction can only be acclaimed after covering the major pitfalls accustomed to current 3D bioprinting procedures.

**CONCLUSION**

Three-dimensional (3D) bioprinting is an upcoming horizon in the world of gastroenterology. The holistic approach would be to target current limitations of GI treatments like inadequacy in results, high cost with long waiting times for transplant, etc., and attempt to apply 3D bioprinting in anatomically acceptable areas of GI. The key word in this aspect is “mimicking.” If a 3D bioprinted scaffold/organ can mimic the affected site of any GI ailment on a cellular, tissue, and nontoxic cluster level, further complex functionality has the potential to reemerge with minimal side effects, helping patients live a normal life. 3D-printing technology, like inkjet bioprinting, laser bioprinting, and computer aided design (CAD) design, is coming with excellent efficacy and application accessibility at national and international levels of research. However, limitations like GI toxicity, lack of accuracy in structural integrity, and cost still remain on the surface. 3D bioprinting shows great potential in GI if further research efforts are dedicated to fulfilling its limitations and increasing its overall accessibility.

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Three-dimensional Bioprinting in Gastroenterology: A Literature Review


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Angiotensin Receptor-Nephrilsyn Inhibitor Therapy and Cardiac Remodeling in Heart Failure: Consensus Statement from India


Received: 26 November 2022; Revised: 08 February 2023; Accepted: 09 February 2023

Abstract

Adverse cardiac remodeling refers to progressive structural and functional modifications in the heart because of increased wall stress in the myocardium, loss of viable myocardium, and neurohormonal stimulation. The guideline-directed medical therapy for Heart failure (HF) includes Angiotensin receptor-neprilsyn inhibitor (ARNI) (sacubitril/valsartan), β-blockers, sodium-glucose co-transporter 2 (SGLT2) inhibitors, and mineralocorticoid receptor antagonists (MRA). ARNI is under-prescribed in India despite its attractive safety and efficacy profile. Therefore, the consensus discusses objectives and topics related to ARNI in the management of cardiac remodeling, and experts shared their views on the early timely intervention of effective dosage of ARNI to improve the diagnosis and enhance mortality and morbidity benefits in cardiac reverse remodeling (CRR).

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**Introduction**

Heart failure (HF) is a significant health concern that impacts 23 million patients globally. The yearly incidence of HF for patients with congestive heart disease (CHD) is about 0.4–2.3%, indicating that 1,20,000–6,90,000 Indians could develop HF due to CHD, presuming none has HF at baseline, and the at risk population does not lessen.

Considerable progress in chronic HF management has been observed with the accessibility of medicines such as angiotensin-converting-enzyme inhibitors (ACEIs), MRA, β-blocker, and Angiotensin II receptor blockers (ARBs). Due to the high rate of morbidity and mortality, there is a great need for newer treatments that are safe to manage HF.

**Remodeling**

The definition of the term “remodeling” has been changing since 1982. A universal consensus forum on cardiac remodeling defined cardiac remodeling as a group of molecular, cellular, and interstitial changes manifest as changes in size, shape, and function of the heart due to cardiac injury. Figure 1 represents the sequence of events that leads to cardiac dysfunction.

**Pathophysiology of Cardiac Remodeling**

Two primary systems in cardiac remodeling—the sympathetic system and renin-angiotensin–aldosterone system (RAAS). Activation of both initiates intracellular signaling pathways, which promote protein synthesis in fibroblasts and myocytes, affecting fibrosis and cellular hypertrophy. Figure 2 represents levels involved in cardiac remodeling. Levels at which remodeling occurs as shown in Figure 2.

**Adverse Remodeling**

Adverse cardiac remodeling refers to progressive structural and functional variations in the heart because of loss of viable myocardium, neurohormonal activation, and increased wall stress in the myocardium.

Characteristically, HF with reduced ejection fraction (HFrEF) shows eccentric remodeling, whereas HF with preserved EF shows concentric remodeling, and both forms may be present irrespective of EF (Fig. 3).

**How Remodeling Affects Prognosis**

Cardiac remodeling, regardless of the conditions used to evaluate it, is believed to be harmful and is related to a poor prognosis. Knowing the magnitude of left ventricular (LV) remodeling can easily assess the prognosis; more the remodeling, the weaker the prognosis. A comparatively modest rise in ventricular volume is related to a significant mortality risk in coronary artery disease/myocardial infarction (MI)/HF patients. In the post-MI population, LV volumes are the most robust prognostic indicators, particularly LV end-systolic volumes. Post-MI patients undergoing consequent morbid conditions had a more significant rise in LV diastolic and LV systolic volumes compared to patients without such events (Fig. 4).

**Reverse Remodeling**

Reverse remodeling indicates the restoration of standard cell size and geometry, resulting in a leftward change of the end diastolic pressure volume relationship (EDPVR) to normal values, with favorable changes in molecular, extracellular matrix (ECM) and metabolic properties of the myocardium.

Properties with distinct reverse remodeling on both sides of ventricles are possible to be controlled by reductions in mechanical stress.
Angiotensin Receptor-Neprilysin Inhibitor Therapy

Journal of the Association of Physicians of India, Volume 71 Issue 4 (April 2023)

Available therapeutic strategies

Renin Angiotensin Aldosterone System Blockade

Angiotensin-converting-enzyme inhibitors (ACEIs) were broadly assessed by the Studies of the Left Ventricular Dysfunction cohort. Patients with LV dysfunction received ACEIs constantly showed a reduced LV volume irrespective of symptomatic condition. Additionally, changes in LVEF, LV end-systolic volume (LVESV), and LV end-diastolic volume (LVEDV) indicated a slender reduction in LV mass (265 ± 82–255 ± 82 gm, \( p < 0.001 \)) and E/A ratio mitral annular (1.3 ± 0.8–1.0 ± 0.7, \( p < 0.001 \)) after administration of enalapril for 1 year.

\( \beta \)-Blockade

\( \beta \)-blockers have the most robust evidence for reverse remodeling in HF. Consistently, as demonstrated in Cardiac Insufficiency Bisoprolol Study, Australia/New Zealand Collaborative Group, and Metoprolol Randomized Intervention Trial in HF when added \( \beta \)-blockers to standard therapy to reduce mortality and improve LV function and volumes.10,11

Mineralocorticoid Receptor Antagonist (MRA)

The MRA action on CRR may be to a lesser extent than ACEI, ARB, and \( \beta \)-blocker counterparts; still, MRA has a crucial part in enhancing morbidity and mortality benefits in HF patients.12 Several postulates, such as Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), states that spironolactone + eplerenone utilize the comparative anti-fibrotic impact in myocardial ECM to further CRR and inhibit adverse-remodeling.13

Predictors of Reverse and Adverse Remodeling in HF

Patients with HFrEF usually undergo serial imaging to monitor LV remodeling, usually through repeated echocardiograms. Identifying dependable predictors for both remodeling allows cardiologists to tailor the approach, which allows for frequent follow-up (F/U) and speedy improvement of treatment in patients with a high possibility for left ventricular EF (LVEF) decline, LV dilation, and vice versa for those with smaller risks.8 For patients having relentlessly modest levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) (BNP \( p < 100 \) ng/L and NT-proBNP <1,000 ng/L), the possibility of forward remodeling is less, the prognosis is favorable, and repeated imaging may be delayed. The risk for LV dilation/LVEF decline is more in those with persistently elevated or rising biomarkers. Regular F/U and treatment could deliver a better yield. On the contrary, stable/dipping levels of the biomarkers indicate reverse remodeling, specifically after initiation of therapy or cardiac resynchronization therapy (CRT) (Fig. 5).8

On the other hand, the same blood perfuses LV and right ventricular myocardium, properties with a related reverse remodeling in both left and right chambers are mostly to be intervened by circulating factors.7

Biomarkers:
- B-type natriuretic peptide (BNP)
- N-terminal pro B-type natriuretic peptide (NT-proBNP)
- Atrial natriuretic peptide (ANP)

HFrEF:
- LV global longitudinal function: M-mode, tissue Doppler-derived mitral annulus systolic velocity,
- LV global longitudinal strain (GLS) and reduced S0 velocity-speckle-tracking
- Echocardiograph
- Magnetic resonance imaging
- Computed tomography

HFrEF:
- Imaging modalities:
  - Echocardiography
  - Magnetic resonance imaging
  - Computed tomography
  - Nuclear cardiology
  - Transthoracic echocardiography (TTE)
  - Left ventricular ejection fraction (LVEF)
  - Left ventricular end-systolic volume index (LVESVI)
  - Left ventricular end-diastolic volume index (LVEDVI)
  - LV mass index (LVMI)

Fig. 3: Adverse cardiac remodeling in HFrEF and HFpEF. ECM, extracellular matrix; MAPK, mitogen-activated protein kinase; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction

Fig. 4: Quantifying remodeling in HFrEF and HFpEF

Fig. 5: Adverse remodeling
Angiotensin Receptor-Neprilysin Inhibitor Therapy

**Sodium-Glucose Transport Protein 2 Inhibitor**

Sodium-glucose transport protein 2 (SGLT2) inhibitors such as dapagliflozin, empagliflozin, and canagliflozin reduce cardiovascular (CV) events and HF hospitalizations among type 2 diabetes mellitus patients.\(^{14-16}\) In dapagliflozin and prevention of adverse outcomes in HF, a mortality benefit was found among patients with HFrEF; nevertheless, questions stayed regarding the mechanism by which the class of drug showed its benefit.\(^{17}\) Both SUGAR-DM-HF and EMPATROPISM suggest that by CRR, drug showed its benefit.\(^{17}\) Both SUGAR-DM-HF regarding the mechanism by which the class of mortality benefit was found among patients prevention of adverse outcomes in HF, a

**Mechanism of Action**

Angiotensin receptor-neprilysin inhibitor (ARNI) improves the physiological effects of natriuretic peptides (NPs) by preventing neprilysin-dependent degradation, which results in raised levels of NPs. As neprilysin degrade BNP even though having no effect on the breakdown of NT-proBNP, patients treated with ARNI have higher plasma BNP levels due to the inhibition of neprilysin activity (Fig. 6).\(^5\)

Ideal patient profile for ARNI:

- Patients with acute HFrEF on RAAS inhibitors.
- Patients with chronic HF on RAAS inhibitors.
- De novo HFrEF (acute or chronic).
- Postacute MI patients with reduced EF.
- Patients with mildly reduced or preserved EF.

The initiation of ARNI, guideline recommendation, and treatment algorithm in the management of HF are discussed below (Figs 7 to 9).

**Frequency of F/U**

Discharged patients following hospitalization for worsening HF, F/U of <7 days is acceptable to lessen rehospitalization. F/U at 12 weeks from discharge is recommended to monitor signs of congestion, tolerability, and initiation/titrate evidence-based therapy.\(^{22}\)

**Reverse Remodeling with ARNI Therapy**

Guideline-directed Medical Therapy (GDMT) for Remodeling and Position of ARNI

Pharmacological therapies have brought advances in CRR in HFrEF, especially in reducing hospitalization and mortality. ACEIs, ARBs, beta blockers (BBs), MRAs, and a new-agent ARNI are extensively accepted and included in guideline-recommended therapeutic approaches in lessening morbidity and mortality in patients with HFrEF. In patients tolerating ACEI/ARB, shift to ARNI before discharge is recommended (Fig. 10).\(^{22,31}\)

- Angiotensin-converting-enzyme inhibitor (ACEI) should be stopped 36 hours before initiating ARNI and should be contraindicated in patients with a history of angioedema/hypersensitivity due to ACEI/ARB.
- Considering the clinical stability, a dose of prior ACEI/ARB, and systemic blood pressure, ARNI can be started at 24/26 mg bid or 49/51 mg bid.
- Double the dose of ARNI every 2–4 weeks, dependent on clinical tolerance and gradually increase the dose before discharge.

