Editorial
Neurological Consequences of COVID influencing the Outcome: A Two-way Process
p11

Articles
Predictive Value of Frailty Index in Comparison to Traditional Markers of Sepsis in Predicting Mortality among Elderly Admitted in Tertiary Care Hospital
p32

Articles
COVID-19 Antibodies as Predictor of Severe Dengue among Hospitalized Children with Dengue Illness in the Post-third-wave Period of COVID-19 Infection in India
p45

Review Articles
Genetic, Epigenetic, and Molecular Biology of Obesity: From Pathology to Therapeutics the Way Forward
p76

Editor-in-Chief: Prof. Dr. Mangesh Tiwaskar
LET YOUR PATIENTS
WAKE UP TO NEW POSSIBILITIES

RYBELSUS®
semaglutide tablets
A GAME CHANGER. A LIFE CHANGER

THE WORLD’S FIRST AND ONLY
ORAL GLP-1 RA

AVAILABLE NOW

GLP 1 RA:
Glucagon-like peptide-1 receptor agonist.

Reference:

Rybelsus is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

• As monotherapy when metformin is considered inappropriate due to intolerance or contraindications;
• In combination with other medicinal products for the treatment of diabetes.

For healthcare professionals only.

For full prescribing information, refer to package insert.

Rybelsus® and The Apis bull logo are registered trademarks of Novo Nordisk A/S. Please refer to latest summary of product characteristics for more details. For the use of a registered medical practitioner or a hospital or a laboratory only.

To get information on the updated package insert, please contact +91 80 4030 3200 or write to us at INAgree@novonordisk.com.
In Newly Diagnosed Hypertensive Patients,

start with

RX ONCE-A-DAY
Stamlo

Amlodipine 2.5mg/5mg/10mg tab.

leader at heart

In Hypertensive patients (with diabetes)

RX Stamlo-T

Amlodipine 5 mg + Telmisartan 40 mg tabs

Powerful & Consistent BP Control

In Hypertensives with increased sympathetic drive

RX Stamlo Beta

Amlodipine 5 mg + Atenolol 50 mg tablets

Prompt and adequate BP control


GGI-Co-Clear-22-30027813-30027813-JA-C22-0331

Dr. Reddy’s Laboratories Ltd., Global Generics - India,
7-1-27, Ameerpet, Hyderabad - 500 016, India; www.drreddys.com
## Contents

**EDITORIAL**

1. Neurological Consequences of COVID influencing the Outcome: A Two-way Process
   Mugundhan Krishnan ................................................................. 11

**ORIGINAL ARTICLE**

2. Neurological Manifestations and Their Effect on Outcome in Second Wave of COVID-19 Pandemic: A Retrospective Cohort Study
   Arti Muley, Sona Mitra, Hema Bhajani, Ashish Bavishi, Dinesh Nakum, Priya Kotwani, Vaibhav Patwardhan, Jahnvi Shah, Shourya Mahendra ... 14

3. Establishment of SMS Dengue Severity Score
   Sudhir Bhandari, Govind Rankanaw, Barkha Goyal, Anurag Lohmror, Vishal Gupta, Ajeet Singh ............................................................. 19

4. Assessment of Visceral Fat Volume and Its Correlation with the Severity of Hepatic Fibrosis in Patients with NAFLD
   Jijo Varghese, Krishnadas Devadas, Rathan Cyrac Joseph, Tharan Tom Oommen, Atul Hareendran, Nibin Nahaz, Vijay Narayan, Bony George ................................................................. 23

5. Kidney Disease Patterns diagnosed by Kidney Biopsy: A Single-center Experience from Central India
   Ritesh Kumar Banode, Piyush Kimmaktar, Charulata Bawankule, Vandana Adamanane, Vishal Ramteke. ...................................................... 25

6. Predictive Value of Frailty Index in Comparison to Traditional Markers of Sepsis in Predicting Mortality among Elderly Admitted in Tertiary Care Hospital
   Ashwariya Muridhadan, Minakshi Dhar, Monika Pathania, Mayank Agarwal, Prativa P Sethi, Vartika Saxena, Nowmeet K Bhat ................................................................. 32

   Ritu Karoli, Sanjay Kumar Bhat, Rohit Srivastava, Anupma Kaul ...................................................... 38

8. COVID-19 Antibodies as Predictor of Severe Dengue among Hospitalized Children with Dengue Illness in the Post-third-wave Period of COVID-19 Infection in India
   Sangeeatha Balasubramanion, Varadaraj Govindaraj, Ritu Agarwal, Amit Pathania, Atul Vij ................................................................. 45

9. Effect of 4-day Online Breath Meditation Workshop on Ballistocardiography-based Sleep and Cardiac Health Assessments among Medical Professionals of a Tertiary Care Hospital in North India during COVID-19
   Monika Pathania, Praag Bhardwaj, Yogesh Arvind Bahurupi, Vyas Kumar Rathaur ................................................................. 49

10. Effects of Intermittent Fasting on Weight Loss in Asian Indian Adults with Obesity
    Sheryl Salis, Syed Shefa, Nitika Sharma, Natasha Vora, Ranjit Mohan Anjana, Viswanathan Mohan, Harish Ranjani ...................................................... 62

**UPDATE ARTICLE**

11. Unmet Need for Further LDL-C Lowering in India despite Statin Therapy: Lipid Association of India Recommendations for the Use of Bempedoic Acid

**REVIEW ARTICLE**

12. Genetic, Epigenetic, and Molecular Biology of Obesity: From Pathology to Therapeutics the Way Forward
    Suranjana Banik, Mainak Bardhan, Suranjana Basak ...................................................... 76

**CASE REPORT**

13. Burkitt’s Lymphoma with an Unusual Cardiac Involvement: A Case Report
    Soham Bhaumik, Nilay Kumar Chatterjee, Mohammad Abul Masud Reza, Arijit Sinha ...................................................... 85

14. Seronegative Autoimmune Limbic Encephalitis: A Case Report
    Deepali Aendole, Jimmy Lalkaka, Jui Jade, Bhim Singh ...................................................... 88

**PICTORIAL CME**

15. Bilateral Calcification of the Vas Deferens and the Seminal Vesicles in a Patient with End-stage Renal Disease
    Ankur Gupta, Mohan Biyani ...................................................... 90

16. Isolated Renal Echinococcosis: A Rare Clinical Entity
    Kamal Gera, Sanjeev Kapoor ...................................................... 92

