Journal of The Association of Physicians of India

VOL NO. 72 | ISSUE NO. 5 | MAY 2024 | ISSN : 0004 - 5772

Editor-in-Chief: Prof. Dr. Mangesh Tiwaskar

JAPI

www.japi.org app: myJAPI Price: ₹ 800

Published on 1st of every month

JAPI
JOURNAL OF THE ASSOCIATION OF PHYSICIANS OF INDIA
Editor-in-Chief: **Prof. Dr. Mangesh Tiwaskar**

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JAPI JOURNAL OF THE ASSOCIATION OF PHYSICIANS OF INDIA
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Subscription Information
Journal of The Association of Physicians of India is published monthly. The annual subscription is ₹12,000 (India) and US $500 (other countries). The Journal is dispatched within India by surface mail and to other countries by sea mail.

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Published and Edited by
Prof. Dr. Mangesh Tiwaskar, on behalf of **The Association of Physicians of India**, Journal of The Association of Physicians of India, Turf Estate, Unit No. 006 & 007, Opp. Shakti Mill Compound, Off Dr. E. Moses Road, Near Mahalaxmi Railway Station (West), Mumbai-400 011.
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Air Pollution: A New Cause of Type 2 Diabetes?

Viswanathan Mohan[1*], Mangesh Tiwaskar[2], Ranjit Unnikrishnan[3]

Winter is the season of air pollution in India. Several Indian cities regularly make it to the list of most polluted places on Earth during this season. The problem has been attracting the attention of policymakers, civil society, medical professionals, and scientists for many years now. Unfortunately, except for a slight dip during the COVID-19-induced lockdowns in 2020 and 2021, there seems to be no let-up in the rising graph of air pollution in India.

Air pollutants are broadly classified into gaseous pollutants and atmospheric particulates. Gaseous pollutants include sulfur compounds, nitrogen compounds, carbon oxides, hydrocarbons, and halogen compounds, and atmospheric particulates include total suspended particulates, inhalable particles (PM10), fine particulate matter (PM2.5), and ultrafine particulate matter. The main sources of air pollution in urban areas include industrial plants, motor vehicles, and construction activities, while in rural areas, the major source is biomass combustion (from cooking as well as burning of crop stubble). As air freely moves from rural to urban areas depending on the prevailing wind patterns, pollution in rural areas can easily spread to nearby cities and *vice versa*.

The health penalties of unhealthy air are immense, with the majority of ill effects pertaining to the respiratory system. Individuals with preexisting respiratory diseases, such as bronchial asthma or chronic obstructive pulmonary disease, are exquisitely sensitive to the detrimental effects of air pollution. In addition, the current evidence suggests that inhaling polluted air has effects far beyond the lungs.

Endocrine Disruptor

Particular interest has been directed to the effects of air pollutants as "endocrine disruptors" leading to type 2 diabetes (T2D). Indeed, a fifth of the burden of T2D worldwide has been attributed to air pollution; 13.4% is derived from ambient PM2.5 and 6.5% from household air pollution.[1] Studies from the United States and Europe reveal that there is a definite link between incident T2D and ambient PM2.5. A systematic review and meta-analysis of 13 studies from these countries showed that the risk of T2D rose by 8–10% per 10 µg/m^3 increase in exposure and that the association was stronger in females.[2] A study from Taiwan showed that compared to the lowest quartile, there was a 1.28 times higher risk of incident diabetes in the second quartile of exposure.[3] However, conclusions drawn from these studies cannot be directly extrapolated to developing countries such as India, as ambient pollutant levels are, in general, much lower in high-income countries.

There have been a few attempts at assessing the risk of diabetes incidence associated with air pollution in developing nations, where the air quality tends to be much poorer. A study from China showed a 15% increased hazard of incident diabetes for every 10 µg/m^3 increase in PM2.5.[4] Another study from China reported an increase in fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) by 0.025 and 0.011 mmol/L, respectively, for every 10 µg/m^3 increase in PM10, and an increase by 0.061 and 0.016 mmol/L, respectively, for every 10 µg/m^3 increase in PM2.5. An analysis of data from nearly 400,000 individuals showed that exposure to higher levels of PM2.5 was associated not only with increased risk of progression from normoglycemia to diabetes but also with mortality risk from baseline, T2D, and its complications.[5]

Indian Evidence

A recent study from India assessed the association of PM2.5 exposure with glycemic markers and incidence of T2D in two large cities, *viz*, Delhi and Chennai. In this study, Mandal et al., in the Centre for cArdiometabolic Risk Reduction in South-Asia surveillance study, followed up 12,064 adults residing in these two cities over a period of 7 years. Daily average ambient PM2.5 concentrations were obtained based on a hybrid satellite-based exposure model, as well as ground monitoring-based assessments of daily average PM2.5.[6] Individuals with normoglycemia at baseline were tested for development of dysglycemia using FPG and HbA1c measurements at the follow-up visits. A 10 µg/m^3 increase in monthly average exposure to PM2.5 was associated with a 0.4 mg/dL increase in FPG and a 0.021 unit increase in HbA1c. An increase in average annual PM2.5 exposure by 10 µg/m^3 was associated with a 22% increased risk of incident T2D.

Possible Mechanisms

What could be the biological mechanisms underlying the increased risk of T2D with exposure to air pollution? Air pollution,

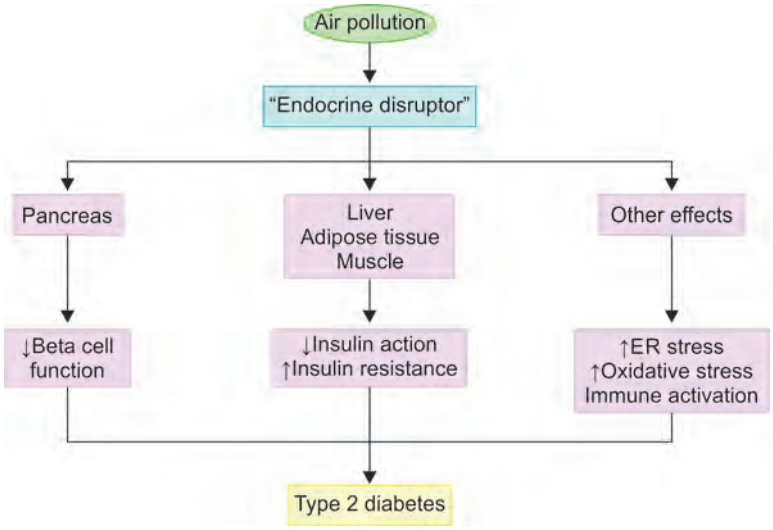

Fig. 1: Link between air pollution and diabetes

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How to cite this article: Mohan V, Tiwaskar M, Unnikrishnan R. Air Pollution: A New Cause of Type 2 Diabetes? J Assoc Physicians India 2024;72(5):11–12.

especially exposure to PM2.5 and nitrogen dioxide, has been shown to adversely affect pancreatic beta cell function as well as insulin sensitivity.[7,8] Other biological mechanisms underlying this association include immune activation, endoplasmic reticulum stress, central nervous system inflammation, and oxidative stress.[9–11] Figure 1 summarizes the putative mechanisms between air pollution and T2D.

With the growing socioeconomic development worldwide, the detrimental health effects of air pollutants are receiving increased attention. T2D and air pollution are both critical public health concerns worldwide. Especially in India, the burgeoning epidemic of T2D threatens to derail healthcare systems across the country. Thus far, the higher prevalence of diabetes in urban parts of India has been attributed to unhealthy diets, sedentary lifestyles, and increased stress levels. The study by Mandal et al. suggests that air pollution may be an additional factor underlying the increased risk for diabetes in urban Indians.[6] Furthermore, this study shifts the focus of modifying environmental triggers for T2D away from individual choices regarding diet and physical activity towards societal and governmental efforts to clean up the air that we breathe.

So what can we do to prevent diabetes knowing the link between air pollution and diabetes?

Firstly, we should try to reduce pollution at the source. We know the major sources of air pollution are either the burning of stubble by farmers, smoke from vehicles, industrial pollution, use of firewood or charcoal in ill-ventilated kitchens, or indiscriminate pollution during festivals like Diwali due to fireworks, etc. All these are potentially modifiable by legislation and education by governmental and nongovernmental agencies. Individuals living in polluted areas, especially those with a high risk of developing T2D (on account of family history/obesity, etc.), should be encouraged to wear good-quality masks as long as the air quality remains poor. These steps are likely to be as easy to implement and as cost-effective as efforts to modify diet and physical activity, and they have the additional benefit of reducing the multisystem morbidity and mortality attributable to air pollution.

These pieces of evidence offer guidance for developing and implementing population- and region-specific policies aimed at lowering ambient air pollution in order to combat the high prevalence of diabetes in low- and middle-income countries like India.

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ORIGINAL ARTICLE

Identifying the Probable Etiology of Acute Undifferentiated Fever through Inflammatory Markers

Varadaraj Govindaraj[1*], Dinesh Poonia[2], Girish Bhardwaj[3], Sangeetha Balasubramani[4], Binoy Michael[5]

Received: 05 September 2023; *Accepted:* 25 October 2023

Abstract

Background: Acute undifferentiated fever (AUF) is defined as any febrile illness with a duration of ≤14 days without evidence of localized infection. Most outpatient services and a significant inpatient load in India are contributed by AUF. COVID-19 has recently added to the existing list of common etiologies of AUF. While the rapid diagnostic test (RDT) kits, which are widely used for the detection of common etiologies of AUF, are unreliable, the rise of various inflammatory markers may help identify the probable etiology. This not only results in better diagnosis but also prepares the physician for close monitoring and pooling of resources.

Aim: To identify the probable etiology of AUF through inflammatory markers.

Objective: To understand the clinical and biochemical parameters as possible predictors of adverse outcomes in AUF.

Materials and methods: This was a prospective observational study carried out in the Department of Medicine in a tertiary care hospital. The total duration of the study was 1 year. A total of 400 AUF patients [both outpatient department (OPD) and inpatient department (IPD)] fulfilling the eligibility criteria were taken up for the study after consent. Various inflammatory markers, namely erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), D-dimer, ferritin, and procalcitonin levels along with basic blood and biochemical tests were measured in all qualifying patients at their first visit. The level of rise of all the measured inflammatory markers was analyzed for clues toward identifying the etiology. Also, the possible predictors of adverse outcomes, as defined in the study, were analyzed.

Outcome variables are described as mean ± standard deviation. All statistical calculations were done using computer programs Microsoft Excel 2007 (Microsoft Corporation, New York, United States of America) and SPSS (Statistical Product and Service Solutions; SPSS Inc., United States of America) version 21.

Results: The common etiologies in our study contributing to AUF were dengue (31.5%), COVID-19 (18.5%), enteric fever (12.7%), scrub typhus (9.0%), and malaria (6.0%). In 76 cases (19%), the fever was undiagnosed. Enteric fever had highly elevated CRP (>30 mg/L) and moderately elevated D-dimer, ferritin, and procalcitonin. Both nonsevere dengue and COVID-19 had highly elevated D-dimer (>750 ng/mL), but in nonsevere dengue, CRP, ferritin, and procalcitonin were only mildly elevated, whereas in COVID-19, CRP and ferritin were moderately elevated with mildly elevated procalcitonin. Scrub typhus had highly elevated CRP and ferritin [more than four times the upper limit of normal (ULN)], but D-dimer and procalcitonin were only mildly elevated. The mean serum procalcitonin level in enteric fever is significantly higher than the other etiologies of AUF.

Our study was correctly able to identify 90.8% of nonsevere dengue, 87.8% of typhoid, 83.6% of COVID-19, and 91.4% of scrub typhus patients based on the inflammatory markers level.

Obesity, diabetes (both types 1 and 2), hypertension, coronary artery disease (CAD), malignancy, chronic kidney disease (CKD), and chronic lung disease were significantly associated with adverse outcomes. A significant delay in visiting the hospital after the onset of fever was found in all etiologies of AUF, which had adverse outcomes.

Conclusion: Our study is one of the few studies comparing the rise in the level of various inflammatory markers among the common etiologies of AUF. The novelty of the study is that it aids in identifying the probable etiology of AUF with good confidence through the levels of inflammatory markers. Also, our study highlights the high-risk factors associated with adverse outcomes in AUF.

Journal of the Association of Physicians of India (2024): 10.59556/japi.72.0523

Introduction

Acute undifferentiated fever (AUF) is defined as any febrile illness with a duration of ≤14 days without evidence of localized infection by history, physical examination, complete blood count, chemistry profile, urinalysis, or chest radiography at the time of initial presentation.[1] The majority of outpatient services and a significant inpatient load in India are contributed by AUF. Unlike Western countries, tropical diseases such as dengue, malaria, and scrub typhus, pose a serious health challenge to the already fragile health system in our country. Most of these diseases are diagnosed by rapid diagnostic tests (RDTs), especially in the rural parts of our country where facilities for microbiological culture or high-end investigations such as polymerase chain reaction (PCR) are not available. It is a recognized fact that diagnosis by RDT is unreliable and has significant false negatives.

While the common etiologies of AUF include dengue, malaria, typhoid, and scrub typhus, COVID-19 has recently added to the list of existing woes. In our study, we aim to identify the probable etiology of AUF through inflammatory markers. Also, the study looks for the predictors of adverse outcomes by using both clinical and laboratory parameters. This not only results in better diagnosis but also prepares the physician for close monitoring and pooling of resources.

Materials and Methods

Place of Study

The study was conducted in the Department of Medicine in a tertiary care Armed Forces hospital in New Delhi.

Study Design

A prospective, observational study.

Sampling Technique and Sample Size

A consecutive type of nonprobability sampling was followed to select study subjects. A total of 400 consecutive patients

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How to cite this article: Govindaraj V, Poonia D, Bhardwaj G, *et al.* Identifying the Probable Etiology of Acute Undifferentiated Fever through Inflammatory Markers. J Assoc Physicians India 2024;72(5):13–16.

fulfilling the eligibility criteria were taken up for the study after informed consent.

Inclusion Criteria

- Age above 18 years.
- All cases of fever satisfy the definition of AUF.

Exclusion Criteria

None.

Methodology

All individuals above 18 years of age meeting the definition of AUF [both outpatient department (OPD) and inpatient department (IPD)] were included in the study.

Various inflammatory markers, namely erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), D-dimer, ferritin, and procalcitonin levels along with basic blood and biochemical tests were measured in all qualifying patients at their first visit. All possible predictors of adverse outcomes such as age, gender, previous comorbidities, and day of presentation to the hospital were documented. Standard diagnostic tests and procedures were used for diagnosis. nonstructural protein 1 antigen and immunoglobulin M (IgM) antibody for dengue, blood culture for typhoid, IgM antibody and PCR for scrub typhus and leptospirosis, rapid antigen test, and reverse transcription PCR for COVID-19 and peripheral blood smear for malaria were used for diagnosis.

Possible laboratory predictors of severe illness, including ESR, CRP, D-dimer, ferritin, and procalcitonin were obtained.

Adverse outcome is defined as:

- Patient requiring 2 or more weeks of hospital inpatient care.
- Also, 3 or more days of hospital ICU care.
- Need for organ support in the form of invasive mechanical ventilation, inotrope use, or dialysis.
- Sequential Organ Failure Assessment (SOFA) score of >6 or change in SOFA score by 2 or more points.
- Results in death of the patient.

Data were analyzed, and predictors of adverse outcomes in AUF were identified.

Statistical Methods of Analysis

Outcome variables are described as mean ± standard deviation. All statistical calculations were done using computer programs Microsoft Excel 2007 (Microsoft Corporation, New York, United States of America) and SPSS (Statistical Package for the Social Sciences; SPSS Inc., Chicago, Illinois, United States of America) version 21.

Duration of Study

The duration of the study was 1 year, from 1st July 2021 to 30th June 2022.

Blinding

Unblinded study.

Ethical Issues

Ethical clearance was obtained from the Institutional Ethics Committee.

Results

A total of 400 consecutive patients with AUF during the period from 1st July 2021 to 30th June 2022 were included in the study.

Discussion

In our study, 400 cases of AUF from the Armed Forces Hospital in New Delhi were included. The common etiologies in our study contributing to AUF were dengue (31.5%), COVID-19 (18.5%), enteric fever (12.7%), scrub typhus (9.0%), and malaria (6.0%). In 76 cases (19%), the fever was undiagnosed (Fig. 1). A small percentage of cases (3.25%) were diagnosed with other diseases such as extrapulmonary tuberculosis (nine cases), leptospirosis (two cases), amoebic liver abscess, and chikungunya (one case each).

Serum ferritin, D-dimer, and CRP are pro-inflammatory markers. They were often studied to prognosticate and as markers of severity among acute febrile illnesses. In our study, we determined a CRP value of >30, 20–30, and 10–20 mg/L as highly elevated, moderately elevated, and mildly elevated, respectively. A D-dimer value of >750 ng/mL was considered highly elevated, 500–750 ng/mL as moderately elevated, and 200–500 ng/mL as mildly elevated. Similarly, a ferritin level of more than four times the ULN was considered highly elevated, and two to four times ULN and more than two times ULN were considered moderately and mildly elevated, respectively. Procalcitonin level of >5 ng/mL was considered highly elevated, 1–5 ng/mL as moderately elevated, and <1 ng/mL as mildly elevated.

In our study, CRP, D-dimer, and ferritin were found to be raised in all etiologies of AUF (Table 1). When compared to other identified etiologies, enteric fever showed the highest quantum of rise in CRP, and scrub typhus showed the highest rise in ferritin and CRP. Both nonsevere dengue and COVID-19 showed the highest rise in D-dimer. However, CRP level was highly elevated in severe dengue. Similarly, among the identified etiologies of AUF, nonsevere dengue had the least rise in CRP, enteric fever had the least rise in ferritin, and scrub typhus had the least rise in D-dimer.

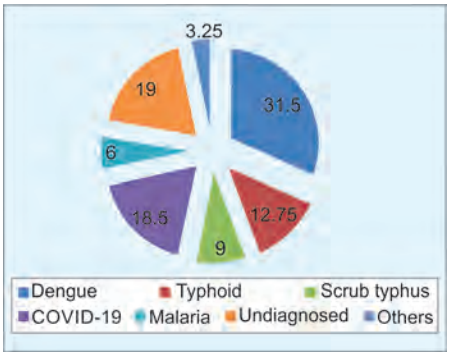

Fig. 1: Various etiologies of AUF

A summary of the probable etiology of AUF based on the levels of inflammatory markers as per our study is given in Table 2.

Our study supports the results of Vuong et al., where higher CRP levels above 34.0 mg/L were associated with severe dengue.[2] In another study by Idhayu et al., a median CRP of 1.65 and 53 mg/dL was seen in uncomplicated dengue and typhoid illness, respectively.[3] Our results substantiate the results by Idhayu et al., where the mean CRP levels are 12.4 and 34.6 mg/L in dengue and typhoid illness, respectively. Similarly, Williams et al. found hyperferritinemia in scrub typhus, the results of which are consistent with our study.[4]

Our study was correctly able to identify 90.8% of nonsevere dengue (109 out of 120), 87.8% of typhoid (43 out of 49), 83.6% of COVID-19 (56 out of 67), and 91.4% of scrub typhus (32 out of 35) patients based on the inflammatory markers level. The study is a novel attempt to identify the etiology of AUF based on inflammatory markers level, and there are no similar studies in the available literature to compare.

A total of 5.25% of the cases developed adverse outcomes during the course of illness (n = 21). Of the 21 patients who had adverse outcomes, there were three fatalities (one dengue, one COVID-19, and one undiagnosed).

While studies showed varying data on the increased severity of dengue among male or female genders, our study did not show any gender predilection for the emergence of adverse outcomes.[5,6] Comparison of variables among different etiologies of AUF is summarized in Table 1. The presence of diabetes was suggested to be a predictor of severe dengue and COVID-19 by Carrasco et al. and Kristan et al.[7,8] A similar observation is made in our study where obesity and diabetes (both types 1 and 2 diabetes mellitus) were found to have a significant association with emergence of adverse outcome in AUF. Among patients who had adverse outcomes, 50% had diabetes in dengue, and it was 7 and

Table 1: Comparison of variables among different etiologies of AUF

S. no.	*Variable (total n = 400)*	*Dengue (n = 126)*	*Enteric (n = 51)*	*Scrub typhus (n = 36)*	*COVID-19 (n = 74)*	*Malaria (n = 24)*	*Others (n =13)*	*Undiagnosed (n = 76)*
1.	Age in years (SD)	49.5 (13.6)	53.1 (14.1)	48.7 (12.9)	57.3 (14.1)	41.3 (11.7)	55.2 (13.5)	57.8 (12.6)
2.	Gender (males) (%)	71 (56.3)	24 (47.1)	17 (47.2)	35 (47.3)	19 (79.2)	6 (46.2)	43 (56.6)
3.	Smoking (%)	32 (25.4)	11 (21.6)	9 (25)	12 (16.2)	2 (25.0)	3 (23.1)	22 (28.9)
4.	Body mass index kg/m^2 (SD)	26.6 (4.4)	25.9 (3.6)	26.2 (4.1)	26.7 (4.5)	26.7 (4.0)	25.8 (4.3)	25.9 (2.7)
5.	Diabetes (%)	39 (30.9)	14 (27.4)	11 (30.6)	29 (39.2)	5 (20.8)	4 (30.8)	21 (27.6)
6.	Hypertension (%)	23 (18.3)	8 (15.7)	5 (13.9)	10 (13.5)	2 (8.3)	2 (15.4)	12 (15.8)
7.	CAD (%)	8 (6.3)	5 (9.8)	3 (8.3)	11 (14.9)	1 (4.2)	1 (7.7)	8 (10.5)
8.	Chronic lung disease (%)	15 (11.9)	7 (13.7)	5 (13.9)	23 (31.1)	1 (4.2)	2 (15.4)	13 (17.1)
9.	Malignancy (%)	5 (4.0)	2 (3.9)	1 (2.8)	6 (8.1)	0 (0)	0 (0)	3 (3.9)
10.	Hypothyroidism (%)	13 (10.3)	7 (13.7)	3 (8.3)	8 (10.8)	0 (0)	1 (7.7)	3 (3.9)
11.	CKD (%)	5 (4.0)	3 (5.9)	2 (5.6)	6 (8.1)	0 (0)	1 (7.7)	4 (5.3)
12.	Hemoglobin in gm/dL (SD)	13.7 (2.1)	12.7 (2.2)	12.9 (4.1)	11.9 (3.6)	13.3 (5.7)	12.7 (3.3)	12.1 (3.8)
13.	TLC in mm^3 (SD)	5127 (4061)	7488 (3981)	8971 (6388)	6824 (3225)	4381 (3376)	8862 (3650)	7695 (5394)
14.	Platelets in lakhs/mm^3	1.6 (1.2)	1.9 (0.9)	1.7 (1.3)	2.1 (1.1)	1.1 (0.8)	2.2 (0.8)	1.8 (0.8)
15.	AST in IU/L (SD)	144 (78)	166 (102)	121 (149)	53 (41)	58 (39)	42 (23)	53 (35)
16.	ALT in IU/L (SD)	72 (41)	186 (133)	86 (91)	58 (69)	66 (43)	87 (51)	55 (67)
17.	ESR in mm/hour (SD)	38 (26)	17 (9)	28 (19)	48 (34)	52 (28)	69 (47)	51 (39)
18.	Serum CRP in mg/L (SD)	12.4 (11.3)	34.6 (17.9)	32.3 (17.1)	25.5 (13.7)	18.9 (16.2)	28.5 (14.9)	25.4 (11.9)
19.	Serum D-dimer ng/mL (SD)	786 (1213)	687 (972)	614 (789)	817 (1652)	655 (861)	657 (1060)	749 (1142)
20.	Serum procalcitonin ng/mL (SD)	0.36 (1.8)	3.21 (4.1)	1.1 (0.7)	0.47 (1.3)	0.27 (1.7)	3.8 (2.7)	1.39 (5.9)
21.	Serum ferritin in ng/mL (SD)	642 (572)	328 (280)	1146 (854)	508 (448)	414 (522)	392 (128)	612 (409)
22.	Average duration from fever onset to first hospital visit (days)	2.9	4.6	4.1	3.7	2.3	4.4	4.1

TLC, total leukocyte count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein

Table 2: Summary of probable etiology of AUF based on the levels of inflammatory markers

	Enteric fever	*Dengue*	*COVID-19*	*Scrub typhus*
CRP	Highly elevated (>30 mg/L)	Normal to mildly elevated (10–20 mg/L)*	Moderately elevated (20–30 mg/dL)	Highly elevated (>30 mg/L)
D-dimer	Moderately elevated (500–750 ng/mL)	Highly elevated (>750 ng/mL)	Highly elevated (>750 ng/mL)	Mildly elevated (200–500 ng/mL)
Ferritin	Moderately elevated (two to four times ULN)	Normal to mildly elevated (less than two times ULN)	Moderately elevated (two to four times ULN)	Highly elevated (more than four times ULN)
Procalcitonin	Moderately elevated (1–5 ng/mL)	Normal to mildly elevated (<1 ng/mL)	Normal to mildly elevated (<1 ng/mL)	Normal to mildly elevated (<1 ng/mL)

*Severe dengue has CRP of >30 mg/L

75% in cases of COVID-19 and undiagnosed AUF, respectively. Similarly, among patients with adverse outcomes, obesity [body mass index (BMI) > 30 kg/m^2] was seen in 66.7% of dengue, 85.7% of COVID-19, and 75% of undiagnosed AUF.

Hypertension (55.4%) and coronary artery disease (CAD) (12.4%) were found to be associated with severe COVID-19 by Sanyaolu et al.[9] Similarly, while 28.6% of COVID-19 patients with hypertension and another 28.6% with CAD had adverse outcome, only 11.9 and 13.4% had hypertension and CAD in COVID-19 patients without adverse outcome. Also, in our study, hypertension was found to be significantly associated with adverse outcomes in dengue.

However, while Zhao et al. suggested that chronic obstructive pulmonary disease (COPD) and smoking contribute to worse outcomes in COVID-19, only COPD but not smoking was significantly associated with adverse outcomes in COVID-19 patients.[10] Also, malignancy and chronic kidney disease (CKD) were seen in a higher proportion of AUF patients with adverse outcomes across various etiologies, similar to the study results of Sanyaolu et al.[9]

Ledika et al. suggested that delay in admission (≥5 days of onset of fever) was significantly higher among the patients with severe dengue.[11] Similarly, in our study, when the mean duration from fever onset to first hospital visit was 2.7 days in dengue patients without adverse outcomes, it was 6.1 days in dengue patients with adverse outcomes. Also, a significant delay in visiting the hospital after the onset of fever was found in other etiologies of AUF, which had adverse outcomes. Ledika et al. also proposed thrombocytopenia (<50,000) to be a predictor of severe dengue. However, the decreased number of platelets was due to the delayed presentation of patients as they are in a critical phase of illness when platelet levels are expected to be at their nadir.

Elevated liver enzymes were reported in dengue, scrub typhus, malaria, and enteric fever. Elevated levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were seen in 11 and 56%, respectively, during the 1st week of typhoid illness in a study by Morgenstern

and Hayes.[12] In our study, 10.2% of patients with enteric fever had elevated AST and ALT levels, majority of them tested in the first week of illness (Table 1). However, in two patients with enteric fever who had adverse outcomes, both had elevated serum transaminases. Elevated AST levels were also a part of the scoring system suggested by Mitra et al. to distinguish dengue and scrub typhus.[13] In our study, elevated serum transaminases (AST and ALT) were seen in all etiologies of AUF having adverse outcomes, including undiagnosed AUF when compared to AUF without adverse outcomes. However, elevated AST levels were more conspicuous in typhoid and dengue when compared to other etiologies (Table 1).

Results of the study by Mishra and Sorabjee showed a median value of serum procalcitonin in enteric fever to be 0.22 ng/mL.[14] Our study differs from the results of Mishra and Sorabjee, and the mean serum procalcitonin level in enteric fever is 3.21 ng/mL, significantly higher than that of the other etiologies of AUF. However, 50–100% of all cases of AUF with adverse outcomes had mildly elevated serum procalcitonin, though not manifold times of normal values as seen in bacterial sepsis.

Strengths and Limitation

The strength of our study is that it is one of the few studies comparing the level of rise in inflammatory markers among the common aetiologies of AUF. It is a novel study that proposes diagnostic importance to the inflammatory markers level in identifying the etiology of AUF.

The major limitation of our study is that it is a single-center study with a limited number of patients, so no recommendations can be made based on the results that were arrived at.

Conclusion

Dengue, enteric fever, COVID-19, scrub typhus, and malaria are the common causes of AUF in urban India. A sizeable proportion of AUF remains undiagnosed due to various reasons, the most common being the nonavailability of a testing facility.

There are subtle differences in the levels of pro-inflammatory markers such as CRP, D-dimer, and ferritin among different AUF etiologies. Careful consideration of the same will help distinguish the possible etiology at an early stage when diagnosis is a challenge. Our study was correctly able to identify 90.8% of nonsevere dengue, 87.8% of typhoid, 83.6% of COVID-19, and 91.4% of scrub typhus patients based on the inflammatory markers level.

The presence of diabetes (both types 1 and 2 diabetes mellitus), obesity, COPD, CAD, and CKD is associated with the emergence of adverse outcomes in patients with AUF. Our study indicates that rising or elevated levels of pro-inflammatory markers in AUF indicate a likely adverse outcome. Resources and monitoring should be intensified in patients with AUF who have elevated CRP, D-dimer, and ferritin.

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ORIGINAL ARTICLE

Study of Association of Erectile Dysfunction with Metabolic Syndrome and Its Correlation with Endothelial Dysfunction in an Indian Population

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Received: 05 July 2022; *Revised:* 18 October 2023; *Accepted:* 20 October 2023

Abstract

Background: Metabolic syndrome (MS) has emerged as a new health risk, and its associated metabolic derangements have detrimental effects on the cardiovascular system. In recent years, MS has been reported to affect reproductive health in males. It has been reported to be associated with erectile dysfunction (ED) and has been attributed to be due to endothelial dysfunction. Poor endothelial function in ED usually affects small-sized vasculature, so it can be looked at as a predictor for the endothelial dysfunction of macro vasculature. The aim of the present study was to determine the association of ED in patients with MS and to determine its correlation with endothelial dysfunction.

Materials and methods: It was a hospital-based case–control study in which 120 male patients with MS and 120 age-matched controls were enroled. Demographic profiles, anthropometry, past illnesses, and medical history of patients were obtained. MS was diagnosed according to the International Diabetes Federation (IDF) criteria and was measured using the flow-mediated dilation (FMD) method with the help of ultrasound used to assess endothelial dysfunction. Diagnosis of ED was based on the International Index of Erectile Function (IIEF) scale.

Results: The study participants had a mean age of 40.91 ± 11.41 years. The majority of cases (57.5%) had ≤6 months of history of MS. The prevalence of ED was 31.7% in cases compared to 5% in controls, thus showing a significant difference between cases and controls. Mean IIEF scores were significantly lower in cases (18.82 ± 5.59) compared to those in controls (23.00 ± 2.57). A moderate positive and significant correlation was observed between FMD and IIEF scores. With an increasing number of MS components, there was a significant increase in the prevalence of ED. Those with ED had significantly lower mean FMD values (5.1 ± 1.1%) compared to those not having ED (10.9 ± 3.3%).

Conclusion: The findings of the present study showed that there is a significant association between ED and MS. We observed that the increase in components of MS increased the prevalence of ED in MS. Endothelial dysfunction measured by FMD was correlated with ED.

Journal of the Association of Physicians of India (2024): 10.59556/japi.72.0535

Introduction

Erectile dysfunction (ED) is defined as the inability to obtain a penile erection sufficient for a satisfactory sexual performance. It is a prevalent disorder affecting >15% of men across the globe.[1] The etiology of ED is multifactorial, and it is more common with increasing age.[2,3] The importance of ED is not only that it has a negative impact on the quality of life in men,[4,5] but epidemiological studies indicate that the occurrence of ED might increase the risk for coronary heart disease and suggests that a diagnosis of ED is a sentinel event that should prompt evaluation of coronary heart disease in the male population.[6,7] The main mechanism underlying the pathophysiology of both ED and cardiovascular disease (CVD) seems to be related to atherosclerosis and endothelial dysfunction.[8,9]

Metabolic syndrome (MS) is a cluster of metabolic abnormalities that starts with insulin resistance and continues with the addition of abdominal obesity, glucose intolerance or diabetes mellitus (DM), dyslipidemia, hypertension, and coronary artery disease. It has been shown to be associated with CVD by directly influencing vascular function. Therefore, it can be hypothesized that patients suffering from MS might have compromised sexual function. There is some literature available to suggest that patients with MS have more propensity for ED.[10–12] There is not much literature available in our population.

Early diagnosis of ED might provide an opportunity to unravel the risk of CVD. Therefore, the aim of our study was to determine the association of ED with MS and assess its correlation with endothelial dysfunction.

Materials and Methods

This study was conducted in the Departments of Medicine, Surgery, and Radiodiagnosis, Era's Lucknow Medical College and Hospital, Era University, Lucknow, Uttar Pradesh, India, which is a medical college hospital, between January 2017 and December 2018.

In this hospital-based cross-sectional study, 120 patients with MS [as per International Diabetes Federation (IDF) criteria] and 120 males as age-matched controls were included after ascertaining compliance with inclusion and exclusion criteria. Following enrolment, demographic information (age, place of residence, occupation, and socioeconomic status) was obtained from all the patients. Among cases, chief complaints and duration since the detection of MS were noted. A past history of medical illnesses was noted in all the cases and control, and they were inquired about their dietary habits and family history of systemic/chronic illness.

Inclusion Criteria

Participant selection—the study included males >18 years and <60 years as cases and controls. The MS was defined according to the IDF criteria.[13] MS by IDF is diagnosed as central obesity [waist circumference (WC) ≥94 cm (male), ≥80 cm or (female)] and any two of the following—blood pressure ≥130/85 mm Hg, triglycerides (TG) ≥150 mg/dL, high-density lipoprotein (HDL) ≤40 mg/dL in men and

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How to cite this article: Karoli R, Fatima J, Verma P, *et al.* Study of Association of Erectile Dysfunction with Metabolic Syndrome and Its Correlation with Endothelial Dysfunction in an Indian Population. J Assoc Physicians India 2024;72(5):17–20.

≤50 mg/dL in women, and fasting blood glucose ≥100 mg/dL.

Exclusion criteria of the study comprised of prostatic disease, peripheral or autonomic neuropathy, patients taking aldosterone receptor antagonists, β-blockers, and thiazide diuretics, nitrates, androgen therapy or alcohol addiction, smoking hypogonadism, history of pelvic trauma, and pelvic surgery. Patients with a history of psychiatric disease, men with debilitating disease, end-stage target organ diseases, and men with unfavorable penile anatomy for sexual acts were also excluded from the study. Written informed consent was obtained from all the study participants, and prior ethical approval for the study was obtained from the Institutional Ethics Committee.

Anthropometric assessment [weight, height, body mass index (BMI), hip and WC] of all the cases and controls was done. Blood pressure measurement, fasting blood glucose, and lipid profile assessments were also performed.

Endothelial Function

Endothelial dysfunction was estimated by flow-mediated dilation in the right brachial artery. This procedure was performed in a cool, dark, and quiet room. The brachial artery diameter was measured in study participants at the baseline in antecubital fossa with the help of B mode ultrasound (7–10 MHz) linear transducer) followed by reactive hyperemia induced by tying the pneumatic cuff for 4 minutes. The second reading was taken after 60 seconds. Three times, the reading was taken in a single participant, and the average was calculated. Flow-mediated vasodilation (FMD) index was calculated according to the following formula[14]:

$$FMD\ index = (post\ occlusion\ diameter - baseline\ diameter) \times 100/baseline\ diameter$$

Erectile Dysfunction

It was assessed by completing questions one through five of the International Index of Erectile Function (IIEF),[15,16] which is a multidimensional questionnaire for assessing ED. The erectile function score represents the sum of questions one through five of the IIEF questionnaire, with a maximum score of 25; a score ≤21 indicates ED.

22–25: No ED.
17–21: Mild ED.
12–16: Mild-to-moderate ED.
8–11: Moderate ED.
5–7: Severe ED.

Statistical Analysis

The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) 20.0 (SPSS Inc, Chicago, United States of America). The normality of the data was checked using the Shapiro–Wilk test. The continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as numbers and percentages. Two groups were compared with the student's *t*-test for continuous variables, and the Chi-squared test was used to test the difference between categorical variables. Pearson correlation was used to test for the correlation between continuous variables. A *p*-value < 0.05 was considered statistically significant. Multivariate logistic regression was used to assess the determining factors of ED.

Results

This was a hospital-based case–control study in which 120 male patients with MS and 120 age-matched controls were enroled. Demographic profiles, anthropometry, past illnesses, and patients' medical history were obtained. Subsequently, with the help of the flow-mediated dilation method, endothelial dysfunction was estimated using ultrasound. All the cases and controls were assessed for ED using the IIEF score.

In the present study, the age of MS patients ranged from 20 to 59 years. The mean age of patients was 40.91 ± 11.41 years (Table 1). The majority of patients were in the age-group 40–59 years (57.5%). The mean age of controls was 40.31 ± 11.33 years. There was no statistically significant difference in the age of cases and controls. The majority of cases and controls were from urban areas (64.2 vs 61.2%). The majority of cases (57.5%) had <6 months of history of MS.

Family history of systemic/chronic illnesses was reported in 19.2% of cases compared to 10% of controls, thus showing a significant difference between the two groups. The mean BMI, waist-to-hip ratio and hip and WC of the cases were significantly higher than those of the controls.

Prevalence of hypertension, glucose intolerance, central obesity, and dyslipidemia (low HDL and raised triglyceride levels) was significantly higher in cases compared to that in controls. Mean FMD values were significantly lower in cases (6.8 + 1.7%) compared to those in controls (12.8 ± 2.8%). With an increasing number of MS factors, a significant decrease in mean FMD values was observed. Prevalence of ED was 31.7% in cases compared to 5% in controls, thus showing a significant difference between the two groups. Mean IIEF scores were significantly lower in cases (18.82 + 5.59) compared to those in controls (23.00 + 2.57).

On univariate analysis, all five components of MS (hypertension, diabetes, central obesity, low HDL, and raised triglyceride levels were found to be significantly associated with ED. Mean BMI, WC, fasting blood sugar, systolic blood pressure, and diastolic blood pressure levels were significantly higher among those with ED compared to those not having ED, whereas mean HDL levels were significantly lower among those having ED compared to those not having ED as shown in Table 2. With an increasing number of MS components, there was a significant increase

Table 1: Clinical parameters in the cases and controls

Variables	*Cases (n = 120)*	*Controls (n = 120)*	*p-value*
Age (years)	40.91 ± 11.41	40.31 ± 11.33	0.12
Urban population(%)	64.2%	61.2	0.07
BMI (kg/m^2)	24.2 ± 1.3	22.2 ± 1.1	0.01
Prevalence of ED	38 (31.7%)	6 (5%)	0.001
IIEF score	18.82 ± 5.59	23.00 ± 2.57	0.03
FMD (%)	6.8 ± 1.7%	12.8 ± 2.8%	0.001

Table 2: Association of risk factors of MS and ED

Serial number	*Parameters*	*ED (n = 44)*		*No ED (n = 196)*		*Significance of differences*	
		Mean	*SD*	*Mean*	*SD*	*"t"*	*"p"*
1	BMI (kg/m^2)	27.62	5.10	23.85	5.53	4.142	0.01
2	WC (cm)	99.84	9.43	86.27	13.76	4.383	0.001
3	Fasting blood glucose (mg/dL)	110.11	12.46	87.33	13.68	3.909	0.001
4	Triglyceride (mg/dL)	207.16	104.95	178.48	91.58	1.826	0.029
5	HDL (mg/dL)	37.28	8.21	48.51	12.80	-6.162	0.001
6	Systolic blood pressure (mm Hg)	148.66	16.45	129.69	15.96	4.977	0.003
7	Diastolic blood pressure (mm Hg)	87.77	11.33	80.45	10.17	3.073	0.032

Table 3: Association of ED and number of components of MS

Serial number		ED (n = 44)		No ED (n = 196)		Total (N = 240)	
		No.	%	No.	%	χ^2	"p"
1	None	4	9.1	66	33.7	31.058	0.001
2	One	2	4.5	41	20.9		
3	Two	0	0.0	7	3.6		
4	Three	17	38.6	43	21.9		
5	Four	9	20.5	22	11.2		
6	Five	12	27.3	17	8.7		

Table 4: Binary logistic regression for association between ED with different components with MS and FMD

	B	Standard error	Wald	Degree of freedom	"p"	OR	95% confidence interval for EXP(B)	
							Lower	Upper
High blood pressure	1.280	1.125	1.294	1	0.255	3.597	0.396	32.651
Glucose intolerance	0.068	1.636	0.002	1	0.967	1.070	0.043	26.431
Raised WC	0.141	9.715	0.000	1	0.988	1.151	0.000	214161246.7
Reduced HDL	1.113	0.879	1.601	1	0.206	3.043	0.543	17.052
High TG	−1.320	0.960	1.889	1	0.169	0.267	0.041	1.754
FMD	−3.159	0.663	22.721	1	0.001	2.34	1.28	4.156
Constant	13.109	20.003	0.429	1	0.512	493332		

EXP(B), Exponentiation of beta coefficients. These are the odds ratios of the variables

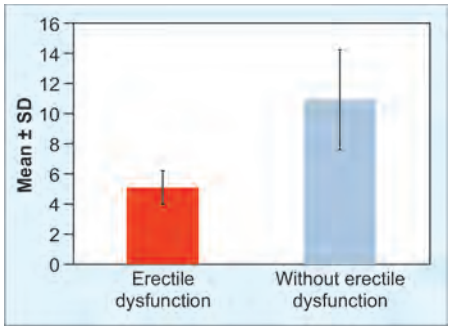

Fig. 1: Levels of FMD (%) in patients with and without ED

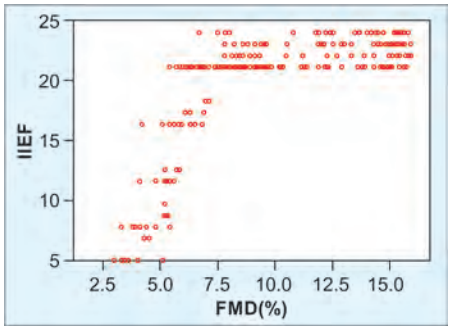

Fig. 2: Correlation between FMD and IIEF scores

in the prevalence of ED (Table 3). Those with ED had significantly lower mean FMD values, as shown in Figure 1 (5.1 ± 1.1%) compared to those not having ED (10.9 ± 3.3%)

On multivariate analysis (Table 4) evaluating the association of ED with hypertension, diabetes, central obesity, low HDL, high TG, FMD, and MS, only lower FMD levels were significantly associated with ED. A significant positive correlation was demonstrated between FMD and IIEF-5 scores ($r = 0.651$; $p = 0.001$) as shown in Figure 2.

Discussion

Erectile dysfunction (ED) is a relatively common health problem but is considerably neglected. As lifestyle diseases such as DM, hypertension, and obesity are increasing, ED has also increased exponentially. In the present study, the prevalence of ED in patients with MS and its correlation with endothelial dysfunction was evaluated.

Erectile dysfunction (ED) is a major health concern in the aging male population across the globe. The prevalence of ED is 10–20% in the overall male population and reaches 50–60% at the age of 70 years.[16,17] The association of ED with CVD can be largely explained by common risk factors such as aging, diabetes, hypertension, obesity, dyslipidemia, and smoking, but ED is an independent predictor of CVD as well.[18]

As widely known, MS represents a cluster of metabolic disturbances such as central obesity, hypertension, impaired glucose tolerance, and dyslipidemia, which are mainly derived from the accumulation of visceral adipose tissue and insulin resistance. MS and ED share a common pathophysiological mechanism; therefore, it is expected that the presence of MS may pose an increased risk of ED. Many previous studies have confirmed this.[19–22]

In the present study, the prevalence of ED among MS patients was 31.7% compared to only 5% in controls. Arrabal-Polo et al., in a case–control study, reported the prevalence of ED to be 64.9 and 9.5%, respectively, among cases and controls.[23]

A large population based on Suarez Arbelaez et al., including 36,911,824 subjects, concluded that MS and its individual components were significant risk factors for various urological disorders.[24]

Heidler et al. in a study of >2,000 men, observed that MS and central obesity are independently associated with an ED.[20]

Costa et al. conducted a study on 179 patients of ED and reported that lower total testosterone circulating levels were correlated with an increasing number of MS components, and the contribution of hypertriglyceridemia and WC was found to be strong.[25]

In the present study, we postulated that endothelial dysfunction could be an underlying reason for ED, and on evaluating and comparing the same between cases and controls, we found that flow-mediated dilation was significantly lower in cases of MS compared to controls.

Metabolic syndrome (MS) is known to affect endothelial function, and the findings of the present study also confirm this. The findings also showed that with an increasing number of components of MS, there was a decreasing trend of FMD values. Mazo et al.[22] in their study found endothelial function to be an important causative factor in the pathogenesis of ED among MS patients. As far as an association of MS components with ED was concerned, Lee et al.[26] highlighted fasting blood glucose levels as the most significant independent factor associated with ED, while Amidu et al.[27] found central obesity and raised blood pressure as the significant MS components associated with ED. In the present study, it was noted that an increase in the number of components of MS in cases was found to be associated with increased prevalence of ED and severity of ED, as suggested by a low IIEF-5 score. Similar results were reported by Lee et al.,[26] who found that with an increased number of MS components, there was a significant decrease in the IIPF-5 score.

It is possible that endothelial dysfunction might be an early marker followed by the development of atherosclerotic disease

and arterial occlusion at a later stage. A link between endothelial dysfunction and ED among MS and future cardiovascular events was shown by various researchers.[11,28–31] In the present study, mean IIEF scores were found to be significantly lower in MS patients, and FMD values showed a significant positive correlation with IIEF values, as reported by Coban et al.[32]

In India, a landmark study conducted by Sood et al. in 357 patients with ED found that ED severity was significantly correlated with the presence of MS. ED was correlated with central obesity, serum TG, and fasting blood sugar.[33]

Another study from India, including 113 subjects of MS, reported that the presence of the various components of MS was associated with increased prevalence and severity of ED.[34]

The findings of the present study showed that there is a significantly increased prevalence of ED in patients with MS, which increases with a number of components of MS. It was noted that endothelial dysfunction was higher in MS patients, and it had a significant correlation with the ED. Hence, it is recommended that among MS patients, endothelial dysfunction should be assessed from time to time, especially among those male patients who complain of sexual problems.

There are only a few studies available in India addressing this issue. This is the only study that has found a correlation between ED and low-flow-mediated dilation in our population. However, the present study has a few limitations, as it is a hospital-based study with a small sample size. Being cross-sectional and observational in design, we could not follow these patients to determine the causal relationship between ED/endothelial dysfunction and CVD. We suggest further research addressing this arena with a large number of patients to validate our data.

Conclusion

The findings of the present study showed that there is a significant association between ED and MS. We observed that an increase in components of MS increased the prevalence of ED in MS. Endothelial dysfunction measured by FMD was correlated with ED.

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ORIGINAL ARTICLE

Adoption of Technology by Healthcare Personnel: An Institutional Survey

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Received: 29 April 2023; *Revised:* 20 October 2023; *Accepted:* 11 December 2023

Abstract

Background: In the current era, technology has a significant influence on healthcare outcomes. Despite that, there are significant barriers and concerns toward the adoption of digital laboratory reporting systems among healthcare professionals in India. The aim of the study was to understand the overall attitude, barriers, and motivators toward the adoption of technology by healthcare personnel.

Methods: The study was conducted through a single-center and prospective questionnaire survey among physicians and surgeons of various specialities, with 107 participants. The electronic laboratory system at the institution, called "AADI," could be accessed across any computer terminal and through a web-based application that could be downloaded on any mobile device.

Results: The results of the study revealed that 98 out of 107 (91.59%) healthcare professionals used the digital platform regularly to access laboratory results, while only 9 (8.4%) did not use it. The mean satisfaction score of the users was 4.62 ± 0.51. The study showed that most users found the digital system to be more secure and reliable, which led to significant time savings compared to the paper-based system. The study also found that age was a determinant of usage, with younger healthcare professionals using the application more frequently.

Conclusion: Overall, the study suggests that digital laboratory reporting systems have significant benefits, and further efforts are needed to increase adoption in healthcare establishments in India.

Journal of the Association of Physicians of India (2024): 10.59556/japi.72.0524

Introduction

Digital reporting of laboratory results or accessing laboratory results electronically through a dedicated platform has several advantages and is gradually replacing old-fashioned paper-based reporting of laboratory results. Ease of access, eco-friendliness, and cost-saving are some of the driving forces behind its widespread adoption. Most first-world countries have already made the transition to electronic laboratory reporting. In India, the initial cost of setting up a digital laboratory information system has deterred establishments from shifting to the modern digital platform for reporting. The efforts of a few healthcare setups in India that have also adopted the technology have been thwarted due to prejudices and reluctance to adapt. Thus, the benefit of an electronic laboratory reporting system remains underutilized even after adopting the system.

While the utility of a digital reporting system has been established, there are mixed views about its adoption.[1] As a prerequisite for greater adoption, it is therefore important to understand the attitudes, barriers, concerns, and motivators that impact widespread adoption of the technology.

Methodology

This was a single-center and prospective study in which a questionnaire survey was conducted among physicians and surgeons of various specialities. The electronic laboratory system at our institution, called "AADI," can be accessed at any computer terminal in the hospital. Moreover, the web-based application can be downloaded to any mobile device. Access control is established through dedicated usernames and passwords, approved and monitored by the institution's information technology support team. Laboratory results can be accessed 24 hours a day, either on-site or remotely, using one of these mechanisms.

The questionnaire was designed and validated by two independent senior clinicians. The questions were prepared on a web-based platform (Table 1) and broadly aimed at correlating usage with demographic factors as well as the operating system and type of mobile devices used. Apart from identifying usage among those surveys, questions were also aimed at identifying barriers and motivators for adoption, as well as toward understanding the perspectives of the users regarding the advantages and disadvantages of the digital system over the previous paper-based system. Any concerns over security breaches were also assessed in the survey.

Statistical Method

An α-level of 5% was taken, and a *p*-value < 0.05 was considered significant. Through a method of random sampling, 125 healthcare professionals were identified to participate in the survey. A timeline of 72 hours was prescribed to record the responses. The responses were analyzed using standard statistical methods. Categorical variables were expressed as the number of patients, and continuous variables were expressed as mean ± standard deviation. Categorical variables were compared across the two groups using Pearson's Chi-squared test, and continuous variables were compared using an unpaired *t*-test. The statistical software Statistical Package for the Social Sciences version 20 was used for the analysis.

Sample Size Calculation

For this survey, the sample size (*n*) was calculated according to the formula:

$$n = z2 * p * (1 - p) / e2$$

Where,

z = 1.645 for a confidence level (*α*) of 90%.

p = proportion was 10% (expressed as a decimal = 0.01).

e = margin of error (0.05).

Using these parameters, *n* [= 1.6452 × 0.1 × (1 − 0.1)/0.052] was equal to 98. Considering that the response rate for online surveys is poor, we included a 25% dropout rate, and the sample size was 123, which was rounded off to 125.

Results

A total of 107 doctors were surveyed, of which 98 (91.59%) reported regular usage of

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How to cite this article: Katragadda NS, Shetty DP, Narayan P. Adoption of Technology by Healthcare Personnel: An Institutional Survey. J Assoc Physicians India 2024;72(5):21–24.

Table 1: Comparison between users and nonusers

	Not using app 9 (8.4%)	*Using app 98 (91.6%)*	*p-value*
Gender			
Male	8 (88.9%)	83 (84.7%)	1
Female	1 (11.1%)	15 (15.3%)	
Years of experience	26.56 ± 10.2	17.46 ± 10.03	0.01
Working specialty			
Physician	4 (44.4%)	50 (51%)	0.001
Surgeon	3 (33.3%)	47 (48%)	
Others	2 (22.2%)	1 (1%)	
Familiarity with technology			
Extremely savvy	8 (88.9%	83 (84.7%)	1
Limited to social media platforms	1 (11.1%)	15 (15.3%)	
Grade			
Senior consultant	8 (88.9%)	66 (67.3%)	0.51
Junior consultant	1 (11.1%)	13 (13.3%)	
Trainee doctor	0	18 (18.4%)	
How helpful is accessing the investigations using the application?			
1 (not helpful)	2 (22.2%)	0	<0.0001
2	1 (11.1%)	0	
3	3 (33.3%)	7 (7.1%)	
4	1 (11.1%)	23 (23.5%)	
5 (extremely helpful)	2 (22.2%)	68 (69.4%)	
Ease of use			
1 (not helpful)	1 (11.1%)	1 (1%)	<0.0001
2	0	1 (1%)	
3	5 (55.6%)	8 (8.2%)	
4	2 (22.2%)	24 (24.5%)	
5 (extremely helpful)	1 (11.1%)	64 (65.3%)	
Perceived improvement in delivery of patient care and/or outcome	2 (22.2%)	93 (94.9%)	<0.0001
Deemed more reliable than receiving the report over phone	7 (77.8%)	93 (94.9%)	0.11
Leads to improvement in patient care	6 (66.7%)	94 (95.9%)	<0.0001
The application leads to time saving	8 (88.9%)	98 (100%)	0.08
Helpful in research	6 (66.7%)	90 (91.8%)	0.05
More secure than accessing results over WhatsApp	7 (77.8%)	87 (88.8%)	0.3

the digital platform to access the laboratory results. Only 9 (8.4%) reported not using the application to access these results.

Summary of Findings among Users

The mean satisfaction score of the users was 4.62 ± 0.51. Of the people who were using the application, 79 (81%) reported using the service on a daily basis, while 11 (11.2%) reported using it few times in 1 week. 6 (6.1%) used it a few times in 1 month, and only 2 (2%) used it more infrequently. A total of 68 (69.4%) of the respondents were using it for >1 year at the time of the survey; 16 (16.3%) were using it for >6 months but <1 year and 14 (14.3%) were using it for <6 months.

All the respondents using the service felt that using the service led to significant time savings, and a vast majority, 93 (94.9%), felt that it led to improvement in the delivery of patient care and/or outcome. A total of 93 (94.9%) of the respondents felt that the result was more reliable than being informed of the results over the phone. A total of 87 (88%) of the users felt that this was a more secure system than sharing investigation results over WhatsApp. Most of the users [94 (96%)] reckoned that they were likely to use the service more often in the future, and 96 (98%) wanted to see other investigation results such as computed tomography (CT) scans, electrocardiograms (ECGs), and X-rays being made available digitally. A total of 70 (71.4%) confirmed that they would not like to go back to results available on paper.