Managing Adverse Events Caused due to ARNI

Symptomatic hypotension:

- Reconsider the need for any vasodilator and decrease the dose or stop.
- If there are no signs/symptoms of congestion, lower the diuretic dose.

Symptom-cough:

- When a troublesome cough develops due to ARNI, ACEI addition of ARB is considered.

Worsening renal function and hyperkalemia:

- An increase in urea, creatinine (Cr), and potassium (K) are to be expected after an ARNI; if the rise is small and asymptomatic, no action is needed.
- If urea, Cr, or K increase excessively, stop concomitant nephrotoxic drugs (e.g., nonsteroidal anti-inflammatory drugs) and other retaining agents such as triamterene or amiloride.
- If there is a large increase in Cr or K despite adjustment of concomitant medications, the ARNI dose should be halved, and blood chemistry should be monitored within 1–2 weeks.
- If K rises to >5.5 mmol/L or eGFR lowers to <30 mL/minute/1.73 m², the ARNI should be stopped.

Need for Consensus

Adverse cardiac remodeling refers to progressive structural and functional modification in the heart because of loss of viable myocardium, neurohormonal activation, and increased wall stress in the myocardium. The GDMT for HF includes ARNI, MRAs, β-blockers, and SGLT2 inhibitors. The medication classes were discussed in previous sections with respect to their effect on cardiac remodeling and their clinical evidence.

In India, ARNI is under-prescribed regardless of its appealing safety and

![Fig. 5: Key predictor for reverse and adverse remodeling in heart failure. HF, heart failure; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction](image-url)
Angiotensin Receptor-Neprilysin Inhibitor Therapy

There is a need for a national consensus on the use of ARNI in patients with HF, especially its effect on CRR. The present expert consensus delivers pragmatic insights on ARNI implementation for the management of HF. Recommendations and criteria for ARNI initiation, up-titration process, monitoring, and identification of side effects, are thoroughly discussed.

**Materials and Methods**

The Indian consensus group included 51 experts, mainly comprising cardiologists, nephrologists, and endocrinologists from...
India participated in the national consensus meeting on 18th September 2022 to discuss the use of ARNI in the current management of HF. Objectives and topics related to ARNI in the management of cardiac remodeling were discussed, and experts shared their views which led to group discussion. The national advisory board meeting was moderated by leading cardiologists of the country, who discussed recommendations with panel members across the country. The final consensus statement was framed after >85% of the experts agreed on the statement.

Panel Discussion

ARNI in HF

The panel of experts agreed with the statement that ARNI is the choice of RAAS inhibitor for treating HFrEF. Due to limited data on HF with preserved EF (HFpEF), experts are ambiguous regarding the benefits of ARNI in HFpEF. According to the experts, CRR remains an important primary therapeutic target in patients with HF, and ARNI can be a game changer for reverse remodeling. ARNI can also benefit CRR if treated for at least 3 months. However, the therapy must be tailored as per individuals’ requirements.

WHEN:

• Patients with HFrEF as a replacement for ACE-I/ARB.
• Patients with HFrEF in those who are ACE-I/ARB naive (de novo use).

HOW:

• Start with a low dose - In some patients, one may consider a reduced starting dose (24/26 mg b.i.d.), namely in those with SBP 100-110 mmHg, ACE-I/ARB naive patients, eGFR 30-60 mL/min/1.73 m².
• Double the dose at not less than 2-week intervals in the community, monitoring tolerability.
• Aim for the target dose or, failing that, the highest tolerated dose.
• Re-check blood chemistry (urea/BUN, creatinine, K) 1-2 weeks after initiation and 1-2 weeks after final dose titration.
• Consider reducing diuretic where appropriate.
• Monitor blood chemistry 4-monthly thereafter.
• Stop uptitration, reduce dose, stop treatment.
• It is very rarely necessary to stop an ARNI, and clinical deterioration is likely if treatment is withdrawn.

Fig. 6: Mechanism of action of ARNI. AT₁, angiotensin II type 1; BNP, B-type natriuretic peptide; RAAS, renin-angiotensin-aldosterone system

Fig. 7: When and how to initiate ARNI
Dosing
Expert panel experienced poor results in HF patients when a suboptimal dose of 25 mg BD of ARNI was recommended. Most patients showed promising results with a 50–100 mg BD dose, and about 40% of patients needed a maximum dose of ARNI (200 mg BD).

Monitoring
During the treatment with ARNI, it is essential to monitor global longitudinal strain (GLS) because it is the hallmark biomarker for structure remodeling LV. After 5–7 days of administration of ARNI, renal function (urea, Cr, sodium, and K) must be monitored. If the parameters are normal, monitoring should be done again after 1 month. Factors deciding up-titration are RFT parameters and availability of patient for F/U.

Future Direction
Experts believe that the higher cost of ARNI is a drawback for the usage of the drug; launching cost-effective ARNI in India could be a game-changer for the management of HF patients. They also believe that ARNI can potentially lower the mortality rate, as in the last 5 years, the mortality rate has increased to 60%.
**Fig. 9:** Treatment algorithm in HF management. ACEI, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; CRT, cardiac resynchronization; GDMT, guideline-directed medical therapy; HF, heart failure; HR, heart rate; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoids receptor antagonist; NYHA, New York Heart Association; therapy; SGLT2, sodium-glucose cotransporter-2 inhibitors

**Final Consensus Statements**

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Statement</th>
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<tbody>
<tr>
<td>1</td>
<td>Reversal of cardiovascular remodeling by therapeutic intervention enhances morbidity and mortality benefits in HF</td>
</tr>
<tr>
<td>2</td>
<td>Cardiac remodeling may be morphological (structural), functional, hemodynamic, biochemical and neurohormonal etc.</td>
</tr>
<tr>
<td>3</td>
<td>There is enormous data to support ARNI-imposed cardiac remodeling reversal leading to mortality and morbidity benefits in HF</td>
</tr>
<tr>
<td>4</td>
<td>HF therapies, including ARNI, SGLT2 inhibitors, β-blockers, MRA, diuretics, ferric carboxymaltose, CRT, and device therapy, all reverse cardiac remodeling</td>
</tr>
<tr>
<td>5</td>
<td>Reversal of cardiac remodeling fosters significant improvement in prognosis</td>
</tr>
<tr>
<td>6</td>
<td>Absence of LBBB, GLS of &gt;10 and early GDMT &lt;3 months are predictors of reverse remodeling</td>
</tr>
<tr>
<td>7</td>
<td>Biomarkers that predict the reversal of remodeling are BNP, NT-pro-BNP, soluble ST2 (biomarkers of myocardial fibrosis and remodeling), high-sensitivity cardiac troponin I, collagen markers, mimcan, etc.</td>
</tr>
<tr>
<td>8</td>
<td>Reversal of remodeling may also postpone the need for CRT and device therapy etc.</td>
</tr>
<tr>
<td>9</td>
<td>Concomitant LV and Left atrium reversal of remodeling with ARNI enhance better prognosis than CRT</td>
</tr>
<tr>
<td>10</td>
<td>ARNI can replace ACEI and ARBs in a reversal of cardiac remodeling</td>
</tr>
<tr>
<td>11</td>
<td>We must shift all patients of HFrEF on ACEI/ARBs to ARNI for better reversal of cardiac remodeling</td>
</tr>
<tr>
<td>12</td>
<td>ARNI helps all components of reversal remodeling by decreasing fibrosis, neurohormonal activation, myocardial injury, inflammation, and myocardial stretch</td>
</tr>
<tr>
<td>13</td>
<td>Hinduja Hospital HF study revealed 6-month F/U data of 152 patients after ARNI. It revealed that ARNI increased LVEF by 5%, decreased LVESV by 15%, LVEDV by 18%, E/e' by 9%, GLS improved by 3%, and NT-proBNP reduced by 20%</td>
</tr>
<tr>
<td>14</td>
<td>ARNIs sustained effect on CRR is ARNI-dependent However, in certain situations, CRR is radically reversed in covid inflicted cardiomyopathy, takotsubo cardiomyopathy, septic cardiomyopathy, and peripartum cardiomyopathy</td>
</tr>
<tr>
<td>15</td>
<td>The magnitude of CRR is proportional to structural and functional improvement and NT-proBNP reduction, which has morbidity and mortality benefits in HF</td>
</tr>
</tbody>
</table>

**Abbreviations:** HF, heart failure; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BNP, B-type natriuretic peptide; CRR, cardiac reverse remodeling; CRT, cardiac resynchronization therapy; E/e', ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity; GDMT, guideline-directed medical therapy; GLS, global longitudinal strain; LA, Left atrium; LBBB, Left bundle branch block; LV, Left ventricle; LVESV, left ventricular end-systolic volume; LVEF, Left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal pro B-type natriuretic peptide; SGLT2, sodium-glucose cotransporter-2 inhibitors
Fig. 10: Treatment algorithm for ARNI in HF. ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure.

CONCLUSION

It is therefore concluded that early timely intervention of effective dosage of ARNI in protocolized manner improves the prognosis and enhances mortality and morbidity benefits in HF with reversal of cardiac remodeling.

AUTHORS’ CONTRIBUTION

All the authors contributed to the concept and design of this consensus document. The manuscript draft was developed and critically reviewed by all the authors. All authors have approved the final draft of the manuscript.

ACKNOWLEDGMENT

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Angiotensin Receptor–Neprilysin Inhibitor Therapy


The human gut is home to a variety of microbes, including bacteria, viruses, fungi, eukaryotes, and archaea, which together form a complex structure. In general, the microbiota that colonizes the gastrointestinal (GI) tract plays a significant role in maintaining human health and has been implicated in the pathogenesis of a number of GI illnesses. The structural integrity and metabolic processes of the alimentary canal are physiologically influenced by the dynamic interactions between the gut and bacteria. GI dysbiosis is a result of an imbalance brought on by a decline in microbial diversity, the loss of helpful bacteria, and an increase in pathobionts. It is crucial to restoring the gut microbiota.

In order to regain the eubiotic state of the microbial flora, varied methods are being researched and implemented. The use of probiotics is one strategy for re-establishing healthy gut flora. Probiotics are "living microorganisms" that improve the health of the host when provided in adequate quantities. There are two types of probiotics—bacteria and yeast-based. The review will look at and summarize the information for yeast-based Saccharomyces probiotics regarding their effectiveness and safety in treating a variety of patient diseases, particularly irritable bowel syndrome (IBS), antibiotic-associated diarrhea, and Helicobacter pylori (HpSA) infection.

The only commercially accessible yeast probiotic, the Saccharomyces strain, which consists of Saccharomyces cerevisiae (S. cerevisiae) and Saccharomyces boulardii (Sb), provides a number of benefits over bacterial probiotics. The significance of Sb as a potent biotherapeutic medication that may be utilized to prevent or treat a variety of GI disorders has been substantiated by several experimental studies and clinical trials.