**MEDICAL PHILATELY**

17. Severo Ochoa and Test Tube RNA
    J V Pai-Dhungat ...................................................... 94

**CORRESPONDENCE**

18. Sudden Blindness in a Victim of Snake Bite
    Rudrajit Paul, Indranil Thakur, Asutosh Ghosh, Manotosh Sutrathar, Subinay Chhaule, Rathindranath Sarkar ...................................................... 97

    Sowmini PR, Mugundhan K, Rajesh Shankar Iyer ...................................................... 95

20. Increasing Melioidosis Cases in India
    Prasanta Raghab Mohapatra ...................................................... 97

21. Is Rivaroxaban Superior to Enoxaparin for Thromboprophylaxis in Hospitalized Patients of COVID-19?
    Kunal Deokar, Meul Kalyia, Karan Vachhani, Sanjay Singhal, Aneri Parekh ...................................................... 99

22. Cascade of Drug Toxicities: A Challenging Case of Tuberculosis and Drug Rash with Eosinophilia and Systemic Symptoms
    Parul Kodan, Nitin Gupta, Himanshu Naranag, Abhishek Singh, Farhan Fazal, Wasiq Khat, Manish Soneja, Ashutosh Biswas, Nawet Wig ...................................................... 97

23. Prescribing, Patient Counselling, and Documentation: A Simple Strategy for Improved Patient Outcomes
    Shambho S Samajdar, Santanu K Tripathi, Jyotirmoy Pol, Sougata Sarkar .... 99

**ANNOUNCEMENTS**

24. Obituary ...................................................... 12

25. Going Green ...................................................... 36

26. Update Mobile Number / Email Id ...................................................... 82

27. Association of Physicians of India, Tripura State Branch ...................................................... 87
CARDIOVIT® AT-102 G2

Easy, Smart and State-of-the-Art

- High resolution 8” colour display
- Touch function keys
- Easy-to-clean sealed alphanumeric keyboard
- More than 8 hours battery capacity with ECG printout
- Resting rhythm up to 10 minutes
- Hook-up adviser with colour-coded waveforms and anatomical model

For enquiries contact: sales@schillerindia.com | Website: www.schillerindia.com | Toll-Free No.: 1-800-2098998
Swiss H.Q.: SCHILLER AG, Altgasse 68, P. O. Box 1052, CH - 6341 Baar, Switzerland.
Indian Corporate Office: SCHILLER Healthcare India Pvt. Ltd., Advance House, Makwana Rd, Off. Andheri Kurla Road, Marol, Naka Metro Station, Andheri (East), Mumbai - 400 059.
Tel.: + 91- 022-283280310, +91-22 61523333/ 29209141 | Fax: +91-22-25209142
Factory: No. 15/S & 15/6, Vazhuthavur Road, Kurumbapet, Puducherry 605009

All registered trademarks acknowledged.
Editorial Board (2022-2023)

Emeritus Editors  
VR Joshi • Shashank R Joshi

Editor-in-Chief  
Mangesh Tiwaskar

Executive Editor  
Milind Y Nadkar

Associate Editors  
Gurpreet Singh Wander • Amit Saraf • Anupam Prakash Vikram Londhey

Assistant Editors  
Jyotirmoy Pal • Amar Pazare • Nihar Mehta
R Rajasekar

Members  
Banshi Saboo • V Palaniappan • Trupti Trivedi
Narayan Deogaonkar • Shobha Itolikar

Ex-Officio  
Shyam Sunder • Agam C Vora

Jt. Secretary  
Rakesh Badade

Advisory Board (2022-23)

Philip Abraham • Ameya Joshi
VK Arora • Sanjay Kalra
S Arulraj • Mala Kaneria
Smrat Bajpai • Nitin Karnik
Nikhil Balankhe • NK Karnik
Tushar Bandgar • SV Khadilkar
D Behera • Umesh Khanna
Ashit M Bhagwati • Uday Khopkar
Sudhir Bhandari • Parvez Koul
Abhay Bhave • SV Kulkarni
Sekhar Chakraborty • Virnda Kulkarni
Drhuv Chaudhry • Charulata V Londhey
MPS Chawla • Anuj Maheshwari
M Chenniappan • Sanjiv Maheshwari
RM Chhabra • Tanuja Manohar
Dwijen Das • Girish Mathur
Alaka Deshpande • Ketan K Mehta
PK Deshpande • Sudhir Mehta
Raja Dhar • AP Misra
Suhas Erande • Minal Mohit
SB Ganguly • JK Mokta
Liyakat Ali Gauri • K Mugundhan
Soumitra Ghosh • VP Munjal
Sujoy Ghosh • A Muruganathan
Udas Chandra Ghosh • Vasant Nagwekar
Nithya Gogtay • SN Narasingan
Yojana Gokhale • G Narsimulu
Virender Kr Goyal • CL Nawal
Rohini Handa • Benny Negalur
DK Hazra • Vijay Negalur
Manish Itolikar • Shailesh Palekar
Bhavin Jankharia • Jayant Kr Panda
SK Jindal • Ghanshyam Pangtey
Vijay Panikar • KK Pareek
Falguni Parikh • Deepak Patkar
Aniruddha Phadke • Munish Prabhatkar
Munish Prabhatkar • YSN Raju
Neelam N Redkar • BB Rewari
Minal Kanti Roy • Manisha Sahay
Rakesh Sahay • Santosh Salagre
Manoj Saluja • SK Sarin
RN Sarkar • Vinayak Sawardekar
PS Shankar • Aman Sharma
Aman Sharma • OP Sharma
Akash Shingada • Archana Sonawale
RR Singh • Ashok Taneja
Pratibha Singhal • Kamlesh Tewary
Rajeev Soman • BB Thakur
Archana Sonawale • Urmila Thatte
Prema Varthakavi • Vijay Viswanathan

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.

Copyright and Photocopying
No part of this publication may be reproduced, or transmitted in any form or by any means, electronic or mechanical, including photocopy without written permission from the Hon. Editor.