Summary of Findings among Nonusers

Only 9 (8.4%) of those surveyed reported not using the service. Interestingly, 8 (89%) felt that using the service would lead to significant time savings. 7 (77.7%) reported using WhatsApp to share the lab results, and all of them felt that accessing the hospital system to access the results would be more secure. More than half of nonusers [5 (55.5%)] mentioned that they were likely to use the service in the future, and 9 (89%) wanted to see other services such as CT scans, ECGs, and X-rays being made available digitally.

Comparing Users and Nonusers

Comparing users with nonusers, it was found that gender, familiarity with the technology, or grade of seniority were not determinants of usage. However, there was a definite trend of increased usage among those younger in age. Only 1 (2.5%) respondent below the age of 40 was a nonuser, while the remaining 38 (97.4%) of those below 40 reported using the

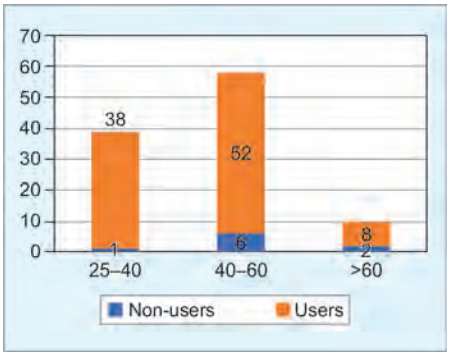

Fig. 1: Correlation between age of user and usage

application. Most of the nonusers [6 (66.7%)] were between the ages of 40 and 60 years (Fig. 1).

Years of experience were also a significant determinant of usage, with more experienced doctors (26.56 ± 10.2) being less amenable to using the application compared to those with fewer years of experience (17.46 ± 10.03, $p = 0.01$). The majority of the users, 68 (69.4%), found the application extremely useful (score 5 out of 5) compared to nonusers, 2 (22.2%), $p < 0.001$. Similarly, the majority of the users found the application and accessing the results extremely easy [64 (65.3%) vs 1 (11.1%), $p < 0.001$] compared to nonusers.

Discussion

Our study found high levels of satisfaction (mean score of 4.62 out of 5) and perceived benefits, including time savings, improved patient care, and increased reliability and security of the results among users. Most users (96%) planned to use the platform more in the future and wanted to see additional types of results available digitally, with most expressing interest in future use. Age and years of experience were found to be significant determinants of usage, with younger doctors and those with less experience more likely to use the platform.

Digital technology has become increasingly important in hospitals for accessing investigations. The key benefits are improved accuracy, speed, and efficiency. Test results can be accessed and shared electronically in real-time, allowing healthcare professionals to make faster and more informed decisions.[2] Furthermore, digital technology improves the efficiency of healthcare services by enabling healthcare professionals to access patient records and test results from anywhere at any time, making it easier to review and analyze patient data.[3] Another significant advantage of digital technology in accessing investigations is that it improves communication and collaboration among healthcare professionals. Patient records and test results can be shared securely and quickly, ensuring that everyone involved in a patient's care has access to the same information. This can lead to better-informed decisions and improved patient outcomes.

Moreover, digital technology in accessing investigations can reduce costs associated with paper-based recordkeeping, such as printing, storage, and shipping. Digital technology can also reduce the need for physical storage space, which can be a significant expense for hospitals.[4] Finally, digital technology can improve patient outcomes when accessing investigations. With more accurate, faster, and more efficient access to patient records and test results, healthcare professionals can make better-informed decisions about a patient's care, leading to earlier detection and treatment of diseases, improved patient safety, and better overall health outcomes.[3]

Digital technology enables access to investigation results and helps create a culture of information exchange within the hospital, which is at the core of health information exchange. It is also paramount in developing clinical decision support systems that are important in enhancing decision-making as well as the clinical workflow. The clinical decision support systems tools include notifications and alerts to doctors, impacting outcomes and cannot be developed without using digital records of investigations.[5]

In our study, the adoption of digital technology was high, with only 8.4% of respondents reporting that they did not use the service. Moreover, the majority of nonusers believed that using it would save them time. Interestingly, many nonusers were likely to use the service in the future and wanted to see other services such as CT scans and X-rays available digitally. Gender, familiarity with technology, and grade of seniority were not determinants of usage, but younger respondents were more likely to use the application. Additionally, years of experience were a significant determinant of usage, with less experienced doctors more likely to use the application. In keeping with our study, it has been shown that those adopting technology are more positively inclined compared to those who have not embraced technology.[6]

Some of the important barriers to the adoption of digital technology are cost, reluctance to change, lack of computer skills,[7] perceived disruption of workflow,[8] lack of technical support, concerns over privacy and security, and interoperability issues.[9] Interoperability is another challenge in the adoption of technology. Interoperability refers to the ability of different technologies to communicate with each other. One of the biggest barriers to the adoption of digital technology in healthcare is the high cost associated with implementing and maintaining these technologies.[10] Lack of interoperability is a significant barrier to the adoption of digital technology in healthcare.[11]

Data Security

The potential loss of hospital data and cyber theft, often associated with ransom attacks, pose significant risks to healthcare institutions. Hospitals store sensitive patient information and rely on digital systems for critical operations. The potential consequences of such events include not only breach of confidential patient data but can also lead to disruption of healthcare services, financial loss, and result in legal and regulatory consequences.

To mitigate these risks, we have implemented a robust set of security features to safeguard user and patient data. These measures encompass input validation to prevent malicious data, authentication and password management for secure access, session management for user session protection, access control for regulating permissions, cryptographic practices to protect sensitive data, error handling and logging to prevent data leaks, data protection, communication security *via* encryption, system configuration, database security, file management, memory management, and general coding practices for code integrity and security. These security measures collectively enhance the app's security and protect sensitive information.

Increasing the popularity of technology among nonusers in healthcare settings involves a combination of strategies that address barriers, promote awareness, and provide support for a smooth transition. The inclusion of training programs and workshops to enhance the digital literacy and technical skills of nonusers is important. Developing intuitive and user-friendly interfaces, communicating the benefits of technology adoption, and providing technical support to assist users in troubleshooting issues and addressing concerns promptly are some of the important measures that can be directed toward nonusers. In addition, assuring nonusers regarding presence of robust data security measures, offering incentives or recognition for healthcare professionals who embrace technology, can make the transition to digital technology more appealing.

Limitations

This was a single-center study carried out at a tertiary care center, and the findings

of the study may not be applicable to all healthcare setups. Even though the number of nonresponders was low (n = 18) and the sample size requirement was met, the nonresponse bias could have influenced the results, potentially skewing them in favor of those more enthusiastic about technology. It is also important to acknowledge that the implementation of digital platforms can be cost-prohibitive, particularly in resource-constrained settings, potentially restricting their adoption to larger urban centers and well-funded hospitals.

Conclusion

In conclusion, digital technology has many benefits when it comes to accessing investigations in hospitals. Its use improves accuracy, speed, and efficiency, reduces costs, and improves patient outcomes. As technology continues to advance, it is likely that the use of digital technology in accessing investigations will become even more critical in providing high-quality healthcare to patients. The adoption of technology in healthcare is not only inevitable but also desirable, as future prospects of technology in healthcare are limitless. The usage of electronic health records, drug traceability, wearable technology, and smartphone apps have the potential to allow interoperable health data exchange. Besides telemedicine and remote monitoring, artificial intelligence and machine learning algorithms are poised to be important drivers for future medical care.

Declarations

Availability of Data and Material

Provided as supplementary files.

Authors' Contributions

NSK contributed toward data collection, analysis, and writing of the first draft; DPS contributed to designing the study and writing the manuscript; and PN contributed to the design, data collection, analysis, and writing of the first draft.

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ORIGINAL ARTICLE

Fear of Coronavirus Disease 2019 among People with Epilepsy

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Received: 02 October 2022; *Accepted:* 28 August 2023

Abstract

Background: Epileptic patients are worried about getting coronavirus disease 2019 (COVID-19) infection and have recurrent thoughts of becoming infected with this virus.

Materials and methods: This study involved 205 patients diagnosed with epilepsy. The questionnaire included questions about sociodemographic information to analyze the demographic composition. The evaluation of the fear of COVID-19 infection was conducted utilizing the Fear of COVID-19 Scale (FCV-19S).

Results: The study enrolled 113 participants (55.10% male and 44.90% female) with an average age of 27.34 years. The mean fear score (FCV-19S) was 14.25, and fear of COVID-19 infection was present in 41 (20%) participants with a mean [standard deviation (SD)] FCV-19S score of 23.19 (3.33). Participants who were >45 years of age, married, graduated, and had low family income were significantly more likely to be fearful of COVID-19. Using logistic regression, education, marital status, and family income were identified as risk factors for having significant fear of coronavirus infection.

Conclusion: Given the notable prevalence of COVID-19-related fear within the epilepsy community, it is advisable to develop a well-thought-out strategy for promptly identifying vulnerable patients who may be at an increased risk of experiencing fear and anxiety.

Journal of the Association of Physicians of India (2024): 10.59556/japi.72.0494

Introduction

Novel coronavirus is responsible for causing coronavirus disease 2019 (COVID-19) infection. The COVID-19 pandemic and the resulting morbidity and mortality have caused significant fears and anxiety among people worldwide.[1]

The people suffering from epilepsy are more prone to additional risks of COVID-19 compared to the normal population, which in turn could complicate the management of COVID-19 as well as epilepsy 1.94 and also possibly lead to a higher incidence of infection.[2,3]

According to a recent study, epilepsy patients encounter an elevated risk of increased severity, with an odds ratio of 1.69, and increased mortality, with an odds ratio of 1.71. They are also more likely to require ventilator support in the intensive care unit (ICU) and experience hospital mortality because of COVID-19 infection.[4] Perceiving COVID-19 infection as a threatening event can lead to persistent worry about catching the infection, resulting in severe illness or death. This fear is likely to aggravate further because the pandemic is still causing high infection and mortality worldwide.[5]

According to a recent study of epileptic patients, 50.8% of epileptic patients were worried about getting COVID-19 infection and had recurrent thoughts of becoming infected with this virus.[6] Since COVID-19 infection may run a severe course in patients with chronic disease and epilepsy being a chronic disease, epileptic patients may experience more anxiety and fear compared to the general population.[1,7]

Presently, there is limited emphasis on the assessment and management of the fear of COVID-19 infection on a global scale.[1] To our knowledge, no previous study has attempted to assess the fear of COVID-19 infection, specifically in individuals with epilepsy. In an effort to address this gap in the current literature, this study was designed to investigate the prevalence of perceived fear related to the COVID-19 virus within the epileptic population during the ongoing pandemic.

Materials and Methods

This research involved a collaborative cross-sectional observational study conducted by the neurology and psychiatry departments at a tertiary care hospital affiliated with a medical college in Rajasthan. The study obtained approval from the Institutional Ethics Committee. Subsequently, after securing written consent, the investigation evaluated consecutively diagnosed cases of epileptic patients aged between 18 and 60 years, encompassing both genders. The study employed the following inclusion and exclusion criteria.

Inclusion Criteria

- People aged 18 years or older.
- Diagnosed cases of epilepsy.
- People who were literate and were able to read Hindi and English language.
- People who gave written consent and were eager to participate.

Exclusion Criteria

- People under 18 years of age.
- History of psychiatric illness or any chronic medical illness other than epilepsy.

After applying inclusion and exclusion criteria, 205 diagnosed cases of epilepsy were finally included in the study.

Assessment Tools

A total of 205 participants initially underwent the administration of a semi-structured proforma specifically designed to collect sociodemographic and clinical data. Subsequently, the following scale was applied to evaluate the fear of COVID-19 infection among participants:

The Fear of COVID-19 Scale (FCV-19S)[1] is a seven-item instrument designed to assess respondents' fear levels related to COVID-19 infections, with higher scores indicating greater levels of fear. Participants rate each question on a 5-point Likert scale. The comprehensive score on the scale has a potential range between 7 and 35. A cutoff score of ≥16.5 on the FCV-19S was used to identify individuals experiencing fear of COVID-19 infection. The scale has demonstrated robust psychometric properties in various studies, with Cronbach's α ranging from 81 to 91.[8]

The gathered data were systematically compiled and subjected to subsequent analysis. Quantitative data underwent analysis based on mean and standard deviation, while qualitative data were evaluated in terms of percentage. IBM Statistical Package for the Social Sciences (SPSS) statistics 23 for Windows was employed for statistical

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How to cite this article: Sureka RK, Gaur V, Agarwal A, *et al.* Fear of Coronavirus Disease 2019 among People with Epilepsy. J Assoc Physicians India 2024;72(5):25–28.

analysis. The data were further analyzed utilizing χ2 analysis and logistic regression. A *p*-value < 0.05 was deemed statistically significant.

Results

The mean age of our patient population was 27.34 ± 10.57, with the majority (*n* = 147, 71.07%) falling within the age-group of 18–30 years. A total of 113 (55.10%) were male, 69 (33.7%) were employed, 113 (55.10%) were educated till 10th class, 107 (52.10%) were married, and 136 (66.3%) were having family income of >17,555 INR per month. A total of 100 patient (48.78%) had <5 years of duration of epilepsy, and 93 (46.34%) had a history of last seizure episode in the previous 4 months. Only 16 participants (7.30%) had a history of comorbid medical illness, and 28 participants (13.70%) had a history of psychiatric illness in the family. Eight participants (3.09%) had a history of COVID-19 infection in the past, while 29 (14.10%) participants believed that COVID-19 infection could increase the chances of having seizures in the future. The overall mean [standard deviation (SD)] FCV-19S score was 14.25 (5.15), and fear of COVID-19 infection was present in 41 (20%) participants with a mean (SD) FCV-19S score of 23.19 (3.33) (Table 1).

Table 1: Descriptive statistics of the variables and their association with fear of COVID-19 infection using the Chi-squared tests

	Fear of COVID-19			
Variables	*n, f (%)*	*FCV-19S mean (SD)*	*Fear of COVID-19 present n (%), mean (SD)*	*p-value*
Total	205 (100%)	14.24 (5.15)	41 (20%), 23.19 (3.33)	
Age-group (years)				0.046*
18–30	147 (71.07%)	14.2 (5.18)	25 (17%)	
31–45	44 (21.05%)	14.05 (5.26)	11 (25%)	
>45	14 (06.08)	16.14 (4.36)	06 (42.9%)	
Sex				0.52
Male	113 (55.10%)	14.35 (5.36)	25 (22.1%)	
Female	92 (44.90%)	14.11 (4.91)	17 (18.5%)	
Occupation				0.27
Employed	69 (33.7%)	13.39 (4.50)	12 (17.4%)	
Nonemployed (students, housewife, retired)	136 (66.3%)	14.67 (5.42)	30 (22.1%)	
Education				0.010**
Till 10th class	113 (55.10%)	13.81 (4.97)	17 (15.0%)	
Till 12th class	37 (18.00%)	13.24 (4.25)	06 (16.2%)	
Graduate and above	55 (26.90%)	15.78 (5.79)	19 (34.5%)	
Relationship status				0.006**
Married	107 (52.20%)	14.82 (5.40)	14 (13.1%)	
Unmarried/divorced/widow, widower	98 (47.80%)	13.71 (4.87)	28 (28.6%)	
Family income (INR) per month				0.008**
≤INR 17,755	69 (33.7%)	15.69 (5.98)	06 (9.4%)	
>INR 17,755	136 (66.3%)	12.98 (3.92)	36 (25.5%)	
Duration of illness				0.179
1–4 years	100 (48.78%)	13.97 (4.92)	19 (19.0%)	
5–10 years	61 (29.76%)	15.28 (5.56)	17 (27.9%)	
>10 years	44 (21.46%)	13.41 (4.96)	06 (13.6%)	
Time since last seizures				0.14
1–4 months	93 (46.34%)	14.55 (5.40)	22 (23.7%)	
5–12 months	23 (11.21%)	15.28 (6.12)	07 (30.4%)	
>1 year	89 (43.45)	13.41 (4.96)	13 (14.6%)	
Comorbid medical illness				0.42
Yes	16 (07.80%)	14.21 (5.20)	04 (25.0%)	
No	189 (92.20%)	14.56 (4.61)	38 (20.1%)	

Contd…

Contd…

Variables	Fear of COVID-19			
	n, f (%)	*FCV-19S mean (SD)*	*Fear of COVID-19 present n (%), mean (SD)*	*p-value*
Psychiatric illness in family				0.275
Yes	28 (13.70%)	14.41 (5.33)	04 (14.3%)	
No	177 (86.30%)	13.14 (3.71)	38 (21.5%)	
Can corona increase seizure in future				0.035**
Yes	29 (14.10)	14.45 (5.34)	02 (6.9%)	
No	176 (85.90)	12.97 (3.66)	40 (22.7%)	
Have you been diagnosed with COVID-19 in past				0.486
Yes	08 (03.9%)	14.26 (5.20)	01 (12.5%)	
No	197 (96.1%)	13.75 (3.91)	41 (20.8%)	

*, significant at 5% level of significance; **, significant at 1% level of significance

Table 2: Results of logistic regression analysis on factors significantly associated with fear

	B	*Standard error*	*Significance*	*Exp (B)*
Age-group	0.582	0.544	0.261	1.790
Education	1.794	0.453	0.001**	6.016
Marital status	0.977	0.364	0.007**	2.657
Family income per month	−1.722	0.567	0.002**	0.179
Can corona increase seizures	−1.601	0.843	0.057	0.202

*, significant at 5% level of significance; **, significant at 1% level of significance

A significant association was identified between FCV-19S scores and various factors, including age-group (p = 0.05), education (p = 0.010), marital status (p = 0.006), family income per month (p = 0.010), and the perception of whether a Corona infection can increase the chances of seizures in the future (p = 0.035). Patients who were >45 years of age, educated till graduation and above, married, having a family income of ≤INR 17,755, and believing that corona infection can increase chances of seizure were significantly fearful of the COVID-19 virus. No significant association between fear of COVID-19 infection and other clinical variable, such as duration of epilepsy illness, time since last seizure, COVID-19 diagnosis, comorbid medical illness, and history of psychiatric illness in the family was found in our study (Table 1).

Regression analysis was conducted to identify the most significant predictors of fear of COVID-19 in patients with epilepsy. The outcomes of the binary logistic regression analysis concerning factors linked to the existence of fear regarding the contraction of COVID-19 infection are presented in Table 2. In our study, factors such as education, marital status, and monthly family income were identified as factors associated with a heightened risk of experiencing fear related to COVID-19 infection.

Discussion

Perceived fear is a very common emotion associated with the COVID-19 pandemic and can affect mood behavior and worsen the physical, social, and cognitive function of the person affected.[9]

There is a scarcity of data in the published literature related to fear of COVID-19 infection among epileptic patients; however, existing literature on fear of coronavirus infection in the general population reported that COVID-19 infection had been associated with significant deterioration in mental health due to anxiety about the lethality of this infection. Similarly, a recent survey conducted on epileptic patients indicated a substantial decline, approximately 65–70%, in the number of outpatient appointments, video electroencephalogram (EEG) monitoring, and surgery for epilepsy. The survey found that around 50% of individuals with epilepsy opted to postpone their scheduled outpatient visits to neurologists, attributing this decision to the perceived fear of contracting this infection.[10]

The results of this study indicate that the ongoing pandemic has instigated notable fear among individuals with epilepsy, as reflected in a mean fear score of 14.92 on a seven-item FCV-19S scale (with a possible range of 7–31). The study identified the presence of fear of COVID-19 infection in 41 (20.5%) participants with a mean (SD) FCV-19S score of 23.19 (3.33).

The mean FCV-19S fear severity score reported by a study conducted on the general population to assess COVID-19 fear was slightly higher than in our sample (16.8 vs 14.92); however, the majority of participants in this study were female (92%) with no preexisting medical condition.[11]

While assessing the factors associated with COVID-19-related fear among people with epilepsy, we found that participants who were >45 years of age, married, studied till graduation, and above, having a low family income were significantly more likely to be fearful of COVID-19. This is probably because older people were experiencing forced isolation, which may contribute to feelings of loneliness and isolation among them. Also, because of the current pandemic, several people have lost their jobs, and participants with low family incomes may face financial difficulties.

Interestingly, those participants who had this belief that the virus can cause seizures in the future were more fearful, which was expected. During the analysis, binary logistic regression was used to explore contributing factors among individuals with epilepsy at an elevated risk of developing fear related to COVID-19 infection. The primary determinants identified included education, marital status, and monthly family income.

Limitations

Firstly, it is important to note that our study involved a modest number of participants, limiting its statistical power. Secondly, participants were chosen through a convenience sampling method, which may not provide a comprehensive representation of the entire population. Moreover, the dependence on participants' self-reporting of fear symptoms constitutes a noteworthy

limitation. This reliance introduces the possibility of disparities between actual experiences and reported information, potentially resulting in inaccuracies within the dataset.

Conclusion

Our study has unveiled a moderate-to-high frequency of perceived fear of COVID-19 infection among individuals with epilepsy. Given the uncertainty surrounding the duration of the current epidemic, we suggest the development of a pre-planned strategy for the early identification of vulnerable epileptic patients who are more prone to encountering heightened levels of fear and anxiety. Replicating this study to a larger sample size would be beneficial. Furthermore, future research endeavors should concentrate on a longitudinal assessment of perceived fear and related anxiety in individuals with epilepsy.

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ORIGINAL ARTICLE

Comparison of Forced Oscillation Technique, Lung Volumes by Body Plethysmography, and Spirometry in Moderate Persistent Adult Asthma

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Received: 16 January 2024; *Revised:* 09 February 2024; *Accepted:* 12 February 2024

Abstract

Background: Spirometry is used extensively, but airway oscillometry is gaining acceptance for evaluating obstructive airway disorders. Moderate persistent asthma requires daily treatment with inhaled corticosteroids (ICS).

Materials and methods: We aimed to examine the relationship between airway oscillometry and lung volumes, which are the markers of lung physiology in obstructive airway disease and spirometry in the real-world clinical setting. A total of 72 adults with moderate persistent asthma followed up in our outpatient department from November 2021 to August 2022, and their clinical details and tests of spirometry, forced oscillation technique (FOT), and lung volumes by body plethysmography (BP) performed before and after bronchodilator administration were analyzed.

Results: The mean age of the study population was 40 years, and the majority (57%) were females. FOT detected airflow limitation in 12 of the 31 patients with normal spirometry. BP detected abnormalities in more patients than both spirometry and FOT (91.6 vs 73.6%, $p < 0.001$). Respiratory resistance 5 (R5) had a negative correlation with functional residual capacity (FRC) and total lung capacity (TLC). Reactance 5 (X5) correlated positively with inspiratory capacity (IC) and TLC and negatively with reserve volume (RV)/TLC ratio. A positive correlation was found between IC/TLC% and postbronchodilator X5 and between R5 and 19 and RV/TLC. R5 had a negative and X5 had a positive correlation with forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), FEV1/FVC, and maximal mid expiratory flow rates (MMEF). ΔX5 had a negative correlation with FEV1, MMEF, and FEV1/FVC. Spirometry detected postbronchodilator responsiveness in more patients than FOT when only the R5 criterion was used and in a comparable number when the X5 criterion was added. ΔX5 and R5–R19/R5 declined significantly after bronchodilators.

Conclusion: We concluded that there is a moderate correlation between FOT and spirometry and lung volumes by BP. FOT and spirometry should be used together to identify airflow obstruction and postbronchodilator responsiveness in asthma. Lung volumes by BP identify more abnormalities in adults with asthma than both spirometry and FOT. Thresholds to define postbronchodilator responsiveness (PBDR) for ΔX5 and R5–R19 need to be defined.

Journal of the Association of Physicians of India (2024): 10.59556/japi.72.0520

Introduction

Physicians have relied on spirometry for the detection of airflow limitation for more than a century. Asthma is characterized by reversible airflow obstruction, and its management relies on spirometry for diagnosis and follow-up. Spirometry is recommended for monitoring airflow limitation and assessing postbronchodilator responsiveness (PBDR) in asthma.[1] However, up to one-third of patients with asthma have normal spirometry.[2] Forced oscillation technique (FOT) was first described in the 1950s and became commercially available much later. FOT has piqued clinicians' interest due to the ease of performance because it only needs tidal breathing with no forceful maneuvers. This feature is especially important in the post-COVID-19 world. FOT may soon be a part of every pulmonary physician's armamentarium, like spirometry.[3,4]

In the middle of the 20th century, around the same time as the establishment of FOT, the technique of body plethysmography (BP) was also refined. BP allowed the measurement of static lung volumes, leading to the diagnosis of hyperinflation and air-trapping, which are consequences of the airflow obstruction that is diagnosed by spirometry. In asthma, BP can detect abnormalities more often than spirometry.[5] FOT and BP are two ends of the spectra of technical ease.

The nomenclature used to describe asthma severity has changed significantly over time but is consistently based on the treatment that patients require to achieve symptom control. Moderate persistent asthma comprises a clinically important subgroup that requires daily inhaled medication for achieving symptom control.[6] These patients are treated with low-dose inhaled corticosteroids (ICS) coupled with long-acting β2 agonists (LABA) as maintenance therapy.[1] This subgroup does not have so severe a disease as to warrant oral corticosteroids or biologics but needs daily medication and may still have symptoms, including night awakenings due to asthma. Due to the need for regular medication and persistent symptoms, this subgroup is important to clinicians.[7] The persistence of airflow limitation and postbronchodilator responsiveness despite treatment have prognostic implications for asthma.[1] Therefore, the sensitivity of tests to detect any airflow limitation or postbronchodilator responsiveness can impact the management of asthma.

The ATLANTIS study was designed to identify small airway dysfunction using spirometry, FOT, and lung volumes. However, the study did not differentiate between measured inspiratory and expiratory resistance and reactance by FOT, lacked data regarding postbronchodilator studies, and used limited parameters from BP to focus only on small airway obstruction.[4] Although small airways are an important site for airflow limitation in asthma and correlate with disease severity, prognostication of asthma requires testing for airflow limitation and postbronchodilator responsiveness across the entire network of conducting airways.

Although spirometry, FOT, and BP have been used in monitoring patients with asthma, to the best of our knowledge, no study has compared the use of these three tests in the real-world clinical setting for moderate persistent asthma. We aim to address the gap in knowledge, albeit

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How to cite this article: Athavale T, Athavale A. Comparison of Forced Oscillation Technique, Lung Volumes by Body Plethysmography, and Spirometry in Moderate Persistent Adult Asthma. J Assoc Physicians India 2024;72(5):29–35.

only partially. In this study, we sought to answer three questions—can we choose a single test with the greatest sensitivity to objectively identify airflow limitation and postbronchodilator responsiveness in moderate persistent asthma; since BP is a technically cumbersome test and requires bulky equipment, is there a role for combining spirometry and FOT (both office-based tests), and would this combination achieve comparable sensitivity; and how do the three tests relate to each other physiologically in the cohort of moderate persistent asthma?

Materials and Methods

Subjects

Medical records of the 72 adults with physician-diagnosed moderate persistent asthma who had followed up with the Department of Pulmonary Medicine and Environmental Pollution Research Centre from November 2021 to August 2022 and who had undergone spirometry, FOT, and BP with baseline and postbronchodilator tests were included. Asthma is diagnosed as per GINA guidelines, with the presence of variable respiratory symptoms of breathlessness, wheezing, chest tightness, or cough, along with variable airflow limitation.[1] Moderate persistent asthma is defined as symptoms on most days with the use of reliever medication or night awakening due to asthma symptoms at least once a week.[6] All patients received GINA step 3 treatment, that is, maintenance and as-needed low-dose ICS-formoterol therapy.[1] Patients with asthma are offered annual pulmonary function testing at our department. These tests are performed during a stable state without exacerbations for at least 3 months. Since there is evidence that FOT may supplement spirometry in asthma, all patients with asthma are offered annual testing with FOT, spirometry, and BP at our department.[4] Clinical details, including demographics, symptoms during the past 3 months, history of illness, and radiographs, are recorded in the pulmonary function laboratory. The inclusion criteria were adult patients with moderate persistent asthma who had all three tests performed within the study period. Patients with a history of exacerbations or hospital admissions within 3 months before lung function testing and those with missing data were excluded. The study was approved by the Institutional Ethics Committee at Seth GS Medical College, and a waiver of consent was granted due to its retrospective nature and absence of direct patient contact.

Study Design

In this observational study, we screened data from the laboratory records and included patients who fit the inclusion criteria. Baseline and postbronchodilator FOT for measuring respiratory resistance (R) and reactance (X), spirometry for measuring forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), ratio of FEV1/FVC and maximal mid expiratory flow rates (MMEF), and BP for measuring reserve volume (RV), functional residual capacity (FRC), total lung capacity (TLC), inspiratory capacity (IC) and RV/TLC and IC/TLC are performed routinely at our center.

Postbronchodilator responsiveness (PBDR) is assessed using salbutamol—either 5 mg nebulized solution or 400 µg delivered through a metered dose inhaler after withholding bronchodilators for appropriate durations. PBDR is tested between 20 minutes and 2 hours of inhalation of salbutamol. Spirometry follows FOT to prevent volume history and forced maneuvers from interfering with FOT and is followed by BP. PBDR testing is performed after ensuring at least 30 minutes gap before FOT. Records of acceptable tests were included in the study.[8]

Forced Oscillation Technique

Airway oscillometry (AO) superimposes sound waves generated with a loudspeaker over tidal breaths to measure R and X using FOT or impulse oscillometry (IO). FOT uses a single frequency, while IO delivers multiple sound frequencies as a square impulse. FOT achieves better resolution.[3] Lower frequencies (e.g., 5 Hz) travel longer than higher frequencies (e.g., 19 Hz) to reach the lungs' periphery. Normally, the resistance at 5 Hz (R5) and 19 Hz (R19) is comparable. An isolated increase in R5 suggests peripheral airway obstruction and predicts the risk of exacerbations of asthma. R is the in-phase, and X is the out-of-phase component of FOT measurements. X comprises the mass-inertive forces of the moving air column (inertance) and compliance of the lung (capacitance). X is measured at 5 Hz (X5). At lower frequencies, the capacitance of the lung dominates and is conventionally denoted with a negative sign. In hyperinflation and fibrosis, X5 is more negative due to capacitive loss.[3] ΔX5 is the difference between X5 in inspiratory and expiratory phases. In obstructive lung diseases, due to expiratory flow limitation (EFL), sound waves cannot pass the choke point in expiration, leading to more negative expiratory X5 and higher ΔX5. Normal ΔX5 is ≤0.07 kPa/L/second, increases to 0.10 kPa/(L/second) in asthma and triples to 0.21 kPa/(L/second) in chronic obstructive pulmonary disease (COPD).[9]

Airway oscillometry (AO) was performed using the Resmon Pro FOT. R5, R19, and X5 are reported as absolute and percentage predicted values using reference equations.[10] The test is standardized with patients seated with hands supporting their cheeks and a nose clip and performing tidal breathing. A minimum of 15 acceptable breaths are analyzed. A mean of three tests is reported. The threshold of coherence of variance is ≤10% at R5. R5 and X5 are recorded in inspiratory and expiratory phases, and total R5 and X5 are reported separately. The predicted values are derived as per Oostveen equations.[10] R ≥ 150% predicted and X5 ≥ 150% predicted is abnormal. R5–R19 is the difference between R5 and R19. ΔX5 is a marker of EFL. PBDR is defined by a decrease in R5 > 40% or an increase in X5 > 50% of baseline.[8] The major limitation of this study is the absence of published reference equations for respiratory resistance and reactance in the Indian population. The current study has also used equations formulated from a Caucasian population.

Spirometry

Spirometry is performed using the Jaeger MasterScreen machine as per ATS guidelines, and Indian standard values are used for reference.[11] FEV1/FVC < 0.75 is abnormal.[1] FVC and FEV1 ≥80% predicted and MMEF of >65% predicted are normal. An increase in FEV1 by >200 mL and >12% suggests PBDR.[1] Global Lung Initiative equations are now routinely employed for reporting spirometry data. However, due to the absence of equations based on the Indian population and due to the significant discrepancy in the use of GLI equations when used in Indian patients, this study has relied on traditional Indian prediction equations.

Lung Volumes by Body Plethysmography

Body plethysmography (BP) measures lung volumes using Boyle's law. The patient seated in the body box breathes against a closed shutter. Pressure changes within the box and at the patient's mouth are used to calculate the thoracic gas volume. Residual volume (RV) and TLC are calculated by subtracting the expiratory reserve volume (ERV) from the FRC and adding IC to FRC, respectively. IC/TLC ratio predicts hyperinflation, is a risk factor for mortality, and has a positive correlation with X5 in COPD.[12]

Medisoft EXPAIR Bodybox 5500 is used to measure lung volumes by BP. RV, TLC, FRC, and IC are measured and reported using Indian standard equations. Values <80% predicted and >120% predicted are abnormal. RV/TLC and IC/TLC ratios are reported. We do not routinely perform respiratory resistance and conductance by BP in patients with asthma

since these parameters have not been found to add to the management of asthma.

Statistical Analysis

Categorial and continuous variables are expressed as percentage and mean ± standard deviation, respectively. Data were checked for normality with Shapiro–Wilk and Kolmogorov–Smirnoff tests. Pearson's and Spearman's rank correlation coefficients were calculated for normal and skewed variables, respectively. Post bronchodilator values were compared with baseline using the paired student *t*-test and Wilcoxon signed-rank test for normal and skewed distributions, respectively. FOT, BP, and spirometry were compared using the exact McNemar test. All analyses were performed at a 95% confidence level, and *p*-values reported.

Results

Baseline Characteristics

Tables 1 and 2 summarize baseline characteristics and lung function data, respectively. The majority were females (57%) with a mean age of 39.8 ± 12.8 years. Cough was the commonest symptom (63%), followed by breathlessness. The mean FEV1/FVC ratio was 77.7± 9.79%, the RV/TLC ratio was 45.89 ± 10.22%, and the RV/TLC% predicted was 148.46 ± 27.71%. Mean R5 was 4.83 cmH_2O/(L/second) and R19 was 4.22 cmH2O/(L/second). Mean R5–R19 was 1.55 cmH_2O/(L/second). Mean X5 was 0.67 cmH_2O/(L/second) and mean ΔX5 was 0.27 cmH_2O/(L/second).

Table 1: Baseline characteristics of the study population

Age, years	39.8 ± 12.8
Sex, female (%)	41 (57)
Body mass index, kg/m^2	23.54 ± 4.75
Symptoms	
Cough, %	45 (63)
Only exertional breathlessness, %	17 (23.6)
Only paroxysmal breathlessness, %	13 (18)
Paroxysmal and exertional breathlessness, %	27 (37.5)
Mode mMRC grade of exertional breathlessness	1
History of wheezing	39 (54.2)
Presence of allergic rhinitis	33 (45.8)
History of smoking	6 (8.3)
Biomass fuel smoke exposure	10 (13.9)
Dust exposure	43 (59.7)
GINA treatment step 3	44 (61.1)
GINA treatment step 4	28 (38.8)
Chest radiograph	
Normal	41 (56.9)
Suggestive of hyperinflation	10 13.8)
Presence of cystic shadows/other abnormality	21 (29.2)
Examination	
Normal	58 (80.5)
Presence of wheeze	8 (11.1)
Presence of comorbidities	
Diabetes mellitus	8 (11.1)
Systemic hypertension	10 (13.8)
History of pulmonary tuberculosis	9 (12.5)
History of COVID-19 infection	2 (2.7)

Continuous variables are expressed as mean ± SD; categorical variables are expressed as the number of patients (percentage); mMRC grade of breathlessness is expressed as mode

Postbronchodilator Responsiveness

Table 2 summarizes PBDR. There was an increase in FEV1 (180 ± 160 mL, $p < 0.001$), FVC (2.60 ± 0.82 vs 2.69 ± 0.82 L, $p < 0.001$), MMEF (1.86 ±1.19 vs 2.28 ± 1.32 L/second, $p < 0.001$), X5 inspiratory [–1.44 ± 0.87 vs 1.23 ± 0.82 cmH_2O/(L/second), $p < 0.001$], X5 expiratory [–1.72 ± 1.25 vs 1.24 ± 0.97 cmH_2O/(L/second), $p < 0.001$], decrease in ΔX5 [0.27 ± 0.91 vs –0.01 ± 0.58, $p = 0.003$], R5 [4.83 ± 1.94 vs 3.85 ± 1.56 cmH_2O/(L/second), $p < 0.001$], R19 [4.22 ± 1.37 vs 3.57 ± 1.06 cmH_2O/(L/second), $p < 0.001$] and RV/TLC ratio (45.89 ± 10.22 vs 43.96 ± 10.48%, $p < 0.01$) but no change in RV, TLC, and FRC.

Correlation of Baseline Lung Function Parameters

Tables 3 and 4 summarize the correlation of baseline lung function parameters. Baseline R5 had negative correlation with FEV1 ($R = -0.62$, $p < 0.001$), FEV1% predicted ($R = -0.42$, $p < 0.001$), FVC ($R = -0.55$, $p < 0.01$), FVC% predicted (–0.3, $p = 0.01$), FEV1/FVC ($R = -0.46$, $p < 0.001$), MMEF ($R = -0.56$, $p < 0.001$), and MMEF% predicted ($R = -0.52$, $p < 0.001$); and X5 positive correlation with FEV1 ($R = 0.62$, $p < 0.001$), FEV1% predicted ($R = 0.51$, $p < 0.001$), FVC ($R = 0.54$, $p < 0.001$), FVC% predicted ($R = 0.37$, $p < 0.001$), FEV1/FVC ($R = 0.46$, $p < 0.001$), MMEF ($R = 0.65$, $p < 0.001$), and MMEF% predicted ($R = 0.58$, $p < 0.001$). ΔX5 had negative correlation with FEV1/FVC ($R = -0.39$, $p = 0.001$), MMEF ($R = -0.36$, $p = 0.002$), MMEF% predicted ($R = -0.38$, $p = 0.001$), and FEV1 ($R = -0.26$, $p = 0.03$) but not with FVC and FVC% predicted. Prebronchodilator inspiratory R5 had a negative correlation with FRC ($R = -0.46$, $p < 0.001$) and TLC ($R = -0.44$, $p < 0.001$). Postbronchodilator inspiratory X5 had a positive correlation with IC ($R = 0.5$, $p < 0.001$).

Correlation between Postbronchodilator Responses

Table 5 summarizes the correlation between postbronchodilator responses. There was negative correlation between change in R5_19 and FEV1 (–0.27, $p = 0.02$), FEV1% predicted ($R = -0.26$, $p = 0.03$), FVC ($R = -0.30$, $p = 0.01$), and between change in X5 and FEV1/FVC ($R = -0.45$, $p < 0.001$), and RV/TLC and FEV1% predicted ($R = -0.30$, $p < 0.001$), FVC ($R = -0.36$, $p < 0.001$), and FVC% predicted ($R = -0.31$, $p < 0.001$).

Contribution of Small Airways to Airway Resistance

The ratio of R5–R19 and R5 was 22.8 ± 108.49%, fell to 5.39 ± 13.68% after bronchodilators ($p = 0.001$). In patients with normal spirometry, the baseline ratio was 1.68 ± 11.32% and paradoxically rose to 2.47 ± 12.5% ($p = 0.34$) after bronchodilators, while with abnormal spirometry, the baseline 38.76 ± 142.09% dropped to 7.6 ± 14.25% after bronchodilators ($p = 0.08$).

Detection of Airflow Limitation

Of the 31 patients (43.1%) with normal spirometry, 10 (32.3%) had abnormal R5 and 2 had abnormal X5. Of the 41 patients with abnormal spirometry, eight had normal FOT. Detection of abnormality by spirometry and FOT was comparable (56.9 vs 62.5%, $p = 0.38$). BP detected airflow limitation in 66 patients (91.6%), in 24 with normal spirometry ($p < 0.001$), and in 40 with normal FOT ($p < 0.001$). BP identified abnormal lung function in 14 more patients than a combination of FOT and spirometry (91.6 vs 73.6%, $p < 0.001$).

Detection of Postbronchodilator Responsiveness

Postbronchodilator responsiveness (PBDR) was detected in 28 (38.8%) patients with spirometry and in 12 (16.6%) by FOT with R5 criterion ($p = 0.02$). When the X5 criterion was added, FOT detected PBDR in 21 (29.1%) patients. FOT detected PBDR in 8 patients who were negative by spirometry, but spirometry detected PBDR in 15 patients who were over FOT.

Detection of Small Airway Obstruction

Maximal mid expiratory flow rates (MMEF) 75/25 is used in spirometry to measure small airway obstruction. RV/TLC is considered a measure of small airway obstruction in BP but is known to lack specificity. RV/TLC was abnormal in more patients than spirometry (63 patients, that is, 87.5% vs 40 patients, i.e., 55.5%; $p < 0.001$). Due to increasing evidence of reliance on MMEF 75/25 on FVC, a corrected value was derived as per reference equations.[13] However, the lower limit of normal derived from these equations failed to detect small airway dysfunction in all patients.

Table 2: Baseline lung function tests and postbronchodilator tests

	Baseline; mean (SD)	*Postbronchodilator; mean (SD)*	*Absolute change; mean (SD)*	*Percentage change; mean (SD)*	*p-value*
FEV1, L	2.04 (0.74)	2.22 (0.75)	0.18 (0.16)	9.99 (8.62)	<0.001
FEV1, % predicted	89.38 (23.35)	97.32 (22.68)	7.94 (6.86)	9.97 (8.63)	<0.001
FVC, L	2.60 (0.82)	2.69 (0.82)	0.09 (0.16)	4.26 (6.86)	<0.001
FVC, % predicted	88.62 (19.41)	92.39 (19.02)	3.77 (6.36)	377.08 (635.72)	<0.001
FEV1/FVC, %	77.7 (9.79)	81.72 (8.65)	4.01 (4.04)	5.56 (5.61)	<0.001
MMEF, L/second	1.86 (1.19)	2.28 (1.32)	0.42 (0.51)	28.26 (29.01)	<0.001
MMEF, % predicted	69.51 (37.58)	86.86 (40.35)	17.35 (15.45)	29.9 (26.41)	<0.001
TLC, L	4.81 (1.16)	4.81 (1.04)	−0.01 (0.55)	3.82 (40.37)	0.88
TLC, % predicted	93.42 (14.97)	92.54 (14.93)	−0.88 (6.8)	−0.71 (7.28)	0.27
RV, L	2.19 (0.59)	4.3 (18.74)	2.09 (18.7)	86.44 (757.03)	0.34
RV, % predicted	137.56 (32.9)	131.7 (34.2)	−5.85 (27.1)	−2.91 (20.95)	0.07
RV/TLC, %	45.89 (10.22)	43.96 (10.48)	−1.94 (6.85)	−3.35 (15.19)	0.01
RV/TLC, % predicted	148.46 (27.71)	142.96 (29.9)	−5.5 (21.42)	−0.96 (14.94)	0.03
FRC, L	2.80 (0.67)	2.78 (0.69)	−0.02 (0.47)	0.43 (17.59)	0.71
IC, L	2.05 (0.83)	2.02 (0.84)	− 0.02 (0.52)	3.56 (39.95)	0.64
IC/TLC, %	42.5 (14.8)	41.2 (12.4)	2.64 (38.05)	–	0.42
R5 total, cmH2O/(L/second)	4.83 (1.94)	3.85 (1.56)	−0.99 (1.25)	−17.07 (21.01)	<0.001
R5 total, % predicted	158.57 (53.4)	125.38 (43.03)	−33.19 (40.84)	−18.14 (21.14)	<0.001
R5 inspiratory, cmH2O/(L/second)	4.8 (1.89)	3.71 (1.37)	−1.09 (1.32)	−18.45 (22.26)	<0.001
R5 expiratory, cmH_2O/(L/second)	4.95 (2.1)	3.94 (1.77)	−1.01 (1.36)	−17.11 (21.42)	<0.001
R19 total, cmH_2O/(L/second)	4.22 (1.37)	3.57 (1.06)	−0.64 (0.85)	−12.9 (17.58)	<0.001
R19, % predicted	138.66 (36.97)	117.94 (29.44)	−20.71(26.88)	−13.1 (17.45)	<0.001
R5–R19*	1.55 (7.66)	0.31 (0.78)	−1.24 (7.64)	−55.2 (143.17)	0.17
X5 inspiratory*	−1.44 (0.87)	−1.23 (0.82)	0.20 (0.74)	−0.78 (80.37)	0.02
X5 expiratory*	−1.72 (1.25)	−1.23 (1.13)	0.49 (0.96)	−13.22 (89.16)	<0.001
X5 total*	−1.68 (0.99)	−1.24 (0.97)	0.37 (0.77)	−10.84 (64.42)	<0.001
Delta X5	0.27 (0.91)	−0.01 (0.58)	−0.28 (0.78)	3.33 (372.43)	0.003

*Wilcoxon signed-rank test

Table 3: Correlation between spirometry and FOT and BP parameters

	FEV 1		*FEV1% predicted*		*FVC*		*FVC% predicted*		*FEV1/FVC*		*MMEF*		*MMEF% predicted*	
	R	*p*	*R*	*p*	*R*	*p*	*R*	*p*	*R*	*p*	*R*	*p*	*R*	*p*
R5 inspiratory cmH_2O/(L/second)	−0.6	<0.001	−0.42	<0.001	−0.53	<0.001	−0.31	0.008	−0.4	<0.001	−0.53	<0.001	−0.5	<0.001
R5 expiratory cmH_2O/(L/second)	−0.59	<0.001	−0.45	<0.001	−0.51	<0.001	−0.30	0.01	−0.49	<0.001	−0.55	<0.001	−0.53	<0.001
R5 total cmH_2O/(L/second)	−0.62	<0.001	−0.42	<0.001	−0.55	<0.001	−0.30	0.01	−0.46	<0.001	−0.56	<0.001	−0.52	<0.001
R5 total % prediction	−0.43	<0.001	−0.40	<0.001	−0.34	0.003	−0.24	0.04	−0.41	<0.001	−0.43	<0.001	−0.48	<0.001
R19 total cmH_2O/(L/second)	−0.50	<0.001	−0.30	0.01	−0.46	<0.001	−0.20	0.09	−0.32	0.006	−0.47	<0.001	−0.44	<0.001
R19% predicted	−0.29	0.01	−0.28	0.01	−0.21	0.07	−0.16	0.17	−0.30	0.01	−0.34	0.003	−0.38	<0.001
R5–R19 cmH_2O/(L/second)	−0.54	<0.001	−0.49	<0.001	−0.47	<0.001	−0.38	0.001	−0.34	0.004	−0.50	<0.001	−0.49	<0.001
X5inspiratory cmH_2O/(L/second)	0.42	<0.001	0.32	0.006	0.41	<0.001	0.31	0.008	0.23	0.05	0.35	0.002	0.32	0.006
X5 expiratory cmH_2O/(L/second)	0.60	<0.001	0.51	<0.001	0.50	<0.001	0.34	0.004	0.50	<0.001	0.65	<0.001	0.60	<0.001
X5 total cmH_2O/(L/second)	0.62	<0.001	0.51	<0.001	0.54	<0.001	0.37	0.001	0.46	<0.001	0.65	<0.001	0.58	<0.001
ΔX5 cmH_2O/(L/second)	−0.26	0.03	0.27	0.02	−0.13	0.29	−0.09	0.45	−0.39	0.001	−0.36	0.002	−0.38	0.001
RV/TLC% predicted	−0.27	0.02	−0.51	<0.001	−0.24	0.04	−0.44	<0.001	−0.23	0.05	−0.22	0.06	−0.35	0.002
RV/TLC%	−0.63	<0.001	−0.61	<0.001	−0.60	<0.001	−0.64	<0.001	−0.39	<0.001	−0.53	<0.001	−0.47	<0.001
IC/TLC%	0.09	0.45	0.06	0.62	0.12	0.32	0.11	0.36	0.02	0.87	−0.03	0.80	−0.05	0.68

Detection of Abnormal Lung Functions in Symptomatic Patients

A total of 61 out of 72 (84.7%) patients had reported the presence of symptoms like cough and breathlessness in the preceding 3 months. Spirometry detected airflow limitation in 33 patients (54%), and FOT was abnormal in 38 patients (62.3%). This difference in the detection of airflow limitation was not statistically significant ($p = 0.25$, McNemar's test). All the 12 patients who had an abnormal FOT but a normal spirometry had respiratory

Table 4: Correlation between FOT and BP

	FRC (L)		*IC (L)*		*RV (L)*		*RV, % predicted*		*TLC (L)*		*TLC, % predicted*		*RV/TLC, %*		*RV/TLC, % predicted*		*IC/TLC, %*	
	R	*p*	*R*	*p*	*R*	*p*	*R*	*p*	*R*	*p*	*R*	*p*	*R*	*p*	*R*	*p*	*R*	*p*
Prebronchodilator R5 inspiratory, cmH_2O/(L/second)	**−0.46**	<0.001	−0.14	0.24	−0.10	0.40	0.14	0.24	**−0.44**	<0.001	0.08	0.53	**0.29**	0.01	0.17	0.16	**0.27**	0.02
Postbronchodilator R5 inspiratory, cmH_2O/(L/second)	**−0.39**	<0.001	−0.18	0.13	−0.15	0.20	0.09	0.45	**−0.39**	<0.001	0.12	0.31	**0.27**	0.02	0.10	0.40	0.08	0.53
Prebronchodilator R5 expiratory, cmH_2O/(L/second)	**−0.40**	<0.001	−0.09	0.45	0.005	0.96	0.16	0.17	**−0.31**	0.008	0.12	0.31	**0.36**	0.001	0.17	0.16	0.11	0.37
Postbronchodilator R5 expiratory, cmH_2O/(L/second)	**−0.33**	0.004	−0.15	0.20	−0.04	0.73	0.11	0.35	**−0.31**	0.008	0.10	0.40	**0.35**	0.002	0.14	0.24	0.02	0.87
Prebronchodilator R5 total, cmH_2O/(L/second)	**−0.42**	<0.001	−0.15	0.20	−0.05	0.67	0.13	0.27	**−0.39**	<0.001	0.14	0.24	**0.35**	0.002	0.10	0.40	0.16	0.17
Postbronchodilator R5 total, cmH_2O/(L/second)	**−0.36**	0.001	−0.17	0.15	−0.08	0.50	0.11	0.35	**−0.35**	0.002	0.11	0.35	**−0.33**	0.004	0.13	0.27	0.04	0.73
Prebronchodilator X5 inspiratory, cmH_2O/(L/second)	0.21	0.07	**0.31**	0.008	0.18	0.13	0.07	0.55	**0.36**	0.001	0.14	0.24	−0.21	0.07	−0.10	0.40	0.08	0.53
Postbronchodilator X5 inspiratory, cmH_2O/(L/second)	0.16	0.179	**0.5**	<0.001	0.16	0.17	0.04	0.73	**0.47**	<0.001	0.06	0.61	**−0.32**	0.004	−0.15	0.20	**0.35**	0.002
Prebronchodilator X5 expiratory, cmH_2O/(L/second)*	0.14	0.24	**0.28**	0.02	−0.01	0.91	−0.02	0.87	**0.29**	0.01	0.08	0.53	**−0.38**	<0.001	−0.20	0.09	0.20	0.09
Postbronchodilator X5 expiratory, cmH_2O/(L/second)*	−0.01	0.91	**0.36**	0.002	0.02	0.86	−0.02	0.85	0.22	0.07	0.04	0.71	**−0.27**	0.02	−0.20	0.10	**0.39**	0.001
Prebronchodilator X5 total, cmH_2O/(L/second)*	0.17	0.16	**0.34**	0.004	0.02	0.84	0.02	0.86	**0.36**	<0.001	0.12	0.32	**−0.39**	<0.001	−0.19	0.10	0.22	0.07
Postbronchodilator X5 total, cmH_2O/(L/second)*	0.07	0.55	**0.44**	<0.001	0.08	0.53	−0.01	0.95	**0.35**	0.002	0.05	0.70	**−0.32**	0.01	−0.20	0.10	**0.38**	0.001
Predelta X5, cmH_2O/(L/second)*	0.001	0.92	0.02	0.85	0.14	0.24	0.08	0.53	0.03	0.79	0.07	0.54	0.22	0.07	0.11	0.35	−0.04	0.75
Postbronchodilator delta X5, cmH_2O/(L/second)*	0.15	0.21	0.09	0.45	0.17	0.16	0.11	0.37	0.21	0.07	−0.03	0.77	0.09	0.45	0.20	0.10	−0.08	0.53
Prebronchodilator R5–R19, cmH_2O/(L/second)*	**−0.27**	0.02	−0.21	0.08	−0.03	0.79	0.08	0.53	**−0.32**	0.01	−0.06	0.60	**0.34**	0.004	**0.28**	0.02	0.002	0.99
Postbronchodilator R5–R19, cmH_2O/(L/second)*	−0.19	0.12	**−0.26**	0.03	−0.06	0.61	−0.10	0.41	**−0.29**	0.01	−0.07	0.58	**0.27**	0.02	0.08	0.53	−0.14	0.24
Prebronchodilator R19, cmH_2O/(L/second)	**−0.49**	<0.001	−0.05	0.67	−0.07	0.55	0.15	0.20	**−0.39**	<0.001	0.16	0.17	**0.27**	0.002	0.10	0.40	**0.33**	0.01
Postbronchodilator R19, cmH_2O/(L/second)	**−0.39**	<0.001	−0.10	0.40	−0.05	0.67	0.17	0.16	**−0.34**	0.004	0.17	0.16	**0.31**	0.008	0.14	0.24	0.13	0.27

*Spearman's rank correlation coefficient; Figures in bold indicate statistical significance

Table 5: Correlation of postbronchodilator reversibility measured by spirometry and FOT and BP

Reversibility	*FEV1, L*		*FEV1, % prediction*		*FVC, L*		*FVC, % predicted*		*FEV1/FVC, %*		*MMEF, L/second*		*MMEF%, predicted*	
	R	*p*	*R*	*p*	*R*	*p*	*R*	*p*	*R*	*p*	*R*	*p*	*R*	*p*
R5 inspiratory, cmH_2O/(L/second)	−0.19	0.12	**−0.25**	0.03	**−0.27**	0.02	**−0.29**	0.01	−0.09	0.45	0.09	0.45	0.13	0.27
R5 expiratory, cmH_2O/(L/second)	−0.19	0.12	**−0.25**	0.03	−0.20	0.09	−0.16	0.17	−0.18	0.13	0.07	0.55	0.12	0.32
R5 total cmH_2O/(L/second)	−0.17	0.16	**−0.26**	0.02	−0.23	0.05	−0.23	0.05	−0.13	0.27	0.07	0.55	0.09	0.45
R5 total, % predicted	−0.21	0.07	**−0.25**	0.03	−0.22	0.07	−0.22	0.07	−0.17	0.16	0.08	0.5	0.13	0.27
R19 total, cmH_2O/(L/second)	−0.09	0.45	−0.17	0.16	−0.09	0.45	−0.08	0.5	−0.15	0.2	−0.01	0.95	0.01	0.95
R19 total, % predicted	−0.09	0.45	−0.14	0.24	−0.07	0.55	−0.06	0.61	−0.15	0.2	−0.01	0.95	0.02	0.85
R5–R19, cmH_2O/(L/second)	**−0.27**	0.02	**−0.26**	0.03	**−0.27**	0.02	**−0.30**	0.01	−0.14	0.23	0.05	0.70	0.03	0.83
X5 inspiratory, cmH_2O/(L/second)	0.14	0.24	0.15	0.2	0.1	0.4	0.19	0.12	0.11	0.35	−0.001	0.99	**−0.24**	0.04
X5 expiratory, cmH_2O/(L/second)	0.12	0.32	0.17	0.16	0.12	0.32	0.11	0.35	0.18	0.13	−0.14	0.24	−0.13	0.27
X5 total, cmH_2O/(L/second)	0.22	0.07	**0.26**	0.02	0.23	0.05	**0.26**	0.02	**−0.45**	<0.001	−0.05	0.67	−0.05	0.67
ΔX5, cmH_2O/(L/second)	0.10	0.40	0.08	0.52	0.12	0.32	0.18	0.13	−0.1	0.41	**0.27**	0.02	**0.25**	0.04
RV/TLC, % predicted	−0.23	0.05	**−0.28**	0.01	**−0.37**	0.001	**−0.32**	0.006	0.08	0.5	−0.03	0.8	−0.05	0.67
RV/TLC, %	**−0.25**	0.03	**−0.30**	0.01	**−0.36**	0.001	**−0.31**	0.008	0.06	0.61	−0.08	0.5	−0.11	0.35
IC/TLC, %	−0.003	0.8	−0.08	0.5	0.02	0.86	−0.01	0.95	−0.10	0.40	−0.10	0.4	−0.17	0.16

Figures in bold indicate statistical significance

symptoms. Spirometry was abnormal in seven symptomatic patients with normal FOT.