Introduction

Many microbes, such as bacteria, fungi, viruses, archaea, and eukaryotes, contribute to the complicated structure of the human gut. The microbiota not only plays a major factor in the pathophysiology of various GI complications but also plays a critical role in healthy living. The internal structure and biochemical activities of the alimentary canal are physiologically influenced by the dynamic interplay between the microbial flora and gut. The gut microbiota is a dynamic ecological system shaped temporarily by physiological life events, namely the mode of delivery, dietary patterns, aging, and interactions with the surrounding environment. The balance could be shifted by exposure to various environmental factors, including dietary changes, toxins, drugs, antibiotics, stress, and pathogens. The imbalance caused by a reduction in microbial diversity and loss of beneficial bacteria with an increase in pathobionts leads to GI dysbiosis. Dysbiosis can be both an effect or a contributor to the pathogenesis of several GI and extra-GI diseases. As a result, it is crucial to try to restore the gut microflora with therapeutic potential in conditions where intestinal microflora dysbiosis appears to be a cause.

Many planned remedies are being researched and put out with the aim of regaining and/or maintaining the eubiotic condition of the microflora gut ecosystem. Probiotic usage is one method for re-establishing healthy gut flora. Live microorganisms that, when given in sufficient quantities, benefit the host’s health are referred to as probiotics. Several probiotics are available for clinical use, out of which yeast-based probiotics appear to confer a specific additional advantage over bacteria-based probiotics. The review will examine and outline the available evidence for Saccharomyces probiotics concerning their efficacy and safety in treating different conditions in patients, specifically irritable bowel syndrome, antibiotic-associated diarrhea, and in HpSA infection. Mechanism of Action of Yeast Probiotics

Competition with gut pathogens is a mechanism by which probiotics limit their growth. Probiotics consume the nutrients which limit their availability to the pathogens as it grows in the gut, producing metabolites that reduce the pH creating a stressful environment for pathogens. Furthermore, probiotics adhere to the intestinal cell wall reducing bacterial pathogenic adherence
and thereby reducing the ability of the bacteria to translocate. Homeostasis is maintained by the gut microbiome, but the exact method by which it does so is not properly known. However, a number of effective mechanisms have been uncovered which directly influence both the host and the response of pathogenic microorganisms by modulating the local and systemic immune responses, regulating intestinal microbial homeostasis, interfering with pathogen colonization, inducing the enzymatic activity that favors absorption and nutrition and stabilizes the GI barrier. The following are the key mechanisms by which yeast probiotics (Sb) function:

- **Competitive exclusion:** Gut microbiota binds to the yeast surface irreversibly, preventing their adhesion to the mucous membranes. Proteolytic and steric hindrance activity of yeast can inhibit adherence of bacteria to mucous. Yeast cell size is 10 times bigger than bacteria, so one yeast can displace 10 bacteria using stearic hindrance.

- **Anti-toxin effect:** Yeast probiotic inhibits the toxin receptor binding site, thereby preventing the toxins from binding to the mucosa. It either stimulates the production of antibodies against the toxins or releases enzymes and proteins, which lead to the proteolysis of toxins.

- **Immune modulation:** Yeast probiotics stimulate the secretion of secretory immunoglobulin (Ig) A levels in the intestine, which thereby reduces the quantum of the pathogen. It interrupts the NF-kB-mediated signal transduction pathway, which then prevents the synthesis of proinflammatory cytokines. Furthermore, the interaction with epithelial cells, monocytes, dendritic cells, lymphocytes, and/or macrophages produces metabolites that stimulate the immune cell via its anti-inflammatory and immunomodulatory response. For instance, in the case of *Clostridium difficile* (C. difficile) infection, Sb inhibits MAP kinase and IL-8 levels and modulates the inflammatory process. Additionally, Sb elevated serum IgA and IgG levels in the presence of *C. difficile* toxins A and B. Restoration of metabolic activities: Yeast probiotics increase the normal short-chain fatty acids (SCFA) production, which exhibits its antimicrobial activity and re-establishes the normal colonic function. It also reduces the intracolic gas produced by the bacteria and metabolizes the nutrient substrate by gas formation as well as improves the colonic propulsion by increasing the intracolic SCFAs production.

### Benefits of Yeast Probiotics over Bacterial Probiotics

Of the several probiotics available, yeast probiotics account for a smaller proportion but are better tolerated when compared with bacterial probiotics. The only yeast probiotic that is commercially available is the *Saccharomyces* strain, that is, *S. cerevisiae* and Sb, which have shown varied benefits over bacterial probiotics. The benefits of yeast probiotics over bacterial probiotics are mentioned in Table 2; they are explained as follows:

- **They are a suitable option for the treatment of antibiotic-associated diarrhea due to their innate resistance to antibacterial antibiotics.** They also reduce the side effects associated with standard triple therapy due to antibiotic use in HpSA infections.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Yeast probiotics</th>
<th>Bacterial probiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival at gastric pH (acidic)</td>
<td>✓</td>
<td>Limited</td>
</tr>
<tr>
<td>Promote IgA production</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Because of greater coverage, the larger cell size makes it appropriate for intestinal protection.</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Barrier effect against pathogen colonization</td>
<td>✓</td>
<td>x</td>
</tr>
<tr>
<td>Natural resistance to antibacterial antibiotics</td>
<td>✓</td>
<td>Very limited</td>
</tr>
<tr>
<td>Use in pediatrics aged ≥ 2 years</td>
<td>✓</td>
<td>Limited</td>
</tr>
<tr>
<td>Anti-toxin effects</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Restores the enzymatic activity of epithelial cells</td>
<td>✓</td>
<td>Limited</td>
</tr>
</tbody>
</table>

### Table 1: PH and temperature stability for Sb

<table>
<thead>
<tr>
<th>Features</th>
<th>Sb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal growth temperature</td>
<td>37°C</td>
</tr>
<tr>
<td>High-temperature resistance (52°C)</td>
<td>Feasibility of 65%</td>
</tr>
<tr>
<td>Resistance to acidic pH (pH = 2 for 1 hour)</td>
<td>Yes, 75% of the time.</td>
</tr>
<tr>
<td>Bile acid tolerance (&gt;0.3%(w/v)) (&lt;0.3%(w/v))</td>
<td>No, survival 0.10% (w/v) or less</td>
</tr>
<tr>
<td>Basic pH resistance (pH = 8)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

### Role of Yeast Probiotics in the Following Conditions

**Irritable Bowel Syndrome (IBS)—IBS** is a common functional GI illness that is characterized by persistent and recurring...
abdominal pain or discomfort as well as changed bowel patterns. An estimated 7–22% of the world’s population suffers from this prevalent, chronic, recurring, and remitting GI condition, with a prevalence of 14% in women and 9% in males. There are a number of qualitative and quantitative alterations in the fecal microbiota in IBS patients, and there is more evidence that substantiates gut dysbiosis as a trigger for IBS. In spite of the range of therapeutic modalities (antidiarrheal, antispasmodics, chloride channel opener, guanylyl cyclase C agonist, and newer gut serotonin modulators), patients continue to suffer from recurrence of symptoms, high relapse rate, and low tolerance threshold to side effects. In view of the association of IBS with dysbiosis, the use of probiotics has also been incorporated into the therapeutic armamentarium for IBS. A major accomplishment is the development of a therapeutic option that, albeit slightly, relieves the disease’s symptoms. The intestinal barrier function, gut-brain axis, immunological activation, and GI motility and sensation are only a few of the pathways that the gut microbiota influences the pathophysiological mechanisms. IBS symptoms, including bloating and abdominal pain, can be alleviated through yeast probiotics like Sb. Additionally, as shown in Table 3, Sb causes a variety of distinct effects, both in a dysbiotic condition and in the avoidance of dysbiosis.

**Efficacy of Yeast Probiotics in IBS**

The effectiveness of yeast probiotics in reducing IBS symptoms is summarized in Table 4. The pooled relative risk for improvement in overall IBS symptoms in 14 probiotic treatment arms was 0.77 (95% confidence interval (CI)—0.62–0.94), according to data from a meta-analysis of 20 randomized clinical trials with 1,404 participants and 23 probiotic treatment arms. Moreover, probiotics were linked to decreased abdominal discomfort when compared to a placebo (Relative Risk (RR) = 0.78; 95% CI—0.69–0.88). The average pain grade and stomach discomfort were observed to be reduced by 38% with the use of *S. cerevisiae* CNCM I-3856. In order to treat IBS, yeast probiotics can alter the intraluminal milieu and reduce inflammation. The effectiveness of the probiotic *S. cerevisiae* in the treatment of IBS was examined in a study by Helo et al. In this trial, *S. cerevisiae* was administered to 177 individuals in doses of 1000 mg each after meals. After 4 weeks of therapy, it was noted that IBS symptoms such as bloating, discomfort, and irregular stools had improved. According to research by Mearin et al., about 15% of people who fulfill the Rome I criteria for IBS have the diarrhea-predominant variant (IBS-D). Sb affects the way microorganisms migrate through the digestive tract. Sb was utilized to treat IBS-D patients in a different double-blind trial by Mupas et al., and the quantity of stools produced decreased (*p < 0.05*), while the consistency of the stools enhanced (*p < 0.05*). In a related trial, mesalazine alone, Sb alone, and mesalazine plus Sb together were used to treat patients. According to reports, adding Sb to mesalazine can improve therapeutic outcomes for IBS, and the probiotic agent has positive benefits on both IBS-related intestinal symptoms and overall quality of life (QoL). Sb has systemic benefits on IBS-D patients that improve their overall health by the suppression of proinflammatory cytokines, which in turn alters the nervous system activity or enhances tryptophan levels.

**Table 3: Mechanism of action of Sb in IBS**

<table>
<thead>
<tr>
<th>Probiotics — creating a beneficial microbiome</th>
<th>Infection and immune activation in IBS</th>
<th>Antimicrobial activity</th>
<th>Trophic action on the intestinal mucosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the case of IBS</td>
<td>In IBS patients, exposure to intestinal infection results in long-lasting, low-grade systemic and mucosal inflammation, which is defined by altered circulating cell populations, immune cell infiltration of the mucosa, and increased cytokine secretion.</td>
<td>Immune activation, gut-brain axis, GI motility and sensation, and intestinal barrier function are pathophysiological processes underlying IBS that are modulated by gut microbiota.</td>
<td>Harms digestive epithelial cells, which are involved in the anti-inflammatory, immune-modulating, and barrier functions of the gut</td>
</tr>
<tr>
<td>Preventive action</td>
<td>Probiotics’ interactions with epithelial cells, monocytes, dendritic cells, lymphocytes, and/ or macrophages result in the production of metabolites that activate the immune cell’s reaction, which is anti-inflammatory and immunomodulatory.</td>
<td>Reduction of bacterial and parasitic development. Reduced pathogen translocation in the intestines. The bacterium virulence factors are neutralized. The suppression of host cell adhesion prevents microbes from colonizing the host.</td>
<td>Decreases the number of infected cells while promoting intestinal cell growth and differentiation in reaction to trophic factors.</td>
</tr>
</tbody>
</table>