Business Correspondence
Enquiries concerning subscription, advertisement, etc. should be addressed to Prof. Dr. Mangesh Tiwaskar, Editor-in-Chief, JAPI, No. 006 & 007, Turf Estate, Dr. E. Moses Road, Opp. Shakti Mill Compound, Mahalaxmi (West), Mumbai-400 011.
Tel.: (022) 6666 3224, 2491 2218
Tel./Fax: 2492 0263
e-mail: onlinejapi@gmail.com/mangesh.japi@gmail.com

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

Advertorial Enquiry:
Prof. Dr. Mangesh Tiwaskar, Editor-in-Chief, JAPI, No. 006 & 007, Turf Estate, Dr. E. Moses Road, Opp. Shakti Mill Compound, Mahalaxmi (West), Mumbai-400 011.
Tel.: (022) 6666 3224, 2491 2218
Mobile: 77381 85750
e-mail: onlinejapi@gmail.com/mangesh.japi@gmail.com

Jaypee Brothers Medical Publishers (P) Ltd.
New Delhi

JAPI App: myJAPI
www.japi.org
### Association of Physicians of India

**GOVERNING BODY (2022-2023)**

<table>
<thead>
<tr>
<th>President Elect</th>
<th>President</th>
<th>Past President</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girish Mathur (Kota) (2023)</td>
<td>Shyam Sundar (Varanasi) (2023)</td>
<td>Kamlesh Tewary (Muzaffarpur) (2023)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vice Presidents</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP Misra (New Delhi) (2024)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hon. General Secretary</th>
<th>Jt. Secretary (HQ)</th>
<th>Hon. Treasurer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agam C Vora (Mumbai) (2025)</td>
<td>Ashit M Bhagwati (Mumbai) (2025)</td>
<td>Charu K Jani (Mumbai) (2023)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Members</th>
</tr>
</thead>
<tbody>
<tr>
<td>Munish Prabhakar (Gurgaon) (2024)</td>
</tr>
<tr>
<td>S Sreenivasa Kamath (Kochi) (2024)</td>
</tr>
<tr>
<td>Narayan Deogaonkar (Nashik) (2024)</td>
</tr>
<tr>
<td>Sekhar Chakraborty (Siliguri) (2024)</td>
</tr>
<tr>
<td>DP Singh (Bhagalpur) (2024)</td>
</tr>
<tr>
<td>Amit Varma (Dehradun) (2024)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Zonal Members</th>
</tr>
</thead>
<tbody>
<tr>
<td>North Zone: Atul Bhasin (New Delhi) (2023)</td>
</tr>
<tr>
<td>North West Zone: Ashok K Taneja (Gurugram) (2023)</td>
</tr>
<tr>
<td>Central Zone: GD Ramchandani (Kota) (2023)</td>
</tr>
<tr>
<td>West Zone: Amit A Saraf (Thane) (2023)</td>
</tr>
<tr>
<td>Mid South Zone: Ravikeerthy M (Bangalore) (2023)</td>
</tr>
<tr>
<td>South Zone: S Chandrashekar (Chennai) (2023)</td>
</tr>
<tr>
<td>East Zone: Jayanta Kumar Panda (Cuttack) (2023)</td>
</tr>
<tr>
<td>Ex-Officio Member: Dean, ICP</td>
</tr>
<tr>
<td>Co-opted Members: Jt. Secretary (President's place)</td>
</tr>
<tr>
<td>Editor-in-Chief, API Text Book</td>
</tr>
<tr>
<td>Dean Deshpande (Mumbai) (2023)</td>
</tr>
<tr>
<td>Director, PRF</td>
</tr>
<tr>
<td>Gurpreet Singh Wander (Ludhiana)</td>
</tr>
<tr>
<td>Armed Forces, Medical Services</td>
</tr>
<tr>
<td>Elected Members</td>
</tr>
<tr>
<td>Prakash Keswani (Jaipur) (2023)</td>
</tr>
<tr>
<td>K Mugundhan (Chennai) (2023)</td>
</tr>
<tr>
<td>Udai Lal (Hyderabad) (2023)</td>
</tr>
<tr>
<td>Narinder Pal Singh (New Delhi) (2023)</td>
</tr>
<tr>
<td>MPS Chawla (New Delhi) (2024)</td>
</tr>
<tr>
<td>Soumitra Ghosh (Kolkata) (2024)</td>
</tr>
<tr>
<td>Sanjeev Maheshwari (Ajmer) (2024)</td>
</tr>
<tr>
<td>R Rajasekhar (Kumbakonam) (2024)</td>
</tr>
<tr>
<td>Ghanshyam Pangtey (New Delhi) (2025)</td>
</tr>
<tr>
<td>Hem Shankar Sharma (Bhagalpur) (2025)</td>
</tr>
<tr>
<td>Ashish Kumar Saha (Kolkata) (2025)</td>
</tr>
<tr>
<td>SV Kulkarni (Raigad) (2025)</td>
</tr>
</tbody>
</table>

### Indian College of Physicians

**FACULTY COUNCIL (2022-2023)**

<table>
<thead>
<tr>
<th>Chairman</th>
<th>Dean</th>
<th>Dean Elect</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Vice Deans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silbendu Kumar Ghosh (Kolkata) (2023)</td>
</tr>
<tr>
<td>Y Satyanarayana Raju (Hyderabad) (2024)</td>
</tr>
<tr>
<td>BB Rewari (New Delhi) (2025)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Jt. Secretary (H.Q.)</th>
<th>Jt. Secretary (Dean's place)</th>
<th>Hon. Treasurer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashit M Bhagwati (Mumbai) (2025)</td>
<td>Rakesh Bhadade (Mumbai) (2023)</td>
<td>Charu K Jani (Mumbai) (2023)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ex-Officio Members</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dean Deshpande (Mumbai) (2023)</td>
</tr>
<tr>
<td>Director - PRF</td>
</tr>
<tr>
<td>Gurpreet Singh Wander (Ludhiana)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Elected Members</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prakash Keswani (Jaipur) (2023)</td>
</tr>
<tr>
<td>K Mugundhan (Chennai) (2023)</td>
</tr>
<tr>
<td>Udai Lal (Hyderabad) (2023)</td>
</tr>
<tr>
<td>Narinder Pal Singh (New Delhi) (2023)</td>
</tr>
<tr>
<td>MPS Chawla (New Delhi) (2024)</td>
</tr>
<tr>
<td>Soumitra Ghosh (Kolkata) (2024)</td>
</tr>
<tr>
<td>Sanjeev Maheshwari (Ajmer) (2024)</td>
</tr>
<tr>
<td>R Rajasekhar (Kumbakonam) (2024)</td>
</tr>
<tr>
<td>Ghanshyam Pangtey (New Delhi) (2025)</td>
</tr>
<tr>
<td>Hem Shankar Sharma (Bhagalpur) (2025)</td>
</tr>
<tr>
<td>Ashish Kumar Saha (Kolkata) (2025)</td>
</tr>
<tr>
<td>SV Kulkarni (Raigad) (2025)</td>
</tr>
</tbody>
</table>