Discussion

Forced oscillation technique (FOT) is an easy and portable test that is expected to gain wider adoption in physicians' practices. There is a gap in the knowledge of how spirometry (hitherto the most commonly performed pulmonary function test) and BP (a technically cumbersome test providing insights into lung volumes) relate to FOT. This study aimed to address this gap in the real-world clinical setting in the cohort of moderate persistent asthma. Patients with moderate persistent asthma need daily treatment with low-dose ICS-LABA and may manifest symptoms despite treatment. Persistent airflow limitation and PBDR, despite maintenance therapy, are associated with a higher risk of exacerbations and adverse outcomes in asthma. Therefore, the sensitivity of tests employed to detect these is important in clinical practice. In this study, we sought to answer three questions—is a single test adequately sensitive to diagnose airflow limitation in patients with moderate persistent asthma; is airway oscillometry sensitive enough to replace spirometry, or should these be used together, and how do these three tests relate to one another physiologically?

We found that BP detected abnormal lung function in significantly more patients (91.6%) even when results of FOT and spirometry were combined (73.6%). BP detected airflow limitation in an additional 14 patients. Spirometry and FOT complemented each other, and spirometry detected PBDR in significantly more patients than FOT when only R5 was used. These findings are in agreement with other studies.[14,15] Using X5 with R5 improved the detection of PBDR to be comparable with spirometry. Since we followed the threshold values of 40 and 50% change in respiratory resistance and reactance, respectively, to define PBDR, using lower thresholds may increase the sensitivity of FOT in detecting PBDR.

Small airway obstructions can affect up to 70% of patients with asthma and lung volumes due to BP, which are sensitive but nonspecific markers of small airway dysfunction.[16] Spirometry correlates moderately with FOT, but FOT is more sensitive in detecting small airway obstruction.[15,17,18] In our study, RV/TLC was more sensitive in detecting small airway dysfunction than spirometry. RV/TLC ratio lacks specificity since it measures air-trapping—a phenomenon that is commonly associated with but not mandatorily due to small airway dysfunction. The ATLANTIS study found that spirometry and FOT were more sensitive to small airway obstruction than RV/TLC but used only RV/TLC and FRC to detect abnormality. This study has included TLC and RV in addition to RV/TLC to define abnormal lung function. FVC-adjusted MMEF values did not detect small airway disease in any patient in our study.

Spirometry and FOT were comparable in the detection of airflow limitation in symptomatic patients. FOT detected abnormalities in 12 and spirometry in seven additional patients. This finding further supports the combined use of these tests in moderate persistent asthma. This combination works in two ways—it detects a greater number of patients with airflow limitation than either test alone and adds to prognostic evaluation; this combination also explains the presence of symptoms in those patients whose airflow limitation would have been missed if only one of the tests were used.

In our study, spirometry had a stronger negative correlation with R5 and a positive correlation with X5 than in other studies.[14,15,19] Our study demonstrated a significant correlation between absolute values of FEV1, FVC, MMEF, and R5. Since the predicted equations for spirometry and FOT may vary, the correlation between absolute values assumes clinical significance. This negative correlation suggests that airflow drops as the resistance of the respiratory system increases.

Small airway dysfunction measured by AOT is associated with bronchial hyperresponsiveness in asthma.[20] Various methods to assess small airways include FEV1/FVC, FOT, BP, and MMEF.[21] R5_19 is a marker of peripheral airway obstruction and small airway abnormality. Kraft and colleagues then found that peripheral airway resistance correlated with asthma severity and an increase in RV.[22] Our study also demonstrated a significant negative correlation between R5–R19 and spirometry and also identified the relationship between absolute values of R5–19 and FEV1, FVC, and MMEF.

The contribution of small airways to the total airway resistance is calculated using the ratio of R5–19 to R5 and varies between 10 and 30%. In COPD, this ratio increases with the severity of airflow limitation and symptom burden.[23] In our study, the R5–19/R5 was 22.8% at baseline and dropped to 5.39% after administering bronchodilators. This highlights reversible small airway obstruction measured by FOT in moderate persistent asthma. A threshold for defining PBDR in R5–R19 shall need further study.

In asthma, premature closure of airways during expiration increases RV. This may occur at the expense of the VC or with an increase in TLC. However, the RV/TLC ratio usually increases. In our study, we found a significant negative correlation between RV/TLC and spirometry parameters. Lung volumes are a reliable complement to FEV1 in identifying severity.[24] We found a significant negative correlation of R5–19 with TLC and a positive correlation with RV/TLC. Therefore, increased peripheral airway resistance correlates with increased air trapping. FOT and spirometry are dynamic tests. Lung volumes by BP are a static test. The correlation between the parameters of dynamic and static tests in this study explains the process of increased resistance and decreased flow that interferes with the patient's breathing, eventually causing changes to static lung volumes.

We have analyzed inspiratory and expiratory parameters in FOT separately. Paredi et al. found that expiratory R5 was higher than inspiratory R5 in asthma and COPD. Transmural pressures that tend to expand the lung during inspiration are smaller during expiration and allow the narrowing of airways. With increased airway resistance, the difference in the transmural pressure during the inspiratory and expiratory phases is accentuated, leading to higher expiratory R5.[9] In this study, the baseline expiratory R5 was higher than the inspiratory R5, but this was not statistically significant (4.95 ± 2.1 vs 4.8 ± 1.89 cmH_2O/(L/second), $p = 0.08$). This difference was significant in the postbronchodilator study (3.94 ± 1.77 vs 3.71 ± 1.37 cmH_2O/(L/second), $p = 0.01$) and needs further investigation in asthma.

Expiratory airflow limitation (EFL) is defined as the absence of an increase in airflow despite an increase in the driving pressures during expiration.[25] Dellaca et al suggested a threshold of ΔX5 of >2.8 cmH_2O/(L/second) in COPD for identifying EFL. Paredi et al. found the mean ΔX5 to be 1 cmH_2O/(L/second) in asthmatic subjects. In this study, the baseline ΔX5 was 0.27 cmH_2O/(L/second) and reduced significantly after bronchodilators to -0.01 ± 0.58 cmH_2O/(L/second), $p = 0.003$. ΔX5 had a negative correlation with flow variables in spirometry. We conclude that ΔX5 is also a marker of airflow limitation in asthma, and a threshold for PBDR should be defined.

The decreased FEV1 in asthma is the result of a myriad of interactions dependent on FVC. FVC is compromised by a disproportionate rise in RV against TLC. This rise in RV at the expense of FVC decreases FEV1. The FVC and, therefore, FEV1 do not fall unless the TLC fails to rise in proportion with RV. Hyperinflation-increase in TLC, defends FEV1 and FVC till the mechanism to prevent overdistension of the chest wall takes over and prevents

further rise in TLC. Therefore, although RV is a reliable complement of FEV1, FEV1 may not always complement RV. In this study, BP detected increased RV and RV/TLC ratio even when the spirometry and FOT were normal in 14 additional patients. BP was thus able to detect airflow limitation in 91.6% of patients compared to 73.6% by spirometry and FOT together.

Resistance 5 (R5) and R19 correlate positively with FRC and TLC. As the airway resistance increases, the respiratory system begins operating at a higher total lung volume till the elastic recoil of the chest wall allows it to do so. X5 is more negative in peripheral airway obstruction and increases, tending towards becoming positive when the obstruction is relieved. In this study, X5 correlated positively with IC and TLC. The correlation with IC is stronger with inspiratory X5, suggesting that patients with less peripheral airway obstruction can breathe in more air, even at a higher TLC. The negative correlation between X5 and RV/TLC explains this further. With worsening airflow limitation, the rise in RV overtakes the rise in TLC, and X5 becomes more negative.

The resting IC depends on end-expiratory lung volume. Casanova et al. proposed a threshold of 25 in COPD. In our study, the mean IC/TLC% was higher than this threshold (42.5 ± 14.8) and did not change significantly with bronchodilators. No significant correlation was found between IC/TLC% and spirometry. There was a significant positive correlation between IC/TLC% and postbronchodilator X5. X5 increased after administering bronchodilators and correlated with IC/TLC%.

This study has some limitations. A major limitation is the absence of published reference equations for FOT in the Indian population. When these equations become available, it will be useful to assess if the use of such equations impacts the results and, therefore, the sensitivity of FOT. Similarly, although GLI equations are now established as the standard for uniform reporting of spirometry, we were unable to use these in our study since they comprised the Indian population. This study is a retrospective one with a limited sample size. Moderate persistent asthma was defined in the study based on symptoms in the preceding 3 months and not based on the more objective scores of the Asthma Control Questionnaire or Asthma Control Test. Therefore, these findings shall have to be confirmed in a prospective study with a larger sample size and objective criteria for asthma control.

Conclusion

Forced oscillation technique (FOT) correlates with spirometry and lung volumes by BP in moderate persistent asthma. FOT and spirometry must be used together since one test may detect airflow limitation or PBDR while the other remains normal. Lung volumes by BP detect abnormalities in more patients than FOT and spirometry in this cohort. Future studies are needed to define a threshold of ΔX5 and R5–R19 for the detection of PBDR.

Acknowledgments

We thank the paraclinical and administrative staff for their contribution to this research.

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ORIGINAL ARTICLE

An Observational Study of the Physical and Biochemical Complications and Socioeconomic Status of Type 1 Diabetic Patients in West Bengal, India: A 25-year Follow-up Report of 224 Patients

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Received: 22 September 2023; *Revised:* 28 December 2023; *Accepted:* 08 January 2024

Abstract

Background: Limited information is available on the total profile of type 1 diabetes mellitus patients in India. The present study has been undertaken, therefore, in search of socioeconomic status, glycaemic status and the state of complications of the type 1 diabetics attending the diabetic clinic run by Calcutta Diabetes and Endocrine Foundation (CDEF), Kolkata.

Objectives: (1) To obtain the glycemic, socioeconomic, and complications status of type 1 diabetic patients; (2) to see any change of the abovementioned parameters in this follow-up period of 25 years; (3) to take necessary action to improve the quality of care and the health condition of the type 1 diabetics attending the clinic.

Study design and setting: A longitudinal observational study. A total of 265 patients were recruited for the study, having been diagnosed or seen within 1 year of diagnosis of type 1 diabetes at the Diabetic Clinic of CDEF. A total of 41 patients were excluded from the study for different reasons, and 224 patients were finally selected. These 224 patients were classified into five separate cohorts according to their first attendance in the diabetes clinic: 1996–2000 (I), 2001–2005 (II), 2006–2010 (III), 2011–2015 (IV), and 2016–2020 (V). Baseline and socioeconomic (based on education and occupational status) data was obtained at the first visit, and mean biochemical parameters were taken from multiple visits. Complications and mortality rates were calculated against the duration of the disease at the end of the study.

Results: Gradual improvement of glycemic status was noted when groups I and V were compared. Delayed development of complications and comparatively long life were also observed.

Conclusion: Several methods of improvement of clinical disease management, including continuous diabetes education with proper training, can improve diabetes care, leading to delays in the development of diabetic complications and ensuring longer as well as healthier life in type 1 diabetes. The development of socioeconomic status might have played some role.

Journal of the Association of Physicians of India (2024): 10.59556/japi.72.0537

Introduction

Type 1 diabetes is considered rare in India compared to the Western world.[1] Not only the incidence of type 1 diabetes but also the quality of patient care is not uniform across the regions of the world. However, because of the huge young population in India, a total number of about 100,000 children are living with type 1 diabetes in India, and this total number is quite significant.[2] As we have crossed a century since the discovery of insulin in 1921, we may turn around to see in the past few decades that there has been significant improvement in understanding the disease and improvement of technical assistance, which helped to improve patient care and the health parameters of type 1 diabetes. In 1925, Lawrence, in his book[3] "A Diabetic Life," declared, "Now modern discoveries, particularly insulin, have completely changed the outlook. There is no reason why a diabetic should not if he can be taught to do so, lead a long, normal life." Unfortunately, the benefits of the discovery, development, and deployment of insulin could not be made possible for all the needy type 1 diabetics, particularly in low-income countries (LIC). India is said to have gradually moved from a LIC to a middle-income country (MIC). On average, about three-fourths of type 1 diabetic children globally were unable to achieve optimized glycemic control.[4] However, the scarcity of representative population-based information in this regard may not fully reflect the true burden of type 1 diabetes.[5] We report our observations on the status of our type 1 diabetic patients in the last 25 years.

Objectives

- To obtain the glycemic, socioeconomic, and complications status of type 1 diabetic patients.
- To see any change of the abovementioned parameters in this follow-up period of 25 years.
- To take necessary action to improve the quality of care and the health condition of the type 1 diabetics attending the clinic.

Study Design and Methods

A total of 265 type 1 diabetic patients visited the Diabetes Clinic of the Calcutta Diabetes and Endocrine Foundation (CDEF) during the period of 1996–2020. They have either been diagnosed in the clinic or seen within 1 year of diagnosis. Type 1 diabetics were diagnosed as per diagnostic criteria, including fasting and postprandial blood glucose (PPBG) level, glycated hemoglobin (HbA1c) level and presence of urinary albumin and/or ketones. In some cases, anti-glutamic acid decarboxylase antibody levels are also estimated as and when necessary. Investigations were advised on their presenting symptoms like polyuria, polydipsia, polyphagia, loss of weight, weakness, dizziness, etc. Baseline clinical parameters, including height, weight, blood pressure, etc., were done for all the patients on their first visit. Height and weight were measured using a prestandardized centimeter scale and weighing machine in kilograms as used for all the patients of the clinic. The patients were asked to stand on the platform on the height scale and weighing

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How to cite this article: Maji D, Ghosh S, Roy RU, *et al.* An Observational Study of the Physical and Biochemical Complications and Socioeconomic Status of Type 1 Diabetic Patients in West Bengal, India: A 25-year Follow-up Report of 224 Patients. J Assoc Physicians India 2024;72(5):36–40.

machine, respectively, with minimum clothes and without shoes, and the parameters were recorded in centimeters and kilograms up to second decimals, respectively. Blood pressure was recorded 10 minutes after rest in a lying position in the left/right arm, which was found to be relatively high after three readings in each arm. The measuring instrument was a mercury sphygmomanometer. The result was expressed in millimeters of mercury.

A detailed personal history, including education, occupation, family history, and history of present and any previous illness, was also taken. Biochemical investigations like fasting blood glucose (FBG), PPBG, HbA1c, serum urea, creatinine, cholesterol, and urine for routine and microalbumin were done at least 3 monthly or as and when necessary with fully automated analyzer COBAS 6000/ COBAS C311 machine. Yearly eye checkups were conducted to exclude retinopathy, and biothesiometry was conducted to exclude peripheral neuropathy. A total of 41 patients were excluded from the study for different reasons, mainly loss of follow-up, lack of compliance, etc. The final study was based on 224 participants. The participants with follow-up were classified into five separate cohorts according to their first visit to the clinic, namely 1996–2000 (group I), 2001–2005 (group II), 2006–2010 (group III), 2011–2015 (group IV), and 2016–2020 (group V) for convenience in data analysis and statistical evaluation. Mean biochemical parameters were tabulated for separate cohorts and analyzed. Developments of complications were analyzed in the total cohort according to the duration of the disease, namely 0–9 years (group I1), 10–14 years (group II1), and 15 years and above (group III1) to show the gradual effect of complications at different timeline of the duration of diabetes. The complications include neuropathy, retinopathy, nephropathy, microalbuminuria, ketosis, infection, hypoglycemic events and any other illness. A total of 24 patients within the study period were expired. Lack of compliance and awareness of diabetes were the main reasons for the development of diabetic complications, which lead to early death. Some of them lead a healthy life with good control. They were fully aware of their disease and continued long, controlled, and healthy lives. The mortality was also observed against the duration of the disease. The results obtained have been expressed in tables and diagrams.

Statistical Analysis

Student's *t*-test and Chi-squared tests were performed to determine the significance of the difference between the variables, and a *p*-value of <0.05 was considered significant.

Results

Baseline demographic data is represented in Table 1. Parameters in different groups are comparable.

Figure 1 shows the male-to-female ratio. There were 111 males and 113 females out of a total of 224 patients. An almost equal number of males and females were recruited.

Mean FBG, PPBG, and HbA1c levels gradually declined, proceeding from groups I to V Table 2. The difference was statistically significant, comparing the results between groups I and V. In other cases (i.e., within groups II, III, and IV), though numerically better control was observed, the statistical differences were not significant (Fig. 2).

Figure 3 shows the improvement of HbA1c from groups I to V.

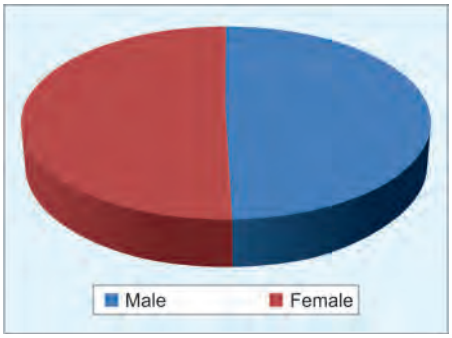

Fig. 1: Male-to-female distribution

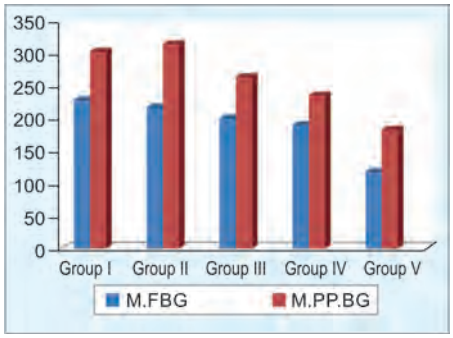

Fig. 2: Comparison of glycemic status; both FBG and PPBG show improvement from groups I to V

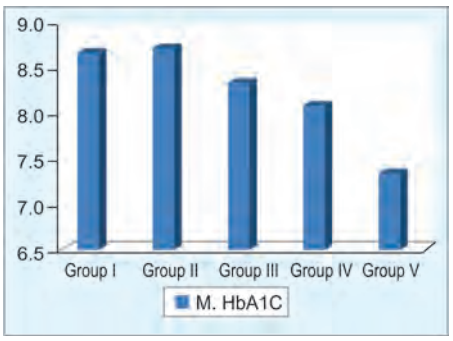

Fig. 3: Comparision of HbA1c Levels

Table 1: Baseline data

Basic vitals	*Group I*	*Group II*	*Group III*	*Group IV*	*Group V*
Mean age in years	22.33 ± 9.67	21.0 ± 9.03	24.48 ± 11.05	22.0 ± 11.57	25.33 ± 5.03
Male/female	19/20	21/23	23/25	22/21	26/24
Mean height in cm	150.20 ± 26.66	153.25 ± 17.70	156.25 ± 7.97	158.68 ± 17.23	159.0 ± 1.73
Mean weight in kg	45.66 ± 13.71	47.74 ± 14.31	53.12 ± 13.34	51.42 ± 15.61	51.66 ± 3.78
Mean SBP in mm Hg	122.79 ± 12.0	125.12 ± 17.87	126.62 ± 8.84	119.47 ± 11.41	105.33 ± 11.54
Mean DBP in mm Hg	81.24 ± 6.70	81.93 ± 7.88	84.37 ± 7.76	78.42 ± 5.28	80.02 ± 8.52

SBP, systolic blood pressure; BP, diastolic blood pressure; cm, centimeter; kg, kilogram

Table 2: Glycemic status

Parameters	*Group I*	*Group II*	*Group III*	*Group IV*	*Group V*	*p-value (Group I and Group IV)*
Mean FBG (mg/dL)	227.85 ± 80.94	216.81 ± 114.28	199.75 ± 78.73	189.31 ± 65.80	117.33 ± 15.01	<0.05 (S)
Mean PPBG (mg/dL)	302.80 ± 101.14	314.31 ± 144.82	263.5 ± 106.6	235.21 ± 102.29	182.66 ± 58.8	<0.05 (S)
Mean HbA1c (%)	8.65 ± 1.20	8.7 ± 1.49	8.32 ± 1.10	8.07 ± 0.94	7.33 ± 0.64	<0.05 (S)

The educational status of the patients of different groups is shown in Table 3. An increasing trend was observed among students who achieved higher degrees except in groups III and IV.

Occupational status has improved over time, as is evident in Table 4. The percentage of permanent service holders and/or businessmen/professionals increased gradually from groups I to V. In other words, more type 1 diabetics are becoming earning members of the family.

Table 5 shows that during the study period, the Indian gross domestic product (GDP) has remarkably increased from 1996 to 2021, which might have played an important role in the improvement of education and economic status of type 1 diabetics, facilitating their quality of care.

Table 6 shows the percentage of different complications developed in three different groups divided according to the duration of the disease. The incidence of neuropathy was nil in group III1. Serum creatinine is similar in all groups. On the contrary, the incidence of retinopathy and microalbuminuria increased from groups I1 to III1. Most interesting observation noted is the incidence of ketosis and hypoglycemia observed lowest in group III1. A Chi-squared test was done to find the statistical significance, and the *p*-value was given in the table.

A comparison of complications among the groups has been expressed in the diagram (Fig. 4).

Table 7 shows a gradual increase in the use of pen devices for insulin injection, glucometers for home monitoring of blood glucose (HMBG) and cell phones to connect with caregivers.

The use of newer devices in the management of type 1 diabetics has increased with time, as shown in Figure 5.

Figure 6 indicates that 24 patients out of 224 expired during the study period. The percentage of death was calculated and divided into three groups according to the

Table 5: India GDP—historical data

Year	*GDP*	*Per capita*
2021	$3.173408B	$2777
2020	$2,667.69B	$1,933
2019	$2,831.55B	$2,072
2018	$2,702.93B	$1,998
2017	$2,651.47B	$1,981
2016	$2,294.80B	$1,733
2015	$2,103.59B	$1,606
2014	$2,039.13B	$1,574
2013	$1,856.72B	$1,450
2012	$1,827.64B	$1,444
2011	$1,823.05B	$1,458
2010	$1,675.62B	$1,358
2009	$1,341.89B	$1,102
2008	$1,198.90B	$999
2007	$1,216.74B	$1,028
2006	$940.26B	$807
2005	$820.38B	$715
2004	$709.15B	$628
2003	$607.70B	$547
2002	$514.94B	$471
2001	$485.44B	$452
2000	$468.39B	$443
1999	$458.82B	$442
1998	$421.35B	$413
1997	$415.87B	$415
1996	$392.90B	$400

Data source, World Bank

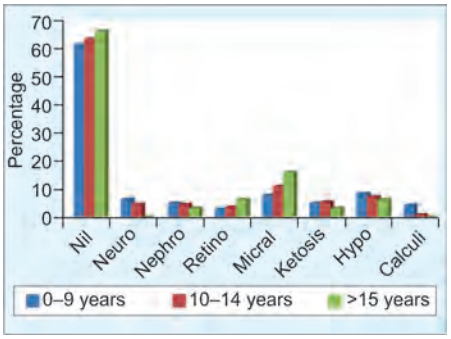

Fig. 4: Comparison of complications

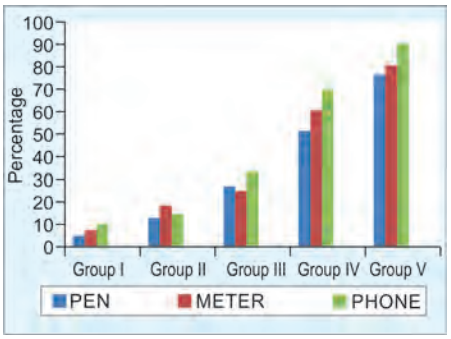

Fig. 5: Showing the advances in management technology

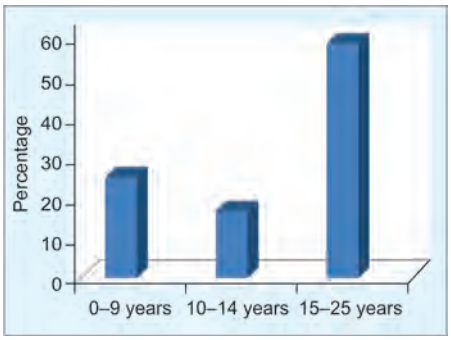

Fig. 6: Mortality status (years after detection of type 1 diabetes)

Table 3: Educational status

Education	*Group I (33)*	*Group II (40)*	*Group III (66)*	*Group IV (58)*	*Group V (27)*
High school	36.54% (12)	47.27% (18)	40.48% (27)	51.11% (30)	16.66% (5)
Higher secondary	36.54% (12)	07.27% (2)	23.80% (16)	8.88% (5)	23.33% (6)
Graduate	21.15% (7)	32.78% (12)	26.19% (17)	24.44% (14)	36.66% (10)
PG and above	05.77% (2)	21.82% (8)	09.52% (6)	15.55% (9)	23.33% (6)

Table 4: Occupational status

Occupation	*Group I (33)*	*Group II (40)*	*Group III (66)*	*Group IV (58)*	*Group V (27)*
Nil	11.54% (4)	2.5%% (1)	02.38% (1)	04.44% (2)	03.33% (1)
Culti/lab.	03.3% (1)	2.5%% (1)	02.38% (1)	04.44% (2)	Nil
Student	38.46% (12)	49.09% (20)	40.48% (26)	44.44% (26)	30.00% (8)
Housewife	23.07% (7)	05.45% (2)	28.57% (18)	06.66% (4)	13.33% (4)
Private tuition	05.77% (2)	12.73% (5)	02.38% (1)	13.33% (8)	06.66% (2)
Service	11.54% (4)	21.82% (8)	21.43% (13)	13.33% (8)	26.66% (7)
Business/profession	09.62% (3)	09.09% (3)	09.52% (6)	13.33% (8)	20.00% (5)

Culti, cultivation; lab., laborer; pvt., private

Table 6: Complications according to duration of diabetes; groups I1 (0–9 years duration), II1 (10–14 years duration), and III1 (15 years and above)

Parameters	*Group I1 (113)*	*Group II1 (72)*	*Group III1 (39)*	*p-value*
No complaint	60.83% (70)	62.72% (45)	65.62% (26)	
Neuropathy	6.29% (7)	4.54% (3)	Nil	<0.01 (S)
Serum creatinine >1.2 mg/dL	4.89% (6)	4.54% (3)	4.12% (2)	>0.05 (NS)
Retinopathy	3.79% (4)	3.68% (2)	7.25% (3)	<0.05 (S)
Microalbuminuria	8.69% (10)	10.9% (8)	12.62% (5)	
Ketosis (with high blood sugar, severe dehydration and presence of ketone bodies in urine)	4.93% (6)	5.45% (5)	3.14% (1)	
Hypoglycemia	8.39% (10)	7.27% (6)	6.25% (2)	

S, significant; NS, non-significant

Table 7: Advances in management technology

Parameters	*Group I*	*Group II*	*Group III*	*Group IV*	*Group V*
Use of pen device	5.13%	13.18%	27.08%	51.16%	76%
Glucometer use	7.70%	18.64%	25%	60.46%	80%
Use of cell phone	10.26%	14.68%	33.46%	69.76%	90%

duration of the disease. The observation is represented in the above diagram.

Discussion

A century after the discovery of insulin, there has been a better understanding of the pathogenesis and management practices related to type 1 diabetes.

Despite much progress, easy access to insulin and related essential technologies for improved management of all type 1 diabetes are still unavailable to all patients in low-middle and LIC like India. Limited data are available globally from the low- and low-middle-income countries (LIC and LMIC, respectively) on evidence of the management of type 1 diabetics with a focus on health and quality of life outcomes.

Worldwide decreasing trends, particularly of overt nephropathy and proliferative retinopathy in type 1 diabetics, have been reported for a period of last 15–20 years.[6–8] The mortality rate has also decreased, probably because of better management and the decline in morbidity. However, Rossing et al. did not find any decreasing trend for diabetic nephropathy[9] and retinopathy[10] after 15 years in a hospital-based cohort, whereas Brown et al.[11] in a comparative study with type 2 diabetics found no change despite improved glycemic control and blood pressure. Here, the type 2 diabetes study was referred to compare the quality of life between type 1 and type 2 diabetes. Improvement in mortality state was also observed in a recently published Indian study.[12]

This study shows that type 1 diabetic patients were gradually improving their educational status, doing professionally better in education, and getting jobs over time, which clearly indicates an improvement in the quality of their lives. Table 7 shows a gradual increase in the use of pen devices for insulin injection and the use of glucometers for HBMG and detecting hypoglycemia episodes, thus preventing an emergency. Also, the increase in the use of cell phones helped them communicate with doctors, caregivers, and peers in any situation and made their lives more comfortable and safe.

Interestingly, there has been almost steady growth of GDP, and the per capita income of persons in India has been observed. This improvement of socioeconomic infrastructure in terms of the increase in GDP of the country might have played an important role in improving the quality of diabetes management in our cohort of type 1 diabetics.[17] Usually, it is thought that quality of life as per financial and related health condition of a person (overall well-being) is related to the increased GDP of the country where he/she belongs as the development status of a country is being determined by its GDP.

Despite downward trends in mortality rates observed in the last 3 decades, a difference still exists between type 1 diabetics and the general population.[18] Untreated and poorly controlled type 1 diabetics have always had risks for the development of diabetic ketoacidosis, hypoglycemia episodes, renal failure, heart attacks, blindness, and neuropathy and its consequences.

A systemic review by Morgan et al.[19] calculated standardized mortality ratios from 23 studies worldwide, ranging from 0 to 8.54, covering time periods from 1970 to 2007. Our group observed in an early study that the mortality rate of type 1 diabetics was about 5/1,000/year, which was lower than that of the general population (7.3/1,000/year in 2017) in India.[20] In this study, the maximum percentage of death occurred at 15–25 years duration, whereas minimum incidence was seen in the middle group (10–14 years duration). The mortality rate was decreased in the second group.

In a longitudinal study, the death of type 1 diabetic patients was registered during a mean follow-up period of 16.8 years. Only 3.1% of the patients died, and the leading cause of death before the age of 30 years was acute complications (34.5%). After 30 years, cardiovascular disease was predominant (33.6%).[21]

The novelty of this study lies in the fact that in West Bengal, India, there is no such 25-year follow-up study on type 1 diabetes involving clinical as well as educational and socioeconomic status.

Conclusion

In this study, it is observed that diabetes care and complications show improvement, leading to fewer long-term complications in patients diagnosed at a later period of time. A coordinated approach, proper education on diabetic lifestyle, diet, physical exercise, psychological care, proper monitoring of all parameters of health, self-monitoring of blood glucose, easy and uninterrupted accessibility to insulin, and modern treatment devices should be the need of the day to improve the quality of life of the type 1 diabetics. Nevertheless, there are many improvements in the management of type 1 diabetes, resulting in improved quality of life for type 1 diabetics, but many stones still remain unturned. In the last 3 decades, there has been immense technological development like the use of pen devices to ease insulin injection with exact doses, the

use of glucometers for home monitoring blood glucose and hypoglycemia detection, and the use of cell phones to communicate, changed the life of type 1 diabetic subjects in this region. Last but not least, the continued growth of India's GDP helped to improve the socioeconomic development of families to meet the demand for the cost of care.

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ORIGINAL ARTICLE

Role of Serum Calcium, Serum Albumin, and Serum Uric Acid as Markers of Initial Neurological Severity and Short-term Outcome Indicators in Acute Ischemic Stroke

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Received: 02 April 2023; *Revised:* 05 August 2023; *Accepted:* 18 August 2023

Abstract

Background and objectives: Stroke is the rapid onset of neurological symptoms that persist for >24 hours or death due to vascular causes. Biochemical alterations indicate stroke severity and outlook. Serum calcium has an important role in signal transduction pathways and may influence the severity of stroke in the acute stages. Serum uric acid acts as an indicator of tissue infarction. However, serum calcium, albumin and uric acid are rarely tested in acute ischemic stroke for severity and short-term prognosis.

Materials and methods: This is a 1-year, observational cross-sectional study of 65 individuals who experienced an acute ischemic stroke within 24 hours of onset. Patients with hemorrhagic stroke, chronic liver, and renal disease were excluded. At admission, serum calcium, albumin, and uric acid were measured along with the National Institute of Health Stroke Scale (NIHSS) severity. The Modified Rankin scale (MRS) grading done at the end of 1st week determined the short-term prognosis.

Results: In our 65-person study, stroke was common among 50–80-year-old patients. Participants included 45 (69.23%) males and 20 (30.77%) females. Male preponderance of the ratio 2.25:1 was observed. A total of 17 (26.15%) individuals had hypertension, 19 (29.23%) had overlapping comorbidities, six (9.23%) had diabetes, and five (7.69%) had coronary artery disease (CAD). Hypertension and diabetes did not show a significant correlation. Only low serum calcium was found to be positively correlated to NIHSS rating. Serum albumin and uric acid did not affect NIHSS severity. All three signals were unrelated to MRS.

Interpretation and conclusion: Low serum calcium exacerbates NIHSS. NIHSS was unrelated to albumin, uric acid, or demography. MRS grades were unaffected by three lab factors. In order to decrease bias and relate these three lab measures to acute ischemic stroke, large-scale prospective research is required.

Journal of the Association of Physicians of India (2024): 10.59556/japi.72.0496

Introduction

A cerebrovascular accident or stroke is a local vascular etiology condition causing abrupt mortality or neurological disability. Stroke will become a major burden on society in the coming years.[1] Serum calcium is a signal transduction cofactor and enzyme cofactor. Cell calcium metabolism during and after ischemia influences the extent of cerebral damage, and thus, serum calcium can predict stroke outcomes.[2] Humans have the most serum albumin, and it provides the nutritional status of the patient. Poor health causes many diseases, including stroke. Protein-energy deficiency worsens stroke outcomes. Antithrombin and heparin cofactors contribute to albumin's anticlotting capability. This enhances the cerebral blood flow.[3] Uric acid is an antioxidant and scavenges free radicals. Increased uric acid is linked to gout, cardiovascular disease, insulin resistance, and metabolic syndrome, but its benefits are still debatable. This uric acid inconsistency may be due to experimental methodology, race, location, culture, sex, or social and economic influences, and further study is needed.[4] Multiple factors affect acute ischemic stroke severity, prognosis, and functional outcome. General health and infarct volume are crucial to patient recovery.[5]

In India, ischemic and hemorrhagic strokes are rising. Simple lab parameters, including serum calcium, albumin, and uric acid, may be used to assess the prognosis of stroke. The main goal is to prevent stroke by identifying and avoiding risk factors and increasing public awareness.

Materials and Methods

The current study is a 1-year hospital-based observational cross-sectional study involving 65 patients from January to December 2020 with the data from the General Medicine and Neurology wards and Intensive Care Unit at KLES Dr Prabhakar Kore Hospital & Medical Research Centre, Belagavi. All participants signed an informed consent form prior to taking part in the study.

All patients >18 years of age having cerebrovascular accident and ischemic stroke as confirmed on computed tomography (CT) or magnetic resonance imaging (MRI) scan within 24 hours of stroke were included in the study. Patients with hemorrhagic stroke, known hepatic/renal disorders, hyperuricemia, and hepatotoxic/nephrotoxic medicines were excluded from this study.

A detailed history was taken, and clinical features were assessed. Basic laboratory tests were conducted, such as complete blood counts, liver function tests, renal function tests, urine routine, and microscopy. National Institute of Health Stroke Scale (NIHSS), total serum calcium, serum albumin, and serum uric acid levels were tested at the time of admission, and the Modified Rankin scale (MRS) was performed at the end of the 1st week.

Statistical Analysis

Data collected using the questionnaire were coded and entered into Microsoft Excel. Data management was done in Microsoft Excel and analyzed using Statistical Package for the Social Science (SPSS) software version 25. Descriptive data is expressed in percentages and frequencies. The Chi-squared test is used for finding the association between categorical variables.

Results

This study was conducted on 65 patients presenting with acute ischemic stroke at KLES

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How to cite this article: Bharamaraddi Chinnammanavar PK, Somannavar VG, Mohan PB. Role of Serum Calcium, Serum Albumin, and Serum Uric Acid as Markers of Initial Neurological Severity and Short-term Outcome Indicators in Acute Ischemic Stroke. J Assoc Physicians India 2024;72(5):41–44.

Dr Prabhakar Kore Hospital & Medical Research Centre, Belagavi. Various demographic factors, comorbidities, habits, clinical presentation with signs, lab parameters, and neuroimaging were compared with NIHSS severity score and lab parameters individually and with MRS grading.

Stroke was common in the age-group of 50–80 years. Male patients were 45 (69.23%), and female patients were 20 (30.77%). Male preponderance was seen with the ratio of 2.25:1. Hypertension was seen in 17 patients (26.15%), overlapping comorbidities were observed in 19 patients (29.23%), diabetes in six patients (9.23%), coronary artery disease (CAD) in five (7.69%) and no comorbidities in 18 patients (27.69%). Hypertension and diabetes did not show any significant correlation to the outcome of the study. Lab parameters like total serum calcium, serum albumin, and serum uric acid when compared with NIHSS scoring (Table 1); a positive correlation was obtained only when low serum calcium levels were correlated with NIHSS. The other two parameters (serum albumin and uric acid) did not show any positive association. Similarly, comparing all three parameters with MRS did not show any positive correlation (Table 2).

Our study confirms that serum albumin and calcium levels within the normal range have a positive outcome, with lower morbidity and early recovery in patients of acute ischemic stroke. However, higher levels of serum uric acid have a negative effect on the prognosis, which can be attributed to the direct adverse impact of high uric acid levels on neurons. Further assessment in studies with larger sample sizes would help confirm the results.

Discussion

In the current study, the maximum number of patients was in the age-group of 51–65 years, 19 in the age-group of 66–80 years, 11 in the age-group of 36–50 years, and five each in the age-group of 21–35 years and ≥81 years, respectively. The mean age was 59.98 ± 15.44 years. Similar results were seen in a study done by Sivasubramaniyam and Umesh[6] with a maximum number of cases between the ages of 55–64 years (*N* = 18).

In our study, out of 65 patients, 45 patients (69.23%) were males, while 20 patients (30.78%) were females. The male preponderance was noted with the ratio of male:female = 2.25:1. Slight male study male preponderance (*N* = 54, 54%) to female (*N* = 46, 46%) was noted in a study by James et al.[7] compared only one parameter (serum albumin).

The clinical presentation of our patients showed that 52 patients (80%) had limb weakness while 50 patients (76.92%) had difficulty in speech. Cranial nerve involvement was seen in 34 patients (52.31%), altered consciousness in 29 patients (44.62%), ataxia in 12 patients (18.46%), and sensory dysfunction in four patients (6.15%). A study by Elbaih et al.[1] in 60 patients found that 55% of them had weakness of both upper and lower limbs, 45% of patients showed speech disturbances, and 45% had altered consciousness.

We observed hypertension as the most common comorbidity in our study, *N* = 17 (26.15%), followed by diabetes *N* = 6 (9.23%), CAD *N* = 5 (7.69%). Around 19 (29.23%) patients had overlapping comorbidities, and 18 patients (27.69%) did not have any comorbidities. This is in sharp contrast to a study by James et al.[7] as seen in their study group where various comorbidities were noted, and hypertension was the most common comorbidity (*N* = 34 patients) followed by dyslipidemia (*N* = 16 patients).

In the current study, 10 patients (15.38%) reported a habit of smoking, seven patients (10.77%) had a history of chewing tobacco, and six patients (9.23%) had a history of alcohol consumption. Overlapping habits were observed in 13 patients (20%), and 29 patients (44.62%) did not have any addictions. When compared to the study by James et al.,[7] observed both smoking and tobacco chewing habits in 35 patients, only alcohol habits in 10 patients, and alcohol with tobacco chewing in three patients.

We attempted to subdivide patients based on NIHSS severity as mild, moderate, moderate-severe, and severe (Table 3); we observed 11 patients (16.92%) with mild severity, 37 patients (56.92%) with moderate severity, and moderate-severe in 17 patients (26.15%). Almost similar results were obtained by Gupta et al.[8] when they compared their patients with NIHSS scoring—15 patients (30%) in mild category, 19 patients (38%) in moderate, and six patients (12%) in moderate-severe and 10 patients (20%) in the severe category.

We tried to categorize our patients based on the MRS grading at 1 week (Table 4), and results obtained showed that a maximum number of patients 25 (38.46%) were in grade IV, followed by 14 (21.54%) in grade I, 10 (15.38%) in grade V, eight (12.31%) in grade III, six (9.23%) in grade II, and only two patients (3%) in grade VI. Gupta et al.[8] in their study have tested the patients with MRS grades and found 12 patients in grade II (24%), 11 patients (22%) in grade IV, 10 patients (20%) in grade I, nine patients (18%) in grade V, five patients (10%) in grade VI, and only three patients (6%) in grade III.

All our patients were subjected to total serum calcium level estimation, and it was found that 31 patients (47.69%) had normal serum calcium levels (8.6–10.2 mg/dL), while the remaining 34 patients (52.31%) had levels below the normal range (≤8.5 mg/dL). Further categorization of serum calcium levels as mild, moderate and severe (Table 5) revealed that 21 patients (32.30%) were in mild category (8.1–8.5 mg/dL), nine patients (13.85%) in moderate (7.6–8.0 mg/dL), and four patients (06.15%) in severe category (≤7.5 mg/dL). A similar study by Sivasubramaniyam and Umesh,[6] who compared all three parameters, found the levels of serum calcium in the normal range in 40 patients (40%), and the remaining 60 patients (60%) had low levels of calcium (≤8.6 mg/dL). The influx of calcium into neuronal cells is a mechanism of ischemic cell death, and massive calcium accumulation triggers direct mitochondrial damage *via* the *N*-methyl-D-aspartate (NMDA) receptor. Free calcium plays a vital role; thus, albumin-corrected calcium should be taken into consideration.

All patients were subjected to serum albumin estimation and were found to have

Table 1: Distribution of patients based on categorization of serum calcium (*N* = 65)

Serum calcium levels (mg/dL)	*Number of patients*	*Percentage of patients*
Normal (8.6–10.2)	31	47.69%
Mild (8.1–8.5)	21	32.30%
Moderate (7.6–8)	9	13.85%
Severe (≤7.5)	4	6.15%

Table 2: Distribution of patients based on categorization of serum albumin (*N* = 65)

Serum albumin levels (gm/dL)	*Number of patients*	*Percentage of patients*
Normal (3.6–5.2)	52	80.00%
Mild (3.1–3.5)	6	9.23%
Moderate (2.6–3)	6	9.23%
Severe (≤2.5)	1	1.54%

Table 3: Distribution of patients based on categorization of serum uric acid (*N* = 65)

Serum uric acid levels (mg/dL)	*Number of patients*	*Percentage of patients*
Normal (≤5.7)	44	67.69%
Mild (5.8–7.2)	10	15.38%
Moderate (7.3–8.5)	7	10.76%
Severe (≥8.6)	4	6.15%

Table 4: Comparison of NIHSS severity with serum calcium levels

Calcium levels	*Mild*	*%*	*Moderate*	*%*	*Moderate-severe*	*%*	*Total*	*%*	χ^2
Normal	6	54.54	23	62.16	2	11.77	31	47.70	16.84
Mild	4	36.36	6	16.21	11	64.70	21	32.30	
Moderate	1	9.01	6	16.21	2	11.77	9	13.85	
Severe	0	0	2	5.40	2	11.77	4	6.15	
Total	11	100.00	37	100.00	17	100.0	65	100.0	

*, $p < 0.05$. *p*-value is 0.0098

Table 5: Comparison of NIHSS severity with serum calcium (mg/dL), serum albumin (gm/dL), and serum uric acid (mg/dL) by one-way one-way analysis of variance (ANOVA)

NIHSS severity	*Serum calcium (mg/dL)*		*Serum albumin (gm/dL)*		*Serum uric acid (mg/dL)*	
	Mean	*±SD*	*Mean*	*±SD*	*Mean*	*±SD*
Mild	8.991	0.550	4.055	0.466	4.636	2.188
Moderate	8.454	0.588	3.916	0.680	5.495	2.311
Moderate-severe	8.406	0.618	3.959	0.520	4.924	1.922
Total	8.532	0.617	3.951	0.603	5.200	2.191
F-value	4.0409		0.2194		0.8294	
p-value	0.0224*		0.8036		0.4411	

Table 6: Comparison of MRS grades with serum calcium (mg/dL), serum albumin (gm/dL), and serum uric acid (mg/dL) by one-way analysis of variance (ANOVA)

MRS grades	*Serum calcium (mg/dL)*		*Serum albumin (gm/dL)*		*Uric acid (mg/dL)*	
	Mean	*±SD*	*Mean*	*±SD*	*Mean*	*±SD*
Grade I	8.86	0.55	4.06	0.46	4.57	1.92
Grade II	8.48	0.48	4.15	0.56	5.20	1.95
Grade III	8.78	0.58	4.36	0.35	5.49	1.68
Grade IV	8.36	0.64	3.76	0.71	5.60	2.58
Grade V	8.30	0.56	3.75	0.53	4.75	2.29
Grade VI	8.75	0.78	4.25	0.49	5.75	0.64
Total	8.53	0.62	3.95	0.60	5.20	2.19
F-value	1.9383		1.8981		0.5106	
p-value	0.1015		0.1083		0.7671	

Table 7: Distribution of patients based on "NIHSS" severity ($N = 65$)

NIHSS severity	*Number of patients*	*Percentage of patients*
Mild	11	16.92%
Moderate	37	56.92%
Moderate-severe	17	26.15%

normal levels (3.6–5.2 gm/dL) in 52 patients (80%). The remaining 13 patients (20%) had low levels of albumin (≤3.5 gm/dL). Further, we categorized serum albumin deficiency (Table 6) as mild (3.1–3.5 gm/dL), seen in six patients (9.23%), moderate (2.6–3 gm/dL) as seen in six patients (9.23%), and severe in only one patient (1.54%). Elbaih et al.[1] found in their study population of 60 patients, 44 (73.34%) had albumin levels between 3.5 and 5 gm/dL, and 16 patients (26.66%) had below 3.5 gm/dL, which is almost in line with our study.

Serum uric acid estimation in all 65 patients revealed that 44 patients (67.69%) had levels below 5.7 mg/dL, and the remaining 21 patients (32.30%) had levels above 5.7 mg/dL. Further, we attempted to categorize our patients as mild (5.8–7.2 mg/dL), moderate (7.3–8.5 mg/dL), and severe (≥8.6 mg/dL), which had 10 patients (15.38%), seven patients (10.76%), and four patients (6.15%), respectively (Table 7). A study by Saadat et al.[9] showed in their population that 57% of the patients had normal levels of serum uric acid, 25% had low levels, and the remaining 18% had higher levels of serum uric acid. The neurons of the brain, when subjected to hypoxia or ischemia, have increased expression of xanthine oxidase. As a result of xanthine oxidase activity, uric acid generation is supposed to be a more potent response to ischemia of neurons in humans. So, it represents a marker of tissue infarction.

In our study, we had a total of 45 (69.23%) middle cerebral artery territory infarcts, 14 (21.54%) posterior cerebral artery territory infarcts, and six (9.23%) intermediate zone infarcts.

Most of the studies we have gone through have not compared NIHSS scoring with age, sex, and clinical presentation (symptoms and signs), whereas we made the comparison with age (*p*-value = 0.190) and sex (*p*-value = 0.753) and found no correlation with the statistically insignificant *p*-value.

However, we did find a correlation between clinical presentation with NIHSS in patients presenting with these clinical symptoms at the time of arrival—limb weakness (*p*-value = 0.00014), speech difficulty (*p*-value = 0.0012), and cranial nerve involvement (*p*-value = 0.00028). There was a correlation between clinical signs and NIHSS in our present study in patients presenting

Table 8: Distribution of patients based on "MRS" grades at 1 week

MRS grades	*Number of patients*	*Percentage of patients*
Grade I	14	21.54%
Grade II	06	09.23%
Grade III	08	12.31%
Grade IV	25	38.46%
Grade V	10	15.38%
Grade VI	02	03.08%

with a motor deficit (p-value = 0.00059), speech disturbances (p-value = 0.0012), cranial nerve palsy (p-value = 0.0028), and altered sensorium (p-value = 0.00193).

There was no association between comorbidities and habits with NIHSS severity in our study population. A study by Manickam et al.[10] found patients with comorbidities (hypertension, diabetes) had an increased risk of stroke in their study population. A study by James et al.[7] found that smoking is a modifiable risk factor for preventing the risk of stroke.

A comparison of serum calcium with NIHSS severity in our study found that low levels of serum calcium had poor outcomes compared with the NIHSS severity score, and the p-value was statistically significant (0.0098) (Table 8). The low levels of serum calcium are associated with either a bigger infarct or poor outcome. Similar conclusions were drawn from studies by Sivasubramaniyam and Umesh[6] and Gupta et al.[8]

Serum albumin did not have any bearing on the NIHSS severity scale in our 65 patients. The p-value was statistically insignificant (0.779). Manickam et al.[10] did not find any correlation between the serum albumin levels and the scoring system in their study. Sivasubramaniyam and Umesh[6] did find an association and quoted that serum albumin independently improves the prognosis of stroke.

A comparison between serum uric acid levels and all three groups, mild, moderate, and moderate-severe NIHSS scores, did not reflect any significant correlation between them. The p-value was statistically not significant (0.5026). Chiquete et al.[11] only found a correlation when both NIHSS and levels of serum uric acid were lower.

We further attempted in our 65 patients comparing all three lab parameters with MRS and found no significant correlation (Table 2). A study by Sivasubramaniyam and Umesh,[6] who compared all three lab parameters in their study, found a positive correlation between higher calcium levels, higher albumin levels, and low uric acid levels in their study population with NIHSS and MRS scoring system.

Studies with larger sample sizes and based on larger areas are required to confirm the results of our study. It is noteworthy that serum calcium, albumin, and uric acid levels represent the quality of overall general health of the patients, including their nutritional status, which might play a significant role in determining their prognosis and morbidity. Therefore, these levels can serve as biomarkers along with other variables.

Conclusion

Total serum calcium levels and stroke severity were the only positively correlated values as per the findings of our study. Diverse sample size in acute ischemic stroke and its comparison with various variables like age, sex, comorbidities, habits, clinical presentation, clinical signs, and size of infarct and lab parameters was worthwhile to see whether these factors have any bearing on neurological status either to predict the prognosis or to see for functional worsening.

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ORIGINAL ARTICLE

A Study of Cerebral Venous Sinus Thrombosis with Special Reference to Newer Risk Predictors

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Received: 03 January 2023; *Accepted:* 13 September 2023

Abstract

Background: Cerebral venous thrombosis (CVT) is an uncommon and frequently unrecognized type of stroke that affects approximately five people per million annually, accounts for 0.5 to 1% of all strokes, and is more commonly seen in young individuals. The exact incidence of CVT in India remains unknown. The risk factors for venous thrombosis in general are linked classically to the Virchow's triad of stasis of the blood, changes in the vessel wall, and changes in the composition of the blood.

There have been numerous studies evaluating long-term as well as short-term outcomes in the presence of these inflammatory mediators. They have been reported to be beneficial in predicting outcome and, hence, potentially in guiding management.

Aims: Evaluation of prevailing risk factors associated with cerebral venous sinus thrombosis (CVST).

Description of the distribution of newer inflammatory markers among the study population and their association with functional and neurologic outcome at 30 days following the occurrence of cerebral VST.

Materials and methods: Approval from the Institutional Review Board was obtained. Written informed consent was given by willing patients, explained in vernacular. Relevant details were obtained *via* a clinical history and laboratory values and imaging data obtained from the hospital's electronic health information system, which were then recorded in the proforma. No personal identifying data was collected. The sample size for this study was lower than originally planned, owing to the coronavirus disease 2019 (COVID-19) pandemic. The patients were called for follow-up after 1 month of the detection of VST, and their neurologic status was recorded on the Glasgow Coma Scale (GCS) and functional status on the modified Rankin Scale (mRS). Descriptive analysis of baseline characteristics was done. Mann–Whitney *U* and Kruskal–Wallis *H* tests of significant difference between means for nonparametric data were used. Linear regression was carried out on the variables found to differ significantly among subpopulations having good and poor neurologic outcomes. Receiver operating characteristic (ROC) curves were then derived for both outcome categories.

Results: The study enrolled 30 patients, with ages from 18 to 70 years, of which 19 (63.3%) were male and 11 (36.67%) were female. No risk factor was identified in 23.3% of cases. The most common risk factor was the presence of substance abuse. Among presenting features, headaches were the most common, followed by seizures and focal neurologic deficits (83.3, 30, and 23.3, respectively).