*Antibiotic-associated Diarrhea (AAD)*

Antibiotic-associated diarrhea (AAD) is associated with the widespread use of antibiotics; hence, its incidence has increased over the years and is reported to be 21.5%. Prevalence of AAD is reported to be in the range of 3.2 to 29% as underlying illness, drugs, surgery, and age alters bowel motility and increase the risk of AAD. Incidence of AAD is more common with clindamycin, cephalosporin, and amoxicillin-clavulanate. Few studies around the world but none from India reported the prevalence of AAD. The most frequent comorbidities of colitis and antibiotic-associated diarrheal (AAD) are colitis and *C. difficile* infection (CDI). From moderate diarrhea to colitis or fulminant pseudomembranous colitis, AAD symptoms might differ. It has been observed that those with other concomitant infections are more susceptible to *C. difficile* antibiotic-associated diarrhea. In a study, it was found that patients with diabetes and hypertension had an estimated 2- and 5-fold higher chance of developing AAD than did people without chronic conditions. For repeated recurrences, fecal replacement therapy and adjunctive treatment with probiotics are recommended. In both a community environment and an institutional environment, Sb, a nonpathogenic yeast, typically grows at body temperature and has been evaluated for its effectiveness in preventing antimicrobial-associated diarrhea. According to reports, Sb can reduce the duration of diarrhea without causing a recurrence through its mechanism of action mentioned in Table 5. Critically ill tube-fed patients can get Sb as a prophylactic therapy, especially those at risk of AAD.
Table 4: Effectiveness of yeast probiotics in treating IBS* 24, 29, 32, 65, 66

<table>
<thead>
<tr>
<th>Reference/author-name</th>
<th>Study type</th>
<th>Treatment group</th>
<th>Study population</th>
<th>Dose</th>
<th>Duration</th>
<th>Outcome</th>
<th>Evidence level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mupas et al., McFarland and Dublin 28</td>
<td>Meta-analysis (double-blind)</td>
<td>two groups: probiotic S. cerevisiae + boulardii and placebo</td>
<td>Patients suffering from IBS-D</td>
<td>9 × 10^9 cfu/day</td>
<td>4 weeks</td>
<td>Improved symptoms were seen</td>
<td>1</td>
</tr>
<tr>
<td>Abbas et al. 65</td>
<td>Randomized, double-blind, placebo-controlled trial</td>
<td>35 patients got the placebo, while 37 patients received Sb.</td>
<td>Patients with IBS-D</td>
<td>Sb 750 mg/day</td>
<td>6 weeks</td>
<td>Interleukin-8 (IL-8) and tumour necrosis factor levels in blood and tissues were significantly reduced in the Sb group (p = 0.001), while anti-inflammatory IL-10 levels increased along with the tissue IL-10/IL-12 ratio.</td>
<td>2</td>
</tr>
<tr>
<td>Choi et al. 29</td>
<td>Randomized, double-blind, placebo-controlled multicenter trial</td>
<td>Patients treated with either Sb (n = 34), or placebo (n = 33)</td>
<td>Patients with IBS-D and IBS-M</td>
<td>Sb at 2 × 10^9 live cells as a daily dose</td>
<td>4 weeks</td>
<td>IBS-related symptoms like bowel movement frequency and stool consistency also improved. Overall IBS-QOL improvement was greater in the Sb group than in the placebo group (15.4 vs 7.0%; p = 0.05).</td>
<td>2</td>
</tr>
</tbody>
</table>

IBS, irritable bowel syndrome; IBS-D, irritable bowel syndrome with diarrhea; IBS-M, mixed irritable bowel syndrome; QOL, quality of life; tid, thrice daily; bid, twice daily; qd, once daily; cfu, colony-forming unit; MG, mesalazine group; MSbG, mesalazine and Saccharomyces boulardii group; SbG, Saccharomyces boulardii group

Table 5: Mechanism of action of Sb in AAD 70, 71

<table>
<thead>
<tr>
<th>Probiotic—creation of a favorable microbiotic environment</th>
<th>Modulation of gut microbiota composition</th>
<th>Increase modulation of bile acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAD mechanism</td>
<td>Antibiotic use alters the composition, function, and biodiversity of the gut’s normal microbiota, which makes it easier for pathogens like C. difficile to colonize.</td>
<td>The main form of bile acid, which is crucial for fat metabolism, is produced by the liver, and the intestinal microbiota converts it into the secondary active form. Antibiotics alter the microbiota, which results in incorrect secondary bile acid conversion.</td>
</tr>
<tr>
<td>Preventive action using probiotics</td>
<td>Combining antibiotics and probiotics (Sb) lessened the change in the composition of the bacteria.</td>
<td>Because Sb alters the gut microbiota, its effects are reversed, allowing the gut bacteria to return to normal and produce secondary bile acid.</td>
</tr>
</tbody>
</table>

Efficacy of Yeast Probiotics in AAD  
Saccharomyces boulardii (Sb) can be prescribed to patients receiving antibiotics as it is naturally resistant to antibiotics. 8 There is a positive trend in the treatment of AAD using Sb for children as well as adults, as results from trials have reported it to be effective in preventing diarrhea caused by various antibiotics such as amoxicillin/clavulanate and by cephalosporins. Surawicz et al. conducted a study to gauge Sb’s efficacy in 180 hospitalized patients consuming different classes of antibiotics. The probiotic was given both during and for two weeks after the antibiotic course. Those receiving Sb experienced significantly fewer episodes of diarrhea (10% compared to 22% in the placebo group; p = 0.038). 8 Adding Sb to β-lactam medicines had a significant preventative effect on diarrhea in hospitalized patients taking antibiotics, according to an additional study by the same author (7% of Sb vs 15% of placebo, p = 0.02). Very few patients on treatment with Sb developed AAD. 44 151 adult patients were enrolled by Can et al. who were taking various antibiotics, and they were randomly assigned to either the Sb or placebo group for the length of the antibiotic treatment. When compared to the control group, it was found that significantly fewer patients receiving Sb had AAD (9 vs 1.4%, respectively; p < 0.05). 45 Decrease in the episodes of diarrhea was one of the most common symptom improvements observed across the studies. Furthermore, Kotowska et al. demonstrated the effect of Sb in children with respiratory tract infection and/or otitis media. It was reported that patients consuming Sb had a decreased prevalence of diarrhea compared to placebo [nine of 119 (8%) vs 29 of 127 (23%)]. 45 The therapeutic probiotic Sb utilized in the treatment and prevention of AAD when given adjuvant to antibiotics has been proven to be beneficial. The efficacy of yeast probiotics in improving AAD symptoms is summarized in Table 6.

Helicobacter pylori (HpSA) Infection  
Almost 4.4 billion people are infected with HpSA worldwide. This microaerophilic gram-negative bacterium colonizes the GI mucosa, 47 and its presence influences the strength of gastric microbial interactions. HpSA is known to cause inflammation and change the microflora, which can lead to a variety of gastric illnesses. In developing nations, HpSA infections are frequently acquired by children and last a lifetime without antibiotic therapy. It is commonly seen that in developing countries, the...
prevalence is high compared to developed nations. HpSA infection leads to gastric inflammation and is associated with disorders like a mucosa-associated lymphoid tumor (maltoma), peptic ulcer, gastric cancer, idiopathic thrombocytopenia, and iron deficiency. HpSA infection by itself and its antimicrobial therapy alters the gut microbial ecological balance. Therefore, gut microbial manipulation to restore a eubiotic state becomes imperative. This is where the role of probiotics comes into play. In individuals with HpSA infection, probiotic supplementation has been seen to increase eradication rates, decrease treatment-related side effects, and alleviate specific symptoms. Though Sb–mediated effects in HpSA infection are not completely understood, it has been speculated that it might work by limiting HpSA adherence to epithelial cells and modulating the gastric immune response, summarized in Table 7.

### Efficacy of Yeast Probiotics in HpSA Infection

According to research by Dinleyici et al., Sb boosts the HpSA eradication rate, minimizes adverse effects, and improves compliance. However, Hurduc et al., employing the Sb strain, reported no effect on the rate of HpSA eradication but positive health effects in the cases of infection. Sb enhanced anti-HpSA antibiotherapy-associated diarrhoea (p < 0.05), epigastric discomfort (p < 0.01), and treatment acceptability, according to Cindoruk et al. Also, the Sb supplement reduced posttreatment dyspepsia symptoms regardless of the presence or absence of HpSA, but it had no discernible impact on the rate of HpSA eradication (p > 0.05). According to Cardenas et al., patients treated with Sb, in addition to triple therapy for HpSA infection, experienced considerably less abdominal discomfort and other GI side effects (p = 0.028). At the termination of antibiotic treatment and one month later, there was a larger abundance of Enterobacteria and a lower abundance of Bacteroides and Clostridia, as well as a greater diversity of bacteria observed (p = 0.0156). Lastly, a study by Duman et al. evaluated the efficacy of Sb vs triple therapy for the elimination of HpSA. According to the study, considerably fewer patients who received Sb (6.9%) than the control group (15.6%, p = 0.007) developed AAD. Sb is generally effective at eliminating HpSA from the human GI tract and minimizing

### Table 6: Efficacy of yeast probiotics for the treatment of AAD

<table>
<thead>
<tr>
<th>Reference/author-name</th>
<th>Study type</th>
<th>Treatment group</th>
<th>Study population</th>
<th>Dose</th>
<th>Duration</th>
<th>Outcome</th>
<th>Evidence level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surawicz et al.</td>
<td>A prospective, double-blind controlled study</td>
<td>Sb and placebo with antibiotics</td>
<td>Hospitalized patients on antibiotics</td>
<td>250 mg capsule bid</td>
<td>Till 2 weeks after the last antibiotic dose</td>
<td>Of the 180 patients, diarrhoea occurred in 14 (21.8%) of 64 (placebo) patients vs 11 (9.5%) of 116 (Sb) patients (p = 0.038). Sb had a 56.7% success rate at avoiding AAD.</td>
<td>3</td>
</tr>
<tr>
<td>Adam et al.</td>
<td>Meta-analysis</td>
<td>Sb vs placebo</td>
<td>388 hospitalized adults</td>
<td>4 x 10^9 (200 mg)</td>
<td>7 days</td>
<td>Compared to 9/199 (4.5) of the patients who received Sb, 33/189 (17.5) of the patients getting a placebo experienced AAD (p = 0.05).</td>
<td>1</td>
</tr>
<tr>
<td>Can et al.</td>
<td>Prospective study</td>
<td>Sb vs placebo</td>
<td>151 hospitalized adult patients</td>
<td>1 x 10^10 (500 mg)</td>
<td>Till 48 hours after the last antibiotic dose</td>
<td>In the study group, the rate of onset of antibiotic-associated diarrhoea was 1.4% (1/73) compared to 9% (7/78) in the placebo group (p = 0.05).</td>
<td>3</td>
</tr>
<tr>
<td>Cremonini et al.</td>
<td>A parallel, triple-blind, placebo-controlled study</td>
<td>Sb vs placebo</td>
<td>43 HpSA + adults on triple therapy</td>
<td>5 x 10^9 (nr)</td>
<td>14 days</td>
<td>In the Sb group, antibiotic-associated diarrhoea occurred in 21% (7/33) and 13.9% (5/36) of cases, respectively (p = 0.05).</td>
<td>2</td>
</tr>
<tr>
<td>Duman et al.</td>
<td>Multicenter, prospective clinical trial</td>
<td>Sb vs placebo</td>
<td>389 adults in Turkey with HpSA + peptic ulcers all received triple therapy</td>
<td>2 x 10^10 (1000 mg)</td>
<td>14 days</td>
<td>Throughout the entire study time, overall diarrhoea rates were 6.9% in the treatment group and 15.6% in the control group (p = 0.007).</td>
<td>3</td>
</tr>
<tr>
<td>Bravo et al.</td>
<td>A prospective, randomized, double-controlled, blinded study</td>
<td>Sb vs placebo</td>
<td>89 adult outpatients on amoxicillin</td>
<td>1 x 10^10 (500 mg)</td>
<td>12 days</td>
<td>Antibiotic-associated diarrhoea in the Sb group was in 3/41 (7.3) patients and 5/45 (11.1) patients in the control group</td>
<td>2</td>
</tr>
</tbody>
</table>