### Physicians Research Foundation

**BOARD OF DIRECTORS (2022-2023)**

<table>
<thead>
<tr>
<th>Chairman</th>
<th>Director</th>
<th>Past Director</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shyam Sundar (Varanasi) (2023)</td>
<td>GS Wander (Ludhiana) (2025)</td>
<td>YP Munjal (Gurugram) (2023)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hon. General Secretary</th>
<th>Jt. Secretary (Director's Place)</th>
<th>Hon. Treasurer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agam C Vora (Mumbai) (2025)</td>
<td>Rajender Bansal (Ludhiana)(2025)</td>
<td>Charu K Jani (Mumbai) (2023)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Members</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM Mehndiratta (New Delhi) (2024)</td>
</tr>
<tr>
<td>Satyabrata Ganguly (Kolkata) (2024)</td>
</tr>
<tr>
<td>Sandeep Garg (New Delhi) (2025)</td>
</tr>
<tr>
<td>Sudhir Mehta (Jaipur) (2025)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Invited Members</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dean, ICP</td>
</tr>
<tr>
<td>Dean Deshpande (Mumbai)</td>
</tr>
<tr>
<td>GS Wander (Ludhiana)</td>
</tr>
<tr>
<td>Editor-in-chief, API Text Book</td>
</tr>
<tr>
<td>Shashank R Joshi (Mumbai)</td>
</tr>
</tbody>
</table>
Rx in Anaemia associated with

- Pregnancy & Lactation
- Menorrhagia
- Nutritional & Iron Deficiency
- Chronic Gastrointestinal Blood Loss
- General Weakness
- Chemotherapy-induced anaemia
- Lack of Appetite
- Chronic Kidney Disease
In T2DM patients inadequately controlled on metformin,

**Vylda-D**

Vildagliptin 100 mg Sustained Release + Dapagliflozin 5/10 mg Tablets

**Double action for better control**

- Every alternate patient achieves ADA target of HbA1c <7%
- Similar Efficacy (HbA1C, FPG and PPG) as FDC of Saxagliptin and Dapagliflozin Combination

Reference: Phase II CLINICAL study report Interim Analysis (8 Week Study Report). Data on file

---

In the management of T2DM

**Dapagza**

Dapagliflozin 5/10mg

**Control the surge of Hyperglycemia**

- Offers Significant Glycemic Control with Weight Reduction


---

For any medical query, please write to us on emqust@emcure.co.in | To report any adverse event or product complaint, please write to Safety.IN@emcure.co.in

Emcure Pharmaceuticals Ltd.
Survey No. 255/2, Phase-4, M.I.D.C., Hinjewadi, Pune - 411057 • Tel: +91 20 30821000 • Website: www.emcure.com

Facebook: /emcurepharmaceutical • Twitter: /emcurepharma • Instagram: /emcurepharma
Neurological Consequences of COVID influencing the Outcome: A Two-way Process

Mugundhan Krishnan

The primary manifestations of COVID-19 are predominantly respiratory in nature, but they can also affect the nervous system. Neurological complications are most frequently reported in critically ill patients with comorbidities. They range from headache, myalgia, anosmia, ageusia, and dizziness to severe neurological manifestations like stroke, myelitis, encephalitis, acute necrotizing hemorrhagic encephalitis, and Guillain–Barré syndrome.

In severe COVID-19, systemic complications like sepsis, hypoxia, respiratory and metabolic acidosis, hypercoagulable states, and disseminated intravascular coagulation are mostly responsible for many of the clinical manifestations, including neurological. Neurological presentations can also be due to prolonged stays in the intensive care unit (ICU) and drug toxicities. But it is not always a one-way process. The neurological complications can also in turn affect the morbidity and mortality in COVID, by its influence on other systems.

There are various routes by which severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is found to infiltrate the central nervous system (CNS), including the olfactory route, the trans-synaptic route, the leukocytic route, and the hemogenetic route. Other possible routes of invasion are via infection of the gastrointestinal tract as well as the vagus nerve. Angiotensin-converting enzyme 2 (ACE2) receptors which are present on endothelial cells of cerebral vasculature act as entry points for the virus.

Various explanations are put forth to throw light on how neurological manifestations and complications affect the severity of COVID.

- Respiratory failure in COVID-19 is explained by impaired spontaneous breathing due to neurological impairment from CNS involvement. This may be caused by the migration of SARS-CoV-2 trans-synaptically from the lungs and nasal epithelium to the medullary cardiorespiratory center, by means of the peripheral nervous system from the lungs and through the cribiform plate from the nasal epithelium.

- Angiotensin-converting enzyme 2, the cell surface receptor for SARS-CoV-2, is located in the rostral ventrolateral medulla (RVLM) and attenuates tonically active glutamatergic input. Its depletion by SARS-CoV-2 would cause overactivity of angiotensin in the RVLM, activating the sympathetic nervous system, increasing blood pressure, causing systemic vasoconstriction, pulmonary capillary leakage, acute respiratory distress syndrome from fluid in the alveoli, and also cardiac failure.

- Guillain–Barré syndrome, occurring as a parainfectious complication of COVID, can lead to respiratory failure by causing upper airway compromise and weakness of pharyngeal and laryngeal muscles leading to difficulty in the clearing of secretions and airway maintenance, thereby also increasing the chances of aspiration. The weakness of inspiratory and expiratory muscles of respiration leads to poor lung compliance, microatelectasis, hypoxemia, and increased risk of infections due to poor coughing ability.

The three abovesaid effects showing the influence of neurological complications on the respiratory system have also been proven by this study by Muley et al., where it was clearly concluded that the need for noninvasive and invasive ventilation was higher in patients with neurological complications.

- Critical illness polyneuropathy (CIN) and critical illness myopathy (CIM) will pose a problem while weaning the COVID patients off the ventilator. CIN and CIM are important to identify since survivors often present with severe residual disability and persistent exercise limitations several years afterward. CIM has a slower or incomplete recovery, and higher mortality rate, whereas patients with CIM often show complete recovery within 6 months. During the acute phase of severe COVID-19 infection, most medical attention is generally assigned to critical care management, and neuromuscular complications such as ICU-acquired weakness and peripheral nerve injuries could be underestimated. When starting post-ICU care for COVID-19 cases, the combination of electrophysiological and imaging studies will be beneficial for evaluating the neuromuscular condition of the patients and help start appropriate interventions.