Coexisting intraparenchymal hemorrhage was seen in 46.67% of patients, with the transverse sinuses most commonly involved (28.77%). The median neutrophil-to-lymphocyte ratio (NLR) was 3.415 [interquartile range (IQR) 2.634–5.637], with median platelet-to-lymphocyte ratio (PLR) 160.728 (IQR 107.728–227.776) and median systemic immune-inflammation index (SII) 1067.883 (IQR 509.694–1522.837). The NLR, PLR, and SII values were found to differ significantly among subgroups having good and poor neurologic outcome on the mRS. PLR and SII significantly differed among subgroups with venous involvement and among subgroups with good and poor neurologic status on GCS, on admission as well as 30-day follow-up. NLR, PLR, and SII values on admission showed a positive association with poor neurologic outcomes.

Conclusion: Here, a significant correlation is seen between the values of complete blood count (CBC)—derived inflammatory markers on admission. Higher-powered studies are needed to assess the potential benefits of incorporating these markers in existing risk stratification models to improve their predictive accuracy.

Journal of the Association of Physicians of India (2024): 10.59556/japi.72.0425

Introduction

Cerebral venous sinus thrombosis (CVST or VST) is a relatively rare condition, reported to be causal in 0.5–1% of all strokes, and an estimated incidence of five per million [American Heart Association (AHA) data; Indian estimates are not currently available]. Incidence is relatively higher in neonates, usually secondary to dehydration/infection, and presentation in this age-group may be solely as seizure episodes.[1] However, it may occur at any age, more commonly <50 years, young women, especially in the puerperal period.

Etiology

Predisposing factors include, but are not limited to, prothrombotic conditions (protein C/S deficiency, antithrombin III deficiency, antiphospholipid antibody (APLA) syndrome, factor V Leiden mutation, hyperhomocysteinemia), pregnancy, drugs [oral contraceptives; danazol, lithium, ecstasy, vitamin A, tamoxifen, L-asparaginase, bevacizumab, heparin-induced thrombocytopenia (HIT)], malignancy, parameningeal infections, coronavirus disease 2019 (COVID-19),[2] mechanical causes (spontaneous intracranial hypotension, lumbar puncture), hematologic disorders [paroxysmal nocturnal hemoglobinuria (PNH), iron deficiency anemia (IDA), nephrotic syndrome), systemic disorders [systemic lupus erythematosus (SLE), Behçet's disease]. No specific contributing factor is found in 15–20% of all cases. Infection-associated cerebral venous thrombosis (CVT) is relatively more common in children.[1,3,4]

Acquired causes include elderly age; sepsis and secondary disseminated intravascular coagulation (DIC); male gender; obesity; malignancies; stasis of flow in the venous system, which may be secondary to prolonged immobilization following major surgical procedures, long-distance travel; pregnancy, use of hormone replacement therapy/oral contraceptives; trauma; myeloproliferative disorders; and polycythemia vera.[5] ~85% of adults may have at least one risk factor for cerebral VST.

Pathogenesis

The genesis of thromboembolism is illustrated by the Virchow's triad—hypercoagulability of

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How to cite this article: Khambholja J, Panchal SS, Gami JI. A Study of Cerebral Venous Sinus Thrombosis with Special Reference to Newer Risk Predictors. J Assoc Physicians India 2024;72(5):45–56.

blood, endothelial dysfunction, and stasis. Microparticles, microvesicles, inflammatory cells, and fibrin structure also contribute to thrombus formation. Many of the thrombogenic risk factors for venous thrombi do not confer a similar increase in risk for arterial thrombotic events.

Inflammation causes disruption of normal endothelial function, causing exposure of the tissue factor and activation of the coagulation cascade, culminating in stable clot formation by fibrin along with thrombin-activated platelets; further extension is normally prevented by the anticoagulant activity of an intact endothelium. This process is regulated by tissue factor pathway inhibitor (TFPI), heparin cofactor II, protein C, and protein S. Dysfunction of any of those factors can result in an increased risk.[5]

The thrombosis causes increased pressure in the cerebral veins, reduced perfusion at the tissue level, and increased local blood, culminating in edema developing due to blood–brain barrier disruption (vasogenic edema) as well as ischemic damage (cytotoxic edema). Hydrocephalus may also result from obstruction of cerebrospinal fluid (CSF) egress through the arachnoid villi.[6]

Clinical Presentation

A high index of clinical suspicion is necessary for appropriate imaging to confirm a diagnosis of VST.

Frequent presentations include—frequent seizures (focal/generalized), localization of focal deficits that do not correspond to an arterial distribution, bilateral signs, and a slow progression of symptoms (median time to presentation from onset—4 days).[4] The diagnosis may be missed if CVT presents with intraparenchymal hemorrhage, idiopathic intracranial hypertension, and isolated mental status changes.

The presenting symptoms may be secondary to the following.

- Raised intracranial tension (ICT): Headache (most common symptom; diffuse, progressive despite symptomatic medication), papilledema, diplopia (abducens nerve palsy), seizures.
- Location of thrombosis (Table 1).

Other conditions having a similar presentation included arterial stroke, meningitis, idiopathic intracranial hyper-/hypotension, and brain abscesses.[4]

Diagnosis

Confirmation is by imaging [computed tomography (CT) or magnetic resonance (MR) venography; either is preferable to digital subtraction angiography (DSA)], which may show either of these features: venous congestion, areas of hemorrhage, edema, areas of infarction (bilateral, multifocal, and involving the gray as well as subcortical white matter). These findings may be local, depending on the sinus involved. A plain CT is frequently normal, with hyperdensity in the region of the affected sinus being the only sign. Magnetic resonance imaging (MRI) is more sensitive overall; a plain MRI may show hypointensities on T2W images, the absence of a normal flow void in the region, or a central isodensity with peripheral enhancement. MR venography allows the thrombus to be seen directly, which is inferred as an area of absent filling on a contrast study. Diffusion-weighted signal abnormalities within the sinuses are predictors of poor recanalization. Cerebral angiography and perfusion imaging may also be used.

A falsely positive finding may be rarely seen on plain imaging, with variations in normal anatomy, such as a hypoplastic sinus, prominent arachnoid granulations, or asymmetric drainage into the sinuses.[4]

The MRI is the most sensitive method for detection of a venous thrombus. It can also assist in dating the clot and assess the extent of parenchymal involvement.

Markers of Inflammation in CVST

The presence and extent of inflammation can be quantified by measurement of acute phase reactants, whose changing levels reflect the status of ongoing inflammation. Conventional markers, such as the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and occasionally serum homocysteine levels, have been used as markers. However, white blood cell-based indices (ratios of the various types on inflammatory cells in the blood, identified on routine hemogram) have also been developed as surrogate markers for systemic inflammation, including, but not limited to, the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-high-density lipoprotein cholesterol ratio (MHR), and systemic immune-inflammation index (SII).[7–10]

$$\text{Neutrophil-to-lymphocyte ratio (NLR)} = \frac{\text{absolute neutrophil count}}{\text{absolute lymphocyte count}}$$

$$\text{Platelet-to-lymphocyte ratio (PLR)} = \frac{\text{platelet count}}{\text{absolute lymphocyte count}}$$

$$\text{Systemic immune-inflammatory index (SII)} = \text{platelet count} \times \frac{\text{absolute neutrophil count}}{\text{absolute lymphocyte count}}$$

Table 1: Clinical manifestations associated with thrombosis of venous sinuses

Sinus affected	*Associated clinical manifestations*
Cortical (superficial cerebral) veins	Fluctuating hemiparesis, incomplete hemianopia, and aphasia may occur. Raised ICP is usually not a feature
Vein of trolard	Parietal lobe involvement
Vein of labbe	Dysfunction of the superior temporal lobe
Dural sinuses	
Sagittal	Features of raised ICP are seen, with headache, vomiting, and papilledema. Cortical involvement (as paraparesis, hemiparesis, or aphasia) is seen only when the thrombosis has extended to involve the superficial veins. On lumbar puncture, the opening pressure may be raised, and the fluid is usually slightly sanguinous
Transverse	Features would be similar to those associated with sagittal sinus involvement
Cavernous	Thrombosis of the anterior part would result in severe chemosis and proptosis, while that of the posterior part would result in lower motor neuron (LMN) palsies of the oculomotor, trochlear, ophthalmic division of the trigeminal, and abducens nerves
Inferior petrosal	The function of the abducens, glossopharyngeal, vagus, and cranial part of the accessory nerves would be impaired
Superior petrosal	The trigeminal nerve is affected
Deep cerebral veins (internal cerebral veins, vein of galen)	Least common type of CVT. Presenting features include inattention, spatial neglect, amnesia, akinetic mutism, apathy, pupillary changes, or coma

Several studies have validated their use in numerous acute and chronic inflammatory conditions, including cardiovascular disease, rheumatoid arthritis, and malignancies.[7–9,11]

Hong et al. studied 95 cases of CVT against 41 controls. Increased levels of high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), NLR, CSF immunoglobulin A (IgA), CSF IgG, and CSF IgM were reported in the patients. They also noted that CSF IgM and NLR were more elevated in patients who eventually had a poor prognosis with NLR cutoff value of 4.205. NLR at admission was associated with a poor outcome and a significantly higher NIHSS score.[12]

Tekeşin and Tunç tested values among 36 patients against 40 controls. Again, the median NLR and PLR values were significantly increased among the patients. ESR and hsCRP values were also found to be raised. The monocyte-to-high-density lipoprotein (HDL) ratio was also tested, but it was not found to differ significantly.[13]

A study by Li et al. in 2020 studied the value of the SII for estimating prognosis among 270 cerebral VST patients. Elevated values were predictive of a reduced likelihood of survival. It was also reported to predict poor outcomes significantly among the puerperal and male populations.[14]

Serum homocysteine levels have been considered a predisposing factor; however, elevated levels have not been shown to independently influence severity of disease.[15]

Management

Guidelines for CVT management have been published by the AHA and American Stroke Association in 2011[4] and the European Stroke Organisation (ESO) in 2017.[16]

Initial anticoagulation is recommended with low-molecular-weight heparin (LMWH), in preference to unfractionated heparin (UFH), even in the presence of an intracranial hemorrhage (ICH). This also applies to pregnant/puerperal women with a prior history of CVT. Steroids may be considered for the management of coexisting autoimmune conditions. Antimicrobials can be used if the CVT is secondary to an infectious etiology. Acetazolamide and diuretics may be used in select cases (prominent signs of raised ICT; routine use is not advised. Antiepileptic drugs can be given in patients presenting acutely with seizures and having supratentorial lesions to reduce the risk of hypoxic injury. Avoiding the use of oral contraceptives is recommended for women of childbearing age with a prior history to reduce recurrence risk. Also, a prior history of CVT is not a contraindication for future pregnancies; however, the risk of recurrent venous thromboembolisms (VTEs) is increased, and LMWH should be considered for primary prevention during pregnancy and puerperium.[4,16]

A retrospective cohort study of pregnant and peripartum patients with CVT, with another cohort of nonpregnancy-related CVT as control, was carried out by Meng et al. They found a higher initial severity of illness in the former, with no statistically significant difference among them in the eventual outcome 12 months after the illness.[17]

Interventional methods (direct catheter thrombolysis, balloon-assisted thrombectomy, catheter thrombectomy, decompressive craniectomy) have been attempted on small scales. Neither of these guidelines endorse their use as part of a routine management algorithm, but they recommend their use may be considered on a case-to-case basis. Ventriculostomy may be required if obstructive hydrocephalus occurs, usually secondary to intraventricular hemorrhage. Decompressive craniectomy to prevent impending parenchymal herniation received a strong recommendation for use in the ESO guidelines. Therapeutic lumbar puncture may be an option in the presence of signs of intracranial hypertension if it is otherwise safe; it has not been explicitly recommended.[4,16]

Prognosis

Mortality in acute CVT has been reported to be 3–15%, with death mainly secondary to transtentorial herniation following a large hemorrhagic lesion due to underlying cerebral edema; other causes being pulmonary embolism, status epilepticus, and other medical events.

Recovery is usually favorable, with complete recovery in 79% of patients. Minor cognitive and language deficits may persist. The secondary headache may take weeks to resolve.

However, in cases having multiple cerebral hemorrhages and/or coma, the disorder is usually fatal.[1]

Prevention

Prevention is primarily focused on avoiding recurrence of thrombotic events.

Severe hereditary thrombophilias (protein C/S deficiency, APLA syndrome, homozygous prothrombin, and Leiden mutations) have been associated with an increased risk of repeat VST. Vitamin K antagonists can be continued with a target international normalized ratio (INR) of 2.0–3.0 for 3–12 months, depending on risk category. In the presence of high-risk factors, lifelong anticoagulation should be considered.

The AHA guidelines also comment on the management of other late complications following a VST—seizures, headaches, visual impairment, and dural arteriovenous fistulae. It is also recommended that repeat imaging be done to exclude recurrent VST.[4]

CVT Risk Score for Outcome Prediction

Ferro et al. devised a prognostic scale called the CVT risk score in 2009, which was derived using data from the ISCVT study cohort. Following a difference in beta values (DFBETA) analysis and Cox proportional hazards regression, a simplified model was derived, which included the following parameters—coma, malignancy, CVT in the deep venous system, male gender, intracerebral hemorrhage, and altered mental status. Risk ratios for each of the factors were rounded off to the nearest whole number (3 or more, assigned a value of 2; 1–3, assigned 1 point), and a total score was calculated for each patient, giving a total score from 0 to 9 (Table 2), with a cutoff score of 3 or more associated with a higher risk of poor outcome (again, defined as an mRS of >2). The investigators carried out validation studies on two cohorts—one from the VENOPORT study and the other being a cohort of patients from hospitals involved in the ISCVT. After testing the score in all three cohorts, an overall sensitivity of 95.5% and specificity of 13.6% was reported, with a receiver operating characteristic (ROC) statistic of 0.77.[18]

An algorithm for the management of cerebral VST incorporates the above risk score (Fig. 1).[6]

Table 2: The CVT risk score as proposed by Ferro et al.

Prognostic variable	*Hazard ratio*	*p*	*Risk points*
Malignancy	4.53 (2.52–8.15)	<0.001	2
Coma	4.19 (2.20–6.28)	<0.001	2
Thrombosis of the deep venous system	3.03 (1.76–5.23)	<0.001	2
Mental status disturbance	2.18 (1.37–3.46)	0.001	1
Male gender	1.60 (1.01–5.23)	<0.001	1
ICH	1.42 (0.88–2.27)	0.148	1

Figures in parentheses are 95% CI

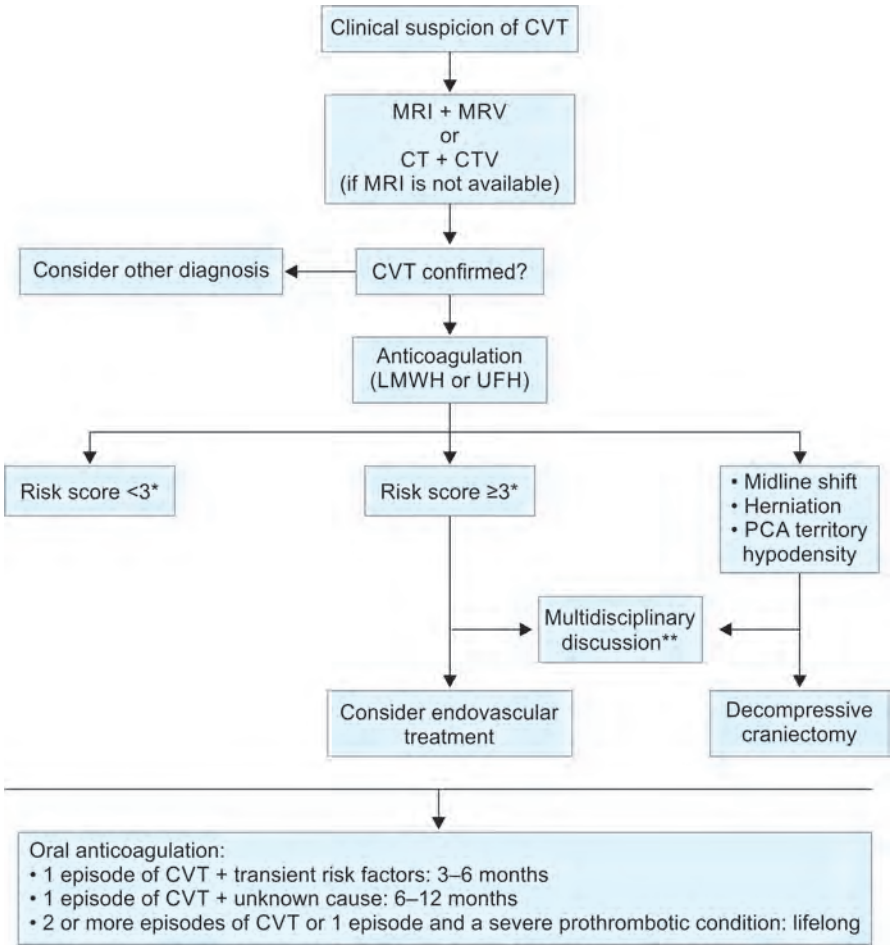

Fig. 1: Proposed management algorithm for cerebral VST

A summary of other prognostic models is shown in Table 3.

Aims and Objectives

- Evaluation of prevailing risk factors associated with cerebral VST.
- Description of the distribution of newer inflammatory markers among the study population and their association with functional and neurologic outcome at 30 days following the occurrence of cerebral VST.

Materials and Methods

This prospective observational study was carried out at the Department of General Medicine at a tertiary care hospital over a duration of 18 months from November 2019 to May 2021.

All patients meeting the following criteria were considered.

Inclusion Criteria

- Inpatients in general medicine or neurology with a newly established diagnosis of CVST as determined on MR venography.
- Patients/relatives willing to give their written informed consent.

Exclusion Criteria

- Pediatric age-group (age <18 years).
- Inpatients with a past history of cerebral VST.
- Cerebral VST occurring secondary to CNS infections (i.e., septic VST).

Methodology

Approval from the Institutional Review Board was obtained. Written informed consent was given by willing patients, explained in vernacular. Relevant details were obtained *via* a clinical history and laboratory values and imaging data obtained from the hospital's electronic health information system, which were then recorded in the proforma. No personal identifying data was collected.

The sample size for this study was lower than originally planned owing to the COVID-19 pandemic, as the hospital was a designated COVID-19 care center.

Overall neurologic status was recorded on the Glasgow Coma Scale (GCS) and the level of responsiveness on the alertness, confusion, drowsiness, and unresponsiveness (ACDU) scale. CVT risk scores were also assigned on admission.

Magnetic resonance (MR) venography was carried out on a Siemens 3 T MRI with two-dimensional (2D) time-of-flight (TOF) technique.

The following laboratory investigations were carried out—complete blood count (CBC) with differential count and absolute white blood cell (WBC) values, prothrombin time (PT)/INR, ESR, CRP, and serum homocysteine.

Complete blood counts (CBC) were carried out on a Siemens ADVIA 2000 Hematology Analyzer.

Treatment and Follow-up

Patients received medical management with anticoagulation—parenteral [unfractionated/low-molecular-weight heparin (UFH/LMWH)] or oral (warfarin). Surgical management (thrombectomy) had been carried out in only one of the patients examined.

They were called for follow-up after 1 month of the detection of VST, and their neurologic status was recorded on the GCS and functional status on the modified Rankin Scale (mRS).

Statistical Analysis

Statistical analysis was done using Microsoft Excel 365, EpiInfo 7.2.4.0, and IBM Statistical Package for the Social Sciences (SPSS) Statistics 25. Descriptive analysis of baseline characteristics (Table 4a and b) was done, with central values reported as means and standard deviations or as medians and interquartile ranges. This analysis was done overall as well as within subpopulations. Mann–Whitney *U* and Kruskal–Wallis *H* tests of significant difference between means for nonparametric data were used. Linear regression was carried out on the variables found to differ significantly among subpopulations having good and poor neurologic outcomes. ROC curves were then derived for both outcome categories, with area under the curve (AUC) <0.5 not disproving the null hypothesis (i.e., not significant). *p*-values < 0.05 (95% confidence level) have been considered statistically significant in all cases.

Table 3: Comparative analysis of prognostic scales for CVT

	Year	*Duration of follow-up*	*Sensitivity*	*Specificity*	*Positive predictive value*	*Negative predictive value*
Saposnik et al.[4]	1992	–	–	–	98% (good prognosis) (0–5/11) 96.0% (poor prognosis) (≥6/11)	
Koopman et al.[23]	2008	6 weeks, 6 and 12 months	88%	70%	96% (good outcome) (<14) 39% (poor outcome)	
Ferro et al.[18]	2009	6 months	96.1%	13.6%	29.4%	94.5%
Barboza et al.[24]	2018	30 days	71.4%	92.9%	50.0%	97.1%

Table 4A: Baseline characteristics and clinical data

	Number of patients (n = 30)
Gender of patient	
Male	19
Female	11
Preexisting risk factors	
Substance abuse	10
Others (trauma, Covishield, etc.)	8
None	7
Recent/current pregnancy	2
Oral contraceptives	2
Known hypercoagulable disorder	1
Clinical features at the presentation	
Headache	25
Seizure	9
Focal neurologic deficit(s)	7
Level of responsiveness	
Alert (A)	21
Confused (C)	6
Drowsy (D)	2
Unconscious (U)	1
Involvement on imaging	
Superficial venous drainage only	24
Superficial and deep venous drainage	6
Venous sinuses involved	
Transverse sinus(es)	21
Sigmoid sinus(es)	17
Superior sagittal sinus	11
Straight sinus(es)	11
Internal cerebral vein(s)	4
Internal jugular vein(s)	3
Vein of galen	2
Vein of labbe	2
Total ISCVT-RS score	
Score < 3	21
Score ≥ 3	9
Modality for management	
LMWH	15
UFH	13
Warfarin	1
Surgical	1
30-day outcome (mRS)	
Good (mRS 0–2)	26
Poor (mRS > 2)	4

Table 4B: Baseline characteristics and clinical data

Number of patients (n = 30)		
GCS	At admission	30 days after event
Mild (GCS 13–15)	25	28
Moderate (GCS 9–12)	3	0
Severe (GCS < 8)	2	2
Hemoglobin (gm/dL)	Mean = 12.25	Standard deviation (SD) = 2.53
12.0–18.0	17	
<12.0	13	
Total WBC count (kU/L)	Mean = 9.81	SD = 3.80
>12.4	4	
5.2–12.4	25	
<5.2	1	
Platelet count (kU/L)	Mean = 298	SD = 170.6
>400	7	
130–400	17	
<130	6	
NLR	Mean = 4.458	SD = 2.868
>3.92	13	
0.83–3.92	17	
PLR	Mean = 181.822	SD = 135.393
>239	6	
61–239	20	
<61	4	
SII	Mean = 1312.384	SD = 1199.828
>1168	14	
189–1168	15	
<189	1	
INR	Mean = 1.17	SD = 0.43
> 1.2	6	
0.8 - 1.2	24	
ESR	Mean = 17.33	SD = 18.63
> 20	8	
< 20	22	
CRP (mg/L)	Mean = 12.25	SD = 19.94
> 6.0	16	
< 6.0	14	
S. homocysteine (mg/dL)	Mean = 23.47	SD = 19.94
> 15.0	16	
< 15.0	14	

Results

Summary statistics of inflammatory markers

NLR	Gender of patient		Clinical severity on Glasgow Coma Scale at admission			Level of responsiveness on ACDU scale at admission				Affected cerebral venous drainage territory		CVT risk score		30-day Outcome on the Modified Rankin Scale (mRS)		30-Day Clinical Status on Glasgow Coma Scale (GCS)	
	M	F	13–15	9–12	< 8	A	C	D	U	Superf. only	Superf. &deep	< 3	≥ 3	0–2	> 2	13–15	< 8
> 3.92	9	4	10	1	2	9	2	1	1	9	4	5	8	9	4	11	2
0.83–3.92	10	7	15	2	0	12	4	1	0	15	2	16	1	17	0	17	0
Mean	7.917	3.309	6.155	5.155	8.738	6.388	5.298	4.367	12.143	6.463	5.281	5.894	7.004	6.113	6.968	6.048	8.738
Median	3.632	2.654	3.409	3.4	8.738	3.421	3.25	4.367	12.143	3.405	4.683	3.091	5.333	3.268	5.782	3.404	8.738

PLR	Gender of patient		Clinical severity on Glasgow Coma Scale at admission			Level of responsiveness on ACDU scale at admission				Affected cerebral venous drainage territory		CVT risk score		30-day Outcome on the Modified Rankin Scale (mRS)		30-Day Clinical Status on Glasgow Coma Scale (GCS)	
	M	F	13–15	9–12	< 8	A	C	D	U	Superf. only	Superf. &deep	< 3	≥ 3	0–2	> 2	13–15	< 8
> 239	4	2	3	1	2	2	2	1	1	5	1	2	4	4	2	4	2
61–239	13	7	18	2	0	17	2	1	0	15	5	15	5	18	2	20	0
< 61	2	2	4	0	0	2	2	0	0	4	0	4	0	4	0	4	0
Mean	230.817	146.54	178.953	161.097	520.171	190.453	136.924	202.75	770.901	194.929	219.862	163.6086	284.6315	174.9035	362.4935	177.0401	520.171
Median	186.055	139.616	168.369	136.059	520.171	168.369	142.749	202.75	770.901	147.786	216.17	139.6161	225.5571	152.9735	238.1124	160.728	520.171

SII	Gender of patient		Clinical severity on Glasgow Coma Scale at admission			Level of responsiveness on ACDU scale at admission				Affected cerebral venous drainage territory		CVT risk score		30-day Outcome on the Modified Rankin Scale (mRS)		30-Day Clinical Status on Glasgow Coma Scale (GCS)	
	M	F	13–15	9–12	< 8	A	C	D	U	Superf. only	Superf. &deep	< 3	≥ 3	0–2	> 2	13–15	< 8
> 1168	11	3	11	1	2	9	3	1	1	9	5	5	9	10	4	12	2
189–1168	8	7	13	2	0	12	2	1	0	14	1	15	0	15	0	15	0
< 189	0	1	1	0	0	0	1	0	0	1	0	1	0	1	0	1	0
Mean	1492.533	946.643	1019.971	1272.749	4726.833	1000.167	1270.637	2054.433	6035	1211.369	1616.39	791.7707	2460.445	1007.674	3142.92	1047.054	4726.833
Median	1289.6	552	983.765	690.2	4726.833	983.765	932.387	2054.433	6035	887.833	1524.947	827.8947	1588.846	932.7197	2503.756	972.5187	4726.833

a, grouping variable: 30-day outcome on the mRS; the difference among means of patients having good and poor outcomes on the mRS was significant for NLR (p = 0.036), PLR (p = 0.031), SII (p = 0.002), and CVT risk score levels (p = 0.005); 30-day outcome on the GCS

a, grouping variable—30-day clinical status on GCS; b, not corrected for ties; the difference in mean values of PLR and SII (p = 0.018 and p = 0.005, respectively) is significant

INR	Gender of patient		Clinical severity on Glasgow Coma Scale at admission			Level of responsiveness on ACDU scale at admission				Affected cerebral venous drainage territory		CVT risk score		30-day Outcome on the Modified Rankin Scale (mRS)		30-Day Clinical Status on Glasgow Coma Scale (GCS)	
	M	F	13–15	9–12	< 8	A	C	D	U	Superf. only	Superf. & deep	< 3	≥ 3	0–2	> 2	13–15	< 8
< 0.8	5	1	5	1	0	0	4	1	1	0	5	1	4	2	6	0	0
0.8–1.2	14	10	20	2	0	2	17	5	1	1	19	5	17	7	20	0	4
Mean	1.22	1.08	1.18	1.14	0	1.13	1.2	1.07	1.17	1.11	1.2	1.04	1.13	1.26	1.18	0	1.08
Median	1.02	1.04	1.01	1.17	0	1.13	1.01	1.03	1.17	1.11	1.05	0.97	1.02	1.12	1.02	0	1.12

ESR (mm/hr)	Gender of patient		Clinical severity on Glasgow Coma Scale at admission			Level of responsiveness on ACDU scale at admission				Affected cerebral venous drainage territory		CVT risk score		30-day Outcome on the Modified Rankin Scale (mRS)		30-Day Clinical Status on Glasgow Coma Scale (GCS)	
	M	F	13–15	9–12	< 8	A	C	D	U	Superf. only	Superf. & deep	< 3	≥ 3	0–2	> 2	13–15	< 8
> 20	5	3	7	1	0	6	2	0	0	6	2	6	2	8	0	8	0
< 20	14	8	18	2	2	15	4	2	1	18	4	15	7	18	4	20	2
Mean	16	20	19	12	4	21	11	3	4	17	18.5	20.62	9.67	18.92	7	18.32	4
Median	7	10	10	9	4	11	7	3	4	8	10.5	9	6	8.5	7	9.5	4

CRP (mg/L)	Gender of patient		Clinical severity on Glasgow Coma Scale at admission			Level of responsiveness on ACDU scale at admission				Affected cerebral venous drainage territory		CVT risk score		30-day Outcome on the Modified Rankin Scale (mRS)		30-Day Clinical Status on Glasgow Coma Scale (GCS)	
	M	F	13–15	9–12	< 8	A	C	D	U	Superf. only	Superf. & deep	< 3	≥ 3	0–2	> 2	13–15	< 8
> 6.0	12	5	12	3	2	9	5	2	1	14	3	10	7	15	0	2	0
< 6.0	7	6	13	0	0	12	1	0	0	10	3	11	2	11	0	2	0
Mean	13.67	10.36	12.66	8.73	15.55	8.67	25.43	16	7.1	9.76	23.27	8.93	20.69	12.78	0	10.39	0
Median	6.54	5.8	5.9	8	15.55	5.8	12	16	7.1	6.37	6.12	5.9	7.1	6.37	0	6.4	0

HCys (mg/dL)	Gender of patient		Clinical severity on Glasgow Coma Scale at admission			Level of responsiveness on ACDU scale at admission				Affected cerebral venous drainage territory		CVT risk score		30-day Outcome on the Modified Rankin Scale (mRS)		30-Day Clinical Status on Glasgow Coma Scale (GCS)	
	M	F	13–15	9–12	< 8	A	C	D	U	Superf. only	Superf. & deep	< 3	≥ 3	0–2	> 2	13–15	< 8
> 15.0	13	3	14	2	0	12	3	1	0	11	5	10	6	14	2	16	0
< 15.0	6	8	11	1	2	9	3	1	1	13	1	11	3	12	2	12	2
Mean	28.41	14.97	25.25	18.59	8.65	27	16.3	13.55	12.4	22.28	28.27	22.27	26.31	22.65	28.89	24.54	8.65
Median	22.2	9.45	18.34	22.2	8.65	18.79	14.17	13.55	12.4	12.9	23.17	13.4	26.04	17.57	30.44	18.57	8.65

HCys, homocysteine

Tests of significance and inflammatory markers.

- **The 30-day outcome on the mRS**

	Test statistics[a]							
	NLR	*PLR*	*SII*	*ESR*	*CRP*	*INR*	*Serum homocysteine*	*CVT score*
Mann–Whitney *U*	18.000	17.000	6.000	37.000	50.000	54.000	47.000	10.000
Exact significance (2-tailed)	0.036	0.031	0.002	0.380	0.919	0.374	0.791	0.005

[a]grouping variable—30-day clinical status on GCS; [b]not corrected for ties

The difference among means of patients having good and poor outcomes on the mRS was significant for NLR ($p = 0.036$), PLR ($p = 0.031$), SII ($p = 0.002$), and CVT risk score levels ($p = 0.005$).

- **30-day outcome on the GCS:**

	Test statistics[a]							
	NLR	*PLR*	*SII*	*ESR*	*CRP*	*INR*	*Serum homocysteine*	*CVT score*
Mann–Whitney *U*	6.000	2.000	0.000	8.500	14.000	66.000	11.000	7.000
Exact significance (2-tailed)	0.074	0.018	0.005	0.129	0.285	1.000	0.193	0.083

[a]Grouping variable: 30-Day Clinical Status on Glasgow Coma Scale (GCS); [b]Not corrected for ties

The difference in mean values of PLR and SII ($p = 0.018$ and $p = 0.005$ respectively) is significant.

- **Gender of patients:**

	Test statistics[a]							
	NLR	*PLR*	*SII*	*ESR*	*CRP*	*INR*	*Serum homocysteine*	*CVT score*
Mann–Whitney *U*	65.500	84.000	68.000	96.000	96.000	54.000	94.500	62.000
Exact significance [2*(1-tailed significance)]	0.094[b]	0.395[b]	0.123[b]	0.735[b]	0.735[b]	0.374[b]	0.672[b]	0.070[b]

[a]Grouping Variable: Gender of patient; [b]Not corrected for ties.)

No statistically significant difference was found in the values of the markers based on gender.

- **Clinical status on admission (GCS)**

	Test statistics[a,b]							
	NLR	*PLR*	*SII*	*ESR*	*CRP*	*INR*	*Serum homocysteine*	*CVT score*
Kruskal–Wallis *H*	3.347	4.675	5.421	2.278	2.850	0.149	2.447	2.053
Exact significance	0.203	0.088	0.049	0.351	0.262	0.746	0.324	0.390

[a]Kruskal Wallis Test; [b]Grouping Variable: Clinical severity on Glasgow Coma Scale at admission

A significant difference was detected in SII values among the clinical categories ($p = 0.049$).

- **Affected venous drainage territory**

	Test statistics[a]							
	NLR	*PLR*	*SII*	*ESR*	*CRP*	*INR*	*Serum homocysteine*	*CVT score*
Mann–Whitney *U*	55.500	33.000	32.000	54.500	68.000	69.000	71.000	51.000
Exact significance (2-tailed)	0.409	0.044	0.038	0.381	0.849	1.000	0.970	0.296

[a]Grouping Variable: Affected cerebral venous drainage territory; [b]Not corrected for ties.

PLR ($p = 0.044$) and SII ($p = 0.038$) were found to differ significantly among those having involvement solely of the superficial venous drainage, and those also having thromboses in the deep venous network.

- **Associated intraparenchymal hemorrhage**

	Test statistics[a]							
	NLR	*PLR*	*SII*	*ESR*	*CRP*	*INR*	*Serum homocysteine*	*CVT score*
Mann–Whitney *U*	42.000	91.000	52.000	104.000	39.000	109.000	90.500	24.000
Exact significance (2-tailed)	0.003	0.400	0.012	0.750	0.002	0.918	0.382	0.000

Mean NLR ($p = 0.003$), SII ($p = 0.012$), CRP ($p = 0.002$), and CVT risk score ($p < 0.001$) were found to differ significantly among cerebral VST patients depending on the presence of coexisting intraparenchymal hemorrhage.

Degree of Association of Inflammatory Markers with Outcome

Linear Regression

Separate linear regression analyses were carried out between NLR, PLR, and SII values (a combined multivariate regression was not conducted as multicollinearity criteria were not satisfied), and mRS on outcome suggested a positive association ($p < 0.001$).

Regression analysis summary for NLR predicting 30-day outcome on mRS

	β	*95.0% confidence interval for B*		*t*	*Significance (p)*
		Lower bound	*Upper bound*		
(Constant)		–0.899	1.091	0.198	0.844
(NLR)	0.419	0.037	0.414	2.445	0.021

R^2 adjusted = 0.146; a significant change is seen in 30-day outcome with change in PLR value

Regression analysis summary for PLR predicting 30-day outcome on mRS

	β	*95.0% confidence interval for B*		*t*	*Significance (p)*
		Lower bound	*Lower bound*		
(Constant)		–0.946	–0.946	–0.418	0.679
(PLR)	0.610	0.003	0.003	4.071	0.000

R^2 adjusted = 0.349; a significant change is seen in 30-day outcome with change in SII value

Regression analysis summary for SII predicting 30-day outcome on mRS

Model	*Standardized coefficients*	*95.0% confidence interval for B*		*t*	*Significance (p)*
	β	*Lower bound*	*Lower bound*		
(Constant)		–0.722	0.490	–0.392	0.698
(SII)	0.722	0.001	0.001	5.527	0.000

R^2 adjusted = 0.505; A significant change is seen in 30-day outcome with change in SII value

Receiver operating characteristic (ROC) curves

ROC for mRS 0-2 at 30 days

Test result variable(s)	*Area*	*Standard error*[a]	*Asymptotic significance*[b]	*Asymptotic 95% confidence interval*	
				Lower bound	*Upper bound*
NLR	0.173	0.085	0.038	0.007	0.339
PLR	0.163	0.085	0.033	0.000	0.330
SII	0.058	0.045	0.005	0.000	0.147

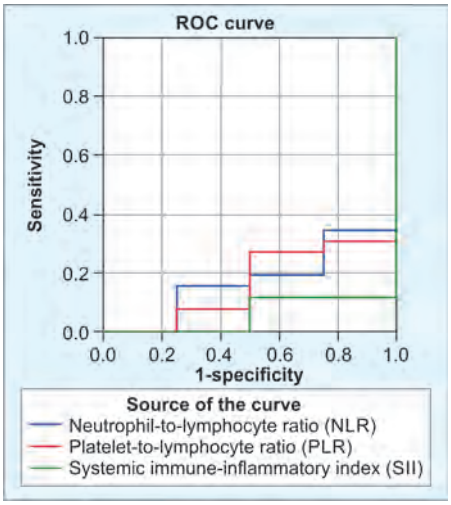

Fig. 2: ROC for mRS 0–2 at 30 days

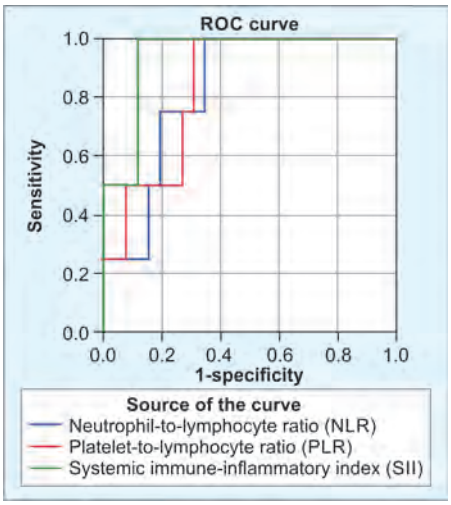

Fig. 3: ROC for mRS > 2 at 30 days

No significant correlation was found between the levels of markers and good outcome on the mRS.

ROC for mRS> 2 at 30 days

Test result variable(s)	*Area*	*Standard error*[a]	*Asymptotic significance*[b]	*Asymptotic 95% confidence interval*	
				Lower bound	*Upper bound*
NLR	0.827	0.085	0.038	0.661	0.993
PLR	0.837	0.085	0.033	0.670	1.000
SII	0.942	0.045	0.005	0.853	1.000

The NLR, PLR, and SII were found to correlate positively with poor outcome at 30 days, with AUC values of 0.827, 0.837, and 0.942, respectively

Discussion

This institute is a tertiary-level health center. Cases were included based on an established diagnosis of CVST and parameters obtained from available investigations. Management was done as per standard protocol. Follow-up was taken after 1 month of diagnosis.

Demography

Most of the patients enrolled in this study were male (63.33%). The ISCVT study of 2004 had 624 patients [of which 465(74.5%) were female] registered over 3 years with a mean age of 39.1 years.[19] The male preponderance here may be related to poorer reporting, a lower clinical suspicion, and a reduced willingness for admission in the local scenario. In this study, no risk factor was identified in 23.3% of cases. The most common risk factor was the presence of substance abuse. Pregnancy and oral contraceptive-related VST was seen in 13.33% of the study population. In the ISCVT study, the most commonly identified risk factor was the presence of a thrombophilia (34.1%; inherited causes—22.4%, acquired causes—15.7%), followed by malignancies (7.4%). Pregnancy, puerperium, and oral contraceptive-related VSTs were found in 6.3, 13.8, and 54.3% of the females aged <50 years. About 12.3% of VSTs were related to sepsis. No risk factor was identified in 12.5% of cases despite an adequate workup.[19] The differing areas of residence and the small sample size may be a factor in the difference seen here. Among presenting features, headaches were the most common, followed by seizures and focal neurologic deficits (83.3, 30, and 23.3%, respectively). The ISCVT study found that the most common symptom reported were headaches (88.8% of participants), seizures were seen in 39.3% of patients, and focal neurologic deficits in 37.2%, followed by visual complaints (vision loss, double vision, papilledema) and stupor (13.9%).[19]

Imaging Characteristics

In this study, all patients included had a confirmed diagnosis of cerebral VST on MRI. Coexisting intraparenchymal hemorrhage was seen in 46.67% of patients. In the ISCVT study, infarcts were seen on imaging (CT/MRI) in 46.5% of all patients and hemorrhage in 39.3% (overall 62.9%), with 18% having bilateral parenchymal lesions.[19] Here, the transverse sinuses were most commonly involved (28.77%), followed by the sigmoid sinuses, and the superior sagittal sinus was affected in ~15% of cases. Among the ISCVT cohort, the superior sagittal sinus was most frequently involved (62.0%), followed in decreasing order of frequency by the transverse sinuses, straight sinus, deep venous system, cortical veins, and jugular veins.[19]

Laboratory Investigations

Normal values for the CBC-based inflammatory markers were taken from the Rotterdam Study.[10] A study by Jhamb et al. carried out at UCMS Hospital New Delhi reports the mean NLR as 1.3–2.5 and mean PLR as 64.82–118.72, with no statistically significant difference among genders. However, the sample size was 500 compared to the ~8700 in the previously mentioned study.[20] In this study, the median NLR was 3.415 [interquartile range (IQR) 2.634–5.637], with median PLR 160.728 (IQR 107.728–227.776) and median SII 1067.883 (IQR 509.694–1522.837). An analysis of inflammatory markers in CVT was carried out by Tekeşin and Tunç, with 36 patients against 40 controls. The median NLR among patients was 2.2 (IQR 1.7–2.9) against 1.5 in the controls (p = 0.000, Mann–Whitney U test), with median PLR 132.9 (IQR 111.1–185.8) against 113.2 in controls (p = 0.003, Mann–Whitney U test). Changes in the absolute neutrophil count were not significant. ESR and hsCRP were also significantly elevated among the patients (ESR—26.0 against 13.5; hsCRP—0.6 against 0.3). The monocyte-to-HDL ratio was also tested, but it was not found to differ significantly.[13] Hence, the MHR has not been analyzed in the present study.

In the study by Hong et al., 95 cases were studied against 41 controls. An mRS of ≤1 was considered a good outcome, and follow-up on the patient's condition was also taken at 3 and 12 months afterward. The markers were tested in the acute, subacute, and chronic phases of illness. Levels of hsCRP (3.3 vs 0.5), IL-6 (9.49 vs 4.32), NLR [2.84 (95% CI 1.86~3.73) vs –2.05], CSF IgA (0.4 vs 0.2), CSF IgG (1.3 vs 0.04), and CSF IgM (3.48 vs 2.34) were all higher in the patients than the controls. They also noted that CSF IgM and NLR were more elevated in patients who eventually had a poor prognosis. Following multivariate logistic analysis, NLR at admission was associated with a poor outcome [adjusted OR 1.339 (1.097–1.784)]. The ROC curve for NLR had a maximal area under curve (AUC) of 0.774 (p = 0.002; 95% CI 0.620–0.928) with an NLR of ≥4.205; patient with higher NLR had a significantly higher

NIHSS score on admission. Further analysis of the subgroups created by the NLR cutoff value showed significant differences in the levels of NLR and CSF IgM (3.45 in the subgroup having higher-than-cutoff NLR, vs 2.45) (Figs 2 and 3).[12] The study by Karahan et al. compared the values of NLR, PLR, and SII at 6 months of follow-up in 51 patients and 51 controls. Increased values of NLR and SII were reported as independently predicting a poor outcome, with NLR having a stronger value (AUC 0.817, $p = 0.002$).[21] The difference in homocysteine levels among patients having good and poor outcomes was not significant in this study. Kalita et al. studied serum homocysteine levels in a cohort of 96 patients, of which 52.1% had raised levels. No significant difference in clinical outcome was found ($p = 0.18$).[22]

Outcome

On the mRS, in this study, four patients (13.33%) had scores greater than 2 at follow-up (indicating a poor prognosis). This was also generally favorable in the ISCVT study, with 12.37% of patients having a poor neurologic outcome at follow-up. Outcome was followed up at discharge, 6 months, and 18 months following the event, measured on the mRS. Cox regression analysis was used for identifying the potential risk predictors.[19]

Conclusion

- The study enrolled 30 patients, with ages from 18 to 70 years, of which 19 (63.3%) were male and 11 (36.67%) were female. Also, 23 (76.67%) patients had one or more preexisting risk factors for the occurrence of cerebral VST, most commonly a history of tobacco use. Headaches, seizures, and focal neurologic deficits were the most common symptoms encountered. Hence, a high index of suspicion should be exercised, especially in the presence of preexisting risk factors.
- Most of the patients (25; 83.33%) had mild impairment of neurologic status on admission, with GCS 13–15. Two patients had severe impairment (GCS of <8).
- About 80% of the cases only had involvement of the superficial venous network (cortical veins, dural venous sinuses), while the remaining also had concomitant involvement of the deep venous system. Coexisting intraparenchymal hemorrhage was seen in 14 cases. The transverse and sigmoid sinuses were the most frequently affected structures. In 26 (86.67%) cases, up to three venous sinuses were thrombosed.
- The CVT risk score was also estimated for patients on admission. A total of 21 cases had CVT scores <3, indicating a good prognosis.
- Values for inflammatory markers were assessed. As inflammatory states are known to predispose to thrombosis, an assessment of the extent of systemic inflammation has been postulated to predict the risk of developing cerebral VST. This study focused on relatively more accessible markers of inflammation (NLR, PLR, SII, ESR, CRP, homocysteine) and thrombosis (INR). These were above normal ranges for NLR, SII, and serum homocysteine.
- Medical management was used in the vast majority, with only one case undergoing thrombectomy.
- A total of 26 of the cases had a good 30-day outcome on the mRS (0 or 1). Similar results were seen on the GCS (28; 93.33%).
- The NLR, PLR, and SII values were found to differ significantly among subgroups having good and poor neurologic outcome on the mRS. PLR and SII significantly differed among subgroups with venous involvement and among subgroups with good and poor neurologic status on GCS, on admission as well as 30-day follow-up. NLR, PLR, and SII values show a positive association with poor neurologic outcome.
- Higher-powered studies are needed to assess the potential benefits of incorporating these markers in existing risk stratification models to improve their predictive accuracy.

Limitations

The study does have several limitations. The presence of a small sample size, owing to restrictions as mentioned earlier, means that the statistical inferences derived may not be accurate and will require further analysis on a larger study cohort before the findings can be applied clinically. Normal values of the WBC-based inflammatory markers are not reliably available, as they vary between genders and increase with age. Also, only large-scale dataset is the Rotterdam Study, whose authors noted the aforementioned. Data for the Indian population on a large scale is not available; hence, comparison groups with local controls would be appropriate. Also, as a validation dataset from this region was not available, a points-based risk model cannot be definitively generated. The values of inflammatory markers on follow-up should aid in increasing prognostic accuracy.

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ORIGINAL ARTICLE

A Study on Drug Prescribing Patterns in Vitiligo Patients of Andhra Pradesh in a Tertiary Care Teaching Hospital

Somanaboina Padmakar[1], Sweta Kumari[2], Biplab Pal[3*]

Received: 20 July 2022; *Accepted:* 21 September 2023

Abstract

Background: Vitiligo is a dermatological condition characterized by the appearance of white spots or patches on the skin due to the loss of skin pigment called melanocytes. The estimated prevalence of vitiligo is about 0.5–2% of the world population, but in India, the prevalence rate varies from 2 to 8%, depending on the region. This study aimed to assess drug prescribing patterns in vitiligo patients.

Materials and methods: A prospective cross-sectional study was carried out in the Dermatology Department of Government General Hospital, Andhra Pradesh, India, from December 2019 to 2020. Patients aged ≥18 years, both genders, and diagnosed and receiving treatment for vitiligo were included in the study. All medicines prescribed to the patients were collected on the predesigned case report form. Ethical approval for this study was taken from the Institutional Ethics Committee of Rajiv Gandhi Institute of Medical Science (RIMS). The collected data were analyzed by using SPSS version 18.

Results: The most commonly prescribed class of drugs was corticosteroids (42.9%), followed by calcineurin inhibitors (13.4%), vitamins (14.6%), basic fibroblast growth factor (BFGF) (9.5%), moisturizers (6.9%), antihistamines (6.5%), and minerals (6.2%). Among corticosteroids, betamethasone was the most commonly prescribed drug, followed by clobetasol propionate. Topical drugs were prescribed more often than orally.

Conclusion: The prescription pattern in vitiligo patients is as per the guidelines and recommendations. However, further studies using multiple centers are recommended to verify our findings.

Journal of the Association of Physicians of India (2024): 10.59556/japi.72.0527

Introduction

Vitiligo is a common, acquired, and progressive depigmentation disorder resulting from the destruction of melanocytes.[1] This condition is characterized by white spots on the skin that develop due to the loss of melanocytes in the skin. These are the cells responsible for skin color. In India, the prevalence of vitiligo is high, ranging from 0.4 to 8.8%.[2] The significant variation in the prevalence of vitiligo in India may refer to the different ethnic backgrounds of the population residing in different geographical regions with different environmental conditions.[3] Vitiligo is categorized into generalized and localized forms by the distribution and degree of lesions. The localized form is further subdivided into focal, segmental or unilateral, and mucosal, while the generalized type is subdivided into acrofacial, vulgaris, and universal,[4] as shown in Figure 1.

Vitiligo is still one of the most complex dermatological conditions to manage. Phototherapy, topical and systemic immunosuppressants, and surgical procedures are therapeutic options that help to halt the disease, stabilize depigmented lesions, and stimulate repigmentation.[5] Therapeutic choices are determined by several factors, including the disease's subtype, severity, distribution of lesion, as well as the patient's age and motivation for treatment. The lesions on the face, neck, trunk, and mid-extremities respond best to treatment, while the lips and distal extremities are more resistant.[6] Topical steroids are effective for lesions located on the face, elbow, and knee where distal extremities respond poorly with topical corticosteroids (TCSs).[7] The factors that contribute to variation in treatment response depend on multiple factors, including skin permeability, residual melanocyte migration from uninvolved skin, melanocyte damage reversibility, especially preservation, and density of follicular reservoirs.[7] In a comparison study with tacrolimus, immunosuppressive therapy using more potent TCSs (e.g., clobetasol) demonstrated moderate treatment effectiveness.[8] Well-known side effects of corticosteroids should be taken into account, particularly in cutaneous atrophy and capillary fragility.[8] Tacrolimus functions on gene expression and suppresses the expression of proinflammatory cytokines like interleukins, tumor necrosis factor α, and interferon γ. Treatment for 24 weeks with 0.1% tacrolimus ointment leads to repigmentation in 68% of patients.[9]

Various research studies have been performed on the prescription pattern of vitiligo in different locations. However, limited studies have been conducted in India. This research will fill a knowledge gap about current prescribing patterns to enhance medicine use, as well as the effective and efficient use of available resources. We, therefore, planned to evaluate the prescription pattern in vitiligo patients.

Materials and Methods

Study Design and Settings

This cross-sectional study was carried out in the Dermatology Department of Rajiv Gandhi Institute of Medical Science (RIMS), a tertiary care teaching hospital located in Andhra Pradesh, India, from December 2019 to 2020.

Study Population

A total of 200 patients' prescriptions were reviewed. All patients aged ≥18 years, of either sex, diagnosed with any type of vitiligo, and receiving treatment were included in the study. Patients with other medical comorbidities and incomplete prescriptions were excluded from the study. We also excluded participants who did not consent to participate in the study.

Ethical Statement

The study was conducted after getting approval from the Institute Ethics Committee of RIMS. Written consent was obtained from all of the subjects after explaining the objectives, importance, and benefits of the research and that participation was voluntary. They were assured that all the collected data would be handled with full

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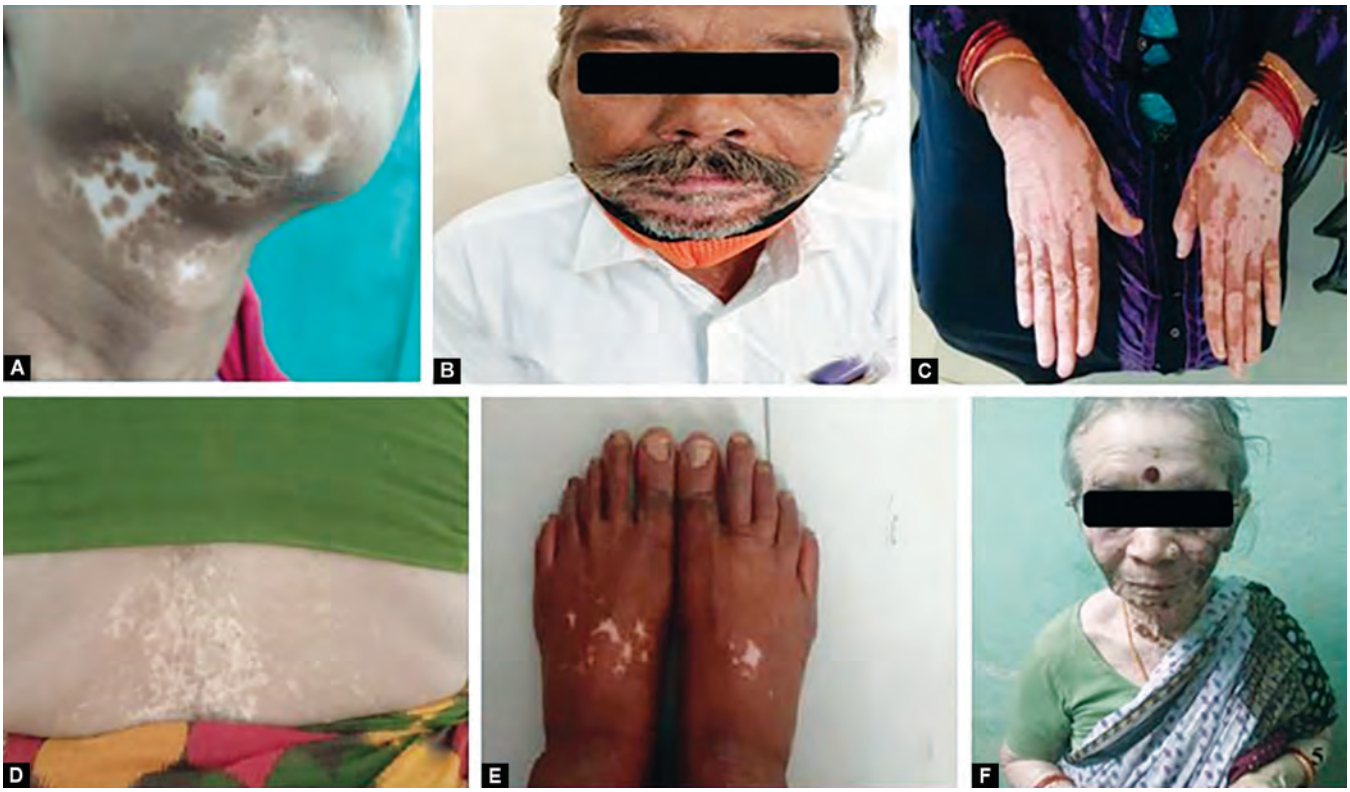
How to cite this article: Padmakar S, Kumari S, Pal B. A Study on Drug Prescribing Patterns in Vitiligo Patients of Andhra Pradesh in a Tertiary Care Teaching Hospital. J Assoc Physicians India 2024;72(5):61–64.