Contd…
The Role of Yeast Probiotics in Gastrointestinal Conditions: An Overview

The mortality rate of up to 20%, is a highly common and dangerous acquired disease of the GIT in very low-birth-weight (VLBW) infants.\(^5\) NEC may result from intestinal ischemia, protein substrate overgrowth in the intestinal lumen, or pathogenic bacterial colonization of the intestine.\(^5\) Probiotics may prevent NEC by ensuring colonization of the gut with essential microorganisms while preventing an excess of pathogens, improving the function of the gut mucosal barrier, and regulating the immune system.\(^6\) Feeding difficulties generally lead to prolonged scarcity of enteral feeds and dependence on total parenteral nutrition which are a severe concern in a preterm infant.\(^5,\)\(^6\)

Necrotizing enterocolitis (NEC), which is characterized by gut wall necrosis and has a mortality rate of up to 20%, is a highly common and dangerous acquired disease of the GIT in very low-birth-weight (VLBW) infants.\(^5,\)\(^6\) NEC may result from intestinal ischemia, protein substrate overgrowth in the intestinal lumen, or pathogenic bacterial colonization of the intestine.\(^5\) Probiotics may prevent NEC by ensuring colonization of the gut with essential microorganisms while preventing an excess of pathogens, improving the function of the gut mucosal barrier, and regulating the immune system.\(^6\) Feeding difficulties generally lead to prolonged scarcity of enteral feeds and dependence on total parenteral nutrition which are a severe concern in a preterm infant.\(^5,\)\(^6\)

### The Role of Sb in Other Disorders

**Acute gastroenteritis**—also known as “acute infectious diarrhea,” this condition is marked by repeated watery stools as a consequence of compromised electrolyte and fluid absorption in the GI tract, which is typically brought on by pathogenic microorganisms, GI tract infections, nutritional deficiencies, allergies, intoxications, or impaired absorption.\(^1,2\) The inclusion of *S. boulardii* to standard rehydration therapy in contrast with a placebo was linked with a decrease in the frequency of diarrhea by almost 24 hours. There was a significant decline in the duration of hospitalization, no. of days with vomiting, frequency of stools, and risk of diarrhea which was evident from the second day onwards. The frequently used dose of *S. boulardii* was at least 500 mg given daily which provided additional benefit than <300 mg dose.\(^1\) According to recent studies, the increase in the immune response of *S. boulardii* may be attributed to changes in the serum levels of IgA, cluster of differentiation 8, and C-reactive protein.\(^5,\)\(^2\)\(^,\)\(^8\)

### Reference/author-name Study type Treatment group Study population Dose Duration Outcome Evidence level

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<tr>
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<th>Outcome</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Cindoruk et al.(^5)</td>
<td>A prospective randomized placebo-controlled double-blind study</td>
<td>Sb vs placebo</td>
<td>124 adults with HpSA + dyspepsia</td>
<td>(2 \times 10^{10}) (1000 mg)</td>
<td>14 days</td>
<td>In the Sb group, antibiotic-associated diarrhoea affected 9.5% of patients, compared to 19.6% of patients in the control group ((p = 0.05)). There were [nine (14.5%) vs 27 (43.5%)] epigastric discomfort cases in the control group ((p = 0.01)). After treatment, the treatment group's GDQ scores were markedly higher (mean ± SD, range—1.38 ± 1.25 (0–5) vs 2.22 ± 1.44 (0–6); (p = 0.01)).</td>
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### Pediatrics

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<th>Reference/author-name</th>
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<tr>
<td>Kotowska et al.(^6)</td>
<td>A randomized, double-blind, placebo-controlled trial</td>
<td>Sb in addition to standard antimicrobial therapy (experimental group; (n = 132)) or a placebo (control group; (n = 137))</td>
<td>269 children (aged 6 months to 14 years) with otitis media and/or respiratory tract infections</td>
<td>Standard antibiotic treatment plus 250 mg of Sb or a placebo</td>
<td>Twice daily for the duration of antibiotic treatment</td>
<td>Additionally, Sb decreased the risk of antibiotic-associated diarrhea when compared to placebo (4 of 119 (3.4%) vs 22 of 127 (17.3%), RR: 0.2; 95% CI: 0.07–0.5). No adverse events were observed</td>
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<td>Riaz et al.(^5)</td>
<td>Double-blind, randomized placebo-controlled clinical trial</td>
<td>For 5 days, Sb 250 mg twice daily was compared to a placebo.</td>
<td>108 children 3–59 months</td>
<td>250 mg bid</td>
<td>5 days or till recovery</td>
<td>When compared to the placebo group, the mean postintervention duration of diarrhoea was considerably (95% CI = 28.13–5.43) shorter in the SB group (52.08±24.57 h) compared to placebo (4 of 119 (3.4%) vs 22 of 127 (17.3%), RR: 0.2; 95% CI: 0.07–0.5). The SB group's first semi-formed feces appeared after less time (39.48±23.09 h; 95% CI: 25.4–3.87) than did for the control group (54.13±28.21 h; p = 0.009).</td>
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**bid, twice daily; Sb, Saccharomyces boulardii; AAD, antibiotic associated diarrhea; SD, standard deviation**

The efficacy of yeast probiotics in treating HpSA infection is summarized in Table 8.

**Role of Sb in Other Disorders**

Acute gastroenteritis—also known as “acute infectious diarrhea,” this condition is marked by repeated watery stools as a consequence of compromised electrolyte and fluid absorption in the GI tract, which is typically brought on by pathogenic microorganisms, GI tract infections, nutritional deficiencies, allergies, intoxications, or impaired absorption.\(^1,2\) The inclusion of *S. boulardii* to standard rehydration therapy in contrast with a placebo was linked with a decrease in the frequency of diarrhea by almost 24 hours. There was a significant decline in the duration of hospitalization, no. of days with vomiting, frequency of stools, and risk of diarrhea which was evident from the second day onwards. The frequently used dose of *S. boulardii* was at least 500 mg given daily which provided additional benefit than <300 mg dose.\(^1\) According to recent studies, the increase in the immune response of *S. boulardii* may be attributed to changes in the serum levels of IgA, cluster of differentiation 8, and C-reactive protein.\(^5,\)\(^2\)\(^,\)\(^8\) Necrotizing enterocolitis (NEC), which is characterized by gut wall necrosis and has a mortality rate of up to 20%, is a highly common and dangerous acquired disease of the GIT in very low-birth-weight (VLBW) infants.\(^5,\)\(^6\) NEC may result from intestinal ischemia, protein substrate overgrowth in the intestinal lumen, or pathogenic bacterial colonization of the intestine.\(^5\) Probiotics may prevent NEC by ensuring colonization of the gut with essential microorganisms while preventing an excess of pathogens, improving the function of the gut mucosal barrier, and regulating the immune system.\(^6\) Feeding difficulties generally lead to prolonged scarcity of enteral feeds and dependence on total parenteral nutrition which are a severe concern in a preterm infant.\(^5,\)\(^6\) The inclusion of *S. boulardii* to standard rehydration therapy in contrast with a placebo was linked with a decrease in the frequency of diarrhea by almost 24 hours. There was a significant decline in the duration of hospitalization, no. of days with vomiting, frequency of stools, and risk of diarrhea which was evident from the second day onwards. The frequently used dose of *S. boulardii* was at least 500 mg given daily which provided additional benefit than <300 mg dose.\(^1\) According to recent studies, the increase in the immune response of *S. boulardii* may be attributed to changes in the serum levels of IgA, cluster of differentiation 8, and C-reactive protein.\(^5,\)\(^2\)\(^,\)\(^8\)
The Role of Yeast Probiotics in Gastrointestinal Conditions: An Overview

**Table 7:** Mechanism of action of Sb in HpSA infection\(^{77,78}\)

<table>
<thead>
<tr>
<th>Probiotic—creation of a favorable microbiotic environment</th>
<th>Adhesion inhibition</th>
</tr>
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<tbody>
<tr>
<td>H. pylori infection mechanism</td>
<td>Due to the fact that HpSA encode the outer membrane proteins sialic acid-binding adherence and blood group antigen-binding adhesion, which can effectively bind to the recognition site and result in long-term colonization, HpSA has the ability to adhere to the epithelial cell. As a result, they can readily invade immune and epithelial cells in unfavorable circumstances.</td>
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<tr>
<td>Prevention action using probiotics</td>
<td>By displaying neuraminidase activity that is specific for sialic acid, Sb eliminates the HpSA binding site and reduces the bacteria’s adhesion to the host cell.</td>
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**Table 8:** Efficacy of yeast probiotics for the treatment of HpSA infection\(^{53–55,67,79}\)