In this study also, the duration of hospitalization was prolonged in patients with neurological complications, which would thus create a vicious cycle, where the prolonged ICU stay worsens the neurological condition, and the worsened neurological condition, in turn, causes hospital stay to be prolonged.

- Neurological complications like stroke, encephalopathy, and seizures can directly influence mortality and morbidity in COVID patients. These are associated with a higher risk of any infections, particularly of respiratory tract and urogenital tract, which might further worsen the outcome of COVID infection. Stroke has been confirmed to increase the risk of pulmonary complications like pneumonia, and other thrombotic phenomena like deep venous system thrombosis which could lead to the fatal outcome of COVID-19 patients.

This has got an implication during the COVID pandemic, as the delay in diagnosis and transport, and the reduced availability of thrombolytic therapy will cause the cerebrovascular accident to be more severe and hence worsen the prognosis.

- In CNS, the leukocytes produce proinflammatory cytokines such as TNF which can damage neurons and/or oligodendrocytes, and chemokines like CCL5, CXCL10, and CXCL11 which can induce chemotraction of activated T cells and/or other leukocytes. After sensing the infection, astrocytes will also produce chemokines, including CCL2, CCL5, and CXCL12, which participate in the further recruitment of more infected leukocytes. SARS-CoV-2 might, hence, initiate an aberrant neuroinflammatory response.

© The Author(s). 2022 Open Access. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by-nc/4.0/). Please refer to the link for more details.
Neurological Consequences of COVID influencing the Outcome: A Two-way Process

loop, which can result in neuropathological damage as well as systemic damage, involving other systems.6

Hence, there is enough evidence and hypotheses to come to a clear understanding that not only respiratory and other systemic complications will lead to neurological manifestations and complications, but also the reverse holds good. Neurological complications, therefore, definitely have a strong influence over the outcome of COVID infection, which is established in this study by Muley et al.

In this study, the severity of COVID disease is well defined based on the Indian Council of Medical Research (ICMR) criteria, and the grading is done accordingly. Definitions for the neurological complications considered in the study were clearly made. No difference was found between the parameters considered in patients with and without neurological symptoms, with regard to the presence or absence of any comorbidity. This emphasizes the fact that neurological manifestations by themselves have got a crucial role in influencing the outcome in COVID patients.

As both the acute and postacute disease burdens of COVID-19 continue to increase, there is an urgent need to better understand the contribution of all factors that influence the course of the disease and how they contribute to CNS complications. Much remains to be explored about the underlying mechanisms leading to SARS-CoV-2-induced neuropathology. Last but not least, raising awareness of the damaging effect of SARS-CoV-2 infection and also on the importance of early neurological management of patients with COVID-19 should be encouraged, as it has a bearing over the outcome. The study also opens the way to follow up with the patients who had survived, to look for the post-COVID neuropsychiatric features, and to establish a relationship between the occurrence of such symptoms and the severity of COVID infection with which they had been hospitalized in the past.

References

Obituary

Dr Ramachandra Dattatraya Lele
(16 January 1928–24 June 2022)
A physician—who pursued excellence

Ramachandra Dattatraya Lele (16 January 1928–24 June 2022) an astute brilliant clinician, great physician, dedicated teacher of teachers, medical researcher, a philosopher, an administrator par excellence, true internist. He was widely known as Pioneer of Nuclear Medicine in India. A stalwart all round personality.

Born in Hyderabad in a middle class Maharashtrian family, pursued his medical education, worked in rural Marathwada and studied further in the United Kingdom. After returning to the motherland, his passion as a teacher and a true disciple of Goddess Saraswati, he adopted the teaching profession. All his students from Aurangabad, Nagpur, Mumbai still recall the memories of his wonderful entertaining teaching.

He was very futuristic and established the Department of Nuclear Medicine at Jaslok Hospital Research Centre in Mumbai and first in India. He had the ability to single-mindedly pursue a new idea, conducted clinical studies, lobbied for policies and pushed the idea at a time when no one knew its value. Today it plays an important and big role in the diagnosis and treatment in clinical medicine. He had a wide intellectual sweep, a curious mind, and an original thinker.

Milestones of his varied intellectual journey are the 13 books he authored covering an astoundingly wide range of topics. On subjects like ayurveda, homeopathy, medical profession and law and rural reconstruction. In 1988 with his book—Computers in Medicine, he displayed foresight to futuristic medicine that speaks of a certain vision well ahead of its times. His last book he wrote in 2021 was History of Medicine in India at the age of 93 years. Bestowed with Padma Bhushan by the President of India in 1992, the third-highest civilian honor in India. His other accolades include - in 1990: Distinguished Community Service Award (from the Rotary Club). 1991: 1st recipient of Gifted Teacher Award (from the Association of Physicians of India (this was very dear to him than his other accolades), 1997: Dhanvantari Award (from the Governor of Maharashtra State), 2000: Honorary Doctor of Science degree (from the NTR University of Health Sciences and Andhra Pradesh), 2008: Homi Bhabha Lifetime Achievement Award (from the Indian Nuclear Society), and 2011: Prof. M. Viswanathan National Award for Medical Teaching and Medical Care.

His autobiography, ‘Pursuit of Excellence’ was published in 2017, which is like another textbook of medicine with many personal touches for every medical professional in the world.