Figs 1A to F: Different types of vitiligo; (A) Unilateral; (B & C) Acrofacial; (D) Vulgaris; (E) Focal; (F) Universal

confidentiality, would be used only for research purposes, and would not affect their treatment. The left thumb impression was taken in the presence of an appropriate witness for illiterate patients.

Sample Size

The sample size was calculated using the formula:

$$n = z^2 p(1-p) / d^2$$

The prevalence of vitiligo was 8%, as taken from a previous study.[3] Where the *Z*-score is 1.96, associated with a confidence level of 95%, sample proportion (*p*) is 8% (expressed as a decimal, 0.08), and the margin of error (*d*) was 4% (expressed as a decimal, 0.04). The calculated sample size was 177. However, to increase the power of the study, a total of 200 patients were recruited.

Data Collection

Patient data were collected from both the outpatient and inpatient Departments of Dermatology. A data collection form was designed incorporating all necessary variables, including age, gender, type of vitiligo, duration since vitiligo developed, current medical conditions, diagnosis, medications prescribed, treatment duration, dosage form, frequency, and route of administration. The patients were examined at the dermatology department by an experienced dermatologist. The diagnosis of vitiligo was based on characteristic loss of skin pigmentation with typical localization and wood lamp examination. All the relevant data were collected from the patient's file.

Data Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS®) software version 18.0. Descriptive statistics such as frequencies, percentages, mean, and standard deviation were used to analyze the data.

Results

In the present study, 200 patient's prescriptions were evaluated, of which 54% (*n* = 108) were females and 46% (*n* = 92) were males. The majority of patients (25.5%) were under the age-group of 45–55 years (*n* = 51), followed by the age group of 25–35 years (*n* = 46). The lowest number of patients was observed in the age group of 65–75 years (*n* = 30) (Table 1).

Acrofacial was the most common type of vitiligo observed in 78 (39%) patients, followed by focal: 46 (23%), vulgaris: 36 (18%), segmental: 29 (14.5%), and universal: 11 (5.5%). Concerning the chronicity of the disease, the majority of the patients, 90 (45%), were suffering for 10 years and above (Table 2).

Table 1: Demographic details of vitiligo patients

Demographic factors	*Categories*	*n (%)*
Age in years	25–35	46 (23)
	35–45	33 (16.5)
	45–55	51 (25.5)
	55–65	40 (20)
	65–75	30 (15)
Gender	Male	92 (46)
	Female	108 (54)
Types of vitiligo	Unilateral	29 (14.5)
	Focal	46 (23)
	Acrofacial	78 (39)
	Vulgaris	36 (18)
	Universal	11 (5.5)

Table 2: Distribution of patients based on the chronicity of the condition

Duration of chronicity (year)	*Number of patients*	*Percentages*
≥2	61	30.5
≥5	49	24.5
≥10	90	45

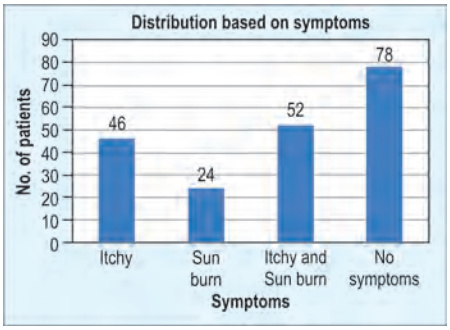


Fig. 2: Distribution based on symptoms experienced by patients of vitiligo

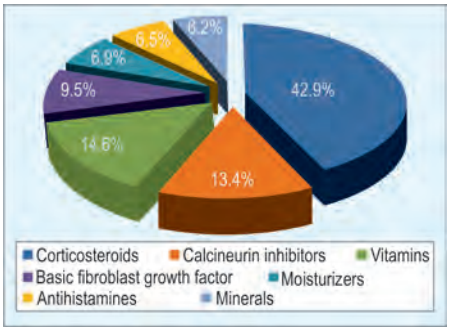


Fig. 3: The most commonly prescribed class of drugs for vitiligo in RIMS General Hospital

Out of 200 patients, 52 (26%) had itchy sunburns in their lesion, 46 (23%) patients had only itchy, and 24 (12%) patients had only sunburns (Fig. 2).

A total of 464 drugs were prescribed to 200 patients. All the drugs were prescribed by generic names. Almost all prescriptions mentioned the strength, the quantity of the drug to be used, the frequency, and the site of application. The most commonly prescribed class of drugs was corticosteroids (42.9%), followed by calcineurin inhibitors (13.4%), vitamins (14.6%), basic fibroblast growth factor (BFGF) (9.5%), moisturizers (6.9%), antihistamines (6.5%), and minerals (6.2%) (Fig. 3). TCSs were prescribed more often than orally. Among corticosteroids, betamethasone was the most commonly prescribed drug, followed by clobetasol propionate. Tacrolimus was secondary to steroids, followed by decapeptide, vitamins A and D, glycerin, chlorpheniramine maleate, B complex, and calcium (Table 3).

Table 3: The most commonly prescribed drugs for vitiligo in RIMS General Hospital, 2020 ($n = 464$)

Drugs prescribed	*Value (%)*
Corticosteroids	
Tab betamethasone	72 (15.5)
Oint betamethasone	68 (14.7)
Oint clobetasol propionate	59 (12.7)
Calcineurin inhibitor	
Oint tacrolimus	62 (13.4)
Vitamins	
Cap vitamins A and D	39 (8.4)
Tab vitamin B complex	29 (6.2)
BFGF	
Lot decapepide	44 (9.5)
Moisturizers	
Lot glycerin	32 (6.9)
Antihistamines	
Tab chlorpheniramine maleate	30 (6.5)
Minerals	
Tab calcium	29 (6.2)

Tab, tablet; oint, ointment; cap, capsule; lot, lotion

Discussion

Prescription auditing is a part of medical auditing and is a quality improvement procedure. It helps to improve patient care and therapeutic outcomes. Prescription auditing is also an educational activity that, if done on a regular basis, can help to improve prescription quality and enable patients to receive high-quality care.[10]

Corticosteroid was the most commonly prescribed drug in our study. Most of the corticosteroids were given topically, followed by oral. This may be due to adverse effects associated with systemic steroid therapy. Topical steroids have added advantages in terms of less systemic absorption, fewer side effects, and convenience to use. Similar to our study, Sarkar et al. also reported that topical steroids were the most commonly prescribed drug for vitiligo.[11] TCS and topical calcineurin inhibitors (TCIs) are important components of evidence-based treatment, resulting in repigmentation of sun-exposed patches in 75% of patients.[12] TCIs (e.g., tacrolimus 0.1% ointment twice a day for 6 months) are indicated to prevent harmful effects on the face and in areas particularly sensitive to corticosteroids.[13] In the present study, betamethasone was the most commonly prescribed corticosteroid, followed by clobetasol propionate. In this study, steroids were prescribed in combination with topical tacrolimus. Tacrolimus is beneficial for younger patients and suitable for sensitive parts of the skin, such as the eyelids.[13] Jang et al. reported that a triple combination of systemic corticosteroids, excimer laser, and topical tacrolimus is effective for recent-onset vitiligo.[14] Early intervention with this combination therapy was likely to prevent the disease's progression and achieve more rapid and full repigmentation.[14]

Tacrolimus ointment is a well-tolerated alternative choice for individuals who were unable to undergo routine phototherapy and were too concerned about the side effects of long-term topical steroids used.[15] The tacrolimus ointment 0.1% was effective in preventing the depigmentation of vitiligo patches and also effective for facial vitiligo.[16,17]

The active BFGF related peptides were investigated as a potential repigmenting agent for vitiligo macules.[18] Shah et al. described that BFGF-related decapeptide solution in combination with tacrolimus was superior to tacrolimus alone among vitiligo patients.[19]

The analogy of vitamin D_3 has also recently been demonstrated to produce good benefits for psoriasis and vitiligo.[20] Vitamin D_3 increases the activity of tyrosinase enzymes and stimulates melanin formation.[21] Vitamin D supplementation is therapeutically helpful for autoimmune diseases in animal models.[22] Thus, a vitamin D supplement may be utilized as a therapy in autoimmune disorders such as vitiligo. A study conducted by Karagüzel et al. illustrated that combined therapy with oral vitamin D and topical tacrolimus was more effective than topical tacrolimus alone for repigmentation.[23]

Conclusion

Most of the patients with vitiligo were treated with topical and systemic corticosteroids, followed by TCIs in combination. Further studies are needed on a regular basis to improve the prescription pattern and develop more effective guidelines that may be beneficial to vitiligo-inflicted patients.

Author's Contribution

- B Pal and Sweta Kumari: Concept, design, supervision of study, analysis, and editing and approval of the manuscript.
- S Padmakar: Literature search, collection, analysis, and interpretation of data, wrote the manuscript.

Acknowledgment

We would like to thank the hospital staff and management for their support and help during the study period.

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ORIGINAL ARTICLE

Association of Diabetic Peripheral Neuropathy with Micronutrients

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Received: 10 April 2023; *Accepted:* 20 October 2023

Abstract

Introduction: Diabetes mellitus (DM) is a common metabolic disorder that has been defined by hyperglycemia. Diabetic patients usually have high levels of oxidative stress. Mitochondrial dysfunction and inflammation of blood vessels are associated with a greater need for micronutrients in diabetic patients. These micronutrients may have an association with the complications in diabetics. The purpose of this study was to show the association of diabetic peripheral neuropathy (DPN) with levels of micronutrients such as copper (Cu), zinc (Zn), magnesium (Mg), and vitamin B_{12} (Vit B_{12}).

Materials and methods: This cross-sectional study was conducted in the Department of Medicine, Lala Lajpat Rai Memorial Medical College, Meerut. A total of 130 randomly selected cases of confirmed type-2 diabetic patients were included in this study. DPN cases were identified using the Michigan neuropathy screening instrument. Out of 130 diabetic patients, 28 patients were found to have diabetic neuropathy. The level of various micronutrients was assessed and correlated with the development of DPN.

Results: The association of DPN with Zn (p-value of 0.02) and Vit B_{12} (p-value of 0.008) was found to be significant, whereas Cu (p-value of 0.57) and Mg (p-value of 0.24) were found to be insignificant.

Journal of the Association of Physicians of India (2024): 10.59556/japi.72.0493

Introduction

Diabetes is a chronic noncommunicable disease that occurs when either our body does not produce enough insulin or insulin, which is produced by our pancreas, is not effectively used by our body.[1]

Uncontrolled blood sugar is commonly associated with many microvascular as well as macrovascular complications. This complication can be prevented or delayed by a healthy diet, physical activity, avoiding smoking and alcohol, and maintaining normal body weight.[2]

Micronutrients are essential nutrients that our body requires in a very small amount on a daily basis. The association of diabetes with trace elements like copper (Cu), magnesium (Mg), vitamin B_{12} (Vit B_{12}), and zinc (Zn) has been seen in many studies. It was found that these trace elements reduce blood glucose levels. Trace elements like Cu, chromium, Mg, vanadium, Zn, manganese, and selenium have many actions on enhancing insulin action, such as (1) serving as a cofactor or component for enzymes that are involved in glucose metabolism, (2) activation of insulin receptor sites, (3) increasing insulin sensitivity, (4) they act as an antioxidant and prevent peroxidation in tissues.[3]

In type 2 diabetes mellitus (T2DM), it was found that the metabolism of trace elements can alter not only blood sugar levels but also have a role in the pathogenesis and progress of the disease.[4]

Diabetic complications can be divided into two broad categories:

- Microvascular complications (they occur due to damage in small blood vessels), for example, diabetic retinopathy, diabetic nephropathy, and diabetic neuropathy.
- Macrovascular complications (they occur due to damage to the larger blood vessels), such as coronary artery disease, peripheral vascular disease, and cerebrovascular disease.[5]

Diabetes mellitus (DM) is associated with a decrease in the antioxidant defense, which increases the production of reactive oxygen species. This oxidative stress is responsible for many diabetic complications.[6,7] Micronutrients play a role in the genesis of oxidative stress, and some minerals and vitamins can be used to decrease oxidative stress and improve glycemic control. Nevertheless, antioxidants and micronutrients can be used as adjuvant therapy in diabetic patients, and strict blood sugar control is the key to preventing these complications. Supplementation of these micronutrients may be more effective when there is a deficiency of these micronutrients.[8]

Therefore, we conducted this study to see the association of micronutrients in patients with diabetic peripheral neuropathy (DPN).

Aims and Objectives

- To see the distribution of DPN in various age and sex groups among diabetics.
- To see the association between DPN and the level of micronutrients among diabetics.

Materials and Methods

A present cross-sectional study was conducted to assess the level of micronutrients in peripheral neuropathy patients among diabetics at Lala Lajpat Rai Memorial Medical College, Meerut. The ethical clearance was taken from Institutional Ethics Committee, Lala Lajpat Rai Memorial Medical College, Meerut, with no SC-1/2022/3970.

The sample size was calculated by taking the prevalence of DM as 8.8, with a 5% allowable error and a 95% confidence interval using the formula.

$$N = (1.96)2PQ / d2$$

The sample size thus calculated came out to be 123. However, it is rounded about to 130.

All the diabetic patients visiting Lala Lajpat Rai Memorial Medical College, Meerut, were included in the study till the desired sample size was achieved.

Inclusion Criteria

- Age 18–65 years.
- Patients consenting to take part in the study.

Exclusion Criteria

- Taking vitamin, mineral supplements, thyroid hormones, estrogens, progesterone, and diuretics.

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How to cite this article: Gautam S, Mittal C, Ranjan A, *et al.* Association of Diabetic Peripheral Neuropathy with Micronutrients. J Assoc Physicians India 2024;72(5):65–67.

- History of myocardial infarction, hepatic disease, psychiatric disorders, and alcoholism.
- Pregnant and lactating female.

Information regarding various biosocial and disease-related variables was collected in a predesigned and pretested questionnaire. All the study participants have undergone complete blood count, liver function test, kidney function test, hemoglobin A1c, blood sugar, both fasting and postprandial, fasting lipid profile, level of Zn, Cu, Mg, and Vit B_{12}.

All the diabetic patients were assessed for DPN by using the Michigan neuropathy screening instrument. A physical examination of both feet was done. The total possible score of physical examination is 8, and patients who had a score of 2.5 or more were considered to have DPN. All the collected information was compiled and tabulated. Statistical analysis was done using the Chi-squared test.

Observations and Results

In the present study, a total of 130 patients were taken. Out of these, 65% were male, and 35% were female. 8.5% belonged to the 18–35 years age-group, while 40% were in the 35–50 years age-group. Around 51.5% of study subjects were >50 years old. Around 67% of study subjects were vegetarian, and 33% were nonvegetarian.

On the basis of the Michigan neuropathy screening instrument, out of 130 study subjects, 28 (21.53%) were found to have DPN. When the age and sex distribution of these patients were assessed, 9.1% of the 18–35 years age-group developed peripheral neuropathy. In the 35–50 years age-group, 9.6% develop DPN. While in the >50 years age-group, 32.8% develop the DPN. The difference of age in the development of DPN was found to be statistically highly significant.

Around 22.4% of males and 20% of females developed DPN. The association between the development of DPN and gender was found to be insignificant.

In Table 1, when the level of various micronutrients was assessed, it was observed that out of 130 diabetic patients, a high Cu level was found in 55.4%, and only 6.2% of patients had a low Cu level. It was observed that out of eight diabetic patients who have low Cu value, four (50%) develop DPN. Out of 50 patients with normal values, only seven (14%) patients developed DPN. Out of 72 patients with high Cu values, 17 (23.6%) developed DPN. The association between the level of Cu in DPN among diabetics was insignificant (*p*-value of 0.57).

Table 2 Out of 130 patients, 47.6% patients had low Zn levels, while 7.6% had high levels of Zn. Out of 62 patients having low Zn levels, 15(24.19%) developed DPN. Out of 58 patients with normal Zn levels, 8 (13.79%) develop DPN, while 50% of patients having high Zn levels develop DPN. The association of the level of Zn with the development of DPN was found to be significant (*p*-value of 0.02).

Table 3 shows that 43.9% of patients had low Mg levels, and only 8.4% were found to have high Mg levels. Out of 57 who had low Mg levels, 14 (24.56%) developed DPN. Out of 62 patients having normal Mg levels, 10 (16.12%) develop DPN. Out of 11 patients having high Mg levels, four (36.36%) develop DPN. The association between levels of Mg in DPN among diabetics is insignificant (*p*-value 0.24).

Table 4 shows that out of a total of 130 diabetic patients, 31.5% had low Vit B_{12} levels, and 6.9% had high Vit B_{12} levels. A total of 17 (41.46%) among those with low Vit B_{12} levels develop DPN. Out of 80 patients having normal Vit B_{12} levels, 10 (12.5%) develop DPN, and among patients having high Vit B_{12} levels, 12.5% patients develop DPN. The Association between Vit B_{12} and DPN was found to be highly significant (*p*-value of 0.0008).

Discussion

In recent years, it has been seen that chronic noncommunicable diseases, especially diabetes, and hypertension, are becoming a major cause of death worldwide. Diabetes affects almost each and every organ system of the body and causes complications. There are various manifestations of diabetic complications in which diabetic neuropathy occurs in almost 50% of long-standing type 1 and T2DM. Diabetic neuropathy can manifest as diffuse peripheral neuropathy, mononeuropathy, and radiculopathy. In diabetic patients, due to high levels of oxidative stress, mitochondrial dysfunction, and inflammation of the blood vessels, there is usually a need for high levels of micronutrients.

In the present study, 65% were male and 35% were female. Almost similar observations were made by Arpaci et al. (57.8% male and 42.2% female).[9]

In the present study, 21.5% of diabetics developed DPN, while Apraci et al. observed 14.1% of diabetics develop DPN.[9]

The DPN was observed to increase significantly with increasing age. Similar findings were observed by Pfannkuche et al., and they concluded older age is a significant risk factor for DPN.[10]

When the level of various micronutrients was assessed, it was observed that out of

Table 1: Association between level of Cu and DPN

Cu value	*Total*	*DPN*	*Percentage*	*χ2*	*p-value*
Low (<70 mg/dL)	8 (6.2%)	4	50%	5.6991	0.57869
Normal (70–155 mg/dL)	50 (38.4%)	7	14%		
High (>155 mg/dL)	72 (55.4%)	17	23.6%		
Total	130 (100%)	28	21.5%		

Table 2: Association between level of ZN and DPN

Zn value	*Total*	*DPN*	*Percentage*	*χ2*	*p-value*
Low (<63.8 mg/dL)	62 (47.6%)	15	24.19%	7.111	0.028
Normal (63.8114 mg/dL)	58 (44.6%)	8	13.79%		
High (>114 mg/dL)	10 (7.6%)	5	50%		
Total	130 (100%)	28	21.5%		

Table 3: Association between levels of Mg in DPN

Mg	*Total*	*DPN*	*Percentage*	*χ2*	*p-value*
Low (<1.3 mEq/L)	57 (43.9%)	14	24.56%	2.8124	0.2450
Normal (1.3–2.1 mEq/L)	62 (47.7%)	10	16.12%		
High (>2.1 mEq/L)	11 (8.4%)	4	36.36%		
Total	130 (100%)	28	21.5%		

Table 4: Association between level of Vit B_{12} and DPN

Vit B_{12}	*Total*	*DPN*	*Percentage*	*χ2*	*p-value*
Low (<160 pg/dL)	41 (31.5%)	17	41.46%	14.078	0.00087
Normal (160–970 pg/dL)	80 (61.6%)	10	12.5%		
High (>970 pg/dL)	9 (6.9%)	1	12.5%		
Total	130 (100%)	28	21.5%		

130 diabetic patients, a high Cu level was found in 55.4%, and only 6.2% of patients had low Cu levels. Similar findings have been observed in other studies, such as Disilvestro[11] and Zarga et al.,[12] 50% of patients with low Cu levels develop DPN. While 23.6% of patients with high Cu values develop DPN, indicating that though Cu levels were higher among diabetics, patients with low Cu levels were found to be more prone to develop neuropathy.

In the present study, 47.6% of diabetic patients had low Zn levels, and 7.6% had high levels of Zn. Hussein et al. also observed similar findings. They found that the mean serum Zn level was significantly lower in the DPN group than in healthy controls (56.95 ± 10.86, 62.09 ± 9.2 µg/dL, respectively) ($p = 0.023$).[13] Among those with low Zn levels, 24.19% develop DPN, while 50% of patients with high Zn levels develop DPN. Hussein et al. also observed lower mean Zn levels in the DPN group than in the non-DPN group.[13]

In the present study, 43.9% of diabetic patients were found to have low Mg levels, and only 8.4% had high Mg levels. Serum Mg has a close relationship with T2DM.[14] It has been shown that lower serum Mg levels are significantly associated with an increased risk of T2DM and with its complications of diabetes, including nephropathy, retinopathy, and foot ulcers.[15] Proportion of patients developing DPN was high among those with high serum Mg levels (36.36%), compared to 24.56% among those with low Mg levels. However, data regarding the relationship between serum low Mg and DPN are limited and controversial.[15]

The present study has shown that Vit B_{12} levels were lower in DPN. These findings are consistent with Khalaf et al., which show a high prevalence of Vit B_{12} deficiency in metformin-treated T2DM patients.[16]

Conclusion

It can be concluded from our study that altered levels of trace elements have a role in the pathogenesis and progression of DM. They also play a significant role in the complications of diabetes especially diabeteic neuropathy.

The decreased blood levels of Zn, Mg, and Vit B_{12} and increased blood levels of Cu, as have been found in the present study, can be utilized for the management of DM. However, these observations require further study because of the important role of trace elements in DM; it is suggested that an adequate supply of these substances in the diet of diabetic patients can be beneficial in the long-term management of diabetic patients, and further study in this field is recommended.

Limitation

The study was a cross-sectional study, so follow-up of the patients could not be done. The sample size was small, so the findings of the study can not be generalized. So, a multicentric study with a larger sample size is needed so that findings can be generalized.

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REVIEW ARTICLE

A Systematic Review and Meta-analysis to Identify Risk Factors for Developing Long COVID-19

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Received: 10 January 2023; *Revised:* 15 February 2023; *Accepted:* 26 December 2023

Abstract

Aim: This systematic review and meta-analysis was undertaken to identify the risk factors of long coronavirus disease 2019 (COVID-19) to provide insight for selecting cases for more aggressive monitoring and treatment after COVID-19 infection and reduce morbidity due to long COVID-19.

Materials and methods: All relevant studies published till July 2022 were searched for in PubMed, Trip database, and the Cochrane Central Register of Controlled Trials (CENTRAL; The Cochrane Library). Reference lists of the studies selected for appraisal were also considered. The National Institute of Health Clinical Database and Google Scholar were searched for unpublished studies. All cohort studies which studied risk factors for long COVID-19 in adults (>18 years age-group) were included. Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines were used for data extraction and bias assessment were. The outcomes were risk factors identified as being related with persistent symptoms 3 months after recovery from COVID-19. Random-effects model (RevMan 5.3) was used to pool the data.

Results: Total nine studies were included with overall quality scores ranging from 16 to 19 out of the maximum 22. Pooled results demonstrated statistically significant association of long COVID-19 with female gender [odds ratio (OR) –1.67; 95% confidence interval (CI) 1.33–2.09], need of hospitalization (OR –1.80; 95% CI 1.22–2.64), and hospital stay (OR 2.41; 95% CI 0.75–4.07).

Conclusion: Female gender, need for hospitalization and duration of hospitalization during acute COVID-19 infection are the risk factors for later development of long COVID-19. There should be specific guidelines for monitoring and treatment of this population after acute COVID-19 infection.

Journal of the Association of Physicians of India (2024): 10.59556/japi.72.0528

Introduction

The pandemic of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection [coronavirus disease 2019 (COVID-19)] resulted in significant mortality and morbidity worldwide.[1] The infection can affect more than one organs and lead to persistence of various symptoms.[2] Pulmonary involvement may lead to chronic cough, lung fibrosis, pulmonary hypertension, and bronchiectasis.[3,4] Cardiac involvement may cause atherosclerosis, hyper-/hypotension, myocarditis, myocardial infarction, pericarditis, arrhythmias, aneurysms, heart failure, and sudden cardiac death.[5,6] Involvement of nervous system results in headache, tremors, difficulty in concentration, reduced attention span, cognitive blunting, and peripheral neuropathy.[7,8] Similarly, advanced COVID-19 disease and prolonged mechanical ventilation may cause weakness, deconditioning, myopathies, neuropathies, delirium, and autoreactivity against various self-antigens.[9,10] COVID-19-associated coagulopathy (CAC) is also seen in the form of arterial or venous thrombosis.[11] It may have psychological impact due to fear and prolonged illness.

About 80% of the COVID-19 infected patients had mild-to-moderate disease. Among the remaining 20% with severe disease, 5% developed critical illness.[12,13] Among the recovered, a few went on to develop "long COVID" syndrome (defined as signs and symptoms that develop during or after COVID-19 infection, continue for >12 weeks post recovery and cannot be explained by an alternative diagnosis).[14,15] In a study, at least one symptom was reported to persist for 60 days.[16,17] In other studies, breathlessness and excessive fatigue were observed even at 3 months post recovery.[18,19] Later, residual symptoms were reported in about 35 and 87% of the outpatient and hospitalized patients, respectively.[20–22]

In a meta-analysis, fatigue, headache, attention disorder, hair loss, and dyspnea were the most common features of long COVID-19 and were seen in 58, 44, 27, 25, and 24%, respectively.[23] Mental health problems like anxiety and depression are also common.[24] Other studies identified female gender, increasing age, and presence of more than five symptoms as the risk factors for developing long COVID-19.[25]

Looking at the impact that COVID-19 has had on the global population, it seems pertinent to gain more insight into the persistent symptoms post COVID-19.[26] Due to a relatively recent appearance on global map, studies addressing this entity are few and even fewer have studied risk factors for development of long COVID-19 syndrome. Hence, we planned this systematic review and meta-analysis to identify the risk factors of long COVID-19 syndrome.

Review Question

What are the risk factors associated with development of long COVID-19 syndrome?

Materials and Methods

An initial limited search of PubMed was carried out using the keywords "long COVID," "post COVID," and "risk factors." Text words in the title, abstract, and index terms of the studies identified were used to form the search strategy. To find relevant published studies, PubMed, Trip database, and the Cochrane Central Register of Controlled Trials (CENTRAL; The Cochrane Library) were searched. The search was restricted to papers published in English language as the authors were unable to translate other languages.

Unpublished studies were searched for in The National Institute of Health Clinical Database and Google Scholar. Studies were also identified from the reference list of all relevant studies retrieved. Authors were contacted in case of incomplete data presented to decide regarding inclusion in the systematic review.

This systematic review included all studies till date which studied persistent symptoms in patients who have recovered from COVID-19. The studies with participants of either gender, >18 years in age with history of COVID-19 infection at least 3 months back

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How to cite this article: Muley A, Mitra S, Bhaliya B, *et al.* A Systematic Review and Meta-analysis to Identify Risk Factors for Developing Long COVID-19. J Assoc Physicians India 2024;72(5):68–74.

were included. The studies with participants <18 years in age were excluded. Post-COVID-19 was defined in accordance with the definition given by WHO as "a condition in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis." (WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1). The outcomes considered were symptoms which persisted and risk factors identified as being related with persistence of symptoms even 3 months post COVID. The results of the search are presented in a PRISMA flow diagram (Flowchart 1).

Data Extraction and Quality Assessment

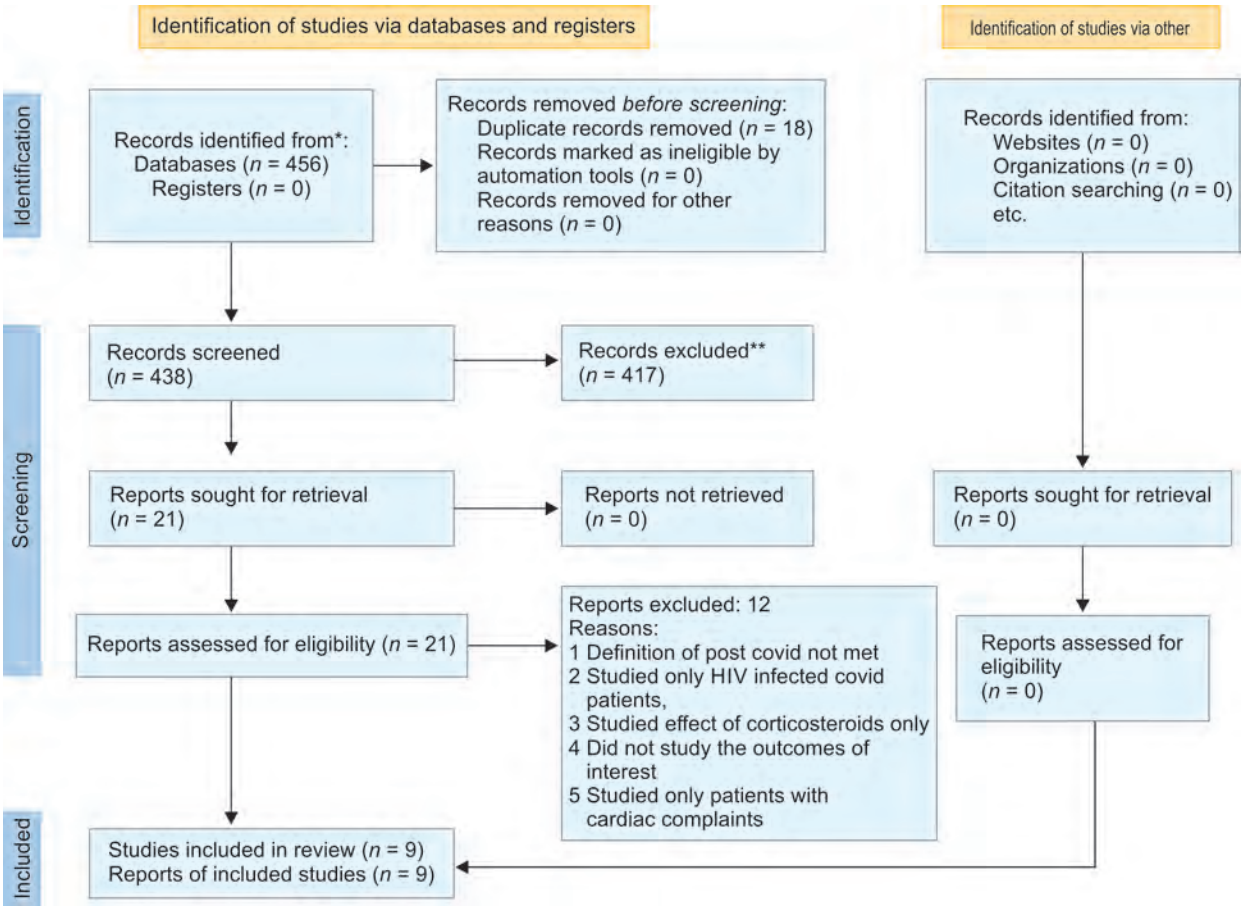
After the completion of searching, all relevant studies identified were collated and duplicates were removed. Two independent reviewers (BB and SM) then screened the titles and abstracts for matching with inclusion criteria. Any disagreements between the two were resolved by discussion. If there was no consensus even after this, a third reviewer (AM) was available and the final decision was based on majority.

Full text of the potentially eligible studies that met the inclusion criteria were retrieved. Other studies that did not meet the inclusion criteria were excluded. Selected studies were critically appraised by two independent reviewers (SM and BB) for methodological quality using the standardized critical appraisal checklist from Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information (JBI SUMARI) for cohort studies. Responses to the appraisal tool (yes—2, no—0, and unsure—1) were recorded. Disagreement was resolved by discussion between the two for both critical appraisal assessments. A score of 22 was the highest possible score for the standardized instrument and indicated a study of higher quality.

Data was extracted and synthesized (where possible) from all included studies. Two independent reviewers (SS and AJ) extracted the quantitative data from the trials included in the review. The data regarding interventions involved, characteristics of study population, context, study duration, study design, and other outcomes of significance to the review question was collected. Authors of trials were requested through mail to provide missing or additional data.

RevMan 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane) was used to pool the data collected for statistical meta-analysis. For results that were not possible to present in a meta-analysis, the findings have been presented in a narrative form. Treatment effect is presented as either odds ratio (for continuous variable) or mean difference (for categorical variable). All studies presented the results either as odds ratio (for continuous variable) or mean difference (for categorical variable). If these values were not given in the study, they were

Flowchart 1: PRISMA 2020 flow diagram showing searching results; *Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers); **If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools; Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372:n71. DOI: 10.1136/bmj.n71; for more information, visit: http://www.prisma-statement.org/



calculated from the number of events with total participants available.

I^2 and χ^2 statistics were used to assess statistical heterogeneity in the meta-analysis. Heterogeneity was considered significant if in the χ^2 test for heterogeneity, $I^2 > 50\%$ and *p*-value < 0.10.37 A random effects model was used in the meta-analysis, when there was significant (>50%) heterogeneity. As only two to three relevant studies could be included in each category of meta-analysis, no subgroup analysis was done and sensitivity analysis was also not needed as there were no outliers.

Results

Results of the Search

The search results identified 125 potential studies (Flowchart 1). After a review of the title and abstract of all 125 studies, 21 trials were identified as relevant for inclusion in the review. After examination of the full text against the inclusion criteria, 12 out of 21 trials were excluded.

Reasons for exclusion were—participants were studied immediately after recovery from COVID-19 to not included the post-COVID-19 time by definition, studied only human immunodeficiency virus (HIV)-infected COVID-19 patients, studied effect of corticosteroids only, did not study the outcomes of interest and studied only patients with cardiac complaints. Nine trials were critically appraised and underwent data extraction and synthesis.

Included Studies

All the nine studies included in the review were cohort studies.[27–35] Two studies were multicenter studies[34,35] and the rest were single-center studies.[27–33] Four studies were conducted in Spain[29,33–35] and the remaining five studies in five different countries—Russia,[27] United kingdom,[28] Iran,[30] United States of America,[31] and Italy.[32] The number of participants varied from 17[32] to 4,681.[30] Of the nine studies, four studies showed male preponderance[30,31,33,34] and four studies showed female preponderance.[27,28,32,35] However, one of the studies did not specify gender distribution.[29] Mean age of patients varied from 41 to 71 years. Inclusion criteria were similar in all studies. All the authors studied presentation of post-COVID-19 symptoms.[27–35] Four studies analyzed quality of life using different questionnaires.[27,29–31] Four studies[27,30,33,34] studied relation of persisting symptoms with female gender, three studies[27,31,33] assessed relation of chronic obstructive pulmonary disease (COPD) with persistent symptoms, three studies[28,31,33] demonstrated relation of hospitalization with persistent symptoms, two studies[30,34] demonstrated relation of number of comorbidities with persistent symptoms, and two studies[30,34] demonstrated relation of stay in hospital with persistent symptoms. Additional variables like serum biomarkers,[33] spirometric analysis[32] and magnetic resonance imaging (MRI) of organ involvement[28] were also analyzed in a few included studies. The follow-up period ranged from 3 months[30] to 1 year (Table 1).[31,32,35]

Risk of Bias in Included Studies

The methodological quality for the nine randomized controlled trials (RCTs) was assessed by two independent reviewers and any disagreement was settled with discussion. Overall quality of the trials was variable. The score ranged from 16 to 19

Table 1: Characteristics of included studies

Author	*Country*	*Study design*	*Follow-up and data collection method*	*Inclusion/exclusion criteria*	*Study population, male/female*	*Mean/median age*	*Outcomes measured*
Munblit et al.[27]	Russia	Longitudinal cohort study	Median 218 days postdischarge By phone surveys	Inclusion: Adult patients (≥18 years of age), with either reverse transcription polymerase chain reaction (RT-PCR)-confirmed SARS-CoV-2 infection and clinically confirmed infection, when the laboratory testing result is negative, inconclusive or unavailable	2649, 1296/1353	56 (46–66)	Symptoms: Fatigue, shortness of breath, forgetfulness, muscle weakness, problem seeing, hair loss, and problem sleeping Dyspnea scale Health status using EuroQol visual analog scale
Dennis et al.[28]	United Kingdom	Prospective observational cohort study	Median 141 days after symptoms Assessment of symptoms by standardized questionnaires and organ specific metrics by biochemical assessment and quantitative MRI	Inclusion: Laboratory-confirmed SARS-CoV-2 infection Exclusion criteria—one symptom of active respiratory viral infection (temperature >37.8°C or three or more episodes of coughing in 24 hours), hospital discharge in the last 7 days, and contraindications to MRI, including implanted pacemakers, defibrillators, other metallic implanted devices and claustrophobia	201, 57/144	44 years (21–71)	Symptoms: Fatigue, breathlessness, muscle aches, headache, cough, joint pain, abdominal pain, nausea, vomiting, chest pain, fever, sore throat, wheezing, runny nose, and inability to walk Organ involvement (MRI findings)—single or multiorgan involvement Severe post-COVID-19 syndrome defined as ongoing respiratory symptoms and/or moderate functional impairment in activities of daily living

Contd…

Contd…

Author	*Country*	*Study design*	*Follow-up and data collection method*	*Inclusion/exclusion criteria*	*Study population, male/female*	*Mean/median age*	*Outcomes measured*
Catalán et al.[29]	Spain	Observational cohort study	1 year after admission, telephonic surveys	Inclusion: Adults ≥18 years with laboratory-confirmed SARS-CoV-2 infection admitted in infectious diseases ward from March to May 2020 Exclusion: Those who died, were unreachable and had cognitive impairment	76		Symptoms like cough, shortness of breath, sore throat, asthenia, forgetfulness, headache, arthromyalgia, nausea/vomiting, diarrhea, chest pain, abdominal pain, loss of smell/taste, insomnia, alopecia, etc. SF-36 questionnaire for quality of life (physical functioning, physical role limitations, bodily pain, social functioning, mental health, emotional role limitations, energy/vitality, and general health perceptions)
Asadi-Pooya et al.[30]	Iran	Retrospective observational study	3 months after discharge By phone surveys	Inclusion: Laboratory-confirmed SARS-CoV-2 infection admitted between 19 February and 20 November 2020) Exclusion: Refusal to participate, below 18 years of age, No response after the second call	4681, 2478/2203	52 ± 15 years	Symptoms (weakness, muscle pain, fatigue, sleep difficulty, palpitation, cough, brain fog, exercise, and walking intolerance) Current health status using Likert scale Other questions: Ability to perform the activity of daily living; concentration and mind workability; studying and reading ability; quality of life; and hope for the future
Kingery et al.[31]	United States of America-New York	Retrospective observational cohort study	1 year after infection, by phone surveys	Adults ≥18 years, RT-PCR confirmed COVID-19 cases hospitalized or presented to emergency room (ER)	530, 294/236	59.2 ± 16.3 years	Self-reported health status Persistent symptoms (brain fog, cough, shortness of breath, sore throat, numbness/weakness, trouble concentrating, headache, muscle aches, nausea/vomiting, diarrhea, sputum production, chest pain, abdominal pain, loss of smell/taste, and insomnia) Effort tolerance
Fortini et al.[32]	Italy	Prospective observational study	1 year after infection Follow-up included structured questionnaire on persisting symptoms, physical examination, pulmonary function tests	COVID-19 positive patients (March–May 2020) who showed a reduction in DLCO (<80% of predicted) at 3–6 months follow-up	17, 8/9	71 years	Exertional dyspnea, cough, and fatigue Spirometric parameters: Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), FEV1/FVC, and diffusing capacity of the lungs for carbon monoxide (DLCO)
Pérez-González et al.[33]	Spain	Prospective cohort study	6 months Follow-up included structured questionnaire on persisting symptoms, physical examination, and blood investigations	Inclusion: Adult patients (≥18 years of age), RT-PCR-confirmed SARS-CoV-2 infection who survived for at least 6 months post discharge Exclusion: Died during follow-up, did not complete follow-up, cognitive impairment	248, 148/100	57 years	Symptoms: Brain fog, mood disorders, sleep disorder, hair loss, cough, shortness of breath, sore throat, numbness/weakness, trouble concentrating, headache, muscle aches, nausea/vomiting, diarrhoea, sputum production, chest pain, abdominal pain, fatigue, etc. Serum biomarkers—LDH, CRP, ferritin
Fernández-de-Las-Peñas et al.[34]	Spain	Multicenter cohort study	8.4 months (SD 1.5) after discharge, by phone survey	Inclusion: Adult patients (≥18 years of age), RT-PCR-confirmed SARS-CoV-2 infection	1969, 916/1053	61 ± 16	Symptoms: Fatigue, dyspnea, memory loss, skin rashes, brain fog, attention disorders, palpitations, gastrointestinal disorders, ocular disorders, anosmia, throat pain, and voice problems
Rivera-Izquierdo et al.[35]	Spain	Prospective multicentric cohort study	1 year after infection	Adults ≥ 18 years with laboratory-confirmed SARS-CoV-2 infection admitted from 1st March to 15th April 2020	453, 260/193	61.2 years	Symptoms: Fatigue, muscle weakness, myalgia, dyspnea, chest pain, pharyngeal symptoms, headache, confusion, memory disturbances, sleep disturbances, anxiety, depressive symptoms, and thrombotic events

(maximum obtainable score 22; Table 1), and all the included studies scored >18 out of the maximum 22 on assessing risk of bias (Table 2).

Effects of Interventions

Relation of Gender with Persistent Symptoms

Four studies[27,30,33,34] studied relation of persisting symptoms with female gender. Pooled results demonstrated statistically significant odds of persistent symptoms in females compared to males [odds ratio (OR) –1.67; 95% confidence interval (CI) 1.33–2.09; $p = 0.003$; $I^2 = 79\%$) (Fig. 1).

Relation of Chronic Obstructive Pulmonary Disease with Persistent Symptoms

Three studies[27,31,33] assessed relation of COPD with persistent symptoms and pooled results from all studies did not show any statistically significant relation between presence of COPD and persistent symptoms after recovery from COVID-19 infection (OR –1.69; 95% CI 0.92–3.08; $p = 0.15$; $I^2 = 47\%$) (Fig. 2).

Relation of Hospitalization with Persistent Symptoms

Three studies[28,31,33] demonstrated relation of hospitalization with persistent symptoms. Pooled results showed statistically significant

Table 2: Assessment of risk of bias

	Asadi-Pooya	*Munblit et al.*	*Fernández-de-Las-Peñas et al.*	*Pérez-González et al.*	*Catalan*	*Rivera-Izquierdo*	*Fortini*	*Dennis et al.*	*Kingery*
Were the two groups similar and recruited from the same population?	Y	Y	Y	Y	Y	Y	Y	U	Y
Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Y	Y	Y	Y	Y	Y	U	Y	Y
Was the exposure measures in a valid and reliable way?	Y	Y	Y	Y	Y	Y	U	Y	Y
Were the confounding factors identified?	U	N	N	U	U	U	N	U	N
Were strategies to deal with confounding factors stated?	U	U	U	U	U	U	U	U	U
Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were the outcomes measured in a valid and reliable way?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the follow-up time reported and sufficient to belong enough for outcomes to occur?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was follow-up complete, and if not, were the reasons to loss to follow-up described and explored?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were strategies to address incomplete follow-up utilized?	U	U	U	U	U	U	U	U	U
Was appropriate statistical analysis used?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Total	19	18	18	19	19	19	16	18	18

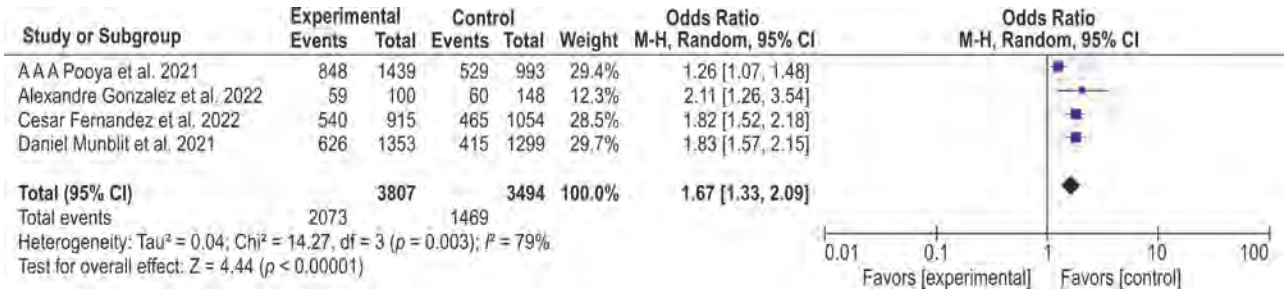


Fig. 1: Relation of persisting symptoms with female gender

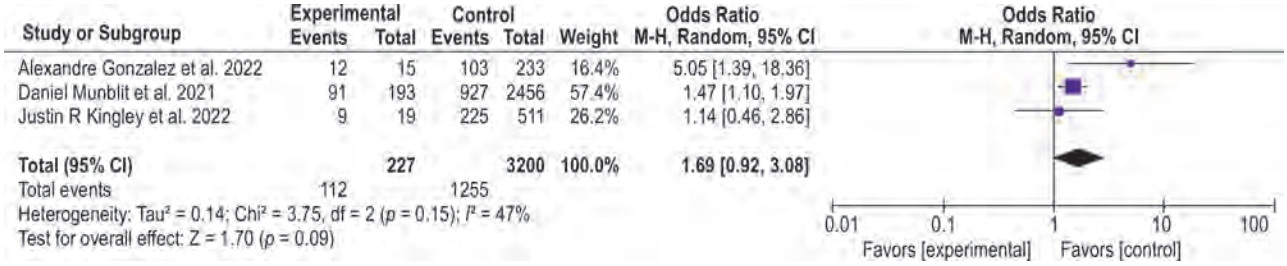


Fig. 2: Relation of COPD with persistent symptoms

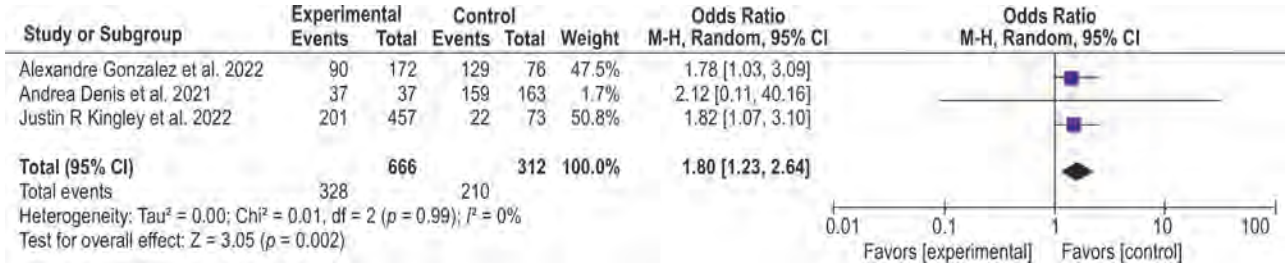


Fig. 3: Relation of hospitalization with persistent symptoms

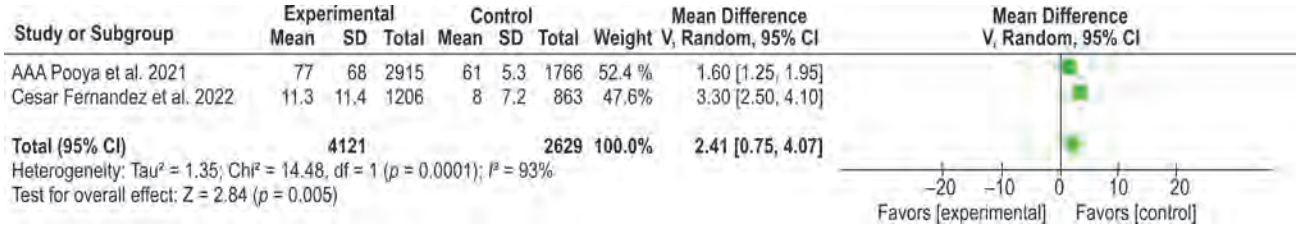


Fig. 4: Relation of stay in hospital with persistent symptoms

relation of need of hospitalization with persistent symptoms (OR –1.80; 95% CI 1.22–2.64; $p = 0.99$; $I^2 = 0\%$) (Fig. 3).

Relation of Stay in Hospital with Persistent Symptoms

Two studies[30,34] demonstrated relation of stay in hospital with persistent symptoms. Pooled results showed statistically significant association [mean difference (MD) 2.41; 95% CI 0.75–4.07; $p = 0.0001$; I^2=93%] (Fig. 4).

Relation of Number of Comorbidities with Persistent Symptoms

Two studies[30,34] demonstrated relation of number of comorbidities with persistent symptoms. Pooled results did not show any significant association between number of comorbidities and persistent symptoms (OR –1.08; 95% CI 1.26; $p = 0.12$; $I^2 = 59\%$).

Discussion

There has been an increase in reporting of persistent symptoms even 1 year after COVID-19 infection.[36] This systematic review was undertaken to study the presentation of long COVID-19 and the associated risk factors. To the best of our knowledge, this is the first systematic review to identify risk factors associated with development of post-COVID-19 syndrome. It included studies which assessed long COVID-19 syndrome. Total nine studies were found eligible for inclusion in the review and observed a significant relation between female gender, need of hospitalization, and duration of stay in hospital individually with persistent symptoms leading to post-COVID-19 syndrome.

The systematic review and meta-analysis were performed after doing extensive search for relevant articles. The included studies showed variable risk of bias mostly due to unclear identification and management of confounding factors. However, all of them scored >18 out of the maximum 22 on assessing risk of bias. Also, meta-analysis, did not show significant heterogeneity across studies. Random effects model was used to account for the heterogeneity. There was significant heterogeneity present in results of previous studies. This could be because of small sample size, differences in ethnicity, living conditions, and possibly socioeconomic status of the individuals.

Pooled results demonstrated statistically significant odds of persistent symptoms in females as compared to males (OR –1.67; 95% CI 1.33–2.09; $p = 0.003$; $I^2 = 79\%$). Recent studies with a higher cohort (single-center and multicenter studies) have also found positive association between female gender and post-COVID-19 symptoms.[12–16] Different mechanisms have been suggested in past to explain why more females than males develop post-COVID-19 symptoms.[37] Most accepted hypothesis is autoimmune hypothesis.[38,39] It has been documented that women are at increased risk of developing autoimmune disease, especially during their reproductive years but are more resistant to infections than men. This is mainly due to sex hormones and genetics causing different immunological response in both genders to the same stimuli. It has been suggested that organ damage caused by excessive inflammatory response due to the virus, is also an autoimmune reaction unmasked by the virus itself perhaps due to molecular mimicry with some components of our body; that could be responsible for the symptoms of long COVID.[25] This stronger immune response for both genetic and hormonal factors in women can act as a double-edged sword—the outcome of acute infection is favorable but autoimmune reactions are more frequent in women thus causing more symptoms.[38–40] Other factors could be isolation, stress, inactivity, and higher health seeking behavior among females compared to males.[37,41]

This study observed statistically significant relation of need of hospitalization with persistent symptoms (OR –1.80; 95% CI 1.22–2.64; $p = 0.99$; $I^2 = 0\%$). Similar observations have been reported by multiple investigators that hospitalization itself is a risk factor for persistent symptoms after COVID-19. In a study done by Carfì et al. in Italy, it was found that 87% of hospitalized COVID-19 patients had persisting symptoms related to COVID-19.[16] Similarly, Ayoubkhani et al. reported that 66% of their hospitalized patients had long COVID-19 symptoms during follow-up.[21]

Pooled results also showed statistically significant association between relation of duration of hospital stay with persistent symptoms (MD 2.41; 95% CI 0.75–4.07; $p = 0.0001$; $I^2 = 93\%$). This can be explained by the fact that severe disease required longer duration of hospitalization. It has been reported by Sudre et al.[25] that those experiencing severe symptoms in 1st week of illness had more long COVID-19 symptoms. Another study[26] reported intensive care unit (ICU) admission (that requires longer hospitalization) to be a risk factor for post-COVID-19 syndrome. This can be explained by two possibilities. Firstly, severe disease causes a more severe immune response and cytokine storm leading to more organ damages.[14,23] Secondly, aggressive treatment

of severe COVID-19 with more medications, corticosteroids can cause an iatrogenic harm/effect, due to invasive ventilation or nosocomial infections leading to long-lasting sequelae. This also indicates that there is a role of systematic multidisciplinary treatment.[42]

This review did not show significant relation of COPD or number of comorbidities with persistence of symptoms although they have been shown to be related to increased hospitalization in acute COVID-19 infection. This may be attributed to the fact that the patients might have had symptoms but could not make out whether they are due to persistence of COVID-19 symptoms or due to their comorbidities leading to underreporting of persistent COVID-19 symptoms. We did not study relationship of persistent symptoms with poor prognostic markers specifically as they are otherwise also related to need of hospitalization which was one of the variables assessed in this study.

Limitations

This systematic review has several limitations—only studies published in English were included, hence, some studies published in other languages may have been missed; majority of the studies included in this review did not report handling of confounding factors clearly; only two or three relevant studies could be identified for each analysis. Also, sample size was quite variable across studies ranging from around 100 to over 4000. Hence, generalizability of the findings is limited. Despite these limitations, the observations and results of this study are important as it addresses a very relevant topic.

Conclusion

Female gender, need for hospitalization, and longer duration of hospitalization during acute COVID-19 infection are the risk factors identified for persistence of COVID-19 symptoms for >3 months. There should be specific guidelines for monitoring and treatment of this population after acute COVID-19 infection to avoid development of long COVID-19.