<table>
<thead>
<tr>
<th>Reference/author-name</th>
<th>Study type</th>
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<td><strong>Adult</strong></td>
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<tr>
<td>Cindoruk et al.(^{54})</td>
<td>A prospective, randomized, placebo-controlled study</td>
<td>Clarithromycin, amoxicillin, and lansoprazole triple treatment with Sb or placebo</td>
<td>124 patients with HpSA infection</td>
<td>1 gm qd (250 mg sachets, 500 mg bid)</td>
<td>2 weeks</td>
<td>The therapy group’s rate of HpSA eradication was higher (71%; 44/62) than the control group’s (59.7%; 37/62) ((p &gt; 0.05)).</td>
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<tr>
<td>Cardenas et al.(^{55})</td>
<td>Single-blind randomized trial</td>
<td>Treatment as usual (amoxicillin, tinidazole, and omeprazole) or treatment as usual + Sb CNCM I-745</td>
<td>18–55 years of patients with typical dyspepsia symptoms</td>
<td>Approximately 22.5 x 10^9 cfu; (n = 2)</td>
<td>2 weeks</td>
<td>When used in addition to the standard triple therapy for Helicobacter pylori infection, Sb CNCM I-745 reduced the incidence of GI side effects that might be caused by alterations in gut microbiota. There were also lower rates of associated GI symptoms ((p = 0.028)) and increased numbers of bacteria with even bacterial diversity ((p = 0.0156)). Eliminated in 16/20 (80%) in the placebo group and in 17/21 (81%) for LGG and blend. For Sb, signs appeared in 4/21 (19%) while they did not in the control group (12/20, 60%). ((p &lt; 0.05)).</td>
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<td>Cremonini F et al.(^{67})</td>
<td>A parallel, triple-blind, placebo-controlled study</td>
<td>Sb (Codex, Smith-Kine Beecham, Italy) in comparison to a placebo, LGG, and a combination (L acid and Bifid lactis)</td>
<td>43 HpSA + adults on triple therapy</td>
<td>5 x 10^9 (nr)</td>
<td>14 days</td>
<td>In the Ab, Sbl, and LB groups, HpSA were eliminated in 66, 12, and 6.5% of the children, respectively. In contrast, no spontaneous clearing was seen in the untreated children. A slight but noticeable change in the? Children who received living Sbl had DOB (−6.31; 95% CI: −11.84—−0.79), but those who received LB (0.70; 95% CI: −5.84–7.24) did not.</td>
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<td>Gotteland et al.(^{79})</td>
<td>Randomized open study</td>
<td>Three groups were randomly assigned to receive either Sbl or LB or antimicrobial therapy (lansoprazole, clarithromycin, and amoxicillin).</td>
<td>182 children (71.7%) who were colonized by Hp, and 141 of them completed their treatment (22.5% dropout)</td>
<td>Children from group LB received a capsule containing 10^9 heat-killed andyophibilized L. For SB: 250 mg of lyophilized Sb</td>
<td>Antibiotics for 8 days or Sbl or LB daily for 8 weeks</td>
<td>In the Ab, Sbl, and LB groups, HpSA were eliminated in 66, 12, and 6.5% of the children, respectively. In contrast, no spontaneous clearing was seen in the untreated children. A slight but noticeable change in the? Children who received living Sbl had DOB (−6.31; 95% CI: −11.84—−0.79), but those who received LB (0.70; 95% CI: −5.84–7.24) did not.</td>
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</tr>
<tr>
<td>Hurduc et al.(^{53})</td>
<td>Prospective, open-label clinical study</td>
<td>Omeprazole/esomeprazole, amoxicillin, and clarithromycin—the standard triple eradication treatment, with or without Sb</td>
<td>90 symptomatic children (range 3–18 years) with HpSA infection</td>
<td>250 mg bid</td>
<td>Triple eradication therapy for 7–10 days; Sb for 4 weeks</td>
<td>Of the 145 children studied, 90 (62%) had HpSA infection; age and socioeconomic position had positive and negative correlations, respectively ((p = 0.002), (p = 0.005)). The overall incidence of HpSA eradication was 87.7% (control group—80.9%; Sb group: 93.3%; (p = 0.750)). In the Sb group, the frequency of side effects was lower—8.3% in the probiotic group compared to 30.9% in the control group ((p = 0.047)).</td>
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bid, twice daily; qd, once daily; cfu, colony-forming unit; DOB, delta (13) CO (2) over baseline value before and after treatment, HpSA: H. pylori stool antigen, LB, Lactobacillus acidophilus, Sbl, Saccharomyces boulardii plus inulin.
neonate. It was observed that Sb reduced the feeding intolerance in VLBW infants, which may be due to the modulation of intestinal motility. It also decreased the incidence of clinical sepsis in VLBW infants but did not affect culture-proven sepsis.59,60

Nonalcoholic fatty liver disease (NAFLD)—the prevalence of NAFLD varies from 6.3% to 37.3% globally and is linked to arterial hypertension, cardiovascular disease, dyslipidemia, peripheral insulin resistance, and abdominal-visceral obesity. It has been observed that disturbance in the balance of the GI microbiota, including SIBO and colon dysbiosis, is linked with the pathogenesis of NAFLD. A possible connection between Bacteroides and NAFLD has been suggested by several clinical trials. It was observed that lyophilized Sb significantly decreased the level of the Bacteroides fragilis in patients with NAFLD, thereby reducing the risk of endotoxemia and averting the progression of steatosis. Consumption of Sb for 90 days also decreased the level of Escherichia coli, which was usually found to be higher in NAFLD patients, thus reducing the possibility of any additional damage to the liver by endogenous alcohol.61

**Discussion**

Dysbiosis can occur when the natural bacteria of the gut are out of balance, as can happen with certain treatments. These treatments generally include triple therapy of antimicrobials such as bismuth, metronidazole, and tetracycline; and pH-sensitive antibiotics like amoxicillin, clarithromycin, and proton pump inhibitors. Other therapies used are bismuth quadruple therapies, four drug regimens, and probiotics which can increase the efficacy when used as a supplement with triple-drug therapy.62 Furthermore, treatments such as fecal microbial transplantation, probiotics, prebiotics, and symbiotics have also proven effective against dysbiosis.

**Probiotics (good bacteria) treat a variety of GI illnesses, including dysbiosis, as demonstrated by recent advancements in medical science.63 When taken orally or intramuscularly, S. cerevisiae and Sb can significantly induce health-promoting benefits in the host body due to their antibacterial, antiviral, anticarcinogenic, antioxidant, antiinflammatory, and immune-modulating characteristics.64 These benefits include natural immunity to antibiotic bacteria, the capability of growth temperature, the ability to sustain, sensitivity to acid and bile salts, cellular hydrophobicity as well as the capacity for auto-aggregation, the capacity for assimilation of cholesterol, and greater cell size in comparison to bacterial probiotics.3,8,17-19,21**

The role of yeast probiotics in GI diseases, primarily IBS, AAD, and HpSA infection, is addressed in the current review. IBS is characterized by frequent, chronic stomach aches or uneasiness and irregular bowel movements. Sb also improves the general health of individuals with IBS by having systemic effects, such as the modulation of proinflammatory cytokines (which in turn modulates nervous system activity) or a rise in tryptophan concentration. It can shorten the duration of diarrhea without recurrence.33 It can be prescribed to severely ill tube-fed patients having risk factors for AAD as a prophylactic.43 Also, it has been noted that Sb supplementation increased eradication rates and decreased side effects from treatment and specific symptoms in individuals with HpSA infection. In adults and children receiving antibiotic treatment, the American Gastroenterological Association supports Sb with a conditional recommendation and low-quality data for preventing CDI.65 According to the World Gastroenterology Organization’s (WGO) Global Guidelines for Probiotics and Prebiotics, the S. cerevisiae strain Sb CNCM I-745 can be used in adults to treat acute and antibiotics-associated diarrhea as well as to prevent diarrhea caused by C. difficile. The WGO also advises Sb CNCM I-745 to be used as coadjuvant therapy for HpSA eradication and for the treatment of IBS. Additionally, it recommends its use in pediatrics to treat acute gastroenteritis, HpSA infection, NEC and to prevent antibiotic-associated diarrhea.66

**Conclusion**

This review emphasizes how numerous clinical trials and experimental investigations have backed the use of Sb as a potent biotherapeutic agent capable of preventing and/or treating a number of GI illnesses. Current research suggests that Sb’s advantages are temporary and independent of host gut colonization, setting it apart from other popular bacterial probiotics in terms of its mode of action. It supports the natural microbiome’s equilibrium and is important for controlling the secretory activities of intestinal epithelial cells, which aids the patient’s nutritional needs. Despite the possibility of fungemia following Sb therapy, none of the clinical trials has revealed any negative outcomes. Patients with immunodeficiency disorders and those at risk for adverse effects, however, should be handled carefully. Several of the unanswered problems regarding the fundamentals of probiotics, the makeup of the human gut flora, survivability and fecal recovery rates, physiological and immunomodulatory impacts, and more must be addressed in future research. Additionally, the most effective dosages, treatment durations, comparisons of various probiotic strains and types, single vs combined probiotics, probiotics combined with prebiotics, the effectiveness of various probiotics in various disease states, and safety of probiotics in patients with compromised gut epithelial integrity need to be assessed.

**References**

The Role of Yeast Probiotics in Gastrointestinal Conditions: An Overview


CASE REPORT

Cardiotoxicity with Yellow Cow Dung Poisoning

Binu MG1*, Anju Paul2

Received: 26 September 2022; Accepted: 11 November 2022

ABSTRACT
Cow dung powder coloring agent poisoning is common in Southern Tamil Nadu. Both yellow and green varieties are common. Yellow cow dung poisoning usually produces central nervous system (CNS) and hepatic involvement as well as gastrointestinal problems. Though cardiac issues like arrhythmias are seen, toxic myocarditis and cardiac failure are not common. We present a case of a 42-year-old lady with yellow cow dung poisoning who developed toxic myocarditis and cardiac failure with complete recovery over a period of time.

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INTRODUCTION
Cow dung has widely been used in Southern India since ancient times due to its germicidal properties. Nowadays it has widely been replaced by synthetic compounds popularly known as saani powder. It is available in two colors—yellow and green. Yellow powder primarily contains auramine O—diarylmethane dye and green powder malachite green—triphenylmethane dye. Cow dung poisoning has commonly been reported in Coimbatore, Erode, and Tirupur districts of Tamil Nadu.1

CASE DESCRIPTION
This 42-year-old lady, with no known comorbidities, hailing from Coimbatore, presented with an alleged history of consumption of yellow cow dung (one teaspoon mixed with banana) poisoning around 3:00 pm at her residence. She had three episodes of vomiting on the way to the hospital. On arrival in the emergency room, she was conscious, oriented, and hemodynamically stable. Systemic examination was unremarkable. Blood investigations revealed normal counts, sugars, renal, thyroid, and liver parameters. Electrocardiogram (ECG) was normal. She was treated with intravenous fluids and other supports.

The following day she developed asymptomatic bradycardia and hypotension. ECG showed sinus bradycardia. A cardiologist’s opinion was obtained, and a bedside echocardiogram (ECHO) (on 2nd day) revealed adequate left ventricle (LV) function with no regional wall motion abnormalities. Since hypotension and bradycardia persisted despite the fluid challenge, dopamine infusion was initiated. Serum electrolytes were normal. As she continued to remain bradycardic and hypotensive, after ruling out dyselectrolytemia, ECG and ECHO were repeated (on 3rd day) which showed new onset ST segment (ECG term) depression in anterolateral leads and global hypokinesia of LV with moderate LV dysfunction and elevated high-sensitive troponin I (1650) and N-terminal pro-brain natriuretic peptide (8670) levels. Toxic myocarditis secondary to yellow cow dung poisoning was suspected. Serial liver and renal parameters were normal. Her cardiac status gradually improved, bradycardia and hypotension improved, and was weaned off inotropes. Repeat ECHO (done on the 10th day) showed adequate LV function and no regional wall motion abnormalities. The patient remained clinically stable and was discharged home.

DISCUSSION
Auramine O is a diarylmethane dye used as a fluorescent stain which is known to induce in vivo deoxyribonucleic acid damage to liver, kidney, and bone marrow cells.2 Easy availability of this product locally, makes it a common household poison in regions in and around Coimbatore. There are very few articles in the literature regarding this common household poisoning, hence, the mechanism of action, clinical presentation, and cause of death are not clearly documented in many textbooks of medicine.

There is no specific antidote for these dyes. Deaths can occur within hours of ingestion due to cerebral edema, resulting in convulsions, coma respiratory, cardiac arrest, and death, or after 2–3 days due to the direct action of dye on the liver causing centrilobular necrosis, resulting in hepatitis and fulminant hepatic failure.3

The common clinical symptoms following auramine poisoning are staining all over the body, especially hands, face, and tongue; nausea, vomiting, abdominal pain, cramps; diarrhea, confusion, and irritability. It is a gastrointestinal tract irritant causing mucosal damage, epigastric pain, and discomfort. It is a neurotoxic poison causing CNS depression leading to altered mentation, coma, seizures, and a low Glasgow Coma Scale.4 Tachypnoea and respiratory distress needing mechanical ventilation have been recorded earlier. Tachycardia, metabolic acidosis, and hyperglycemia were also observed with auramine poisoning.5 Ventricular dysrhythmias, such as monomorphic ventricular tachycardia, were noticed, particularly in patients with underlying cardiac diseases. Muruganathan et al. in their study noticed 55.1% of patients developed hypotension during their course of treatment which responded well to fluids and dopamine infusion.6

Though tachycardia, hypotension, and arrhythmias mainly ventricular tachyarrhythmia have been recorded, no cases of bradycardia or toxic myocarditis have been reported with auramine O poisoning so far. Our patient had no recorded cardiac abnormality at the time of admission and had complete recovery of cardiac dysfunction at the time of discharge points out in favor of the unusual cardiotoxicity of this molecule.