We all pay a humble salute to a clinical giant on behalf of all physicians of India. An era ended with him, our most humbled bows to the teacher of teachers

To sir with love, regards and respects

SV Kulkarni, Shashank R Joshi
In the management of Heart Failure and T2DM with multiple CV risk factors

Emil

EmilDap

Dapagliflozin 5mg/10mg Tablets

Empower Heart

In Hypertension associated with CHF — Post MI

METPURE-TEL

S(+)Metoprolol PR 25 mg & Telmisartan 20/40 mg Tablets

Controls Hypertension, Ensures Cardiac PROTECTION

In Hypertension with Diabetes,

Temsan-AM

Telmisartan 40 mg & S(+)Amlodipine 2.5/5 mg Tablets

Swift BP Reduction, Assured Control

For any medical query, please write to us on emquest@emcure.co.in | To report any adverse event or product complaint, please write to Safety.M@emcure.co.in

Emcure Pharmaceuticals Ltd.
Survey No. 255/2, Phase-I, M.I.D.C., Hinjewadi, Pune - 411057 • Tel: +91 20 39821000 • Website: www.emcure.com

/EmcurePharmaOfficial /Emcurepharma /Emcurepharma
Neurological Manifestations and Their Effect on Outcome in Second Wave of COVID-19 Pandemic: A Retrospective Cohort Study

Arti Muley1, Sona Mitra2, Hema Bhojani3, Ashish Bavishi4, Dinesh Nakum5, Priya Kotwani6, Vaibhav Patwardhan7, Jahnavi Shah8, Shourya Mahendru9

Received: 24 January 2022; Revised: 16 June 2022; Accepted: 27 June 2022

ABSTRACT

Aim: There is a need for a better understanding of the relation of various neurological symptoms and complications with outcomes of coronavirus disease 2019 (COVID-19). Hence, we planned this study to get an insight into the relation of neurological manifestations and COVID-19.

Materials and methods: This was a retrospective study. All patients ≥18 years in age, admitted with reverse transcription-polymerase chain reaction (RT-PCR) confirmed COVID-19 were included in the study. Their clinical records were accessed for collecting demographic and laboratory data. The data collected were analyzed for prevalence and pattern of neurological symptoms at admission and neurological complications developed during hospitalization. It was also analyzed to find the relation of neurological manifestations with duration of hospital stay, requirement of bilevel positive airway pressure (BiPAP) or ventilator, severity of disease, development of neurological complications, and mortality.

Results: A total of 440 patients were included. The mean age was 59.28 ± 13.28 years. The most common neurological symptom at presentation was headache while the most common neurological complications were altered sensorium, cerebrovascular stroke, seizure, and encephalitis. Significantly, more patients with neurological complications than those without had severe disease and needed ventilation. Duration of hospitalization was significantly longer (16.26 ± 5.15 vs 12.73 ± 4.89, p = 0.0173) and mortality was also significantly higher (OR 6.59, 95% CI 2.23–19.43; p = 0.0006) in patients with neurological manifestations.

Conclusion: The presence of neurological manifestations is associated with greater morbidity and mortality in patients with COVID-19 and thus warrants more aggressive treatment. However, a study of association of individual neurological manifestation with severity of COVID-19 will provide a more meaningful insight regarding the approach to the management of such patients.

INTRODUCTION

The outbreak of COVID-19 began in Wuhan, Hubei Province in December 2019 and rapidly spread throughout the world. It is caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is similar to the zoonotic SARS-CoV from 2002 and the Middle East respiratory syndrome coronavirus (MERS-CoV) from 2012. On 11th March 2020, the World Health Organization declared COVID-19 as a global pandemic.

The initial clinical descriptions of COVID-19 have given evidence of potential neurologic involvement in SARS-CoV-2, manifested by symptoms such as anosmia, dysgeusia, muscle pain, and headache during the early course of the disease. These neurologic symptoms have led to many hypotheses on how the virus reaches the nervous system, including its potential entry via the olfactory groove or the bloodstream. It has been suggested that like other coronaviruses, COVID-19 may also infect the nervous system and skeletal muscle since they have angiotensin-converting enzyme 2 (ACE-2) receptors as in the respiratory system. It has also been hypothesized that acute respiratory failure seen in COVID patients may be due to neuroinvasion by the virus.

Critically ill patients with severe COVID infections often have elevated D-dimer levels and severe thrombocytopenia, which make them prone to acute cerebrovascular events. Moreover, many neurological diseases [multiple sclerosis, Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and myasthenia gravis] have immunological pathogenesis and might be exacerbated or triggered by COVID. Many factors like delay in diagnosis, transport to hospitals, decreased thrombolytic and thrombectomy treatments, and proinflammatory and prothrombotic status in stroke patients with COVID may also worsen the prognosis.

All these observations point toward the necessity of a better understanding of the relation of various neurological symptoms and complications with manifestations and outcomes of COVID-19. Hence, we planned this study to investigate the occurrence of neurological manifestations in patients with COVID-19 and their relation.

MATERIALS AND METHODS

This was a retrospective study conducted at a tertiary care hospital in Gujarat from 1st May 2021 to 31st May 2021 in patients diagnosed with COVID-19 disease. It was conducted after getting approval from the Institutional Ethics Committee.

All patients ≥18 years in age who were admitted with RT-PCR confirmed COVID-19 disease were enrolled in the study. Their clinical records were accessed for collecting demographic and laboratory data. The cases with incomplete data were excluded and the rest of the cases which had enough data entered in records were included. Data abstracted included age, gender, exposure history, history of diabetes and other underlying comorbidities (hypertension, cardiovascular disease, cerebrovascular disease, chronic pulmonary disease, chronic kidney disease, chronic liver disease, etc.), symptoms (general symptoms like fever, cough, breathlessness, etc. and neurological symptoms like headache, dizziness, loss of taste, loss of smell, myalgia, etc.), vital

© The Author(s). 2022 Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by-nc/4.0/). Please refer to the link for more details.
Neurological Manifestations of COVID and Its Outcome

One of (1) respiratory rate: >24/min, (2) SpO₂ <90% on room air; severe disease—any one of (1) respiratory rate: >30/min, (2) SpO₂ <90% on room air. Cerebrospinal fluid. Stroke was diagnosed based on CT or MRI findings.

The data collected were analyzed for prevalence and pattern of neurological symptoms at admission and neurological complications developed during hospitalization. The patients were divided into two groups, first—without any neurological symptoms and second— with neurological symptoms. These two groups were compared for their duration of hospital stay, requirement of BiPAP or ventilator, severity of disease, development of neurological complications, and mortality. Similar parameters were compared between patients with neurological complications and age- and gender-matched patients who did not develop neurological complications.

Results are presented as mean ± standard deviation (SD) for continuous variables and as percentages for categorical variables. Comparability of groups was analyzed by Chi-square test, Student’s t test, or Mann–Whitney U test as appropriate. IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA) software was used for statistical analyses.