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CONSENSUS STATEMENT

Consensus Statement from India on the Renal Benefits of ARNi, SGLT-2i, and Bisoprolol in Chronic Kidney Disease

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Received: 30 March 2024; *Accepted:* 03 April 2024

Abstract

Chronic kidney disease (CKD) is a major contributor to morbidity and mortality in India. CKD often coexists with heart failure (HF), diabetes, and hypertension. All these comorbidities are risk factors for renal impairment. HF and CKD are pathophysiologically intertwined, and the deterioration of one can worsen the prognosis of the other. There is a need for safe renal pharmacological therapies that target both CKD and HF and are also useful in hypertension and diabetes. Neurohormonal activation achieved through the activation of the sympathetic nervous system (SNS), the renin–angiotensin–aldosterone system (RAAS), and the natriuretic peptide system (NPS) is fundamental in the pathogenesis and progression of CKD and HF. Angiotensin receptor neprilysin inhibitor (ARNi), sodium-glucose cotransporter 2 inhibitors (SGLT-2i), and selective β1-blocker (B1B) bisoprolol suppress this neurohormonal activation. They also have many other cardiorenal benefits across a wide range of CKD patients with or without concomitant HF, diabetes, or hypertension. This consensus statement from India explores the place of ARNi, SGLT-2i, and bisoprolol in the management of CKD patients with or without HF and other comorbidities.

Journal of the Association of Physicians of India (2024): 10.59556/japi.72.0543

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How to cite this article: Chopra HK, Khullar D, Nair T, *et al*. Consensus Statement from India on the Renal Benefits of ARNi, SGLT-2i, and Bisoprolol in Chronic Kidney Disease. J Assoc Physicians India 2024;72(5):77–88.

Background

Chronic kidney disease (CKD) is a major contributor to global and Indian morbidity and mortality.[1,2] CKD prevalence in India shows regional disparity; CKD affects one in every five adults in high CKD prevalence areas.[2]

Chronic kidney disease is often diagnosed late in India, thereby increasing the burden of renal failure. Approximately, 210,000 new renal failure cases are diagnosed each year.[3] Morality rates are high in renal failure patients, with 9–13% of those on hemodialysis in India dying within 1 year. The all-cause mortality rates of dialysis patients are 6.3–8.2 times higher than that of the general population.[4] Diabetes, hypertension, and cardiovascular disease (CVD) were all significantly associated with increased renal failure deaths in India.[5]

A CVD is present in approximately 50% of stage 4 and 5 CKD (Table 1; stages of CKD) patients, and 40–50% of the total mortality cases in stage 4 and 5 CKD are due to CV-related mortality.[6] Approximately, 17–21% of patients with CKD have a new onset heart failure (HF).[6]

Targeting renal parameters in CVD, such as HF and CV parameters in CKD, is essential for optimal management and prognosis of these conditions.[7,8] Further, renal impairment/CKD restricts optimum pharmacological management for HF.[6,9]

Despite the high prevalence of HF in CKD (especially stage 2–4 CKD or renal replacement therapy), most HF trials that have shaped the current pharmacological management of HF excluded patients with severe renal impairment [i.e., estimated glomerular filtration rate (eGFR) ≤30 mL/minute/1.73 m^2].[6,10]

Moreover, patients with HF with reduced ejection fraction (HFrEF) and advanced CKD have the worst prognosis. However, HFrEF patients with CKD receive less evidence-based guideline-directed medical therapy (GDMT) for HFrEF than patients without CKD.[11]

Interplay between Chronic Kidney Disease and Heart Failure

As the renal and cardiac pathophysiology/function are bidirectionally interlinked, the disease of one organ can initiate, precipitate, or accentuate the disease of the other organ and create a vicious cycle of cardiorenal deterioration.[6–8,12,13] Several common mechanisms for cardiorenal deterioration in HF and CKD have been postulated, such as inflammation, oxidative stress, and neurohormonal activation, such as activation of the sympathetic nervous system (SNS), the renin–angiotensin–aldosterone system (RAAS), and natriuretic peptide system (NPS) (Fig. 1).[6–8,12,13] Further, CKD can lead to venous congestion, and therefore HF, because of salt and water retention and altered hemodynamics.[6] Therefore, both CKD and HF often coexist and serve as a risk factor for each other.[7,11]

Moreover, the reciprocal association between the two organs may occur in the presence of comorbidities that simultaneously affect both cardiac and renal function, such as diabetes, hypertension, and atherosclerosis.[6,7,11,12] The Indian CKD Study ($N = 4,056$) reported that 87% of patients with CKD had hypertension, 37% had diabetes, and 22% had CVD.[1]

Table 1: Classification of CKD*#[85]

Stage	*GFR in mL/minute/1.73 m^2*	*Description*
1	≥90	Kidney damage# with normal or increased GFR
2	60–89	Kidney damage# with mild decreased GFR
3	30–59	Moderately decreased GFR
4	15–29	Severely decreased GFR
5	<15 (for dialysis)	Kidney failure

*GFR <60 mL/minute/1.73 m^2; #pathological abnormalities or marker of damage (e.g., proteinuria or urine sediments) or abnormal imaging with small kidney, scarring, bilateral cystic changes); GFR, glomerular filtration rate

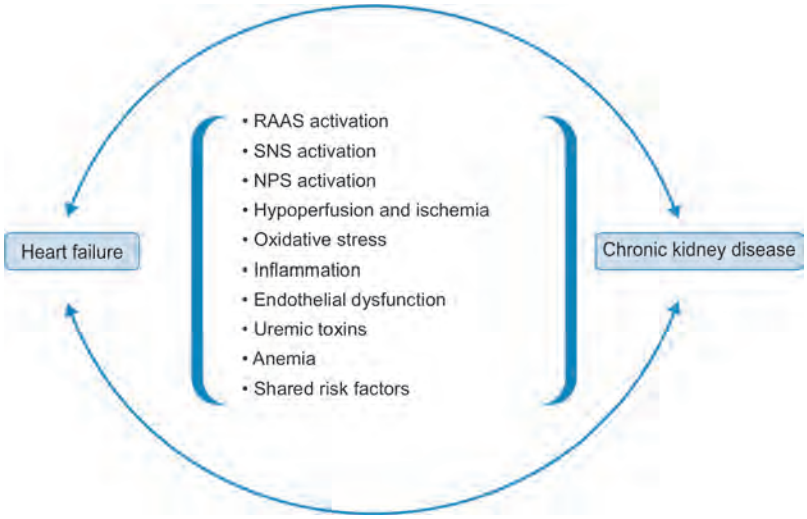

Fig. 1: The bidirectional interlink between CKD and HF[6,7,12,13,86]; NPS, natriuretic peptide system; RAAS, renin–angiotensin–aldosterone; SNS, system sympathetic nervous system

Thereby, there is a need for therapies that target both renal and cardiac pathophysiology and are also helpful in managing the commonly co-occurring comorbidities.

Selecting Multitargeted Therapies with Cardiorenal Benefits in CKD

Evidence shows that angiotensin receptor neprilysin inhibitor (ARNi), sodium-glucose cotransporter 2 inhibitors (SGLT-2i), and a selective β1-blocker (B1Bs) (bisoprolol) can be used for the management of HF in patients with grades 1–3 CKD, but should be used with caution and in consultation with a nephrologist in grades 4 and 5 CKD.[6,14] Coadministration of ARNi with SGLT-2i or β-blockers (BB) has been found to be renal safe in patients with HF and/or CKD.[15–17]

It is postulated that ARNi, SGLT-2i, and BBs exert interrelated and independent cardiorenal effects that improve renal blood flow (RBF), GFR, cardiac output (CO), and mean arterial preswsure (MAP), and preserve filtration fraction (FF) (Fig. 2).[11]

The use of RAAS inhibitors is limited in CKD due to their potential to increase serum creatinine or cause hyperkalemia. ARNi (sacubitril/valsartan) overcomes these challenges through concomitant angiotensin II (RAAS blockade) by valsartan and neutral endopeptidase neprilysin inhibition by sacubitril.[9,18] This dual inhibition augments NPS, which could provide potentially beneficial counter-regulation in states of RAAS activation, such as chronic HF and CKD.[18,19] Further, ARNi are more effective than RAAS inhibitors in reducing blood pressure in CKD patients and improving the prognosis in HF patients.[17]

Thus, ARNi provides several renal benefits in terms of functional adaptations and structural remodeling mediated via increased bioavailability of natriuretic peptides (Fig. 2).[9,20]

The exact mechanism of renal protection conferred by SGLT2 inhibition is poorly understood. A number of direct and indirect effects of SGLT-2 inhibition may contribute to preventing or delaying a progressive decline in renal function (Fig. 2).[21–23]

Sodium-glucose cotransporter 2 inhibition counteracts the inappropriate RAAS and SNS activation, a critical factor in the pathogenesis of renal disease associated with diabetes, and also improves renal function by reducing inflammation and fibrosis.[21,23,24]

β-blockers play a key role in reversing adverse atrioventricular and vascular remodeling (cardiac remodeling) in HF by suppressing the β-1 adreno receptor activation and inhibiting the characteristic neurohormonal activation in HF.[25,26] Selective B1Bs, such as bisoprolol, attenuate both sympathetic overdrive and RAAS activation involved in adverse cardiac remodeling have a direct effect on MAP and CO, and positively influence renal hemodynamics (Fig. 2).[27]

This consensus from India discusses the evidence-based renal benefits of ARNi, SGLT-2i, and Bisoprolol in the current management of CKD with or without HF and highlights the importance and need for renal-friendly pharmacological therapies in this patient population.

Methodology

The national consensus meeting was organized on 6th August 2023 to discuss the renal benefits of bisoprolol, ARNi, and SGLT-2i in patients with CKD. A total of 77 experts from India in the fields of nephrology, cardiology, endocrinology, and intensive care specialties attended this meeting. The experts highlighted the dual burden of CVD and type 2 diabetes (T2DM) in CKD patients.[5] A senior nephrologist presented comprehensive and updated evidence of renal benefits of ARNi, SGLT-2i, and bisoprolol in patients with CKD with or without CVD or T2DM. The experts discussed the presented literature and guidelines to understand the rationale and mechanisms of the renal benefits of bisoprolol, ARNi, and SGLT-2i in the management of CKD. They also shared their clinical experience of managing CKD patients with these drugs. Leading nephrologists, cardiologists, and diabetologists moderated the panel discussion. With focused discussion and deliberation, expert opinions were formulated and accepted by all participating faculty members.

Panel Discussion: Evidence for the renal benefits of ARNi in CKD

Evidence shows renal benefits of ARNi over a RAAS inhibitor in patients with grades 2–4 CKD[28] across comorbidities such as various HF scenarios (Table 2)[29–37] and hypertension.[38,39]

Table 2: Renal benefits of angiotensin receptor/neprilysin inhibitor across the HF scenario

Chronic HF (CHF)[31]
HFrEF[29,30]
Acute decompensated HF (ADHF)[32]
HF with preserved ejection fraction [HFpEF])[33–37]
HF with mitral regurgitation[35]

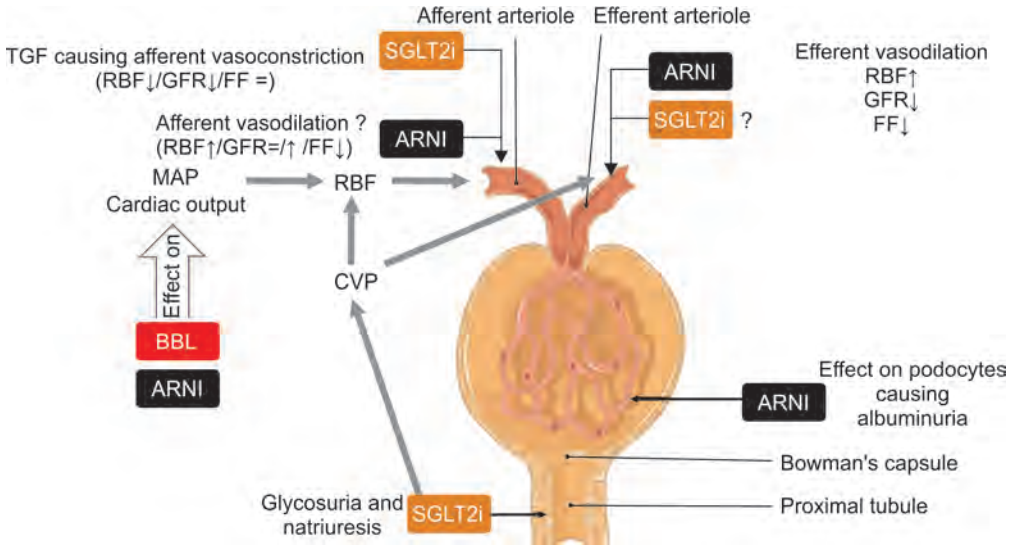

Fig. 2: Overview of potential mechanisms of cardiorenal benefits of ARNI, SGLT-2i, and BBL; BBL, β-blocker; CVP, central venous pressure; FF, filtration fraction; GFR, glomerular filtration rate; MAP, mean arterial pressure; RBF, renal blood flow; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; and TGF, tubuloglomerular feedback

Renal Benefits of ARNi in Heart Failure

The renal benefits of ARNi in HF are outlined in Table 3.

A meta-analysis of three HFrEF trials demonstrated that combined neprilysin/RAAS inhibition was associated with a significantly reduced composite outcome of death or HF hospitalization (HHF; $p = 0.013$) and reduced all-cause mortality ($p = 0.021$) vs RAAS inhibition alone.[40] HF management in CKD is complicated by a high risk for anemia and hyperkalemia.[6] However, the side effect profile too favored ARNi with a lower incidence of renal dysfunction, GFR decline, hyperkalemia, and elevated serum creatinine than RAAS inhibition. The three included trials comparing ARNi with RAAS were IMPRESS [omapatrilat (ARNi) vs lisinopril (RAAS), OVERTURE [omapatrilat vs enalapril (RAAS)], and PARADIGM-HF [sacubitril/valsartan (ARNi) vs enalapril].[40]

In patients with HFrEF, the sacubitril/valsartan group reported a significantly lower decline in eGFR during the follow-up of the PARADIGM-HF trial than enalapril (–1.61 vs –2.04 mL/minute/1.73 m^2/year; $p < 0.001$).[41] Renal parameters had no impact on the benefits conferred by sacubitril/valsartan on the decrease in CV death or HHF. These benefits in the sacubitril/valsartan group were seen even in patients with CKD. There was a 30% risk reduction in progression to end-stage renal disease (ESRD) with sacubitril/valsartan. Further, the renal benefits of sacubitril/valsartan were seen despite an increase in urinary albumin/creatinine ratio (UACR) (the increase was considered clinically insignificant).[41]

Though the renal benefits of sacubitril/valsartan in HFrEF are seen independent of diabetes status, they are likely to be more profound in patients with diabetes.[41,42] The PARAGON-HF trial showed that sacubitril/valsartan attenuated eGFR decline and reduced clinically relevant kidney outcomes (eGFR decline of ≥50%, ESRD, and death due to renal causes) over 192 weeks, similarly in patients with and without diabetes.[42] However, the renal benefit (eGFR decline of ≥50%, ESRD) of sacubitril/valsartan in the PARADIGM-HF trial was twice as large in patients with T2DM than in those without T2DM.[43] This impact is clinically relevant because the presence of diabetes doubles the rate of eGFR decline in HF patients.

The renal benefits of ARNi over other GDMTs for HFrEF were confirmed in a real-world study of 54 patients. The study demonstrated that the renal function significantly improved after 12 months with sacubitril/valsartan compared to other GDMTs such as RAAS inhibitors, BBs, mineralocorticoid receptor antagonists, and diuretics (p for interaction <0.001).[44]

Renal Benefits of ARNi in Patients with Concomitant Heart Failure and Chronic Kidney Disease

There is ample high-quality evidence from meta-analyses demonstrating that ARNi significantly improves eGFR and significantly reduces systolic blood pressure (SBP), diastolic blood pressure (DBP), and N-terminal prohormone brain natriuretic peptide (NT-proBNP) in concomitant HF and CKD.[19,45]

Of these, one was a systematic review and meta-analysis of 10 randomized controlled trials (RCTs) comparing sacubitril/valsartan with other RAAS inhibitors [angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB)] for renal outcomes (eGFR or serum creatinine if eGFR was not available and renal adverse events) in 16,456 patients with CKD and HF. The meta-analysis showed a 30% lower risk of renal dysfunction and progressive eGFR decline over other RAAS inhibitors (pooled odds ratio = 0.70, $p < 0.001$) (Fig. 3).[19]

Another meta-analysis of three RCTs in 3,460 patients with concomitant HF and CKD concluded that patients on ARNi had significantly higher eGFR than those on irbesartan, valsartan, or enalapril ($p = 0.02$), with additional CV benefits of greater decrease in SBP, DBP, and NT-proBNP ($p < 0.001$ for all).[45] There were no significant differences between groups in adverse events.

A real-world study in 661 patients with HFrEF and baseline eGFR <30 mL/minute/1.73 m^2 reported that eGFR and left ventricular ejection fraction at 1 year were significantly higher in the ARNi treated versus non-ARNi treated ($p = 0.04$ and $p < 0.001$, respectively). Those treated with ARNi had significantly lower risks of 1-year all-cause mortality ($p = 0.02$) and total

Table 3: Renal outcomes of sacubitril/valsartan in HF and CKD

Trial	*Comparator RAAS inhibitor*	*Definition of renal events/follow-up or duration of treatment*	*Population*	*Subgroup (N)*	*Rate of renal events, %*		*p-value*	*HR (95% CI)*
					Sacubitril/valsartan	*Comparator*		
PARADIGM-HF[41]	Enalapril (ACEi)	↓eGFR ≥50%, ESRD	Chronic HFrEF, LVEF ≤40%	All (8,399)	0.9	1.4	**0.028**	0.63 (0.42–0.95)
				eGFR 30 to <60 (3,061)	1.2	1.8	NA	0.64 (0.34–1.19)
				eGRF ≥60 (5,338)	0.7	1.1	NA	0.63 (0.36–1.01)
PARAGON-HF[37,38]	Valsartan (ARB)	↓eGFR ≥50%, ESRD, renal death	Chronic HFpEF, LVEF ≥45%	All (4,796)	1.4	2.7	**0.001**	0.50 (0.33–0.77)
				eGFR 30 to <60 (2,341)	1.4	2.7	NA	0.50 (0.28–0.92)
				eGFR ≥60 (2,454)	1.4	2.6	NA	0.51 (0.29–0.93)
PARAMOUNT[36]	Valsartan (ARB)	↑Serum creatinine >0.3 gm/dL and >25%	Chronic HFpEF, LVEF ≥45%	All (301)	12	18	0.18	NA
PIONEER-HF[32]	Enalapril (ACEi)	↑Serum creatinine ≥0.5 gm/dL and ↓eGFR ≥25%	ADHF, LVEF ≤40%	All (881)	13.6	14.7	NA	0.93 (0.67–1.28)
UK HARP-III[28]	Irbesartan (ARB)	↓eGFR ≥25%/12 months	CKD, eGFR 20–60	All (414)	34	32	0.75	NA

ACEi, angiotensin-converting enzyme inhibitor; ADHF, acute decompensated heart failure; ARB, angiotensin II receptor blocker; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate (in mL/minute/1.73 m^2); ESRD, end-stage renal disease; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; LVEF, left ventricular ejection fraction; NA, not available; PARADIGM-HF, Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure; PARAGON-HF, Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction; PARAMOUNT, Prospective Comparison of ARNI with ARB on Management of Heart Failure with Preserved Ejection Fraction; PIONEER-HF, Patients Stabilized from an Acute Heart Failure Episode; RAAS, renin–angiotensin–aldosterone system; UK HARP-III, United Kingdom Heart and Renal Protection-III; Bold values signify significant p-value ($p < 0.05$); ↑, increase; ↓, decrease

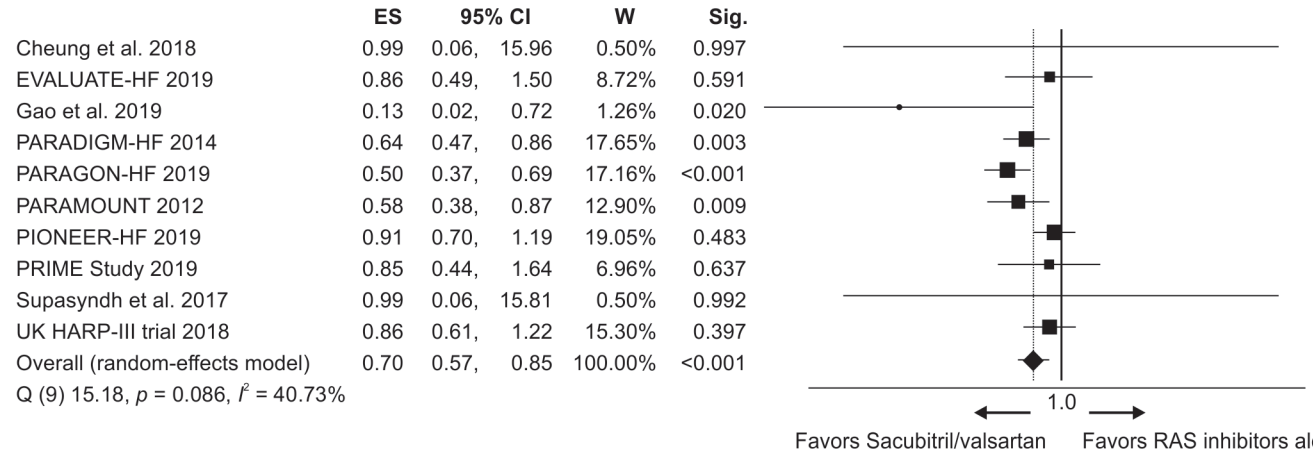

Fig. 3: Individual and overall effect size (ES) of RCTs comparing sacubitril/valsartan with RAAS inhibitors on the renal outcome[19]; Trials: Cheung et al. (2018; vs olmesartan)[38]; EVALUATE-HF (2019; vs enalapril)[29]; Gao et al. (2019; vs valsantan)[31]; PARADIGM-HF (2014; vs enalapril)[30]; PARAGON-HF (2019; vs valsartan)[33]; PARAMOUNT (2012; vs valsantan)[34]; PINONEER-HF (2019; vs. enalapril)[32]; PRIME study (2019; vs valsartan)[35]; Supasyndh et al. (2017; vs olmesartan; elderly Asian patients); UK HARP-III trial (2018; vs irbesartan; eGFR) 20–60 mL/minute/1.73 m^2)[28]

HF rehospitalizations ($p = 0.01$) than non-ARNi treated.[46]

Panel Discussion: Evidence for the Renal Benefits of SGLT-2i in Chronic Kidney Disease

Cardiorenal Benefits of SGLT-2i

Initially approved as a glucose-lowering drug for patients with T2DM, the immense cardiorenal benefits provided by SGLT-2i have made them an attractive option in patients with CKD and/or HF, irrespective of their diabetes status. Of the globally extensively researched SGLT-2i, only three SGLT-2i, dapagliflozin, empagliflozin, and canagliflozin, are approved in India,[47–53] and hence, the evidence-based discussion centered around these three SGLT-2i.

The cardiorenal efficacy of these three SGLT-2i has been well-established in CKD patients irrespective of T2DM and HF status through landmark renal outcome trials such as CREDENCE (canagliflozin vs placebo),[54,55] DAPA-CKD (dapagliflozin vs placebo),[56,57] and EMPA-KIDNEY (empagliflozin vs placebo).[58] Table 4 captures the details of renal and CV parameters investigated in these trials and the benefits seen.

Sodium-glucose cotransporter 2 inhibitor (SGLT-2i) were found to be renoprotective in T2DM patients with or without established CVD (including those at high CVD risk) irrespective of CKD status through landmark trials such as CANVAS program (canagliflozin vs placebo)[54] and EMPAREG-OUTCOME (empagliflozin vs placebo)[59] (Table 5). Further, SGLT-2i were found to be cardio- and renoprotective in HF patients irrespective of T2DM or CKD status and irrespective of ejection fraction through landmark cardiovascular outcome HF trials such as DAPA-HF,[60] EMPEROR Reduced (empagliflozin vs placebo)[61], and EMPEROR Preserved (empagliflozin vs placebo)[62] (Table 6). Moreover, the clinical benefits were seen irrespective of baseline albuminuria, along with a reduction in new-onset anemia and hyperkalemia and a good safety and tolerability profile.[6,63]

The renal benefits of SGLT-2i demonstrated in clinical trials were mirrored in a large international (Asian: Israel, Japan, Taiwan, and European: Italy, United Kingdom) real-world study of 35,561 patients with T2DM.[64] The study showed that compared to other GLDs, the use of SGLT-2i was associated with a slower decline in kidney function and lower risk of major kidney events (50% eGFR decline or ESRD) ($p < 0.0001$ for both).

Importantly, the clinical benefits of SGLT-2i in CKD are seen even at stage 4 CKD.[63] In 624 patients with baseline eGFR of 25–30 mL/minute/1.73 m^2, the DAPA-CKD trial demonstrated a 27% reduction in the primary composite endpoint (50% eGFR decline, ESRD, or kidney/CV death) and 28% reduction in ESRD risk. The renal benefits were seen within 16 months of dapagliflozin therapy, and it was suggested that SGLT-2i be continued until the patient is on dialysis.[63]

Panel Discussion: Evidence for the Renal Benefits of Bisoprolol in Chronic Kidney Disease

Renal Benefits of Bisoprolol in Chronic Kidney Disease and End-stage Renal Disease Nondialysis Patients

A systematic review and meta-analysis of six placebo-controlled HF trials enrolling patients with CKD stages 3–5 concluded that BBs reduced the risk of CV mortality [risk ratio (RR): 0.66, 95% cofidence interval (CI): 0.49–0.89; $p = 0.006$] and all-cause (RR: 0.72, 95% CI: 0.64–0.80; $p < 0.001$), but increased the risk of hypotension (RR: 5.08, 95% CI: 3.48–7.41) and bradycardia (RR: 4.92, 95% CI: 3.20–7.55).[65] The analysis included one trial with patients on dialysis and five trials of nondialysis patients, of which one study included 1,119 patients on bisoprolol [the Cardiac Insufficiency Bisoprolol Study II (CIBIS II)]. There was minimal heterogeneity between different BB trials for all-cause mortality ($I^2 = 0\%$, $p = 0.601$) and a moderate level of heterogeneity for CV mortality ($I^2 = 64.2\%$, $p = 0.045$). There was no significant improvement in all-cause mortality on removing the patients on dialysis (RR: 0.72, 95% CI: 0.64–0.81, $p < 0.001$; $I^2 = 0\%$, $p = 0.435$), but there was significant and consistent improvement in CV mortality (RR: 0.76, 95% CI: 0.64–0.90, $p = 0.001$; $I^2 = 0\%$, $p = 0.92$) when only nondialysis patients were included.[65] The systematic review and meta-analysis demonstrated that BBs, including bisoprolol, were effective in reducing CV and all-cause mortality in nondialysis HF patients with stages 3–5 CKD.

A subanalysis of the CIBIS II trial showed that bisoprolol reduced the risk of all-cause mortality ($p = 0.81$), the composite of all-cause mortality or HF hospitalization ($p = 0.66$), and HF hospitalization alone ($p = 0.71$) across all ranges of baseline eGFR (<45, 45–60, 60–75 and ≥75 mL/minute/1.73 m^2).[66]

Another metanalysis of 10 randomized, double-blind trials in 16,740 patients with HFrEF demonstrated that in patients in sinus rhythm ($n = 13,861$), BBs reduced mortality vs placebo for eGFR 45–59 mL/minute/1.73 m^2 and for eGFR 30–44 mL/minute/1.73 m^2 [hazard ratio (HR) 0.73 vs 0.71; $p < 0.001$ for

Table 4: Renal and cardiovascular outcomes of SGLT-2i in CKD

Trial	*Population (N)*	*Definition of renal events (n)*	*Renal event rates per 1000 patient years*	*p-value*	*HR (95% CI)*	*Definition of CV events (n)*	*CV event rates per 1000 patient years*	*p-value*	*HR (95% CI)*	*Remarks*
Summary from kidney outcome trials: SGLT-2i are cardio- and renoprotective in pts. with CKD irrespective of T2DM and HF status										
CREDENCE (canagliflozin vs placebo)[54]	T2DM and CKD; eGFR 30 to <90 mL/minute/1.73 m^2 (*N* = 4,401)	Kidney failure*, a sustained doubling of serum creatinine level or death due to kidney conditions (*n* = 377)	34% lower in the canagliflozin group	$p < 0.001$	0.66 (0.53–0.81)	CV death and HHF (*n* = 432)	31.5 vs 45.4	$p < 0.001$	0.69 (0.57–0.83)	Canagliflozin significantly reduced the risk of renal failure and CV events in pts. with T2DM and CKD
		ESRD (*n* = 281)	32% lower in the canagliflozin group	$p = 0.002$	0.68 (0.54–0.86)	HHF (*n* = 230)	15.7 vs 25.3	$p < 0.001$	0.61 (0.47–0.80)	
		Kidney failure*, a sustained doubling of serum creatinine level, or death due to kidney or CV conditions (*n* = 585)	30% lower in the canagliflozin group (43.2 and 61.2)	$p = 0.00001$	0.70 (0.59–0.82)	CV death, MI, stroke (*n* = 486)	38.7 vs 48.7	$p = 0.01$	0.80 (0.67–0.95)	
CREDENCE analysis according to the history of HF (canagliflozin vs placebo)[55]	T2DM and CKD; eGFR 30 to <90 mL/minute/1.73 m^2 (*N* = 4,401)	History of HF (*n* = 652): kidney failure*, a sustained doubling of serum creatinine level, or death due to kidney conditions	62.4 vs 65.5	*p* interaction >0.150	0.89 (0.61, 1.31)	History of HF (*n* = 652): CV death and HHF	39.3 vs 48.9	*p* interaction >0.150	0.76 (0.48, 1.22)	Canagliflozin reduced the risk of renal failure and CV events in pts. with T2DM and CKD, irrespective of HF status
		No history of HF (*n* = 3,749): kidney failure*, a sustained doubling of serum creatinine level, or death due to kidney conditions	39.9 vs 60.5		0.66 (0.55, 0.79)	No history of HF (*n* = 3,749): CV death and HHF	11.7 vs 21.5		0.54 (0.39, 0.75)	
DAPA-CKD (dapagliflozin vs placebo)[56]	CKD with or without T2DM; eGFR 25–75 mL/minute/1.73 m^2 (*N* = 4,304)	↓eGFR ≥50%, ESRD, kidney failure* or death due to kidney or CV conditions (*n* = 509)	9.2 vs 14.5%	$p < 0.001$	0.61 (0.51–0.72)	CV death and HHF (*n* = 238)	2.2 vs 3	$p = 0.009$	0.71 (0.55–0.92)	Dapagliflozin significantly reduced the risk of renal failure and CV events in pts. with CKD, irrespective of T2DM status
		↓eGFR ≥50%, ESRD, kidney failure* or death due to kidney conditions (*n* = 385)	3.3 vs 5.8	$p < 0.001$	0.56 (0.45–0.68)					
DAPA-CKD analysis of pts. with HF vs no HF(dapagliflozin vs placebo)[57]	CKD with or without T2DM; eGFR 25–75 mL/minute/1.73 m^2 (*N* = 4,304)	HF patients (*n* = 82): ↓eGFR ≥50%, ESRD, kidney failure* or death due to kidney or CV conditions	6.5 vs 11	*p* interaction = 0.59	0.58 (0.37–0.91)	HF patients (*n* = 84): CV death and HHF	7.1 vs 10.1	*p* interaction = 0.90	0.68 (0.44–1.05)	Dapagliflozin reduced the risk of renal failure and CV events in pts. with CKD, irrespective of T2DM status
		No HF (*n* = 427): ↓eGFR ≥50%, ESRD, kidney failure* or death due to kidney or CV conditions	4.4 vs 7		0.62 (0.51–0.75)	No HF (*N* = 154): CV death and HHF	1.6 vs 2.2		0.70 (0.51–0.97)	
EMPA-KIDNEY (empagliflozin vs placebo)[58]	CKD with eGFR 20 but <45 mL/minute/1.73 m^2 or at least 45 but <90 mL/minute/1.73 m^2 with UCAR of at least 200 (*N* = 6,609)	↓eGFR ≥40% from baseline or sustained decrease in eGFR to <10 mL/minute/1.73 m^2, ESRD, or death due to kidney or CV conditions (*n* = 990)	6.85 vs 8.96	$p < 0.001$	0.72 (0.64–0.82)	CV death and HHF	2.04 vs 2.37	$p = 0.15$	0.84 (0.67–1.07)	Empagliflozin significantly reduced the risk of progressive kidney disease and reduced CV events in pts. with CKD
		eGFR slope decline over 1 year	−1.25 ± 0.11 vs −2.62 ± 0.11 mL/minute/1·73 m^2	$p < 0.001$	1.36 (1.06–1.66)					

*Kidney failure defined as eGFR of <15 mL/minute/1.73 m^2, sustained initiation of continuous renal replacement therapy or renal transplantation; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate (in mL/minute/1.73 m^2); ESRD, end-stage renal disease; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; h/o, history of; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NA, not available; pts., patients; T2DM, type 2 diabetes mellitus; UACR, urinary albumin-to-creatinine ratio

Table 5: Renal and cardiovascular outcomes of SGLT-2i in T2DM patients with established CVD or at high risk of CVD

Trial	*Population (N)*	*Definition of renal events (n)*	*Renal event rates per 1000 patient years*	*p-value*	*HR (95% CI)*	*Remarks*
Summary: SGLT-2i is renoprotective in T2DM pts. with or without established CVD (including those at high CVD risk) irrespective of CKD status; renoprotective even in pts. without CKD						
CANVAS Program (canagliflozin vs placebo)[54]	T2DM at high risk of CV events and eGFR of <60 mL/minute/1.73 m^2 (*N* = 2,039)	Composite of doubling of serum creatinine, ESRD, and death from renal causes (*n* = 73)	49.4 vs 66.9	NA	0.53 (0.33–0.84)	Canagliflozin reduced the risk of renal events in T2DM and CKD pts. at risk of CV events
		+macroalbuminuria (*n* = 698)	15.1 vs 27.4	NA	0.58 (0.50–0.67)	
		+CV death (*n* = 518)	13.2 vs 15.8	NA	0.82 (0.68–0.97)	
		↓eGFR 40%, ESRD, renal death (*n* = 249)	5.5 vs 9	NA	0.60 (0.47–0.77)	
DECLARE-TIMI 58 (dapagliflozin vs placebo)[87]	T2DM at high risk of CV events or established CVD and eGFR >60 mL/minute/1.73 m^2 (*N* = 17,160)	Change in UACR over time (≤15, >15 to 300 mg/gm)	UACR improved from baseline to 4.0 years with dapagliflozin across all UACR and eGFR categories	all $p <$ 0.0001	1.45 (1.35–1.56) for ≥1 category improvement in UACR	Dapagliflozin had a favorable effect on UACR and renal-specific outcomes across all baseline UACRs, including normal albumin excretion; suggests role of SGLT-2i in primary prevention of DKD
		↓eGFR ≥40% to <60 mL/minute/1.73 m^2, ESRD, renal or CV death	Reduced for subgroups of UACR ≥30 mg/g	$p < 0.0125$, $p_{interaction} =$ 0.033	0.73 (0.57, 0.94)	
		↓eGFR ≥40% to <60 mL/minute/1.73 m^2, ESRD, renal or death	Reduced for all UACR groups	$p < 0.05$, $p_{interaction} =$ 0.480	Different HR across categories	
EMPAREG-OUTCOME (empagliflozin vs placebo)[59]	T2DM with established CVD and eGFR ≥30 mL/minute/1.73 m^2 (*N* = 7,020)	Composite of ↓eGFR ≥40%, ESRD, kidney failure* or death due to kidney/cardiac conditions or sustained progression to macroalbuminuria or doubling of serum creatinine (*n* = 4,199)	Composite of renal and CV outcomes: 43.1 vs 75.2	$p < 0.001$ for a composite of all	0.56 (0.49–0.64)	Empagliflozin significantly improved renal and CV outcomes in T2DM pts. with established CVD, irrespective of CKD status

*Kidney failure defined as eGFR <15 mL/minute/1.73 m^2, sustained initiation of continuous renal replacement therapy or renal transplantation; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate (in mL/minute/1.73 m^2); ESRD, end-stage renal disease; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; h/o, history of; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NA, not available; pts., patients; T2DM, type 2 diabetes mellitus; UACR, urinary albumin-to-creatinine ratio

both]. The study excluded patients with eGFR <30 mL/minute/1.73 m^2. Hence, the study concluded that BB can be safely prescribed in moderate-to-moderately severe CKD (eGFR of 30–59 mL/minute/1.73 m^2).[67] The analysis included two cardiac insufficiency bisoprolol studies in HFrEF, *viz*, CIBIS I and CIBIS II.[68,69]

A Swedish Heart Failure Registry cohort study compared the mortality/morbidity benefit with evidence-based BB [i.e., bisoprolol (41% of patients), carvedilol, or metoprolol] in severe CKD (*n* = 3775; eGFR of <30 mL/minute/1.73 m^2) vs moderate CKD (*n* = 15,346; eGFR 30 to <60 mL/minute/1.73 m^2) in HFrEF and HF with preserved ejection fraction (HFpEF).[70] The study demonstrated lower risk of death {adjusted HR 0.85 [95% confidence interval (CI), 0.75–0.96]} and cardiovascular mortality/HF hospitalization [0.87 (0.77–0.98)] only in HFrEF patients and not in HFpEF.[70] There were similar benefits in both advanced and moderate CKD, suggesting that BBs, including bisoprolol, could be safely used across the entire spectrum of CKD patients not on dialysis.

Renal Benefits of Bisoprolol in End-stage Renal Disease Dialysis Patients

More than half the patients on dialysis are on BBs due to comorbidities like hypertension, atrial fibrillation, coronary artery disease, and HF.[71] BBs provide cardioprotection in patients with ESRD, and therefore reduce the risk of CV events in ESRD patients.[72] Bisoprolol (cardioselective/moderately dialyzable) and carvedilol (noncardioselective/poorly dialyzable) are the two most commonly prescribed BBs in the hemodialysis population.[71,72] Compared to carvedilol, bisoprolol use in hemodialysis patients was associated with a lower 2-year risk of death and major adverse cardiovascular events (MACEs) [HR 0.85 (95% CI 0.80–0.91)], mainly attributed to lower risk of HF [HR 0.83 (95% CI 0.77–0.91)] and ischemic stroke [HR 0.84 (95% CI 0.72–0.97)].[72]

Table 6: Renal and cardiovascular outcomes of SGLT-2i in HF trials

Trial	*Population (N)*	*Definition of renal events (n)*	*Renal event rates per 1000 patient years*	*p-value*	*HR (95% CI)*	*Definition of CV events (n)*	*CV event rates per 1000 patient years*	*p-value*	*HR (95% CI)*	*Remarks*
Summary from cardiovascular outcome trials: SGLT-2i are cardio and renoprotective in HF patients irrespective of T2DM or CKD status										
DAPA-HF (dapagliflozin vs placebo)[60]	HFrEF with or without T2DM and eGFR ≥30 mL/minute/1.73 m^2 (*N* = 1,742)	↓eGFR ≥50%, kidney failure* or death due to kidney conditions (*N* = 67)	0.85 vs 1.2	*p* = 0.17	0.71 (0.44–1.16)	CV death and HHF in pts. with CKD (eGFR < 60 mL/minute/1.73 m) (*n* = 445)	14.5 vs 20	*p* for interaction = 0.54	0.71 (0.59–0.86)	Dapagliflozin reduced the risk of kidney failure and CV events in pts. with HFrEF, irrespective of T2DM status
		Rate of decline in eGFR between day 14 and 720	−1.09 (−1.40 to −0.77) vs −2.85 (−3.17 to −2.53)	*p* < 0.001		CV death and worsening HF in pts. without (*n* = 443)	9.9 vs 13		0.77 (0.64–0.93)	
			The decline was seen irrespective of T2DM	*p* for interaction = 0.92						
EMPEROR Reduced (empagliflozin vs placebo)[61]	HFrEF with/without CKD (*N* = 3,730)	↓eGFR ≥40%, kidney failure* in pts. with CKD (eGFR < 60 mL/minute/1.73 m^2 or UACR >300 mg/gm) (*n* = 48)	2 vs 3.8	*p* for interaction = 0.78	0.53 (0.31–0.91)	CV death and HHF in pts. With CKD (*n* = 491)	18.4 vs 23.6	*p* for interaction =0.63	0.78 (0.65–0.93) and	Empagliflozin reduced the risk of kidney failure and CV events in pts. with HFrEF, irrespective of CKD status
		↓eGFR ≥40%, kidney failure* in pts. without CKD (*n* = 30)	1.1 vs 2.3		0.46 (0.22–0.99)	CV death and HHF in pts. without CKD (*n* = 329)	13 vs 18		0.72 (0.58–0.90)	
		eGFR slope decline over 1 year in pts. with CKD vs without CKD	1.11 (0.23–1.98) vs 41 (1.49–3.32) mL/minute/1.73 m^2/year							
EMPEROR Preserved (empagliflozin vs placebo)[62]	HfpEF; HfpEF + CKD (eGFR <60 mL/minute/1.73 m^2 (*N* = 2,988)	↓eGFR ≥40%, kidney failure* (*n* = 220)	2.1 vs 2.2	NA	0.95 (0.73–1.24)	CV death and HHF (*n* = 926)	6.9 vs 8.7	*p* <0 .001	0.79 (0.69–0.90)	Empagliflozin significantly reduced the risk of eGFR decline and CV events in pts. with HFpEF and CKD
		eGFR slope decline over 1 year	−1.25 ± 0.11 vs −2.62 ± 0.11 mL/minute/1.73 m^2	*p* < 0.001	1.36 (1.06–1.66)					

*Kidney failure defined as eGFR <15 mL/minute/1.73 m^2, sustained initiation of continuous renal replacement therapy or renal transplantation; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate (in mL/minute/1.73 m^2); ESRD, end-stage renal disease; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; h/o, history of; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NA, not available; pts., patients; T2DM, type 2 diabetes mellitus; UACR, urinary albumin-to-creatinine ratio

Consensus Recommendations for ARNi, SGLT-2i, and Bisoprolol in Chronic Kidney Disease

Consensus Recommendations for ARNI: Indian cardiologists recommend the use of ARNI in patients with HF and CKD not on dialysis due to its potential benefits in reducing cardiovascular risk and improving eGFR compared to ACEI/ARBs.[73]

The Chinese expert consensus on the use of ARNi in CKD patients also recommends the use of ARNi in nondialysis CKD patients with HF (grade IA) or hypertension (grade IB) or in hemodialysis patients with HF (grade IB) or hypertension (grade 2D).[17]

No dose titration is recommended for mild renal impairment. In patients with moderate to severe renal impairment, 20–50 mg twice daily is recommended based on the patient's blood pressure. Thereafter, the dose is doubled every 2–4 weeks until a target maintenance dose of 200 mg twice daily is reached.[17,73]

Detailed recommendations from the Chinese consensus are outlined in Table 7.

Consensus Recommendations for SGLT-2i: In 2021, the UK Kidney Association (UKKA) Clinical Practice Guideline on the use of SGLT-2i in CKD provided grades 1A, 1B, or 2B recommendations for their use across various CKD clinical scenarios (Table 8).[74] The Kidney Disease Improving Global Outcomes 2022 guideline and the 2023 American Diabetes Association (ADA) guidelines recommended SGLT-2i for patients with T2DM and CKD with an eGFR of at least 20 mL/minute/1.73 m^2.[75,76] The ADA guidelines also recommend SGLT21i

Table 7: Chinese expert consensus on switching to ARNi in CKD patients being treated with ACEi/ARB[17]

Patient population	*Recommendation*	*Grade*
Nondialysis		
CKD patients with HF	"Can be switched to ARNI, as long as there is no contraindication, to improve eGFR, reverse cardiac remodeling, and reduce the risk of end-stage renal disease and cardiovascular events"	IA
CKD + HF showing a trend toward developing hyperkalemia	"We recommend switching to ARNI after serum potassium levels decrease to the normal range so as to reduce the risk of hyperkalemia"	2B
CKD + HF serum creatinine increased by >50% or ≥266 μmol/L	"We recommend discontinuing ACEI/ARB, monitoring renal function, and switching to ARNI after renal function stabilizes or improves, so as to reduce the risk of entering end-stage renal disease"	1B
Overhydrated CKD patients	Suggestion: "We suggest switching ACEI/ARB to ARNI to improve volume control"	1C
CKD with uncontrolled blood pressure	"We suggest switching ACEI/ARB to ARNI to further improve blood pressure control"	1B
CKD and poor nocturnal blood pressure control	"We suggest switching ACEI/ARB to ARNI to further improve nocturnal blood pressure control"	1B
Maintenance dialysis patients		
With HF	"ARNI is recommended for improving myocardial remodeling, controlling the symptoms of HF, protecting residual renal function, and reducing the risk of cardiovascular events"	1B
With hypertension	Suggestion: "ARNI can be used to lower blood pressure, protect cardiac function, and reduce the risk of cardiovascular events"	2D

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor neprilysin inhibitor; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure; SGLT-2i, sodium-glucose cotransporter 2 inhibitor

Table 8: UK Kidney Association Clinical Practice Guideline on the use of SGLT-2i in CKD[74]

	People with type 2 DM	*Grade*
1	The guideline recommends that SGLT-2i should be initiated in people with CKD and T2DM, irrespective of primary kidney disease, for any of the following 4 clinical scenarios: • eGFR: 20–45 mL/minute/1.73 m^2. • eGFR: >45 mL/minute/1.73 m^2 and UACR: ≥25 mg/mmol[b]. • Symptomatic HF, irrespective of ejection fraction. • Established coronary disease.	1A
2	The guideline suggests initiating SGLT-2i to modify CV risk and slow renal function decline rate in people with an eGFR of >45–60 mL/minute/1.73 m^2 and a UACR of <25 mg/mmol, recognizing limited glycemic control	2B
3	The guideline suggests clinicians should consider initiating SGLT-2i in people with eGFR <20 mL/minute/1.73 m^2 to slow CKD progression	2B
	People without DM	
1	The guideline recommends initiating SGLT-2i in people with CKD, irrespective of primary kidney disease[a] for any of the following clinical scenarios: eGFR: ≥20 mL/minute/1.73 m2 and UACR: ≥25 mg/mmol[b]; symptomatic HF, irrespective of ejection fraction	1A
2	The guideline recommends initiating SGLT-2i slow renal function decline rate in people with an eGFR of 20–45 mL/minute/1.73 m^2 and UACR of <25 mg/mmol[b]	1B
3	The guideline suggests clinicians consider initiating SGLT-2i in people with an eGFR of <20 mL/minute/1.73 m^2 to slow CKD progression	2B

CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; SGLT-2i, sodium-glucose cotransporter 2 inhibitor; T2DM, type 2 diabetes mellitus; UACR, urinary albumin-to-creatinine ratio

for T2DM patients with HF or established atherosclerotic CVD (ASCVD), multiple ASCVD risk factors and CKD.[77] The ADA guidelines give a grade A recommendation for urinary albumin ≥200 mg/gm creatinine and a grade B recommendation for urinary albumin normal to <200 mg/gm creatinine.[76,77]

Consensus Recommendations for Bisoprolol: B-blockers has proven efficacy (and guideline recommendations) for HFrEF in patients requiring secondary prevention of CKD following myocardial infarction, hypertension, and arrhythmias.[71,78–83] Hypertension guidelines from the European Renal Association and the International Society of Hypertension also recommend the use of BBs in patients with CKD if they have CV risk or established CVD.[82,83]

The "Medical Officers" Manual for Prevention and Management of Chronic Kidney Diseases" under the "National Programme for Prevention and Control of Noncommunicable Diseases" by the Ministry of Health and Family Welfare, Government of India, recommends that the dose of hydrophilic BBs such as acebutolol, atenolol, Bisoprolol, and nadolol should be reduced by 50% when GFR is <30 mL/minute/1.73 m^2.[84]

Thus, it is evident from literary evidence and from guideline recommendations that ARNi, SGLT-2i, and B1Bs are effective and safe for a wide population of CKD patients with or without HF (Fig. 4).

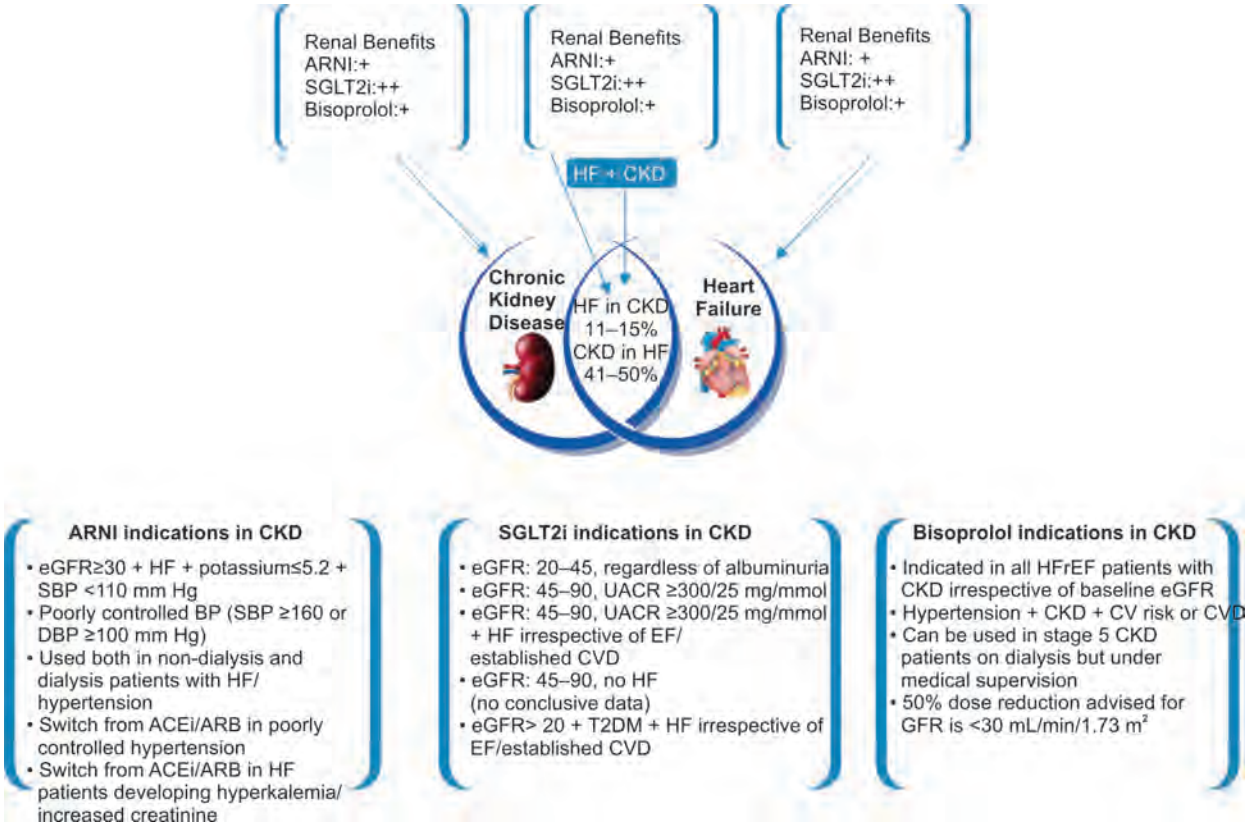

Fig. 4: Patient profiles likely to benefit from cardiorenal protection of ARNi, SGLT-2i, and bisoprolol in CKD, HF, and concomitant CKD + HF[6,7,12,13,17,23,63,74,84] + clinical evidence of benefits; BP, blood pressure; CVD, cardiovascular disease; DBP, diastolic blood pressure; SBP, systolic blood pressure

Conclusion

Heart failure is a considerable health burden in India. CKD is a major contributive factor of morbidity and mortality in association with HF. Pathophysiology of HF and CKD are interconnected; deterioration of one can worsen the prognosis of the other. ARNI, SGLT-2i, and bisoprolol reduce the neurohormonal activity in several shared pathways and have enormous cardiorenal metabolic benefits across CKD patients with or without concomitant HF, DM, and hypertension. It is, therefore, proposed to incorporate ARNI, SGLT-2i, and bisoprolol in the management of HF with CKD in a meticulous protocolized manner guided by clinico-echo, NT Pro BNP, eGFR navigation to improve the morbidity and mortality benefits.

Ethics Compliance

This is a consensus statement and, hence, does not require EC approval.

Funding

Funding for medical writing support was provided by Alembic Pharmaceuticals Ltd.

Medical Writing Assistance

The authors thank Dr Kokil Mathur and Dr Punit Srivastava of Mediception Science Pvt. Ltd. for providing medical writing support in the preparation of this publication.

Conflict of Interest

Dr Onkar Swami, Dr Sanjay Jain, and Dr Priyank Shah are full-time employees of Alembic Pharmaceuticals Limited, which actively markets Bisoprolol, SGLT-2i, and ARNI.

Consensus Statements

- Chronic kidney disease is a major contributory factor for morbidity and mortality in India and globally.
- Chronic kidney disease is commonly associated both with HFpEF and HFrEF, along with uncontrolled hypertension and or uncontrolled diabetes.
- Around 17–21% of CKD patients have a new onset of HF. The prevalence of CKD is one in five adults in high CKD prevalence areas.
- Heart failure and CKD are double jeopardy and pathophysiologically interconnected, and deterioration of one can worsen the prognosis of the other.
- Angiotensin receptor neprilysin inhibitor, SGLT-2i, and selective β1 blocker bisoprolol suppress this neurohormonal activation, thereby improving the prognosis by reducing morbidity and mortality.
- Angiotensin receptor neprilysin inhibitor, SGLT-2i, and B1Bs can be used in HF with grades 1–3 CKD but may be used with grades 4 and 5 CKD under strict vigilance with nephrologists.
- Angiotensin receptor neprilysin inhibitor, SGLT-2i, and B1Bs can be used together in HF with or without CKD.
- Angiotensin receptor neprilysin inhibitor, SGLT-2i, and B1Bs independently and interdependently have cardiorenal metabolic benefits by improving RBF eGFR, CO and mean atrial blood pressure, blood sugar control, and reduction microalbuminuria.
- Meticulous protocolization and titration of doses of ARNI in HF with CKD is the need of the hour. No dose titration is recommended for mild renal impairment. However, with severe renal impairment, 25–50 mg twice daily is recommended based on blood pressure.
- The use of ARNi has been shown to be beneficial in HFrEF and HFpEF by reducing hospitalizations with HF, cardiac mortality, all-cause mortality, and eGFR decline.
- Angiotensin receptor neprilysin inhibitor may cause initial renal dysfunction with elevated serum creatinine in grades 3–4 CKD followed by improvement in the renal functions, including eGFR, as eGFR is a significantly variable entity.
- Hyperkalemia in stage 4 and 5 CKD and dehydration are commonly seen when ARNi is used in HFpEF or HFrEF.