CONCLUSION
The treatment of poisoning caused by an uncommon compound is always challenging and the situation becomes graver when the patient develops an unexpected complication and does not respond properly to treatment. Further studies are necessary to elucidate this fatal poison in a broader aspect and this article will serve as a guide for future research.

1Professor, Department of General Medicine, KMCH Institute of Health Sciences and Research; 2Resident, G Kuppuswamy Naidu Memorial Hospital, Coimbatore, Tamil Nadu, India; *Corresponding Author
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Hon. General Secretary
An Unusual Case of Telangiectasias

Varsha Shirish Dabadghao1*, Suresh Kumar Sharma2, Satbir Kaur Malik3, Vikrant B Khese4

Accepted: 28 December 2016; Accepted: 26 December 2022

Abstract

Background: Telangiectasias are defined as persistent dilatation of small capillaries in the superficial dermis. Case: A 26-year-old woman presented with red lesions, epistaxis, joint pains, color changes of the hands, and breathlessness. On clinical examination and investigations, a final diagnosis of mixed connective tissue disease (MCTD), with interstitial lung disease (ILD), with telangiectasias, and epistaxis was made. Telangiectasias and epistaxis are rare presentations of MCTD.

Introduction

Telangiectasias are defined as persistent dilatation of small capillaries in the superficial dermis that is visible as fine, bright, nonpulsatile red lines, or net-like patterns on the skin.1 The dilated vessels are commonly seen on the face around the nose, cheeks, and chin. Telangiectasias can be congenital or acquired. Congenital causes are nevus flammeus, Von Hippel–Lindau syndrome, axatia–telangiectasia, Sturge–Weber syndrome, hereditary hemorrhagic telangiectasia (HHT), etc. Acquired causes are Cushing’s syndrome, venous hypertension, acne rosacea, connective tissue disease, carcinoid syndrome, radiation exposure, or chemotherapy.2 Epistaxis is a common complaint, the etiologies of which are mostly local nasal lesions, arteriovenous malformations, bleeding, coagulation disorders, leukemias, and Wegener’s granulomatosis.3 Connective tissue diseases (CTD’s) form a rare cause of both these complaints.4 Telangiectasias mostly occur in systemic sclerosis (SSC) (calcinosis, Raynaud’s phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia syndrome or localized SSC).5 Epistaxis can occur due to nasal telangiectasias or as concomitant Von Willebrand disease (VWD). MCTD, a separate entity, which comprises features of systemic lupus erythematosus (SLE), SSC, rheumatoid arthritis (RA), and polymyositis (PM), is a relatively rare cause of both these complaints.5 In most studies on such patients, only periangual telangiectasias6,7 were found. Here, we report a rare case of a young woman who presented with telangiectasias all over the face and upper body, along with epistaxis that occurred together.

Case Description

A 26-year-old female patient came with complaints of reddish colored lesions over face and palms since 10 months. She had joint pains and swelling involving small joints of hands with early morning stiffness lasting for 40 minutes since 9 months. She complained of color change (white to red skin) in the fingers of both hands on working in cold water since 9 months, which was suggestive of Raynaud’s phenomenon. She also had multiple oral ulcers and epistaxis since 9 months. Bouts of epistaxis occurred at least thrice weekly with a loss of a quarter teaspoon of blood. There was a history of breathlessness on climbing stairs since 3 months. She had no history of breathlessness on any other site. There was no history of bleeding or coagulation disorders in the family. No h/o photosensitivity, hematuria, decreased urine output, or thrombotic episodes. There was a history of breathlessness on climbing stairs since 3 months. She had no history of (h/o) photosensitivity, hematuria, decreased urine output, or thrombotic episodes. There was no history of bleeding from any other site. There was no history of bleeding or coagulation disorders in the family. No h/o similar lesions over the body in any family member.

On general examination, she was moderately built and nourished. Her vitals were stable, mild pallor was present. Multiple oral ulcers 1–2 mm were present over buccal mucosa and inside of lips. Red lesions, small, around 1 mm in diameter, blotty not raised, blanching on pressure suggestive of telangiectasias were present over the face, hands, and including palms. Similar red lesions were seen inside the oral or nasal cavity; on preliminary examination, they were likely to be telangiectasias.

On musculoskeletal examination, her skin appeared stretched, and could not be pinched up over her fingers, up till wrist. Tenderness over all metacarpophalangeal joints and proximal interphalangeal joints. No swelling was noted.

On bathing her hands with cold water, Raynaud’s phenomenon was induced.

On nose and throat examination, telangiectasias were noted in the nasal cavity. There were no local lesions or arteriovenous malformations. On ophthalmology examination, no uveitis or telangiectasias were seen (Figs 1 to 4).

On account of multisystem involvement—Raynaud’s, numerous telangiectasias, skin tightening, inflammatory joint pains, dysphagia, and dyspnea, the patient appeared to have scleroderma, but for oral ulcers and epistaxis, further investigations were warranted. Her hemoglobin was 9.8 gm%. Total leukocyte count was 7,800/cumm, platelets were 2.6 lakh/cumm, and peripheral blood smear was normocytic and normochromic. Erythrocyte sedimentation rate was 24 mm. Her Liver and renal functions were normal. Her serum electrolytes were normal. Her blood sugar level was 191 mg%. Her urine showed no albumin and sugars. Her bleeding time, clotting time, prothrombin time, and activated partial thromboplastin time were normal. Iron studies and vitamin B12 were normal. Her pulmonary function test showed moderate restriction, and the 6-minute walk test was normal (no significant desaturation). The helium dilution study (diffusing capacity study) were normal. High-resolution computed tomography thorax was done, which showed diffuse ground glass opacities, reticular opacities, and fine areas of honeycombing with subpleural sparing noted in the bilateral lower lobes suggestive of nonspecific interstitial pneumonitis. Although barium swallow showed a suggestion of lower esophageal stricture, this was ruled out on upper gastrointestinal endoscopy.

Based on the clinical features and investigations, she was finally diagnosed with MCTD, with extensive ILD, and epistaxis. She was treated with prednisolone 1 mg/kg/day tapered gradually and maintained at 10 mg/day, azathioprine 50 mg once a day (OD), hydroxychloroquine 200 mg OD, and nifedipine 10 mg were started. She reported improvement in her symptoms. Her telangiectasias had reduced in visible number, while no further lesions appeared. Her epistaxis episodes were reduced in frequency.

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An Unusual Case of Telangiectasias

Characteristic initial presentation is Raynaud’s phenomenon associated with puffy fingers. Skin rashes suggestive of SLE-like malar rash or of dermatomyositis like heliotrope rash on eyelids and oral ulcer. Pulmonary fibrosis and isolated pulmonary arterial hypertension (PAH) or secondary PAH may develop. Other features include periungual telangiectasias, esophageal dysmotility, arthritis, pericarditis, and renal disease. Such extensive telangiectasias are relatively rare in MCTD. Telangiectasias have many causes, of which MCTD forms a rare part. HHT is the most important differential for a patient with multiple telangiectasias. Our patient did not have a family history, and so this differential was ruled out, as were others. Patients of MCTD can sometimes have epistaxis due to telangiectasia in the nasal mucosa. There are also reports of acquired VWD in patients with CTD, which may cause bleeding (epistaxis).

Glucocorticoids remain the mainstay of treatment. ILD mostly responds to low to moderate dose steroids and if needed cyclophosphamide pulses are used.

<table>
<thead>
<tr>
<th>Disease category</th>
<th>Symptom</th>
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<tbody>
<tr>
<td>SLE</td>
<td>Polyarthritis</td>
</tr>
<tr>
<td></td>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td></td>
<td>Malar rash/facial erythema</td>
</tr>
<tr>
<td></td>
<td>Mericarditis or pleuritis</td>
</tr>
<tr>
<td></td>
<td>Thrombocytes of &lt;100–10^9/1 or leukocytes of &lt;4.0–10^9/1</td>
</tr>
<tr>
<td>Progressive SSC</td>
<td>Sclerodactyly</td>
</tr>
<tr>
<td></td>
<td>Long fibrosis or restrictive lung disease (VC &lt; 80%) or carbon monoxide diffusion of &lt;70%</td>
</tr>
<tr>
<td></td>
<td>Esophageal hypomotility or dilatation</td>
</tr>
<tr>
<td>PM</td>
<td>Muscle weakness</td>
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<tr>
<td></td>
<td>Elevated serum levels of myogenic enzymes</td>
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<td>Myogenic pattern on electromyography</td>
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</tbody>
</table>

MCTD criteria are met in case of Raynaud’s phenomenon or presence of swollen hands or fingers or positivity for anti-U1 small nRNP-antibodies and at least one symptom in two of three disease categories. VC, vital capacity. Kasukawa, R. Excerpta Medica. 1987

References

Discussion

Mixed connective tissue disease (MCTD) is a distinct rheumatic disorder with features of SLE, RA, SSC, and PM in varying proportions and high titers of uridine (U1) nuclear ribonucleoprotein particle (NRRNP). Three criteria are used for diagnosis—Kasukawa (Table 1), Sharp, and Alarcon-Segovia.
Mounier-Kuhn syndrome (MKS) is an extremely rare congenital disorder characterized by the loss of smooth muscle and elastic connective tissue of the tracheobronchial tree. This leads to progressive tracheobronchomegaly and bronchiectasis. The disease is more common in males and is usually diagnosed in adult life. There are only a handful of reported cases of MKS from India.

A 65-year-old male patient was admitted to our hospital with an acute respiratory tract infection. He had had similar episodes frequently in the past for the last 15 years. He was not a smoker. On examination, oxygen saturation was 83%. There were Rhonchi and coarse crepitations bilaterally in the chest, with the maximum intensity in the lower zones. Grade 2 clubbing was present in all fingers. A chest X-ray was done, which showed (Fig. 1) bilateral lower zone honeycombing with enlarged tracheal shadow. A high-resolution computed tomography (HRCT) scan of the thorax was done, which showed (Fig. 2) features suggestive of MKS. The patient was treated with intravenous antimicrobial agents, nebulization, and respiratory physiotherapy. After recovery, pneumococcal and influenza vaccines were advised.

Mounier-Kuhn syndrome (MKS) is a very rare condition, which was first described in 1932. Presentation of the condition can be protean, from completely asymptomatic subjects to severe respiratory failure and death. Because of the rarity, the etiology of the condition is not fully known, but it is hypothesized to be autosomal recessive in some cases. However, most of the reported cases are sporadic, as in our case.

The main complication of MKS is recurrent lower respiratory tract infections and bronchiectasis. The abnormal tracheobronchial dilatation causes ineffective cough reflex, and mucociliary clearance is also impaired. This is thought to be responsible for respiratory complications.

Certain conditions like Marfan syndrome, Ehlers-Danlos syndrome, cutis laxa, and Kenny-Caffey syndrome can cause secondary tracheobronchomegaly. Also, severe fibrosis in the upper lobes may cause tractional tracheal enlargement. Such secondary causes must be ruled out before the diagnosis of MKS.