Results

A total of 440 hospitalized patients with COVID-19 confirmed by RT-PCR were included in this study. The mean age of the patients was 59.28 ± 13.28 years, 260 (59.1%) of the total patients were males and 180 (40.9%) were females. The number of patients with mild, moderate, and severe disease were 121 (27.5%), 242 (55.1%), and 77 (17.5%), respectively. A total of 209 (47.5%) patients presented with at least one comorbid condition; the most common of which was hypertension seen in 132 (30%), followed by diabetes in 106 (24.1%), chronic obstructive pulmonary disease (COPD) in 77 (17.5%), obesity in 62 (14.1%), cardiovascular disease in 23 (5.2%), chronic liver disease in 23 (5.2%), chronic kidney disease in 20 (4.5%), thyroid disease in 22 (5%), and stroke in 12 (2.7%) (Table 1). No statistically significant difference was found between patients with and without neurological symptoms with regard to the prevalence of comorbidities (Table 1).

The most common general symptoms at presentation were fever seen in 328 (74.5%), cough in 320 (72.7%), shortness of breath in 210 (47.7%), sore throat in 188 (42.7%), and fatigue in 185 (42.1%). Less common symptoms were rhinorrhea, seen in 103 (23.4%), diarrhea in 48 (10.9%), nausea/vomiting in 36 (8.2%), and abdominal pain in 34 (7.7%). A total of 326 (74.1%) patients had at least one neurological symptom. The most common neurological symptom at presentation was headache which was seen in 167 (37.9%) followed by myalgia in 159 (36.1%), loss of taste in 113 (25.7%), loss of smell in 104 (23.6%), and dizziness in 52 (11.8%) (Table 2).

Out of the 440 COVID-19 patients, 38 (8.6%) developed neurological complications during hospitalization. The most common complication was altered sensorium which was seen in 21 (55.3%) followed by ischemic stroke in six (15.8%), seizure in six (15.8%), hemorrhagic stroke in three (7.9%), and encephalitis in two (5.3%) (Table 2). None of the patients with mild disease developed any neurological complications.

In comparing the morbidity and mortality between patients presenting with at least one neurological symptom on admission with those who had none, we found no significant difference between the two groups in terms of severity of disease (OR 1.13, 95% CI 0.63–2.02, p = 0.6788), need for invasive ventilation (OR 2.45, 95% CI 1.01–5.94, p = 0.68), or mortality (OR 0.98, 95% CI 0.52–1.84, p = 0.9401). However, a significantly more number of patients with neurological symptoms on admission developed neurological complications during hospitalization (OR 4.59, 95% CI 1.39–15.22, p = 0.0126) leading to a significantly longer duration of hospital stay in these patients (14.71 ± 6.04 vs 10.65 ± 4.60 days; p = 0.0419) (Table 3).

In comparing the morbidity and mortality, the patients who developed neurological complications and age- and gender-matched controls who did not develop neurological complications, it was found that a significantly more number of patients with neurological complications had severe disease (OR 9.21, 95% CI 3.23–26.27; p < 0.001), needed noninvasive ventilation/BiPAP (OR 4.43, 95% CI 1.57–12.50; p = 0.0049), invasive ventilation (OR 3.92, 95% CI 1.13–13.58; p = 0.0309), and mortality (OR 6.59, 95% CI 2.23–19.43; p = 0.0006) than those without neurological complications. Duration of hospitalization was also found to be longer in patients with neurological symptoms (16.26 ± 5.15 vs 12.73 ± 4.89, p = 0.0173) which was probably due to a greater number of neurological complications seen in these patients (Table 4).

Discussion

This study describes the neurological symptoms at admission and neurological complications during hospitalization of patients with confirmed COVID-19 in the Western part of India. In this cohort of 440 patients admitted with COVID-19 disease, 74.1% of patients presented with at least one neurological symptom. Similar observations were made by Flores-Silva et al.18 and Fan et al.,19 who reported neurological manifestations at the time of admission in 69.3% and 62.8% of patients, respectively. Others have shown a much lower incidence of neurological symptoms, for example, Mao et al.,20 Luigetti et al.,21 and Karadaş et al.22 reported neurological manifestation in only 36.4%, 30%, and 36.7% of patients, respectively. This difference may be because of the different effects of different strains of the SARS-CoV-2 virus.

In this study, headache (37.9%) was the most common neurological manifestation, followed by myalgia (36.1%), loss of taste (25.7%), loss of smell (23.6%), and dizziness (11.8%). A similar observation was made by Karadaş et al.22 and Flores-Silva et al.18 who found headache to be the most common manifestation (26.7% and 41.7%, respectively). Consistent with the previous studies,18–22 muscle symptoms were also common in our study.

In hospital neurological complications involving the central nervous system (CNS) were seen in 8.6% of patients. Delirium/alterned sensorium was the most common complication, seen in 4.7% of patients. All of them needed invasive ventilation as they could not tolerate noninvasive ventilation. Other complications observed in this study were ischemic stroke (15.8%), seizure (15.8%), hemorrhagic stroke (7.9%), and encephalitis (5.3%), which were similar to the observations made by Fan et al.18 who reported delirium to be the most common neurological complication.

Many mechanisms have been suggested to explain the neurologic damage caused by SARS-CoV-2, like (1) direct damage to specific receptors, cytokine-related injury, secondary...
Neurological Manifestations of COVID and Its Outcome