- Renal benefits of ARNi in HF are very well documented in various studies (Paradigm HF, IMPRESS, OVERTURE, UACR studies).
- Significant improvement in eGFR with reduction in SBP and DBP and NT pro-BNP had been documented concomitantly in patients of HF with CKD.
- Hyperkalemia, if it occurs, can be managed by optimizing the dose of ARNi, a loop diuretic, K-Bind resin, and the usefulness of patiromer.
- Heart failure with reduced EF with eGFR of ≤30 mL/minute/1.73 m^2 significantly lowers 1-year all-cause mortality and rehospitalization than non-ARNi treated patients.
- Utility of SGLT-2i in HF has enormous cardio reno metabolic benefits, irrespective of all spectrums of ejection fraction. It also has a renovascular remodeling reversal benefit.
- Cardiorenal benefits of SGLT-2i (dapagliflozin, empagliflozin, and canagliflozin) are very well established in HF with CKD, irrespective of type 2 DM (CREDENCE, DAPA CKD, EMPA KIDNEY, CANVAS, EMPA REG OUTCOME, EMPEROR PRESERVE, and DAPA EMPAEROR REDUCED trials).
- Sodium-glucose cotransporter 2 inhibitor in HF with CKD has shown a reduction in HF hospitalization, CVD mortality, and all-cause mortality.
- Sodium-glucose cotransporter 2 inhibitor is very well tolerated; it does not cause hyperkalemia, has weight reduction potential, and is used as a single dose; no dose titration is required.
- Clinical benefits of SGL2i in CKD are seen even in stage 4 CKD with eGFR of 25–30 mL/minute/1.73 m^2.
- Sodium-glucose cotransporter 2 inhibitor may be continued in dialysis patients if the patient is already on SGLT-2i therapy.
- Bisoprolol reduces cardiac mortality by cardiac (atrial, ventricular, and vascular) and renovascular remodeling reversal.
- β1-blocker (bisoprolol) is effective in reducing CV, all-cause mortality, and sudden cardiac death in nondialysis HF patients with stages 3–5 CKD and reduces HF hospitalization across all ranges of eGFR (<45–60, 60–75 mL/minute/1.73 m^2 (CIBIS I, II trials).
- Bisoprolol safety has been documented across the entire spectrum of CKD patients who are not on dialysis.
- Bisoprolol can be used in hemodialysis patients to reduce mortality and MACEs.
- Bisoprolol has proven efficacy in HFrEF in patients with secondary prevention of CKD following MI, arrhythmia, and hypertension.
- Overall, bisoprolol is superior β1 super selective BB with robust survival benefits and enormous morbidity and mortality reduction, HF hospitalization reduction, MACE, and arrhythmias with enormous renal benefits in HF.
- Angiotensin receptor neprilysin inhibitor, SGLT-2i, and B1Bs are safe and effective, with enormous morbidity and mortality benefits in the population of CKD patients with HF.

Acknowledgments

All authors meet the International Committee of Medical Journal Editors criteria for authorship for this manuscript, take responsibility for the integrity of the work, and have given final approval for the version to be published.

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POINT OF VIEW

Deliberate Problem-solving with a Large Language Model as a Brainstorm Aid Using a Checklist for Prompt Generation

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Received: 21 November 2023; *Accepted:* 04 December 2023

Abstract

Large language models (LLMs) use autoregression to generate text in response to queries. Crafting an appropriate prompt to elicit the desired response from these generative artificial intelligence (AI) models to solve a clinical problem can be a challenge to clinicians who may be unfamiliar with this technology. The use of checklists to generate carefully worded queries can leverage the potential of LLMs as a brainstorming aid for medical problem-solving. Systematically using different prompts to generate the most appropriate differential diagnoses for selected clinical case scenarios, a potential checklist for prompt generation has been created and is reported here.

Journal of the Association of Physicians of India (2024): 10.59556/japi.72.0518

Introduction

Large language models (LLMs) are a form of generative artificial intelligence (AI) trained on large data sets to produce new text using the statistical model of autoregression, which uses past values of a series to predict future values.[1,2] LLMs code a sequence of words into a numerical vector and, based on this, predict the next set of words and thus formulate a meaningful text output in response to a query.[2] It is important to remember that LLMs are able to generate output by string prediction tasks based on the context rather than true natural language understanding.[3]

Large language models (LLMs) encounter errors primarily due to the limitations associated with language understanding and generation. Ambiguity in context, biased and insufficient training data in certain domains like medicine, along with the phenomenon of catastrophic forgetting, which is the loss of previously learned information, could lead to erroneous outcomes.[4,5] Despite these drawbacks, LLM can be used as a tool to brainstorm as these models have access to a rich knowledge database. This can be useful in both clinical practice and medical education for experienced clinicians and doctors in training. For instance, when tested with questions from the United States Medical Licensing Exam, the performance of an LLM like ChatGPT was not only adequate to pass the examination but was able to generate valid clinical insights.[6] Thus, understanding both the opportunities and limitations of using LLMs as a tool to generate differential diagnoses in the medical domain is paramount.

To be able to use LLM effectively in clinical problem-solving, a deeper understanding of prompt engineering is crucial, as the answers generated are heavily dependent on the way the queries are phrased. Prompt engineering consists of techniques which can optimize the output from LLMs. A few tips for effective prompt generation include being as descriptive as feasible, offering sufficient context, and even asking LLMs for prompts that would result in the best answer.[7]

As medical technology advances, teaching an efficient, prompt generation to inexperienced but tech-savvy clinicians may become part of the curriculum. Particularly in India in the primary healthcare setup, where access to experts and even peers may be limited, LLM can work as a brainstorming aid for a doctor faced with a clinical dilemma. Thus, our aim was to create a checklist for prompts that could be utilized to produce an accurate set of differential diagnoses for a specific clinical scenario frequently encountered in practice so that inexperienced clinicians could utilize LLMs to their fullest potential.

Materials and Methods

Using sample case scenarios of both common and rare diagnoses, we prompted ChatGPT (ChatGPT 3.5, OpenAI) to build a comprehensive differential diagnosis for each case scenario. We systematically reiterated the prompts until we were able to generate a set of acceptable differentials for each case scenario. Based on this experience, a comprehensive checklist that resulted in the optimal set of differentials from the LLM for a particular clinical problem was generated. A sample of the case scenarios, prompts used, and the LLM output are available as supplementary material.

Results

The checklist is enumerated in Table 1 and summarized below.

Providing Adequate Medical Context

A description of the clinical case scenario encompassing all available details of history, including chief complaints, past history, personal history, and relevant physical examination findings and test results with appropriately used medical terminology, led to an LLM output of a more precise differential diagnosis for a given case scenario. For example, to elicit appropriate differentials, a prompt of "a patient presents with a sore throat, difficulty in swallowing, pain in the neck, and low-grade fever for the last 2 days" could be described in greater detail as "a 30-year-old male patient presents with a sore throat, difficulty in swallowing, pain in the neck, and low-grade fever since the last 2 days. On clinical examination, there is congestion of the posterior pharynx, and his neck has a 2 × 1 cm tender swelling. He also has a past history of penicillin allergy."

Accounting for Pretest Probability

Large language models (LLMs) can produce a set of differentials ranked according to pretest probability if specifically prompted to generate clinical diagnoses in order of Bayesian probability or likelihood ratios. We found that using the keywords "list the differential diagnoses in order of Bayesian probability" at the end of the case scenario led to better results. Prompting the LLM for evidence in favor of and against each differential diagnosis is also crucial. When asked for points to justify the stated differential diagnosis, it is an opportunity for the novice to look through the clinical reasoning behind the generated differential, both for learning

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How to cite this article: Muralidharan J, Thomas T. Deliberate Problem-solving with a Large Language Model as a Brainstorm Aid Using a Checklist for Prompt Generation. J Assoc Physicians India 2024;72(5):89–90.

Table 1: Prompt checklist to generate appropriate of differential diagnoses for a case scenario

Ensure correct medical terminology is used. Medicalize keywords
Provide context in the following headings: • Demographic data • Chief complaints • Brief history of presenting illness • Past history, personal history, medication history • Relevant physical examination findings • Relevant test result findings if available
Use the words "generate a clinical diagnosis in order of Bayesian probability/likelihood ratios/pretest probability"
Prompt for points for and against each differential diagnosis • Prompt for pathognomonic clinical features for each differential diagnosis • Prompt for a table to differentiate the top differential diagnosis generated *via* history and clinical examination
Prompt specifically for the most dangerous differential diagnosis that could lead to catastrophic consequences if missed • Ask for any additional history or examination that need to be done to pickup this diagnosis
If there is an unusual aspect of history or examination, prompt specifically for any differentials which could be related to this aspect • If there is a suspicious cluster of symptoms/events, prompt specifically for any differential diagnosis which could link these in any way

clinical insights and identification of errors in logic that an LLM may commit. In this regard, prompting for the pathognomonic clinical feature of each differential diagnosis, as well as a table to distinguish between the top differentials based on history and clinical examination, may also be useful.

Refining the Differential Diagnosis

It is imperative to prompt for any differential diagnosis that, if overlooked, could lead to catastrophic consequences and prompt explicitly for clinical differentiating points to identify such a diagnosis. For example, "an 80-year-old female patient with 20 pack-year smoking history with acute onset shortness of breath with a recent history of percutaneous vertebroplasty for an L2 vertebral compression fracture" may correctly generate differential diagnoses of pulmonary thromboembolism and pneumonia, but additional prompting for adverse effects of the percutaneous vertebroplasty could offer cement embolism as an additional differential diagnosis to be kept in mind. Furthermore, in a patient with an unusual cluster of signs and symptoms, it is important to leverage the wide knowledge database the LLMs can access to specifically prompt for any possible relation in the symptoms to identify a rare diagnosis. For example, for a patient on doxorubicin as a chemotherapeutic agent presenting with diabetic ketoacidosis, the elevation in sugars may not be attributed to the chemotherapy drug if the knowledge base of drug adverse effects is limited.

Limitations of Large Language Models

When employing LLMs for differential diagnosis generation, it is vital to exercise caution, as we noted that both the list of differentials generated and the explanations for supporting or refuting differentials may occasionally be erroneous. For example, when a case scenario of a young male student with clinical features suggestive of a toxidrome like ketamine abuse was provided, the LLM did not generate drug abuse as a differential or suggest the possible causative drug. In that case scenario, a high potassium level was also misinterpreted as hypokalemia, which could have disastrous consequences. We noticed, despite explicit prompting, that LLMs may still confuse pathological and etiological headings for differentials, for example, by listing streptococcal sore throat and pharyngitis as two separate differentials. LLMs are not trained on up-to-date medical data and may generate erroneous differential diagnoses, especially with changes in the domain. Thus, it is important to use sound clinical judgment when using an LLM, and utilizing an LLM as a brainstorming aid while cross-referencing its output with credible medical resources is a judicious approach for a junior clinician.

Conclusion

A novice doctor could search and extend their knowledge base using LLMs as a tool to generate an appropriate set of differential diagnoses. Using a checklist to craft appropriate prompts could leverage LLMs as a tool to achieve this objective. It is imperative to understand the limitations and pitfalls of LLMs and to use sound clinical judgment when considering the output of an LLM. Research to evaluate how LLMs could support clinical problem-solving is the need of the hour, as the use of LLMs as a brainstorming aid will increase tremendously in healthcare practice in the future.

Declarations

- Availability of data and materials: The LLM output is provided as supplementary files.
- Competing interests: The authors have no competing interests to declare.
- Authors' contributions: Both authors (JM and TT) have contributed equally to the conception, data analysis, and writing and revision of the manuscript.

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CASE SERIES

Immunoglobulin A Nephropathy Presenting in Young Adults as Advanced Chronic Kidney Disease and Posttransplant Early Recurrence: A Case Series

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Received: 08 February 2023; *Accepted:* 15 January 2024

Abstract

Immunoglobulin A nephropathy (IgAN) is the most common glomerular disease, leading to chronic kidney disease. The disease is characterized by microscopic hematuria, gross episodic hematuria, hypertension, and subnephrotic proteinuria with or without renal function impairment. It affects individuals of all age groups, commonly seen in 10–40 years of age. It is progressive in nature and leads to chronic kidney disease, necessitating renal replacement therapy. This case series of in a tertiary care hospital in Western India highlights the presentation of this disease in young adults, its aggressive course, its rapid progression, and its early recurrence in the posttransplant period. It also summarizes the treatment recommendations for IgA recurrence in kidney recipients. The disease is known to have a high chance of posttransplant recurrence. Optimizing renin-angiotensin-aldosterone system (RAAS) blockade, blood pressure control, and increasing immunosuppression in rapidly deteriorating cases are the strategies recommended to treat IgA recurrence in kidney transplant recipients.

Journal of the Association of Physicians of India (2024): 10.59556/japi.72.0525

Introduction

Immunoglobulin A nephropathy (IgAN), or Berger's disease, is the most common glomerular disease worldwide. It was first described by Berger in 1768. The disease is characterized by microscopic hematuria, gross episodic hematuria, hypertension, and subnephrotic proteinuria with or without renal function impairment. It affects individuals of all age groups, commonly seen in 10–40 years of age. The definitive diagnosis is the presence of mesangioproliferative glomerulonephritis on renal biopsy specimen, with predominant IgA deposits on Immunofluorescence and mesangial immune complex deposits on electron microscopy. It is progressive in nature and leads to chronic kidney disease, necessitating renal replacement therapy. This case series of IgAN in a tertiary care hospital in Western India highlights the aggressive course of the disease, its rapid progression, and its early recurrence in the posttransplant period.

Case 1

A 27-year-old male patient first presented to us in January 2014 at 23 years of age with a history of upper respiratory tract infection followed by gradually worsening pedal edema, oliguria, and renal dysfunction. On evaluation, he was found to have a blood pressure of 160/100 mm Hg, requiring two antihypertensive drugs. Urinalysis showed nephrotic range proteinuria with microscopic hematuria. His serology was negative for antinuclear antibody (ANA), antineutrophilic cytoplasmic antibody, Anti-glomerular basement membrane antibody, and normal complement levels. He had advanced renal failure with uremic features and required to be initiated on maintenance hemodialysis. Ultrasound revealed normal-sized kidneys with poor corticomedullary gradient. A kidney biopsy was done, which showed diffuse global glomerulosclerosis with >50% interstitial fibrosis and tubular atrophy, as seen in Figure 1. Immunofluorescence showed C3, IgA codominant 3+. A diagnosis of end-stage kidney disease secondary to IgAN, M0E0S2T2C0, was made.

The patient underwent live related renal transplant with the donor being the mother, ABO compatible, one haplotype match. No induction was given. The patient was on triple-maintenance immunosuppression of tacrolimus, azathioprine, and corticosteroids. The posttransplant course was uneventful, and the patient had stable graft functions, and he was discharged at a baseline serum creatinine of 1.2 mg/dL with no evidence of proteinuria.

A total of 2 years posttransplant, in September 2017, the patient started noticing frothing of urine. His 24-hour urine protein quantification was 810 mg/day. In view of stable graft functions, renin-angiotensin-aldosterone system (RAAS) blockers were added at low doses as tolerated by the patient. However, his proteinuria continued to worsen and increased to 2.1 gm/day. His allograft biopsy was done, which revealed 14 glomeruli, of which one was globally sclerosed, and the remaining 12 glomeruli showed an increase in mesangial matrix with mesangial hypercellularity, with mild acute tubular injury, and vessels showed hyaline arteriosclerosis, as seen in Figure 2. Immunofluorescence showed IgA 3+ and C3 3+, confirming the recurrence of IgAN, M1E0S0T0C0.

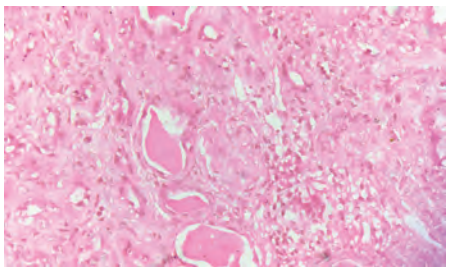

Fig. 1: Hematoxylin and eosin staining; 40× magnification; light microscopic image of kidney biopsy showing diffuse global glomerulosclerosis

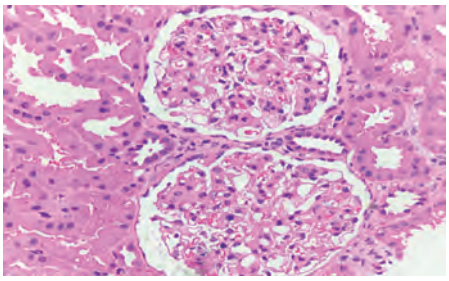

Fig. 2: Hematoxylin and eosin stain; 40× magnification; light microscopic image of allograft biopsy showing mesangial hypercellularity and increase in mesangial matrix in two glomeruli seen in the image

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How to cite this article: Gala R, Ahmad S, Mehta KS, *et al.* Immunoglobulin A Nephropathy Presenting in Young Adults as Advanced Chronic Kidney Disease and Posttransplant Early Recurrence: A Case Series. J Assoc Physicians India 2024;72(5):91–94.

The patient's immunosuppression was continued at the same doses. His dose of angiotensin-converting enzyme (ACE) inhibitors was optimized with antihypertensive medications, statins for lipid control, and fish oil capsules were added.

He continues to have proteinuria of 1.5 gm/day with a stable graft function of 1.2 mg/dL.

Case 2

A 17-year-old male presented with an insidious onset of rapidly worsening pedal edema and anasarca, headache with blurring of vision, not preceded by any upper respiratory infection, not associated with hematuria or oliguria. On evaluation, he was found to have a blood pressure of 210/100 mm Hg, which needed four antihypertensive medications for control of blood pressure. Urinalysis revealed nephrotic range proteinuria with active urinary sediments. His serology was negative for ANA and anti-double stranded DNA. Complements were normal. His serum creatinine was 4.9 mg/dL. His kidney biopsy was done, which revealed diffuse global glomerulosclerosis with >50% interstitial fibrosis and tubular atrophy with strongly positive IgA in immunofluorescence studies. A diagnosis of chronic kidney disease secondary to IgAN was made. The patient continued to have refractory hypertension on four antihypertensive drugs at maximum dosages. He was kept on conservative management in view of advanced renal failure and was counseled about renal replacement therapy options, including transplant and hemodialysis.

March 2016: He underwent live-related ABO compatible renal transplant surgery with his mother being the donor with bilateral native nephrectomy done for resistant hypertension. No induction was given. Triple-maintenance immunosuppression was given, which includes corticosteroids, mycophenolate mofetil, and tacrolimus.

Posttransplant, his course was uneventful. A total of 2 months posttransplant, he had new onset proteinuria 3.3 gm/day with acute allograft dysfunction serum creatinine 3.1 mg/dL. An allograft biopsy was done. Light microscopy showed occasional tubulitis and patchy interstitial infiltrates <15% containing lymphocytes and occasional neutrophils, with acute tubular injury.

Immunofluorescence studies showed 3+ mesangial staining of IgA, confirming the recurrence of native kidney disease, that is, IgAN.

However, clinically, his proteinuria resolved over the next 1 month. The most likely explanation for the resolving proteinuria could have been attributed to the native kidney disease. He did not have any persistent proteinuria or graft dysfunction. Thus, this patient showed histopathological recurrence but no clinical recurrence. He was continued on triple immunosuppression therapy, with close monitoring of proteinuria and graft functions. The patient was continued on triple immunosuppression, tacrolimus, mycophenolate mofetil, and corticosteroids.

Case 3

A 37-year-old male patient, symptomatic at 30 years of age with edematous illness and newly detected young hypertensive. He had a history of one isolated episode of macroscopic painless hematuria at 8 years of age; however, he was not evaluated then. On evaluation of this episode, he was found to have advanced renal dysfunction with a serum creatinine value of 6 mg/dL. His urinalysis showed subnephrotic range proteinuria with active urinary sediments. In view of these findings, a kidney biopsy was performed. Light microscopy examination revealed 19 glomeruli, of which 10 were globally sclerosed. Three glomeruli showed segmental cellular crescents and one fibrocellular crescent, with marked mesangial hypercellularity, marked interstitial fibrosis, and tubular atrophy. Immunofluorescence had 3+ IgA and C3 codominant deposits in the mesangium, confirming IgAN with diffuse global glomerulosclerosis with crescents.

He underwent a live-related renal transplantation in 2011, with his mother being the voluntary kidney donor. It was ABO compatible donor with a one-sixth human leukocyte antigen (HLA) mismatch. The transplant was done with no induction given on triple immunosuppression of tacrolimus, prednisolone, and mycophenolate mofetil (MMF).

On postoperative day 3, the patient had a recurrence of proteinuria, 10 gm on quantification. Serum albumin reports were normal. To rule out native disease recurrence vs rejection, a graft biopsy was performed. Histopathology showed focal mesangial proliferation of glomeruli; the rest of the glomeruli were unremarkable. Immunofluorescence did not show any immune deposits or C4d positivity, ruling out any evidence of rejection. The patient was empirically given 3 days of pulse methylprednisolone, to which the proteinuria responded and was absent by day 15 postoperative. The patient achieved nadir creatinine of 1.2 mg/dL. Graft functions were stable on triple drug immunosuppression. In 2015, 4 years posttransplant, the patient again had worsening of proteinuria to 6.2 gm/day with stable graft functions. Suspecting a recurrence of native kidney disease, the patient underwent a graft biopsy. Light microscopy showed 13 glomeruli, three of which were globally sclerosed. One glomerulus showed a fibrous crescent with mild to moderate mesangial proliferation and acute lymphocytic tubulointerstitial inflammation. Immunofluorescence showed IgA and C3 codominant granular mesangial deposits, thus confirming IgAN recurrence. He was started on RAAS blockade and fish oil capsules, with renal functions and serum potassium monitoring. The proteinuria

Table 1: Summarizes the demographic, clinical, and histopathological features of the three cases

	Case 1	*Case 2*	*Case 3*
Age at onset (years)	23	17	30
Gender	Male	Male	Male
Serum creatinine at presentation (mg/dL)	9.0	4.9	6.0
Progression to ESRD from disease onset	At presentation	5 months	6 months
Kidney biopsy: light microscopy	Diffuse global glomerulosclerosis	Diffuse global glomerulosclerosis	Diffuse global glomerulosclerosis with crescents: three cellular and one fibrocellular
Immunofluorescence studies	IgA 3+; C3 3+	IgA 3+; C3–	IgA 3+; C3 3+
Dialysis vintage (months)	18	15	12
Disease recurrence posttransplant (months)	24	2	48
Recurrence type	Clinical	Histopathological	Clinical
Management	RAAS blockade, lipid-lowering statins, fish oil capsules	–	RAAS blockade, fish oil capsules
Immunosuppressive	No modification	No modification	No modification
Proteinuria at last follow-up (mg/dL)	1500	210	1200

stabilized to 1.2 gm/day with stable graft functions. Blood pressure was well controlled on two antihypertensive drugs (Table 1).

Discussion

Immunoglobulin A nephropathy (IgAN) is the most common cause of primary glomerulonephritis, causing chronic kidney disease all across the world. The clinical course of this disease is variable, ranging from mild to severe renal involvement at presentation. Also, the disease progression to end-stage renal disease (ESRD) varies from patient to patient, seen usually in 15–40% of those affected. While some patients maintain normal renal function for years, others have been found to rapidly worsen their kidney function, necessitating renal replacement therapy.[1] It has been estimated that 10–15% of patients with IgAN progress to ESRD within 10 years and 20–40% within 20 years.[2]

The prevalence of IgAN in the Asian population is higher than in individuals of Caucasian and African–American ethnicity. The mean prevalence of IgAN in India is 16.5%.[3] The prevalence of IgAN in China and Japan countries is around 45%, while it was noted to be around 10% in the United States of America and 13.3% in African countries.[3]

Kidney transplantation is the best option for renal replacement therapy for patients having ESRD on maintenance hemodialysis secondary to IgAN. However, the recurrence of native kidney disease after a kidney transplant can affect graft outcomes and lead to poorer allograft survival. Recurrence of IgAN as the primary disease postkidney transplant has been reported to be as high as approximately 60% in a few studies.[4] Also, the outcomes in patients with recurrent disease have shown allograft loss to be about 30%.[5]

Recurrent disease is diagnosed by a combination of clinical and pathological findings. Clinically, recurrent IgAN manifests as microscopic hematuria and new or worsening proteinuria exceeding 0.5 gm/day but usually remains below the nephrotic range or an increase in serum creatinine. Pathologically, in addition to the mesangial IgA deposition, mesangioproliferative glomerulonephritis must also be observed in the kidney allograft biopsy to meet the diagnostic criteria of recurrent IgAN.[4] In rare cases, recurrent IgAN presents as crescentic glomerulonephritis with rapidly progressive renal allograft failure.[4] Patients who had a rapidly progressive course of ESRD in their native kidney tend to recur early after transplantation, with significant clinical manifestations.[6] Those with early allograft loss from recurrent IgAN may also be at risk of rapid recurrence after retransplantation.[7]

Possible risk factors for the recurrence of IgAN after transplantations include living donors, in particular receiving living-related donor kidneys compared with deceased donor kidneys and 6/6 HLA matching.[8] An analysis of the European Transplant Registry revealed that the 10-year graft survival was significantly lower among patients with IgAN and HLA-B8 and HLA-DR3.[9] Data from the Australian and New Zealand registry of 1,354 patients with ESRD caused by IgAN showed that zero HLA-mismatched living donor recipients were more likely to develop recurrence. Studies have shown an association between pretransplant donor-specific antibodies (DSA) [hazard ratio (HR) 2.74, 95% confidence interval (CI) 1.22–6.14] and de novo DSA (HR 6.65, 95% CI 3.33–13.27).[10]

The TANGO study (posttransplant glomerular disease) demonstrated that the risk of graft loss was higher in IgA recurrence than in those who did not have a recurrence (HR 3.69, 95% CI 2.04–6.66).[10,11] A study of posttransplant IgA recurrence demonstrated the median time from diagnosis of disease recurrence to allograft failure to be 3.1 years.[10]

The case series here depicts the nature of the disease, IgAN, its progression to ESRD, and its posttransplant course. The young age of disease onset, uncontrolled blood pressures requiring multiple drugs, significant proteinuria, and microscopic or macroscopic hematuria, the rapidity of progression of disease leading to ESRD, with or without treatment.

Treatment

The treatment recommendations for recurrence of IgAN posttransplant are extrapolated from the treatment of the primary glomerular disease. Initial management includes initiation of RAAS blockade, that is, ACE inhibitors or angiotensin receptor blockers (ARBs). It delays the disease progression in transplant recipients.[12,13] A retrospective analysis of 75 renal transplant recipients with IgA recurrence benefitted from ACE or ARBs with a higher than 5- and 10-year allograft survival rate; however, it was not statistically significant.[13]

There have been anecdotal case reports of fish oil having a favorable outcome on disease progression in IgA recurrence; however, larger studies are still needed to support its routine use.[14]

Dietary restriction of salt intake to 2 gm/day is advocated for better control of hypertension. Antihypertensive drug optimization to maintain a blood pressure of 130/80 mm Hg is advised.

Immunosuppressive Therapy

Immunosuppressive therapy in IgA recurrence is indicated in selected patients who develop rapidly worsening graft function in biopsy-proven recurrence or nephrotic range proteinuria despite RAAS blockade optimization.

Treatment is pulse methylprednisolone for 3 days and/or high-dose glucocorticoids (1 mg/kg/day) given for a duration of 6–8 weeks followed by slowly tapering back to low doses.[15]

Patients with rapidly worsening graft functions despite high dose glucocorticoids or cellular crescents on allograft biopsy may benefit from cyclophosphamide in oral or intravenous form. During this time, the antimetabolite (MMF or azathioprine) needs to be withheld to balance the net state of immunosuppression. Some patients may benefit from an increase in the dose of mycophenolate mofetil.[15] The use of rituximab in transplant recipients with disease recurrence is yet to be studied. A randomized controlled trial of patients with IgAN (nontransplant) compared rituximab with supportive therapy in one arm with supportive therapy alone in the second arm did not show any improvement in disease outcomes.[16]

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CASE REPORT

Langerhans Cell Histiocytosis Presenting with Pneumothorax and Diabetes Insipidus

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Received: 28 August 2023; *Revised:* 17 October 2023; *Accepted:* 23 October 2023

Abstract

Secondary spontaneous pneumothoraces occur in patients with known underlying lung disease. Patients with emphysema, bullae, and cystic lesions in the lungs are at high risk of developing pneumothorax. Cystic lung diseases like Langerhans cell histiocytosis (LCH) can present with complications like pneumothorax. Other common presenting features include maculopapular rashes and bone lesions. It can also be associated with endocrinopathies, most commonly central diabetes insipidus (CDI). We here present a case of a 22-year-old male who presented with pneumothorax, polyuria, and polydipsia. He was diagnosed with LCH on transbronchial lung biopsy, associated with CDI, and was treated with thoracoscopy-guided autologous blood patch for persistent air leak and subcutaneous cytarabine.

Journal of the Association of Physicians of India (2024): 10.59556/japi.72.0541

Introduction

Langerhans cell histiocytosis (LCH) is characterized by monoclonal proliferation of immature dendritic cells that infiltrate into different organs. Its clinical presentation may range from isolated skin rashes and bony lesions to life-threatening multisystem disease. Pulmonary manifestations of LCH include dyspnea, nonproductive cough, bizarre-shaped lung cysts, spontaneous pneumothorax, and pulmonary hypertension in advanced stages. It can also involve the hypothalamic–pituitary axis resulting in complications like central diabetes insipidus (CDI).[1] The diagnosis of LCH is histopathological, made by the presence of markers such as CD1a and/or CD207 (langerin) on biopsy.[2]

Case Presentation

A 22-year-old male patient, nonsmoker, presented with sudden onset left-sided chest pain. On examination, the patient had tachypnea, tachycardia, and an oxygen saturation of 95% on room air. Chest X-ray revealed a pneumothorax on the left side for which an intercostal drainage (ICD) tube of 20 French was inserted in the left pleural space. Computed tomography (CT) scan of the thorax (Fig. 1) was suggestive of multiple bizarre-shaped cysts in bilateral lung fields with paraseptal emphysematous changes along with pneumothorax. Based on the CT scan findings and age of the patient, the differential diagnoses were alpha-1 antitrypsin deficiency and LCH. The alpha-1 antitrypsin levels were normal.

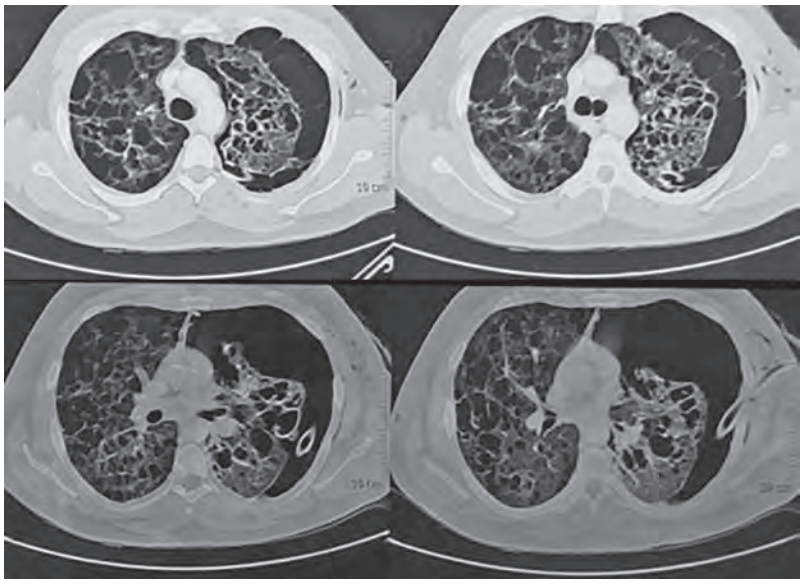

Fig. 1: CT scan of thorax: multiple bizarre-shaped cysts in bilateral lung fields with paraseptal emphysematous changes, pneumothorax on left, and ICD tube *in situ*

The patient also gave a history of polyuria and polydipsia for 7 years for which the patient had never been investigated. The urine output of the patient was found to be 7 L/day. His serum sodium level was 147 mmol/L, serum osmolality was 305 mOsm/kg, and urine osmolality was 65 mOsm/kg. Based on high serum and low urinary osmolality, the patient was suspected to have diabetes insipidus (DI). This was confirmed by a water deprivation test in which the patient lost 4% of his body weight in merely 6 hours. His magnetic resonance imaging (MRI) brain was suggestive of partially empty sella along with the absence of the posterior pituitary bright spot.

A bronchoscopy and a transbronchial lung biopsy with intercostal tube *in situ* were performed. The immunohistochemistry (IHC) of the lung biopsy was positive for CD1a, S100, and langerin, and the diagnosis of LCH was confirmed (Fig. 2). The patient was then started on injectable subcutaneous cytarabine at a dose of 100 mg/m^2 of body surface area and desmopressin for DI. The patient had persistent air leak via the ICD. A thoracoscopy (Fig. 3) was performed, and autologous blood patch instillation was done. Subsequently, the patient's air leak subsided, and once the chest X-ray showed a completely expanded lung, a pleurodesis using betadine was done to prevent recurrence of pneumothorax.

Discussion

Langerhans cell histiocytosis is a disease of the monocyte–macrophage system characterized by the proliferation of CD1a-positive immature dendritic cells.[3] Common clinical presentations include cystic lung diseases, skin rashes, and bony lesions. LCH can occur at any age but is most common from birth to age 15 years.[4] LCH can have a waxing and waning course, which can cause

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How to cite this article: Kedia Y, Madan M, Ish P, *et al.* Langerhans Cell Histiocytosis Presenting with Pneumothorax and Diabetes Insipidus. J Assoc Physicians India 2024;72(5):95–96.

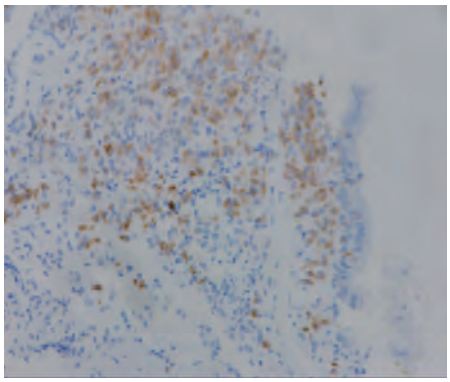

Fig. 2: Transbronchial lung biopsy positive for langerin

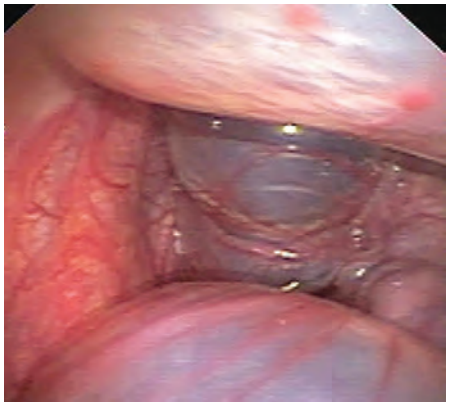

Fig. 3: Thoracoscopy image showing bullae

long-term complications such as DI and neurodegenerative disease. CDI has been reported in almost 12% patients with LCH.[5] BRAF V600E mutation has been identified in 30–60% cases of pediatric LCH and is an independent predictor for disease relapse and a candidate for targeted therapy with disease relapse and multisystem disease. MAP2K1 is another common mutation seen in LCH and may be seen with BRAF-negative cases.[6] In adults, LCH is considered to be associated with cigarette smoking. This association was demonstrated in a murine model where mice were passively exposed to tobacco smoke, and their level of Langerhans cells (LCs) increased by 20-fold.[7] In humans, macrophage activation occurs due to various toxins from cigarette smoke, which secrete tumor necrosis factor alpha (TNF-α) and granulocyte-macrophage colony-stimulating factor (GM-CSF), and these in turn cause proliferation of LCs.[8] Recently, clonal proliferation in LCH has been reported with the presence of BRAF V600E oncogenic mutation as well. Although, in our case, the patient was a nonsmoker, and genetic testing for mutation analysis could not be performed due to lack of facilities.

Pulmonary LCH (PLCH) mostly presents with nonspecific respiratory symptoms like dyspnea and cough. Pneumothorax as a complication can occur in 10% of the patients.[9] Typical chest radiographic features of PLCH include upper and middle zone reticulonodular opacities with cystic lesions. PLCH lung nodules can be hypermetabolic on fluorodeoxyglucose (FDG) positron emission tomography–computed tomography (PET–CT), and thus differentiating from other malignant lesions can be difficult.[10]

Diabetes insipidus is the most common central nervous system (CNS)-related complication in LCH. CDI is diagnosed when there is evidence of plasma hyperosmolality, urine hypoosmolality, and polyuria. The water deprivation test helps to confirm the diagnosis.[5] Patients with primary polydipsia can concentrate their urine with deprivation of water intake, while those with CDI or nephrogenic DI (NDI) continue to excrete dilute urine. After administration of desmopressin, patients with CDI are able to concentrate their urine, while those with NDI continue to pass diluted urine due to end-organ resistance to the action of vasopressin or its analogs.

Histologic features of LCH include histiocytes with elongated, grooved nuclei and are CD207 (langerin)- and CD1a-positive on IHC.[2]

For unifocal LCH, local therapies may be sufficient to treat.[11] Management of PLCH can be complex and take into consideration respiratory symptoms, the degree of lung function impairment, and the radiologic extent of disease. Smoking cessation is the most effective way to achieve complete remission and prevent long-term complications related to tobacco. Combined inhaled corticosteroid and bronchodilators like long-acting β2-agonist therapy may provide benefit to patients with wheezing. Pneumothorax may recur in half of the patients and may present with persistent air leak (air leak for >5–7 days) in some cases. As for other chronic respiratory illnesses, seasonal influenza, pneumococcal, and COVID-19 vaccinations are recommended for all patients.

The systemic chemotherapy options for LCH are cladribine, cytarabine, or vinblastine plus prednisone, with the first two being preferred because of relatively high overall response rates and the potential for long-term remissions with limited cycles of treatment.

Use of cladribine has been associated with improved lung function and is the preferred systemic therapy. Combination therapies including methotrexate plus cytarabine have been tried in some trials. Cladribine used as primary therapy or in cases with disease relapse has shown high response rates (79–90%) in recent retrospective studies.[12]

Among patients with BRAF V600E mutated LCH, targeted therapy with BRAF inhibitors is a novel therapeutic approach. In a phase II trial using vemurafenib in four patients with relapsed LCH, one patient had a complete response, whereas three had partial responses.[13] A case report of an adult patient with relapsed or refractory disease has shown that the patient responded to dabrafenib and trametinib after progression from vinblastine to prednisone.[14]

Conclusion

Langerhans cell histiocytosis is a multisystemic disorder which can present with life-threatening complications like pneumothorax along with multisystem involvement. Extrapulmonary manifestations may be the initial or the only presentation. Once diagnosed, a detailed screening for other organ involvement should be done. Therapies using cladribine and cytarabine have been shown to reduce disease activity and improve life expectancy. New reports are emerging on the potential role of BRAF inhibitors, and good response has been seen with this novel therapy.

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CASE REPORT

Late-onset Chorea with a Rare but Identifiable Cause

Advait Aniruddha Gitay[1*], Prashant Dubey[2]

Received: 07 January 2023; *Accepted:* 03 July 2023

Abstract

Chorea is a very commonly encountered movement disorder; it has various etiologies, and it can have autoimmune, vascular, degenerative, or paraneoplastic etiology. Our patient had acute onset chorea and a strong history of smoking, which made us suspect first vascular followed by paraneoplastic cause. After ruling out common vascular and metabolic causes, his whole body positron emission tomography (PET) scan revealed a mass in the right upper lobe, a biopsy revealed a small cell carcinoma lung and a paraneoplastic panel showed antibodies positive for collapsin response mediator protein 5 antigen (CRMP-5/CV2); the patient was started on immunomodulation, chemotherapy with the variable response, he succumbed to a cardiac event after treatment.

Journal of the Association of Physicians of India (2024): 10.59556/japi.72.0508

Introduction

Chorea is a common movement disorder encountered in neurological practice and has different etiologies. It can present in various age-groups, and etiologies vary according to age-groups; treatable causes should be kept as a first differential before moving toward degenerative etiologies.[1] With acute onset, vascular and metabolic etiologies should be considered. Autoimmune etiologies should be considered in each and every patient; in adults, autoimmune chorea is one of the leading causes of adult-onset chorea behind Huntington's disease (HD) and vascular etiologies.[2,3]

Case Description

We had a 72-year-old male with no previous comorbidities presented with acute onset and progressive involuntary movements involving the right upper limb, right lower limb, and mood disturbances. The patient didn't have any past history suggestive of diabetes mellitus or toxin exposure. Personal history revealed he had a history of smoking. There was no history of cognitive impairment/depression/similar complaints in the family. The patient denied any history of neuroleptic/antiemetic drug intake. Examination revealed he had a normal mini-mental status examination. Motor examination revealed choreiform movements involving the right upper limb, right lower limb, and tongue.

The patient underwent an extensive workup including brain magnetic resonance imaging (MRI) with and without contrast, electroencephalogram (EEG), cerebrospinal fluid (CSF) analysis, antistreptolysin O, serum/urine copper, ceruloplasmin, thyroperoxidase antibody, rapid plasma regain, veneral disease research laboratory (VDRL) and vitamin B_{12} levels. A chest X-ray also was normal. The patient was started on the tab. Tetrabenazine and diphenhydramine with no improvement. CSF routine/microscopy was normal.

In view of the history of smoking and considering his age, we asked for a whole body positron emission tomography (PET) scan to rule out paraneoplastic cause. A whole-body PET scan revealed a mass in the right perihilar region and multiple mediastinal lymph nodes, suggestive of carcinoma lung, and metastasis was not seen anywhere in the body (Fig. 1). He underwent a computed tomography (CT)—guided biopsy, which revealed small cell carcinoma lung. A paraneoplastic panel was sent, which revealed antibodies against CRMP-5/CV2.

The patient was started on dexamethasone and chemotherapy, following which his chorea subsided. The patient succumbed to a cardiac event after 2 months.

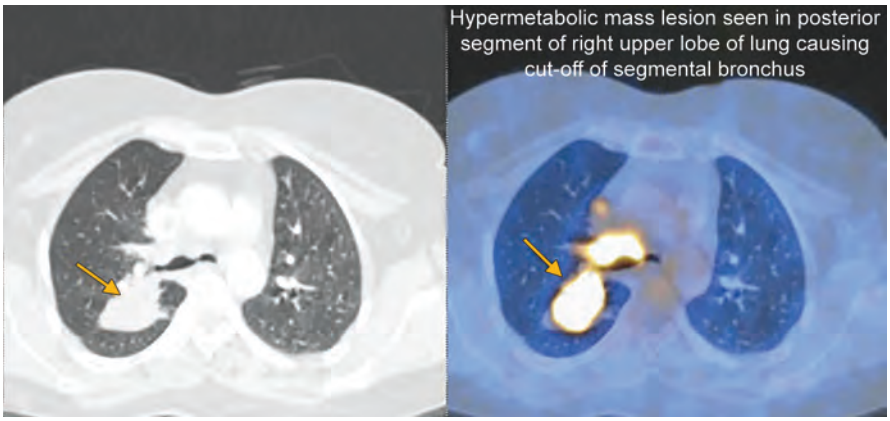

Fig. 1: Positron emission tomography (PET) scan showing a hypermetabolic mass in the the right upper lobe

Discussion

Paraneoplastic basal ganglia disorders are a very rare occurrence. Chorea is mainly associated with anti-CRMP5/CV2 antibodies. The associated paraneoplastic syndrome can include chorea (11% of patients), cranial neuropathy, peripheral and autonomic neuropathy, cerebellar ataxia, neuromuscular junction disorders, and subacute dementia.[4] Anti-CRMP-5/CV2 immunoglobulin G is the most common paraneoplastic cause of chorea, followed by anti-Hu/antineuronal nuclear autoantibody (ANNA)-1.[5]

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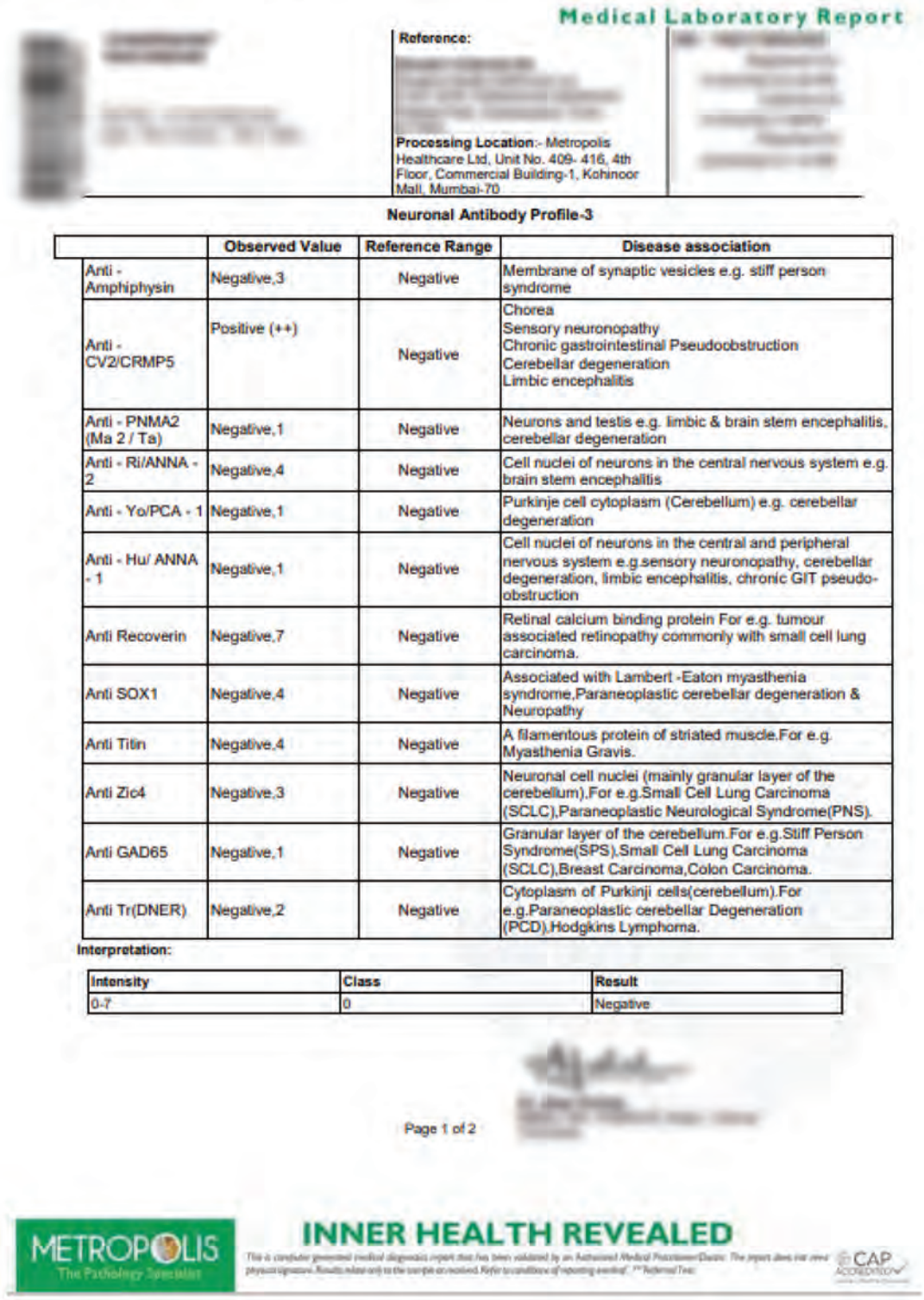
How to cite this article: Gitay AA, Dubey P. Late-onset Chorea with a Rare but Identifiable Cause. J Assoc Physicians India 2024;72(5):97–100.

Supportive reports :

Paraneoplastic panel and PET scan report -



Medical Laboratory Report

Reference:

Processing Location:- Metropolis Healthcare Ltd, Unit No. 409- 416, 4th Floor, Commercial Building-1, Kohinoor Mall, Mumbai-70

Neuronal Antibody Profile-3

	Observed Value	Reference Range	Disease association
Anti - Amphiphysin	Negative,3	Negative	Membrane of synaptic vesicles e.g. stiff person syndrome
Anti - CV2/CRMP5	Positive (++)	Negative	Chorea Sensory neuronopathy Chronic gastrointestinal Pseudoobstruction Cerebellar degeneration Limbic encephalitis
Anti - PNMA2 (Ma 2 / Ta)	Negative,1	Negative	Neurons and testis e.g. limbic & brain stem encephalitis, cerebellar degeneration
Anti - Ri/ANNA - 2	Negative,4	Negative	Cell nuclei of neurons in the central nervous system e.g. brain stem encephalitis
Anti - Yo/PCA - 1	Negative,1	Negative	Purkinje cell cytoplasm (Cerebellum) e.g. cerebellar degeneration
Anti - Hu/ ANNA - 1	Negative,1	Negative	Cell nuclei of neurons in the central and peripheral nervous system e.g.sensory neuronopathy, cerebellar degeneration, limbic encephalitis, chronic GIT pseudo-obstruction
Anti Recoverin	Negative,7	Negative	Retinal calcium binding protein For e.g. tumour associated retinopathy commonly with small cell lung carcinoma.
Anti SOX1	Negative,4	Negative	Associated with Lambert -Eaton myasthenia syndrome,Paraneoplastic cerebellar degeneration & Neuropathy
Anti Titin	Negative,4	Negative	A filamentous protein of striated muscle.For e.g. Myasthenia Gravis.
Anti Zic4	Negative,3	Negative	Neuronal cell nuclei (mainly granular layer of the cerebellum).For e.g.Small Cell Lung Carcinoma (SCLC),Paraneoplastic Neurological Syndrome(PNS).
Anti GAD65	Negative,1	Negative	Granular layer of the cerebellum.For e.g.Stiff Person Syndrome(SPS),Small Cell Lung Carcinoma (SCLC),Breast Carcinoma,Colon Carcinoma.
Anti Tr(DNER)	Negative,2	Negative	Cytoplasm of Purkinji cells(cerebellum).For e.g.Paraneoplastic cerebellar Degeneration (PCD),Hodgkins Lymphoma.

Interpretation:

Intensity	Class	Result
0-7	0	Negative

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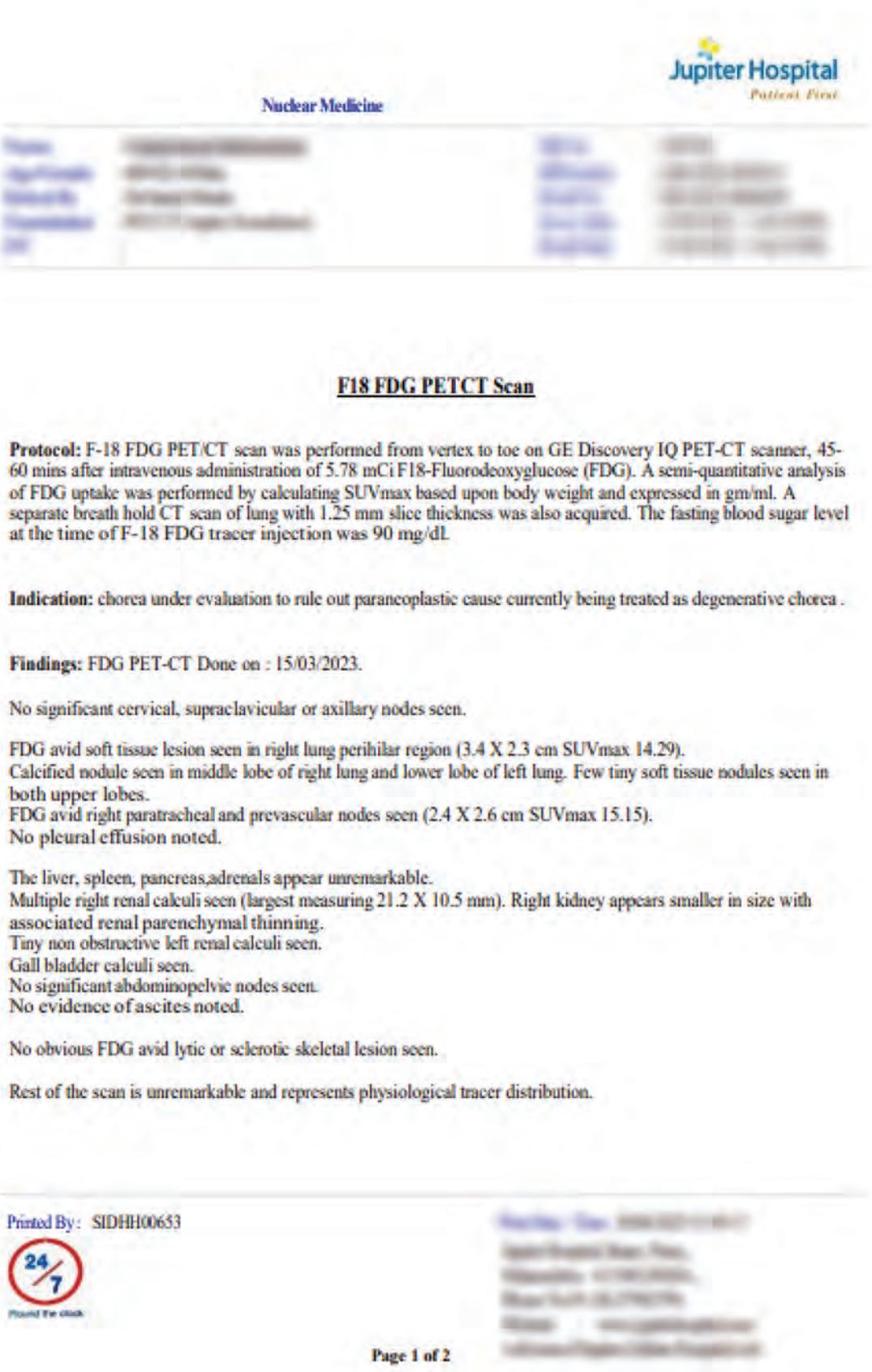
METROPOLIS The Pathology Specialist

INNER HEALTH REVEALED

CAP ACCREDITED

Fig. 2: Paraneoplastic panel with anti-CRMP5 positive



Jupiter Hospital
Patient First

Nuclear Medicine

[redacted]

F18 FDG PETCT Scan

Protocol: F-18 FDG PET/CT scan was performed from vertex to toe on GE Discovery IQ PET-CT scanner, 45-60 mins after intravenous administration of 5.78 mCi F18-Fluorodeoxyglucose (FDG). A semi-quantitative analysis of FDG uptake was performed by calculating SUVmax based upon body weight and expressed in gm/ml. A separate breath hold CT scan of lung with 1.25 mm slice thickness was also acquired. The fasting blood sugar level at the time of F-18 FDG tracer injection was 90 mg/dL

Indication: chorea under evaluation to rule out paraneoplastic cause currently being treated as degenerative chorea .