Computed tomography (CT) scan of the thorax is essential in the diagnosis of the
condition. Bronchoscopy can also be used to demonstrate tracheal dilatation.\(^2\) Treatment is mainly supportive, and interventions like tracheal stenting are rarely successful.\(^2\)

**REFERENCES**


Paraquat is a rapidly acting, inexpensive, nonselective, easily available herbicide and is a leading cause of fatal poisoning. Its chemical formula is N,N'-dimethyl-4,4'-bipyridinium dichloride. The tongue appearance following swallowing of Paraquat or spitting it without swallowing results in a typical tongue change called “Paraquat tongue.” The formulation strength, dose ingested and time since ingestion are important in determining the outcomes.

The oral lesions depend upon the amount of Paraquat taken. The mouth and pharynx are to be examined for any necrosis, inflammation, or ulceration. The onset of oropharyngeal and Paraquat tongue features may be delayed a number of hours (possibly up to 12) and reach maximum severity some days later. A 27-year male attended triage with a history of ingestion of Paraquat with suicidal intent. He spat it immediately as the taste was bitter. In this patient, the tongue was initially normal with a mild coating (Fig. 1A) and then evolved over a week into ulcerations and bleeding with glossodynia (Fig. 1). It may even evolve into large or multiple ulcers on the dorsum of the tongue.1,2 Large ulcerated tongue signifies a significant amount of Paraquat ingestion and severe upper gastrointestinal (GI) injuries. In this case, upper GI endoscopy revealed grades I–IIA injuries. It was managed symptomatically, and the patient took left against medical advice discharge after 10 days. At discharge, his tongue lesions, as well as renal, pulmonary, and hepatobiliary parameters, were improving towards normalcy.

Learning Point
Ulcerations, bleeding and glossodynia of the tongue is a common sequela after oral ingestion of Paraquat. The presence of a Paraquat tongue should warrant a clinician to carefully look for GI injuries and multi-organ dysfunction. The extent of tongue lesions correlates with the severity of GI mucosal injuries.

References

Arun Agarwal*
Director, Department of Internal Medicine, Fortis Escorts Hospital, Jaipur, Rajasthan, India; *Corresponding Author
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Amanita phalloides: The Death Cap

Rohit Bansal¹, Priya Bansal²

Amanita phalloides (A. phalloides), Spain, 1994

Amanita phalloides (A. phalloides), Republic of Tchad

Amanita phalloides (A. phalloides). Malawi, 2008

Amanita phalloides (A. phalloides). Hungary, 1986

Amanita phalloides (A. phalloides). Ghana

About 5% of all known mushroom species are poisonous. Most fatal ingestions are due to the consumption of Amanita phalloides (A. phalloides), commonly known as “death cap.” It is widely distributed across Europe and other parts of the world. These toxic mushrooms resemble several edible mushrooms, most notably Caesar’s mushroom and paddy straw mushroom. As little as half a mushroom contains enough toxin to kill an adult human. In general, poisoning incidents are unintentional and result from errors in identification. Roman Emperor Claudius in AD 54, Holy Roman Emperor Charles VI, and some other historical figures are alleged to have died from A. phalloides poisoning as assassination plots.

Its heat-stable amatoxins withstand cooking temperatures and inhibit ribonucleic acid (RNA) polymerase II and, subsequently, protein synthesis. Death caps have been reported to taste pleasant. This, coupled with delay in the appearance of symptoms (>6 hours)—during which time internal organs are being severely, sometimes irreparably damaged, makes it particularly dangerous. Initial symptoms include colicky abdominal pain, diarrhea, nausea, vomiting, and dehydration, followed by jaundice and hypoglycemia. The liver is principally affected, as it is the organ first encountered after absorption in the gastrointestinal tract. Later kidney failure also ensues. Amatoxins can be measured directly in the serum, urine, and gastric aspirate of a poisoned patient.

Treatment is mainly supportive. High-dose intravenous penicillin G may displace amanitin from plasma binding sites. Intravenous silibinin, an extract from the herb, blessed milk thistle, prevents the uptake of amatoxin by liver cells, thereby protecting undamaged liver tissue. It also stimulates deoxyribonucleic acid-dependent RNA polymerase, and RNA synthesis, thus may prove useful when started within 96 hours of ingesting this poisonous mushroom. Thiocytic acid may also have some antidotal effects. A liver transplant may prove lifesaving in some cases.

Commonly consumed mushrooms on a day-to-day basis in India are white button mushrooms—Agaricus bisporus. There are certain characteristics of the death cap that help in its identification. It has white gills that don’t turn brown as the mushroom matures. It has a white cap with a greenish or yellowish tint. It has a cup-like volva at the base. There may be a large loose skirt-like membrane on the top of the stalk. Its immature forms are egg-like. Its spore print is white and may have an ammonia-like odor. But most important of all, if one suspects that a mushroom may be a death cap, do not eat it. It may very well turn out to be one’s last meal.

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How to cite this article: Bansal R, Bansal P. Amanita phalloides: The Death Cap. J Assoc Physicians India 2023;71(4):100–100.
Morvan’s Syndrome after Siddha Drug Intake

Mangalapalli Vijay, Sowmini Padmaja Raman, Sakthi Velayutham Saravanan, Malcolm Jeyaraj Krishnasamy, Vivekasaran Raju, Mugundhan Krishnan

Sir,

Morvan’s syndrome is a disorder of the central and peripheral nervous system caused by voltage-gated potassium channel (VGKC) autoantibodies. We report a case of a woman who presented with symptoms of Morvan’s syndrome after 2 months of Siddha medicine intake. She presented with burning feet sensation, insomnia, and dysautonomia. She tested positive for VGKC antibody. Her symptoms improved with a course of steroids and intravenous (IV) immunoglobulins. This case report highlights the association between VGKC antibody and Siddha medicine intake.

Augustine Marie Morvan, a French physician, first used the term “la chorée fibrillaire” in 1890 to describe a syndrome characterized by peripheral nerve hyperexcitability, fluctuating delirium, dysautonomia, and insomnia. Autoantibodies against VGKC complex proteins, contactin-associated protein-like 2 (CASPR2), and leucine-rich glioma-inactivated 1 (LGI1) are considered strongly in the pathogenesis of Morvan’s syndrome. A large number of case reports and case series about the association between intake of native medicines or heavy metal poisoning with neuromyotonia-like presentation has been documented.

A 30-year-old woman presented with complaints of myalgias, muscle weakness, easy fatigability, muscle twitchings, paresthesias of bilateral lower limbs, and mood and sleep disturbances of 2 months duration. The pain was crampy in nature, causing difficulty in standing, walking, wearing footwear, lifting objects, and mixing food. She had muscle twitchings in bilateral arms, flanks, and thigh muscles occurring 30–40 times/day. She complained of paresthesias of bilateral lower limbs in the form of pins and needles as well as a burning sensation. She had a low mood with frequent crying spells and had sleep disturbances. About 1 month after the onset of the above symptoms, she had frequent episodes of giddiness whenever she stood up from sitting or lying position associated with profuse sweating. The patient gave a history of Siddha medicine usage for complaints of primary infertility prior to her presentation.

Examination revealed significant postural hypotension. Her mini-mental state examination score was 30/30. She had ripping myokymic muscle movements on her arms, forearms, and thighs. She had hyperesthesia of both feet. Electromyography showed spontaneous activity in the form of doublets and triplets. Nerve conduction studies were normal. A clinical diagnosis of Morvan’s syndrome was made and a VGKC antibody was done. The test was positive for high titers of CASPR2 antibody. Baseline blood investigations were normal. Antinuclear antibodies screening, extractable nuclear antigen profile, and antineutrophil cytoplasmic antibodies profile were negative. Heavy metal screening in urine was negative. Magnetic resonance imaging (MRI) brain and MRI whole spine were normal. Computed tomography chest and abdomen were normal. MRI brain and MRI whole spine were normal. Computed tomography chest and abdomen were normal.

She was initially treated with IV methylprednisolone 1 gm IV once daily for 5 days, followed by oral steroids. Due to persistent symptoms, IV immunoglobulins were administered at a dose of 0.4 gm/kg/day for 5 days. Oral prednisolone was slowly tapered over a period of 2 months. The patient’s symptoms resolved completely.

Morvan’s syndrome is a disorder of autoimmunity associated with VGKC autoantibodies involving the central, peripheral, and autonomic nervous system. In the pathogenesis of Morvan’s syndrome, VGKC complex proteins, CASPR2, and LGI1 are strongly implicated. CASPR2 is expressed mainly in the peripheral nervous system, whereas LGI1 is expressed both in the central and peripheral nervous systems. In Morvan’s syndrome, antibodies are directed usually against CASPR2, LGI1, or both, but CASPR2 antibodies dominate. Three autoantibodies bind to multiple regions in the brain, thereby explaining the multifocal clinical features of this disorder. Morvan’s syndrome is clinically characterized by neuropathic pain, neuromyotonia, dysautonomia, and neuropsychiatric features.

A large number of case reports are available about the association between native medicine intake or heavy metal poisoning like gold, lead, mercury, and silver with neuromyotonia-like presentation. In a study from Northwest India, 20 patients of neuromyotonia had an association with ayurvedic drug intake. In a country like India, where Siddha and ayurvedic drugs are used in abundance, such a treatable condition should not go unrecognized when patients with similar clinical features present to the general practitioner.

References
API Announcement

Elections of API, ICP and PRF

(Full details circular No. 1 & 2/2023)

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

Governing Body of API:
President-Elect: One; Vice President: One; Elected Members: Six

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

Board of PRF:
Director Elect: One; Board members: Two

Separate nominations must be submitted for each post.

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

Requirements for eligibility contest of election to Board of PRF

**Director Elect:** A member of API for at least 10 years with research experience and having 10 research publications in peer reviewed indexed journals.

**Board Members:** A Member of API for at least 10 years with research experience and having 5 research publications in peer reviewed indexed journals.

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

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

Requirements for eligibility for the contests of election to ICP

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

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

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

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

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

Every member is supplied with a nomination form. The nomination form completed in all respects should reach the API Office not later than 31st May 2023. For every post on the Governing Body/Faculty Council/Board of PRF, the nomination must be accompanied by a sum of Rs. 7500/- + 1350/- (GST) (Rupees eight thousand eight hundred fifty only) nonrefundable in the form of Demand Draft payable at Mumbai. The nomination paper NOT accompanied by the Bank Draft of Rs. 8850/- will be deemed invalid.

Important

Canvassing in any form should not be done by the candidate for the election. Instead, they are requested to send a short bio-data NOT MORE THAN 200 words along with the nomination paper which will be printed and circulated along with the ballot paper. Excess of bio-data beyond the first two hundred words shall be deleted. Canvassing in any form or in favor of the candidate shall not be permitted. THE CANDIDATE WILL HAVE TO CERTIFY AND SIGN THAT THE INFORMATION PROVIDED IN HIS/HER BIODATA IS CORRECT.

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

DEAD LINES OF ELECTION PROCEDURE

- Last date to receive the nomination at API Office: 31st May 2023
- Last date for withdrawal: 20th June 2023
- Last date to receive ballot papers at API Office: 31st August 2023

Dr. Agam Vora
Hon. General Secretary
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