Findings: FDG PET-CT Done on : 15/03/2023.

No significant cervical, supraclavicular or axillary nodes seen.

FDG avid soft tissue lesion seen in right lung perihilar region (3.4 X 2.3 cm SUVmax 14.29).
Calcified nodule seen in middle lobe of right lung and lower lobe of left lung. Few tiny soft tissue nodules seen in both upper lobes.
FDG avid right paratracheal and prevascular nodes seen (2.4 X 2.6 cm SUVmax 15.15).
No pleural effusion noted.

The liver, spleen, pancreas,adrenals appear unremarkable.
Multiple right renal calculi seen (largest measuring 21.2 X 10.5 mm). Right kidney appears smaller in size with associated renal parenchymal thinning.
Tiny non obstructive left renal calculi seen.
Gall bladder calculi seen.
No significant abdominopelvic nodes seen.
No evidence of ascites noted.

No obvious FDG avid lytic or sclerotic skeletal lesion seen.

Rest of the scan is unremarkable and represents physiological tracer distribution.

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24/7 Round the clock

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Page 1 of 2

Fig. 3: Description of PET scan report showing lesion in right lung


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Impression:

Scan findings reveal:

- **Metabolically active soft tissue lesion seen in right lung perihilar region - likely neoplastic etiology. Suggested histopathological correlation.**
- **Few tiny bilateral lung nodules seen - too tiny to characterize.**
- **Metabolically active mediastinal nodes - likely metastatic.**
-

Suggested clinical correlation.

[redacted]

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Page 2 of 2

Fig. 4: PET scan report

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CASE REPORT

An Unusual Hematological Complication of Typhoid Fever Case Report

Sanju John[1*], Aleena V[2]

Received: 08 February 2023; *Accepted:* 05 September 2023

Abstract

Typhoid fever is caused by *Salmonella* species. The most common hematological complications described are anemia and disseminated intravascular coagulation. Splenic infarction is an unusual complication of typhoid fever, and this presentation is rarely described. We report the case of a young female who presented with complaints of severe left upper quadrant pain after being diagnosed with typhoid fever. Computed tomography (CT) revealed multiple wedge-shaped splenic infarcts. She was treated with antibiotics and was also started on antiplatelets. She had a complete recovery with this management, and antiplatelets were tapered off on subsequent visits.

Journal of the Association of Physicians of India (2024): 10.59556/japi.72.0498

Introduction

Typhoid fever is caused by the organism *Salmonella enterica* subspecies enterica serovar Typhi, a systemic infection transmitted predominantly through water or food contaminated by human feces. Typhoid fever presents clinically with a variety of symptoms and signs, including fever, abdominal pain, nausea, and vomiting, and it also presents with complications.[1] The development of severe disease depends on host factors (immunosuppression, antacid therapy, previous exposure and vaccination), strain virulence and inoculum, and choice of antibiotic therapy. Unusual complications include Guillain–Barré syndrome,[2] acute transverse myelitis,[3] sick sinus syndrome,[4] glomerulonephritis,[5] and rhabdomyolysis.[6] Splenic infarction is a very rare complication of typhoid fever.

Case Description

A 25-year-old female patient with no known comorbidities was referred to our hospital with complaints of high-grade fever for 9 days, which was associated with loose stools. She was diagnosed with typhoid fever from the referring hospital and was started on ceftriaxone. She then started complaining of left-sided abdominal pain, chest pain, and breathlessness. She had a family history of rheumatoid arthritis in her mother. On examination, she was conscious and oriented, febrile, and had a temperature of 104°F. Her blood pressure was 130/80 mm Hg, her pulse rate was 70 beats/minute, and her respiratory rate was 25 breaths/minute. Her abdominal examination showed tenderness over the left hypochondrium, and her respiratory system showed signs of left-sided pleural effusion.

She was admitted, and baseline blood investigations were conducted. Complete blood count showed hemoglobin—11.6, packed cell volume—35.4, total leukocyte count—9600, and platelet count—201. She had raised inflammatory markers, and there was no evidence of sickling or hemolysis. Chest X-ray shows features of mild to moderate left pleural effusion. Serum electrolytes, renal functions, liver functions, coagulogram, amylase, and lipase levels were within normal range. Her blood culture confirmed the diagnosis of *Salmonella* Typhi, which was sensitive to the antibiotic. Her serology for other tropical illnesses, such as dengue, malaria, leptospirosis, and scrub typhus, was negative.

On further evaluation, an ultrasound of the abdomen was done in view of the abdominal pain and was found to have hepatomegaly, mild splenomegaly with? Evolving abscess of size 8 × 7 cm (Fig. 1A). It was followed by contrast enhanced computed tomography (CBCT) of the abdomen (Fig. 1B) and chest, which revealed multiple wedge-shaped splenic infarcts and mild pleural effusion (Fig. 1C). Echocardiogram was unremarkable, and thrombophilia panel were within normal range.

She was treated with antibiotics, nonsteroidal anti-inflammatory drugs, and fluid resuscitation and was put on oral antibiotics on discharge. An opinion was taken from a hematologist and rheumatologist to exclude blood-borne malignancy, hypercoagulable states, autoimmune diseases and collagen vascular diseases. She was initiated on antiplatelets and continued for 6 months. Her follow-up ultrasound of the abdomen revealed a normal splenic echotexture and size.

Discussion

Splenic infarction is rarely seen as a complication of tropical fevers. Common causes of splenic infarction include blood-borne malignancy, hypercoagulable states, thromboembolic disorders, blunt abdominal trauma, and pancreatic disorders; additionally, autoimmune diseases and collagen vascular diseases have been noted to cause splenic infarction.[7] The exact pathophysiology of splenic infarction in infectious diseases is unknown but is postulated to be due to inadequate blood supply and transient production of antiphospholipid antibodies.[8]

Splenic infarction can have a variable presentation, but the most common is left-sided abdominal pain (50%) and tenderness (32%).[8] Abdominal ultrasonography can be used for its identification, but it is less sensitive. CECT abdomen can precisely identify the low attenuation defects and is the current modality of choice for accurate diagnosis.[9]

Although the mainstay of diagnosing typhoid fever is a positive blood culture, the test is positive in only 40–50% of cases, usually early in the course of the disease. Stool and urine cultures become positive after the 1st week of infection, but their sensitivity is much lower. The classic Widal test is a simple test but lacks sensitivity and specificity.[10]

The management of splenic infarction requires only supportive measures. Surgical treatment is required only if the patient is in hemodynamic instability. Patients presenting with splenic infarct are a challenge to physicians. We emphasize the workup of splenic infarction after the obvious predisposing etiologies have been ruled out.

Conclusion

Splenic infarction is an unusual complication of typhoid fever, and there are only very few

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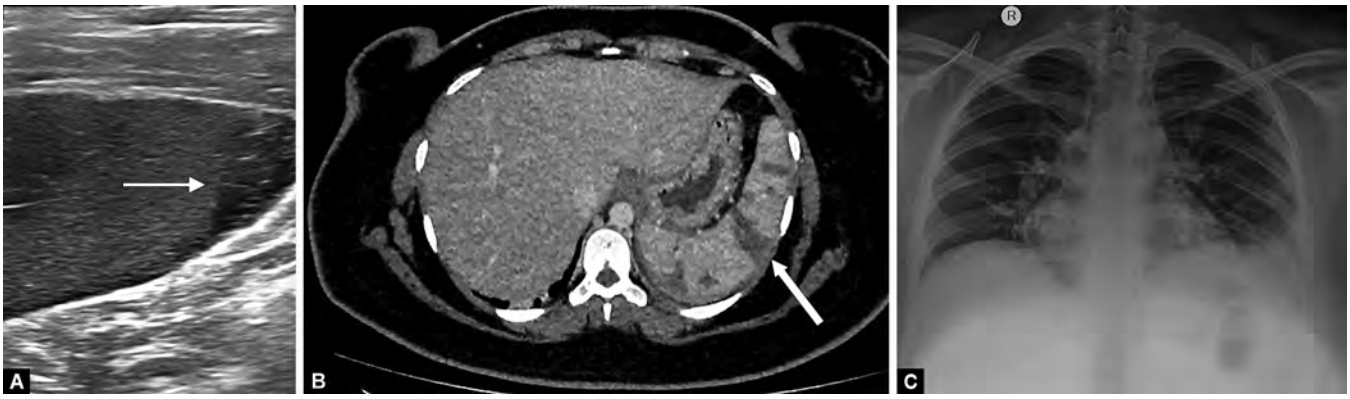
How to cite this article: John S, V A. An Unusual Hematological Complication of Typhoid Fever Case Report. J Assoc Physicians India 2024;72(5):101–102.



Figs 1A to C: (A) Ultrasound of spleen with high-frequency probe showing hypoechoic lesion involving splenic pole (white arrow); (B) Computed tomography of abdomen in venous phase showing multiple wedge-shaped nonenhancing areas involving spleen extending toward hilum consistent with splenic infarcts; (C) X-ray chest showing blunting of left CP angle region with silhouetting of left hemidiaphragm

literatures mentioned for the same. Common presentation is left-sided abdominal pain and tenderness. CT scan is the imaging modality of choice for suspected patients. It is also crucial to exclude other common causes of splenic infarction. In our patient, we have found a benefit with antiplatelet therapy and supportive treatment.

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CASE REPORT

Septal Artery Strangulation Causing Brugada Phenocopy: A Rare Presentation

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Received: 05 April 2023; *Accepted:* 18 August 2023

Abstract

Brugada phenocopies are conditions that have an electrocardiography (ECG) pattern that mimics typical patterns seen in Brugada syndrome (BS). We report a rare case of a patient who had a Brugada-like ECG pattern caused by ischemia due to strangulation of the septal artery. The patient was treated with thrombolytic therapy after a probable diagnosis of ST-elevation myocardial infarction (STEMI), which resulted in hematologic complications.

Journal of the Association of Physicians of India (2024): 10.59556/japi.72.0507

Introduction

Brugada syndrome (BS) is a cardiac channelopathy associated with potentially fatal ventricular arrhythmias in a structurally normal heart.[1] Brugada phenocopies are clinical conditions that have an etiology unrelated to BS but result in electrocardiography (ECG) patterns identical to those seen in BS.[2] We report a patient who presented with chest pain having Brugada-like ECG pattern and was diagnosed as ST-elevation myocardial infarction (STEMI). The patient was treated with thrombolytic therapy, following which he developed hematologic complications.

Case Presentation

A 53-year-old male was referred to Apollo Hospitals, Chennai. He had reported to another hospital with complaints of atypical chest pain at rest lasting a few minutes, with spontaneous subsidence. ECG done at the presenting hospital revealed ST elevation in leads V1–V3 (Fig. 1) and a diagnosis of anteroseptal STEMI was considered.

He was administered thrombolytic therapy (tenecteplase 30 mg) at that hospital. A subsequent ECG at our center revealed J-point-ST elevations in leads V1–V3 (Fig. 2).

Serial ECGs did not reveal any labile changes. Serial biomarkers (hs-troponin I) were negative. A perusal of his old ECG taken 3 months prior to presentation during a routine health check-up revealed the same ECG changes.

Coronary angiography (CAG) revealed a normal left main coronary artery with irregularities in the proximal and mid-left anterior descending artery. About 50% systolic compression (myocardial bridging) was observed in the distal left anterior descending artery. Severe myocardial bridging was noted in septal branch S1 with near total systolic obliteration/compression of septal artery. The left circumflex and right coronary arteries were normal. Doppler echocardiography revealed normal size and function of the ventricles with no regional wall motion abnormalities and normal strain imaging with left ventricular ejection fraction of 60%. Figure 3 represents CAG findings.

The patient reported after 6 days with ecchymoses involving the forearms and thighs (Fig. 4).

The patient was advised genetic analysis following suspicion of BS. The genetic test results were negative for channelopathies.

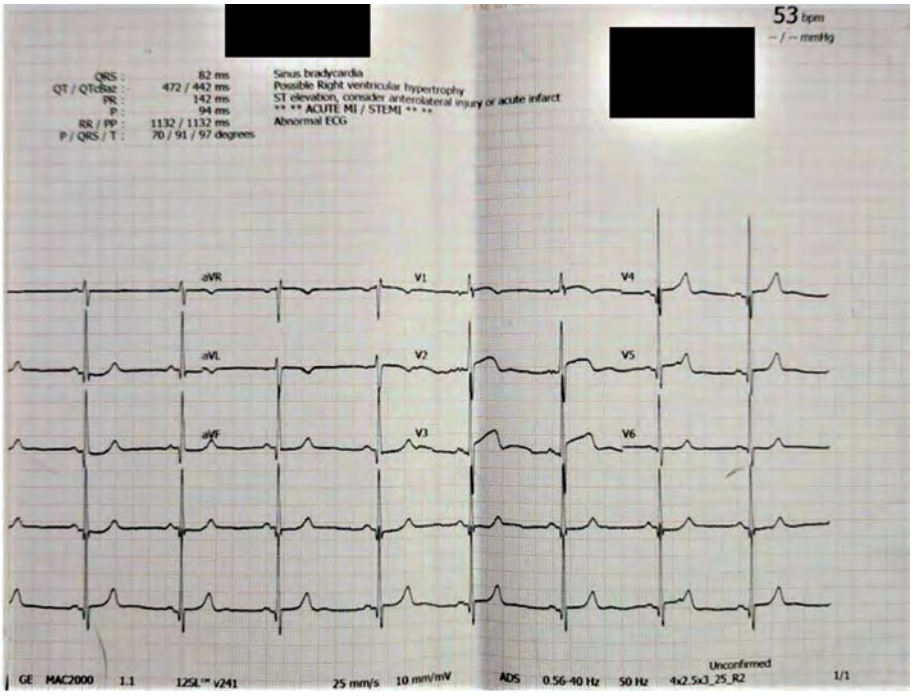

Fig. 1: Electrocardiography (ECG) depicting ST-elevation in leads V1–V3

Discussion

Brugada syndrome (BS) was first described by Dr Pedro Brugada and Dr Joseph Brugada in a series of eight patients with episodes of sudden death with common clinical and ECG features.[3] The term "Brugada syndrome" was coined in 1996.[4] Typically, the characteristic ECG pattern reveals ST-segment elevation in ≥1 right precordial leads positioned in the second to fourth intercostal space observed spontaneously or after provocative drug tests with intravenous sodium channel blocker.[5] The clinical spectrum of SCN5A mutations include long QT syndrome, BS, and

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How to cite this article: Vijayachandra Y, Sreeram J, Wilson A, *et al.* Septal Artery Strangulation Causing Brugada Phenocopy: A Rare Presentation. J Assoc Physicians India 2024;72(5):103–105.

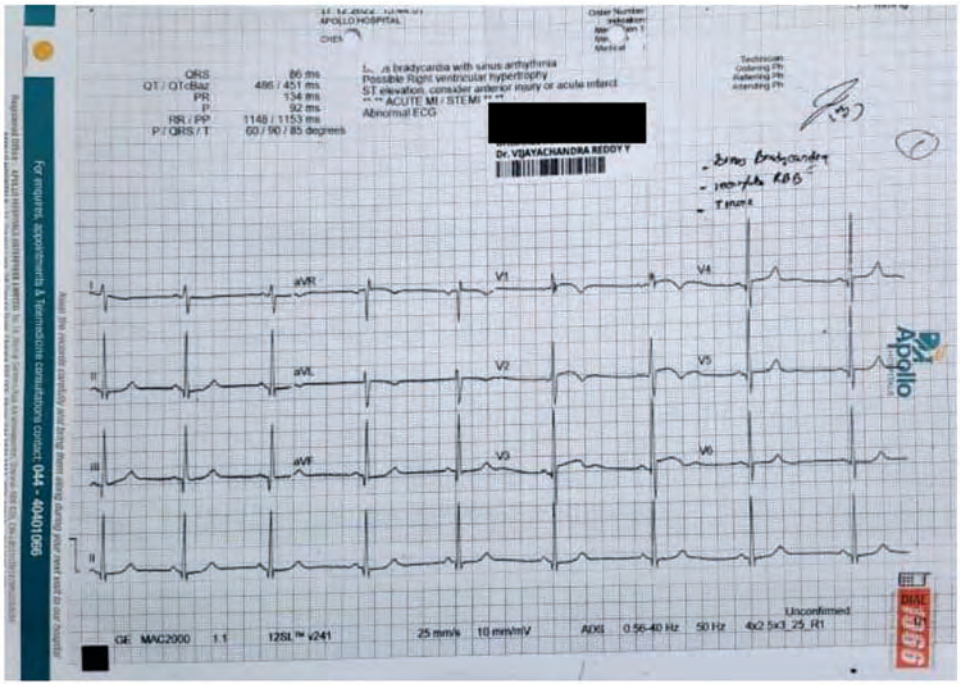

Fig. 2: Electrocardiography (ECG) depicting "Brugada-like" pattern with J-point and ST-elevations in leads V1–V3. Serial ECGs do not show labile changes

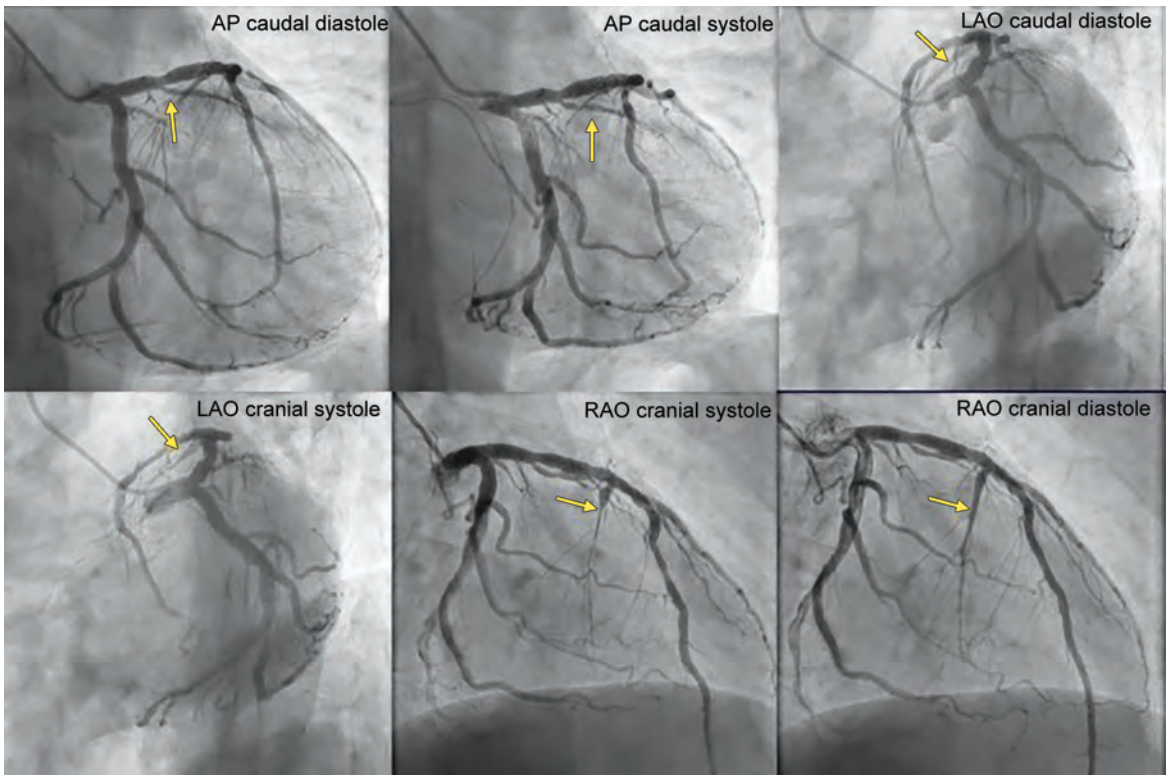

Fig. 3: Multiple angiographic views depict severe myocardial bridging with near total systolic compression/obliteration of septal artery

cardiomyopathy. SCN5A codes for α-subunit of cardiac voltage-gated sodium channel.[6] Variants in >40 genes have been associated with BS.[7]

Clinical entities that mimic Brugada pattern on ECG are referred to as "Brugada phenocopies." The International Registry of Brugada Phenocopies maintains an online database for patient documentation and follow-up. The etiological classification of Brugada phenocopies include metabolic imbalance, mechanical compression, ischemia and pulmonary embolism, myocardial and pericardial disease, ECG modulation, and miscellaneous reasons.[8] About 50% myocardial compression in the distal left anterior descending artery, and severe myocardial bridging with near total

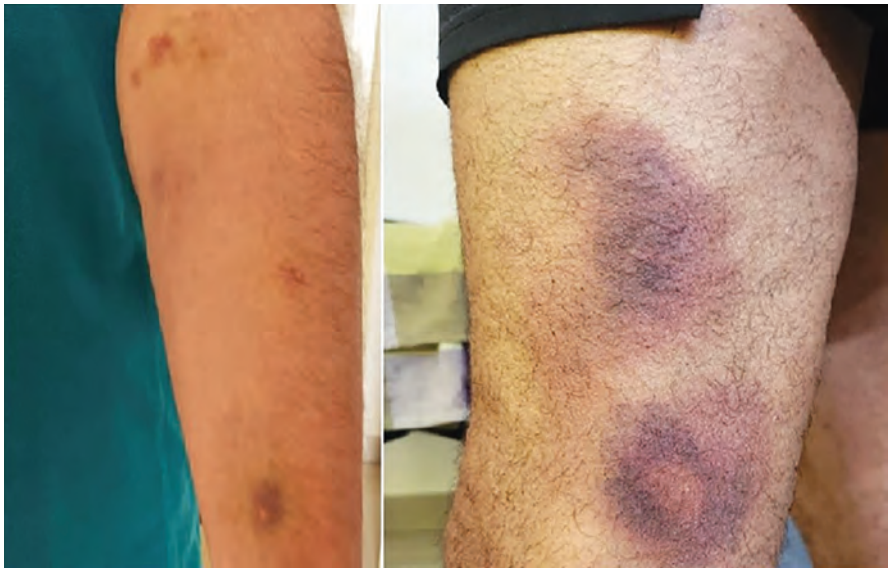

Fig. 4: The patient reported with ecchymosis on the forearm and thigh following thrombolytic therapy

obliteration of septal artery might have led to presentation of Brugada-like ECG in this patient. It is to be noted here that myocardial bridging is generally considered an incidental at coronary arteriography with no clinical relevance. This is because coronary flow in left anterior descending (LAD) is predominantly diastole except in states of tachycardia. It is possible that myocardial fibers overlying the tunneled coronary segment cause its compression and sometimes complete obliteration during systole, which may persist into diastole and reduce the early hyperemic diastolic flow.[9,10] Myocardial bridges have been linked to stable or unstable angina pectoris, acute myocardial infarction, complete atrioventricular block, and sudden death.[11–13] It is important to use systematic diagnostic criteria to differentiate between BS and Brugada phenocopies as ECG findings are identical.[14] Low pretest probability of BS was confirmed using symptoms, patient history, and family history.[8] It is to be noted that our patient was an athlete with vigorously active lifestyle, and he reported no medical comorbidities, and there was no history of sudden death or syncope in the family. It is also possible that the critical septal bridging might have occurred due to high levels of physical activity as seen in individuals involved in sports. Additionally, the results of genetic testing were negative for SCN5A and other variants known to be involved in the causation of BS. Hence, it is imperative to consider "Brugada phenocopy" a differential diagnosis in such rare circumstances where patients present with such ECG features in the absence of the other features of BS.

Another point of interest is the potential error of mistaking the Brugada pattern on ECG to be anteroseptal STEMI, as was in our case and in other case report.[15] The patient presented with ecchymoses following thrombolytic therapy. As thrombolytic therapy may lead to potentially serious complications such as intracranial hemorrhage and even mortality, it is important to consider the entity of "Brugada phenocopy" in all patients of anteroseptal STEMI, especially when there are no typical ischemic symptoms, serial ECG changes or positive biomarkers or echocardiographic changes of STEMI.

Conclusion

We report a rare case of Brugada phenocopy ECG due to systolic obliteration of septal artery in an athlete which was mistaken for STEMI and thrombolyzed. It is crucial to recognize BS as well as Brugada phenocopies as differential diagnoses in patients presenting with characteristic ST elevations in leads V1–V3 on ECG. While the entity of BS has captured the attention of the physician community, the entity of the more common "Brugada phenocopies" has not received the requisite attention and needs to be emphasized. Negative genetic testing for channelopathy genes would be emphatic in ruling out BS in those with ECG abnormalities and no other criteria and adding credence to the diagnosis of "Brugada phenocopy." Correct diagnosis of patients presenting with "Brugada phenocopy" on ECG helps prevent the unnecessary and potentially dangerous usage of thrombolytic therapy (mistaking for STEMI) as well as the implementation of unnecessary and expensive strategies like implantable cardiac defibrillator (mistaking for BS).

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CASE REPORT

Perforation of Jejunal Metastasis from Primary Lung Carcinoma with Brain Metastasis: A Rare Case

Ankur D Modi[1*], Chintan Godhani[2], Trupal Desai[3], Jainesh Shah[4], Jitesh Rathod[5]

Received: 04 January 2022; *Accepted:* 20 July 2023

Abstract

A case describes a 49-year-old male patient who underwent emergency exploratory laparotomy for small intestinal perforation. Peritonitis was present due to perforation of the jejunal tumor. Resection of the jejunal tumor with perforation was performed followed by end-to-end anastomosis of the jejunum. The resected jejunal tumor was identified in the histopathological examination as metastatic from a clear cell variant of squamous cell/large cell carcinoma of the lung. It was associated with metastatic lesions in the brain. Metastasis from the lung carcinoma in the jejunum is a very rare condition predisposing to small intestinal perforation which is also associated with brain metastasis.

Journal of the Association of Physicians of India (2024): 10.59556/japi.72.0477

Introduction

Jejunal metastasis from primary carcinoma of the lung is rare.[1] The most common histological types resulting in metastasis are large cell carcinoma, adenocarcinoma, small cell carcinoma, and squamous cell carcinoma.[1] Primary lung carcinomas can metastasize to another lung (50%), liver (37%), adrenal gland (31%), bone (29%), kidneys (18%), and brain (12%) and rarely to the digestive tract (2.8–8.8%).[1] A small intestinal metastatic tumor can present as obstruction, malabsorption, hemorrhage, or perforation.[1]

The majority of the patients are males with a median age of 63 years (range 40–70 years).[2] Among small intestines, jejunum is the most common site of metastasis (79%).[3] When it involves the upper gastrointestinal tract, the most common symptom is bleeding, but when it involves the small intestine, the most common manifestation is intestinal obstruction or perforation.[4] A metastasis to the gastrointestinal tract occurs mainly *via* the hematogenous and lymphatic routes. Such metastatic lesions are more commonly encountered in the advanced stages of the disease and majorities are associated with unfavorable prognosis.[4] When compared with the histological distributions of primary lung cancer, patients with large cell carcinoma exhibited the highest elevated risk of gastrointestinal metastases [relative risk (RR), 4.07].[5]

Brain metastasis in the case of primary lung carcinoma is also rare. The total incidence proportions percentage of brain metastases was 9.6% for all primary sites in combination and highest for lung (19.9%). Its incidence is higher among African Americans.[6]

Case Description

A 49-year-old male presented with a history of generalized abdominal pain for 3 days which was sudden in onset, intermittent, colicky in nature, and was associated with two episodes of vomiting containing food particles. He was having a generalized weakness. He did not have any history of fever, diarrhea, constipation, or urinary complaints. The patient was a known case of ischemic heart disease. His per abdominal examination was suggestive of abdominal distention with generalized abdominal tenderness and signs of peritonitis. Abdominal ultrasound was suggestive of changes of jejunitis with surrounding inflamed fat and echogenic free fluid in the interbowel region with a possibility of hollow viscus perforation. For which an emergency exploratory laparotomy was performed. On exploration, perforation of approximately 1 × 1 cm was found 15 cm distal from the ligament of Treitz over the antimesenteric aspect of the proximal Jejunum. About 3 × 2 cm of submucosal growth was palpable surrounding the perforation (Fig. 1). Rest of the abdomen was found normal. A jejunal growth with perforation was resected with a tumor-free margin of approximately 5 cm on either side and on the mesenteric aspect. The jejuno–jejunal anastomosis was performed (Fig. 2). The abdominal drain was kept and closure was done. Peritoneal fluid was taken and sent for cytology which showed many neutrophils, few lymphocytes, and macrophages in the background of few red blood cells (RBCs). No atypical cells were seen. It was negative for malignant cells.

Chest X-ray was suggestive of a well-defined soft tissue density lesion with a broad base toward the pleura in the right upper lung zone suggestive of neoplastic etiology. So we used high-resolution computed tomography (HRCT) thorax which showed a large well-defined heterogeneous soft tissue

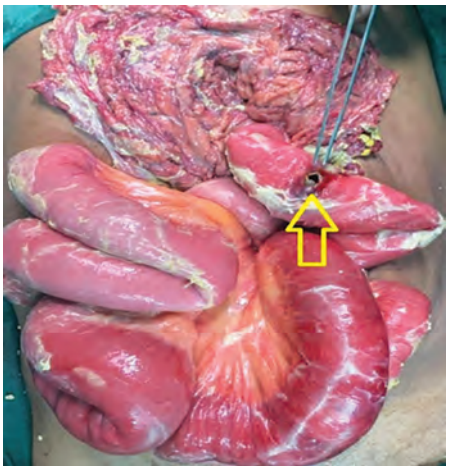

Fig. 1: On exploration, we found perforation of about 1 × 1 cm over the antimesenteric aspect of the proximal jejunum which was about 15 cm distal from the ligament of Treitz. About 3 × 2 cm of submucosal growth was palpable surrounding the perforation

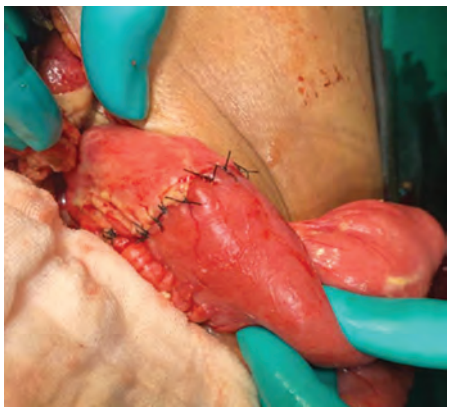

Fig. 2: Jejuno–jejunal anastomosis

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How to cite this article: Modi AD, Godhani C, Desai T, *et al.* Perforation of Jejunal Metastasis from Primary Lung Carcinoma with Brain Metastasis: A Rare Case. J Assoc Physicians India 2024;72(5):106–108.

density mass lesion of approximate size (52 × 63 × 57) mm with few internal calcified foci involving an apical segment of the right upper lobe. It was encasing subsegmental bronchi. Posterolaterally, the lesion invaded the chest wall at the level of the right first, second, third, and fourth ribs with invasion of intercostal muscles and caused lytic erosion of the posterior aspect of the right second and third ribs. Superiorly, the lesion was lying in close relation with the right subclavian vessel with the preserved fat plane. Multiple enlarged lymph nodes were noted in the right upper and lower paratracheal and right hilar region, the largest measuring 15 × 19 mm in the right lower paratracheal region. Left adrenal hypodense lesion of approximate size 33 × 24 mm. Left-sided moderate pleural effusion with a maximum thickness of 38 mm. Right-sided minimal pleural effusion with a thickness of 4 mm was noted. Marked emphysema with multiple bulla formation was noted in bilateral upper lobes (Fig. 3).

A resected specimen was sent for histopathological study. Histopathological findings showed submucosal and muscular layers infiltrated with nests and cords of large polygonal atypical cells with a high N: C ratio, open chromatin, and irregular nuclear membrane at places of prominent nucleoli. The cytoplasm of the cell was clear. These nests of cells were also present in the mucosal layer of the intestine. The presence of necrosis along with degenerated neutrophils in the surroundings was seen which was suggestive of "metastasis in the small intestine with possibility from clear cell variant of squamous cell/large cell carcinoma of lung" (Fig. 4).

Contrast (gadolinium) enhanced magnetic resonance imaging (MRI) of the brain with T1, T2, and flair images were obtained. It showed approximately 72 × 45 × 58 mm well-defined peripherally enhancing altered signal intensity cystic lesion with perilesional edema seen in the right high frontoparietal lobe parafalcine region. The lesion appeared hyperdense on T2W images and dark on T1W and flair images (Fig. 5). No evidence of restriction on the diffuse weighted image was seen. The lesion leads to a mass effect in the form of compression over the right lateral ventricle with a midline shift of approximately 6 mm toward the left side. A few small similar characteristic lesions were seen in bilateral high frontal lobes and the right cerebellar hemisphere. These findings were in favor of metastatic lesions in the brain.

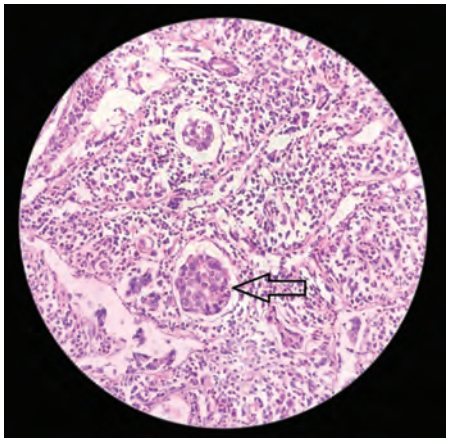

Fig. 4: Hematoxylin and eosin stain shows atypical polygonal cells

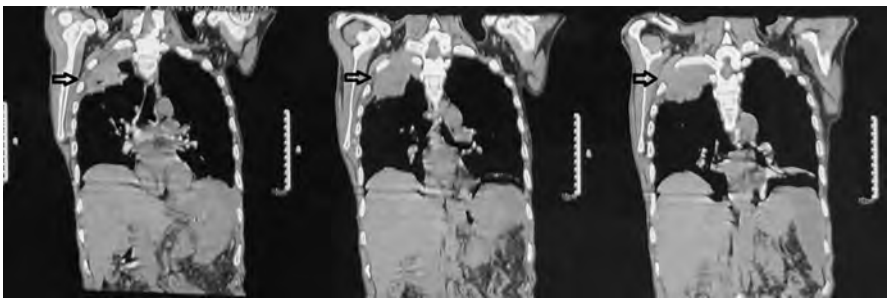

Fig. 3: The HRCT thorax shows a malignant mass lesion involving the apical segment of the right upper lobe causing chest wall invasion

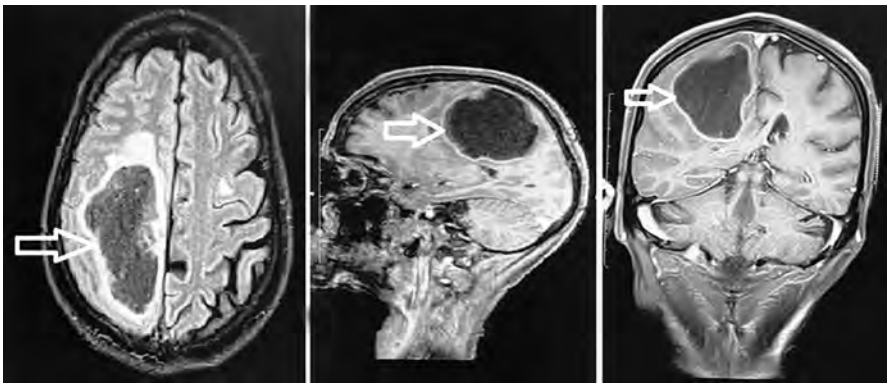

Fig. 5: The MRI of the brain with T1, T2, and flair images were in favor of metastatic lesions in the brain

Discussion

Metastasis to the small intestine from primary lung carcinoma is very rare. Small intestinal metastasis is commonly present with perforation.[7] In small intestinal metastasis, 39% of patients present with large cell lung carcinoma followed by 12.3% with adenocarcinoma, 8% with small cell carcinoma, and 7.5% present with small cell lung carcinoma.[1,7] Jejunum is the most common site of metastasis and the most common presentation is perforation of the small intestinal metastasis with poor prognosis if the patient was undiagnosed or diagnosed with lung carcinoma and had not taken prior treatment for primary lung carcinoma.[1,3,8]

Gastric metastasis is extremely rare (0.2–0.5%) and remains asymptomatic in the early period as it starts from the submucosal layer, and becomes symptomatic in later stages as it causes obstruction, ulceration, perforation, or hemorrhage.[9] Lee et al. reported that the median duration from diagnosis of primary lung carcinoma to gastrointestinal metastasis was 3 months and the average duration from diagnosis of gastrointestinal metastasis to death was 2.8 months.[10] The majority of small bowel metastases that present with acute abdomen cannot be diagnosed until exploratory laparotomy.[10] In small bowel metastases presenting with perforation undergo surgical management, keeping in mind definitive or palliative care. In spite of this, perioperative mortality is very high (22%) with poor prognosis.[1,8,10]

The incidence of brain metastasis is found highest in primary lung carcinoma (19.9%).[6] Cagney et al. reported that among lung carcinomas, lung adenocarcinoma is 26.8%, nonsmall cell lung cancer not otherwise specified is 25.6%, small cell lung cancer is 23.5% and squamous cell carcinoma of the lung is 15.9%.[11] Overall survival (OS) of patients after the diagnosis of brain metastases remains poor due to significant clinical problems.[12]

Matthias et al. reported that in the treatment of brain metastasis due to nonsmall cell lung cancer and anaplastic

lymphoma kinase rearrangements, tyrosine kinase inhibitors (TKIs) like crizotinib, ceritinib, alectinib or brigatinib can be used. The combination therapy of radiotherapy and TKIs or immunotherapy is a promising treatment but it needs validation.[12] Surrounding tissues of brain metastases should be targeted by microscopic total resection with an additional 5 mm margin which improves local control rate.[12]

Conclusion

Small intestinal metastasis from primary lung cancer is a very rare condition in which a patient may present with acute abdomen due to perforation. The prognosis is very poor. Aggressive surgical treatment can provide effective palliation and may improve survival. For brain metastases, the treatment of choice will greatly influence the overall prognosis. The combined modality of treatment will have an improvement in OS.

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Pellagra: Is It Here or is It Rare?

Rahul Kumar[1*], Tanvi Batra[2], Atul Kakar[3]

Received: 01 December 2023; *Accepted:* 03 February 2024

A 36-year-old male presented to the outpatient department (OPD) with a history of nonproductive cough for 2 days, low-grade fever, and sore throat for 1 day. On examination, his vitals were stable; his throat was erythematous and congested. A clinical diagnosis of acute viral pharyngitis was made, and symptomatic treatment was started. Further examination revealed hyperpigmented scaly lesions on the forehead, face, upper chest, and both forearms and hands (Figs 1A to C). The lesions typically involved the sun-exposed areas. On further questioning, the patient gave a history of on and off loose stools for the last 3 months. He was also irritable and had difficulty concentrating on his routine activities. He gave a history of alcohol intake for the last 10 years. A clinical diagnosis of pellagra was made, and the patient was started on B-complex vitamins and referred to de-addiction center. Pellagra was first described by the Spanish physician Gaspar Casal in 1735.[1] The name pellagra was coined by Frapolli in 1771, from the Italian "pelle" for skin and "agra" for rough, describing the roughened appearance of skin resembling sunburn, which is characteristic of this disease.[2] It is a nutritional disease resulting from deficiency of niacin, which manifests as a classical triad of diarrhea, dermatitis, and dementia.[3] It is often seen in a state of poor nutrition, which has reduced with fortification of food, but still sporadic cases appear among alcoholics, homeless, patients suffering from malabsorption (Crohn's disease, bariatric surgery, or anorexia nervosa), carcinoid syndrome, Hartnup disease, and certain drugs (isoniazid, ethionamide, chloramphenicol, 6-mercaptopurine, 5-fluorouracil).[4] The symptoms and skin lesions show rapid improvement with nicotinamide supplementation.

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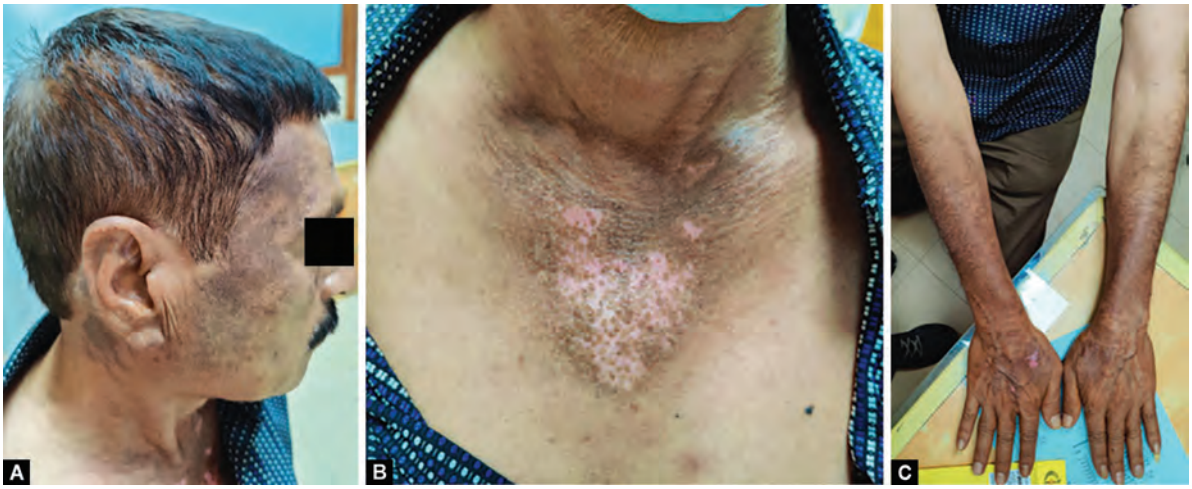
How to cite this article: Kumar R, Batra T, Kakar A. Pellagra: Is It Here or is It Rare? J Assoc Physicians India 2024;72(5):109–109.



Figs 1A to C: (A) Hyperpigmented scaly lesion on the sun-exposed area of the face. (B) Hyperpigmented collar around the neck called the "Casal's collar" with areas of depigmentation. (C) Hyperpigmented lesion in sun-exposed area of both hands and forearms

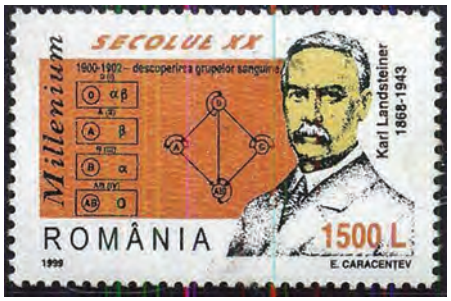
Levaditi: Unknown Immunology Pioneer

J V Pai-Dhungat

Constantine Levaditi; Romania, 1962

Constantin Levaditi (1874–1953) was born in Galați, Romania, and obtained his medical degree from Davila University of Medicine and Pharmacy, Bucharest, where he studied under Victor Babe. He then had training at the College de France in Paris, where he received his MD in 1902, and later, he spent 1 year working with Paul Ehrlich in Frankfurt. He was then accepted by Metnichoff to work in his team at the Pasteur Institute in Paris. Sometime later, Emile Roux, the director of the famous institute, gave Levaditi the opportunity to create an independent laboratory where he had served his entire life. He became head of the laboratory of the Pasteur Institute in 1910 and, in 1926, its chef de service.

The experimental work of Levaditi was multilateral, and it involved cooperation with numerous colleagues. Levaditi studied the epidemiology of poliomyelitis and discovered



Karl Landsteiner and blood groups; Romania, 1999

the presence of the poliovirus in nonnervous tissues with Karl Landsteiner in 1909. His contribution to the epidemiology and eradication of poliomyelitis was of utmost importance. His pioneering experiments formed the scientific basis for the discovery of the relevant vaccines.

This Romanian bacteriologist also dealt with syphilis and was the first to demonstrate the presence of *Treponema pallidum* in a newborn with congenital lues. He is best known for his silver staining method for *T. pallidum* in syphilis (1905), the Levaditi stain. Subsequently, he introduced new serological techniques for the diagnosis of the disease and pioneered syphilis therapy with bismuth and arsenical compounds.

Among other subjects, his long-lasting scientific career includes the study of lethargic encephalitis, recurrent fever, and erythema multiforme.

Constantin Levaditi never gained the fame that his scientific work deserved because of his modesty and his selfless devotion to medical research. In the poliomyelitis research, his name was overshadowed by the relevant work of Landsteiner.

After 1928, he continued his work in Romania where he taught at the University of Medicine and Pharmacy as an honorary member.

Stop poliomyelitis, Nigeria 19**

Postretirement from Pasteur Institute in 1940, he devoted his efforts to the organization against venereal diseases until his death at the age of 79 in 1953.

Many consider him to be one of the most significant European researchers in immunology and virology.

Professor of Medicine (Retired), Department of Medicine, Topiwala National Medical College and Bai Yamunabai Laxman Nair Charitable Hospital; Honorable Physician, Bhatia Hospital, Mumbai, Maharashtra, India

How to cite this article: Pai-Dhungat JV. Levaditi: Unknown Immunology Pioneer. J Assoc Physicians India 2024;72(5):110–110.

The Trend of Using AI Language Models such as ChatGPT in Research and Publication: How to Keep it in Check?

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Dear Editor,

We are writing to you as concerned researchers and contributors to the Journal of the Association of Physicians of India to address an emerging issue in the field of academic publishing—the inclusion of text generated by artificial intelligence (AI) language models such as ChatGPT in scholarly articles. While AI language models can offer valuable insights and assistance, ensuring the authenticity and reliability of the content they produce has become a pressing concern.

The potential for including ChatGPT-generated content in scholarly articles necessitates thoughtful consideration to maintain the integrity of academic discourse. We would like to propose a discussion on strategies to prevent the inclusion of unreliable or misleading content from AI language models such as ChatGPT. By implementing the following measures, we can enhance the transparency and trustworthiness of published articles:

- Disclosure: Authors should transparently disclose the utilization of AI language models such as ChatGPT in the generation of text. This disclosure allows readers and reviewers to understand the origin of the content and assess its validity accordingly.
- Verification and fact-checking: Authors should independently verify and fact-check any information generated by ChatGPT before incorporating it into their articles. External sources, databases, and established research should be used to confirm the accuracy of the information provided.
- Citation and attribution: Proper citation and attribution should be provided for any text generated by ChatGPT. This includes citing the AI language model itself, mentioning the specific version used, and acknowledging the model's contribution to the content.
- Peer review and expert input: Editors should encourage thorough peer review and seek expert opinions when articles include text generated by AI language models. Peers and experts can help identify any potential biases, inaccuracies, or concerns arising from the AI-generated content.
- Ethical considerations: Authors, editors, and reviewers must be mindful of the ethical implications associated with using AI-generated content. Issues such as data privacy, intellectual property rights, and potential biases introduced by AI models should be carefully considered.

By incorporating these strategies, we can work together to prevent the inadvertent inclusion of misleading or unreliable content from AI language models such as ChatGPT in scholarly articles. This will strengthen the credibility and authenticity of the Journal of the Association of Physicians of India and ensure that it remains a trusted source of knowledge in the medical community.

We believe that initiating a dialogue on this topic will greatly benefit the academic community and help establish best practices for handling AI-generated content in the realm of scholarly publishing. We look forward to the thoughtful consideration of these suggestions and the continued pursuit of excellence in academic discourse.

Thank you for your attention to this matter.

Uncommon Localization of Ewing Sarcoma: A Case of Primary Extraskeletal Pleural Involvement

Gursimran Singh Anand[1], Ekta Mishra[2]

[1,2]Junior Resident, Department of Radio-diagnosis, Government Medical College and Hospital, Chandigarh, IndiaUncommon Localization of Ewing Sarcoma

Dear Editor,

An 18-year-old male patient presented to the pulmonary medicine outpatient department with the chief complaints of shortness of breath and chest pain for 3 months with few episodes of massive hemoptysis in the last 1 week. On auscultation of the chest, breath sounds were markedly reduced on the left side.

The patient was referred to the department of radiology for a chest radiograph. The chest radiograph revealed a large homogeneous opacity in the left middle and lower lung zones silhouetting the left mediastinal border, left heart border with obscuration of the left hemidiaphragm and left costophrenic angle (Fig. 1). No significant mediastinal shift was seen on the chest radiograph. A provisional diagnosis of moderate to gross pleural effusion was kept; however, in view of the history of episodes of hemoptysis, the patient was referred for an urgent contrast enhanced computed tomography (CECT) of the chest before attempting a left pleural tap.

Contrast enhanced computed tomography of the chest revealed a large, relatively well-defined, heterogeneously enhancing, pleural based, soft tissue density mass with internal nonenhancing areas of necrosis involving and expanding the left pleural cavity. The mass was seen causing passive collapse and significant volume loss of the left lower lobe and apicoposterior segment of the left upper lobe with abutment of the posterior shafts of the left 5th–9th ribs. No obvious extrapleural infiltration was seen. Moderate associated hypoattenuating pleural effusion was also seen (Figs 2 to 4).

The patient further underwent ultrasound (USG)-guided biopsy of the left pleural cavity mass as well as diagnostic fluid aspiration from pleural effusion. The pleural fluid

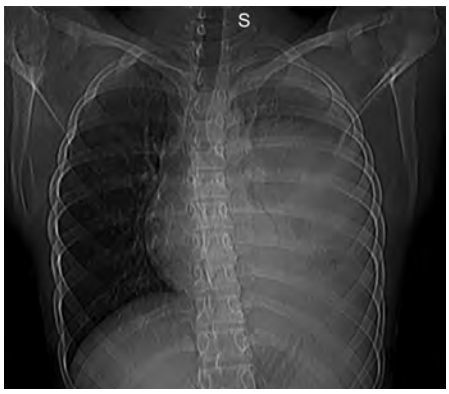

Fig. 1: Chest radiograph shows a large homogeneous opacity in the left middle and lower lung zones

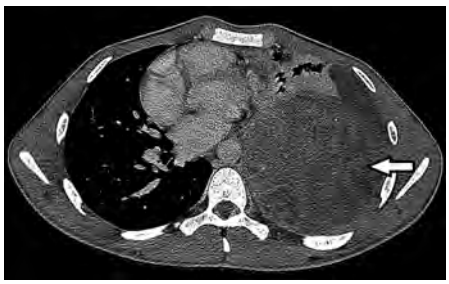

Fig. 2: Axial contrast enhanced section of the chest in mediastinal window shows a large, heterogeneously enhancing soft tissue mass in the left pleural cavity (white arrow)

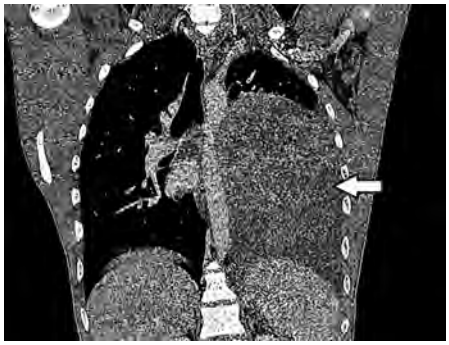

Fig. 3: Coronal contrast enhanced section of the chest in mediastinal window shows a large, heterogeneously enhancing soft tissue mass in the left pleural cavity (white arrow)

aspirate revealed malignant cells on cytology reports.

Histopathological examination revealed an invasive tumor consisting of small round cells arising from the pleura.

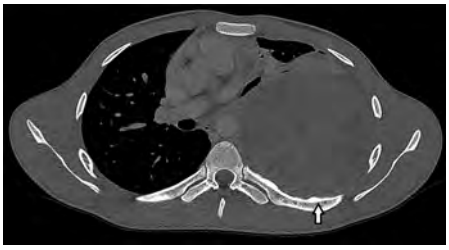

Fig. 4: Axial contrast enhanced section of the chest in bone window shows solid periosteal reaction along the anterior border of the posterior shaft of the left 5th rib (white arrow)

Immunohistochemistry revealed strong and diffuse membranous positivity for CD99; however, it was negative for desmin, vimentin, and leukocyte common antigen, suggesting the diagnosis of extraskeletal Ewing sarcoma (EES).[1–3]

The patient was started on chemotherapy and was planned for radiotherapy followed by surgical resection. However, no follow-up imaging could be done as the patient was lost to follow-up.

Very few cases have been reported about the primary EES presenting as a pleural mass. It is considered to be a highly malignant tumor with a poor prognosis. The diagnosis is difficult and easily misdiagnosed due to the lack of specificity in clinical manifestations and imaging examination.

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API Announcement

Elections of API, ICP and PRF

(Full details circular No. 1 & 2/2024)

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

Governing Body of API:
President-Elect: One; Vice President: One; Hon. General Secretary: One; Elected Members: Six

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

Board of PRF:
Board members: Two
Separate nominations must be submitted for each post.

Requirements for eligibility contest of election to the Governing Body of API

1. **President Elect:** To contest for the post of President Elect the candidate should be a life member of API for at least 10 years and have completed at least two full terms of 3 years each in any elected position in the Governing Body.
2. **Vice President and Hon. General Secretary:** To contest for the post of Vice President and Hon. General Secretary, 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

Board Member: A Member of API for at least 10 years with research experience and having 5 research publications in peer reviewed indexed journals.
The members contesting for the PRF election must attach copies of the Research Papers as mentioned above is mandatory.

Nominations shall be made on prescribed forms stating the office for which nominations are filled. The nominations for API/PRF posts shall be proposed by one valid member and seconded by another valid member of API and duly signed by them and shall also be signed by the candidate 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*:**
i. A member of API for at least 15 years and
ii. A Founder Fellow or a Fellow of the College of 7 year standing and
iii. 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*:**
i. A member of API for at least 12 years and
ii. A Founder Fellow or a Fellow of the College of 5 year standing and
iii. 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 years 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, Hon. General Secretary; Member of the Governing Body) (Dean-Elect; Vice Dean; Joint Secretary HQ 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 2024. 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 2024
Last date for withdrawal	20th June 2024
Last date to receive ballot papers at API Office	31st August 2024

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Hon. General Secretary

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