Table 1: Clinical characteristics of patients with COVID-19

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Total (n = 440)</th>
<th>With neurological symptoms (n = 326)</th>
<th>Without neurological symptoms (n = 114)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD (years)</td>
<td>59.28 ± 13.28</td>
<td>62.47 ± 12.80</td>
<td>56.25 ± 14.44</td>
<td>0.1637</td>
</tr>
<tr>
<td>&lt;50 years</td>
<td>152 (34.5%)</td>
<td>106 (32.5%)</td>
<td>46 (40.3%)</td>
<td>0.1615</td>
</tr>
<tr>
<td>&gt;50 years</td>
<td>288 (65.5%)</td>
<td>220 (67.5%)</td>
<td>68 (59.6%)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>260 (59.1%)</td>
<td>193 (59.2%)</td>
<td>67 (58.8%)</td>
<td>0.9357</td>
</tr>
<tr>
<td>Female</td>
<td>180 (40.9%)</td>
<td>133 (40.8%)</td>
<td>47 (41.2%)</td>
<td></td>
</tr>
<tr>
<td>Type of diseases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>121 (27.5%)</td>
<td>81 (24.8%)</td>
<td>40 (35.1%)</td>
<td>0.047</td>
</tr>
<tr>
<td>Moderate</td>
<td>242 (55%)</td>
<td>188 (57.7%)</td>
<td>54 (47.4%)</td>
<td>0.073</td>
</tr>
<tr>
<td>Severe</td>
<td>77 (17.5%)</td>
<td>57 (17.5%)</td>
<td>27 (23.7%)</td>
<td>0.9886</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>132 (30%)</td>
<td>97 (29.8%)</td>
<td>35 (30.7%)</td>
<td>0.9432</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>106 (24.1%)</td>
<td>86 (26.4%)</td>
<td>20 (17.5%)</td>
<td>0.0764</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>23 (5.2%)</td>
<td>15 (4.6%)</td>
<td>8 (7.02%)</td>
<td>0.4513</td>
</tr>
<tr>
<td>COPD</td>
<td>77 (17.5%)</td>
<td>51 (15.6%)</td>
<td>26 (22.8%)</td>
<td>0.1120</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>20 (4.5%)</td>
<td>16 (4.9%)</td>
<td>4 (3.5%)</td>
<td>0.7217</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>23 (5.2%)</td>
<td>17 (5.2%)</td>
<td>7 (6.1%)</td>
<td>0.8926</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>12 (2.7%)</td>
<td>8 (2.5%)</td>
<td>4 (3.5%)</td>
<td>0.7940</td>
</tr>
<tr>
<td>Obesity</td>
<td>62 (14.1%)</td>
<td>40 (12.3%)</td>
<td>22 (19.3%)</td>
<td>0.0891</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>22 (5%)</td>
<td>17 (5.2%)</td>
<td>5 (4.4%)</td>
<td>0.9205</td>
</tr>
<tr>
<td>General symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>328 (74.5%)</td>
<td>251 (76.9%)</td>
<td>77 (67.5%)</td>
<td>0.1172</td>
</tr>
<tr>
<td>Cough</td>
<td>320 (72.7%)</td>
<td>235 (72.1%)</td>
<td>85 (74.6%)</td>
<td>0.6975</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>210 (47.7%)</td>
<td>158 (48.5%)</td>
<td>52 (45.6%)</td>
<td>0.6775</td>
</tr>
<tr>
<td>Sore throat</td>
<td>188 (42.7%)</td>
<td>126 (38.7%)</td>
<td>62 (54.4%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Fatigue</td>
<td>185 (42%)</td>
<td>145 (44.5%)</td>
<td>40 (30.7%)</td>
<td>0.014</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>103 (23.4%)</td>
<td>73 (22.4%)</td>
<td>30 (26.3%)</td>
<td>0.4697</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>48 (10.9%)</td>
<td>31 (9.5%)</td>
<td>17 (14.9%)</td>
<td>0.1561</td>
</tr>
<tr>
<td>Vomiting</td>
<td>36 (8.2%)</td>
<td>22 (6.7%)</td>
<td>14 (12.3%)</td>
<td>0.0976</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>34 (7.7%)</td>
<td>22 (6.7%)</td>
<td>12 (10.5%)</td>
<td>0.2729</td>
</tr>
</tbody>
</table>

Table 2: Neurological symptoms and complications in patients with COVID-19

<table>
<thead>
<tr>
<th>Parameters</th>
<th>N = 440</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>167</td>
<td>37.9</td>
</tr>
<tr>
<td>Dizziness</td>
<td>52</td>
<td>11.8</td>
</tr>
<tr>
<td>Loss of smell</td>
<td>104</td>
<td>23.6</td>
</tr>
<tr>
<td>Loss of taste</td>
<td>113</td>
<td>25.7</td>
</tr>
<tr>
<td>Myalgia</td>
<td>159</td>
<td>36.1</td>
</tr>
<tr>
<td>Neuralgia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neurological complications</td>
<td>N = 38</td>
<td>Percentage (%)</td>
</tr>
<tr>
<td>during hospitalization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>6</td>
<td>15.8</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>3</td>
<td>7.9</td>
</tr>
<tr>
<td>Seizure</td>
<td>6</td>
<td>15.8</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>2</td>
<td>5.3</td>
</tr>
<tr>
<td>Impaired consciousness</td>
<td>21</td>
<td>55.3</td>
</tr>
</tbody>
</table>

hypoxia, and retrograde travel along nerve fibers. Like its expression on lung epithelial cells, the expression of ACE2 on endothelial cells of the blood-brain barrier can also allow viral binding, facilitating viral entry into the CNS by attacking the vasculature. (3) the binding of SARS-CoV-2 at the pulmonary epithelial cells generates a global systemic inflammatory response, producing increased levels of interleukin (IL)—6, IL-12, IL-15, and tumor necrosis factor-α; activating glial cells; and producing a massive proinflammatory CNS state. In particular, IL-6 levels have been correlated with increased systemic effects in COVID-19. These systemic effects combined with localized lung alveolar damage result in severe hypoxia, which can lead to cerebral vasodilation and may decompensate into cerebral edema and ischemia.
We found that a significantly higher number of patients with neurological complications had severe disease, greater need for noninvasive ventilation/BiPAP/invasive ventilation, and mortality than those without neurological complications. Duration of hospitalization was also found to be longer in patients with neurological complications.

### Table 3: Odds of morbidity and mortality in patients with neurological symptoms vs those without neurological symptoms

<table>
<thead>
<tr>
<th>Severe disease</th>
<th>With neurological symptoms (n = 326)</th>
<th>Without neurological symptoms (n = 114)</th>
<th>Odds ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe disease</td>
<td>Yes</td>
<td>57</td>
<td>1.18 (0.63–2.02)</td>
<td>0.6788</td>
</tr>
<tr>
<td>No</td>
<td>269</td>
<td>96</td>
<td>1.18 (0.63–2.02)</td>
<td>0.6788</td>
</tr>
<tr>
<td>BiPAP requirement</td>
<td>Yes</td>
<td>39</td>
<td>2.45 (1.01–5.94)</td>
<td>0.048a</td>
</tr>
<tr>
<td>No</td>
<td>287</td>
<td>108</td>
<td>2.45 (1.01–5.94)</td>
<td>0.048a</td>
</tr>
<tr>
<td>Ventilator requirement</td>
<td>Yes</td>
<td>23</td>
<td>1.01 (0.44–2.32)</td>
<td>0.9892</td>
</tr>
<tr>
<td>No</td>
<td>303</td>
<td>106</td>
<td>1.01 (0.44–2.32)</td>
<td>0.9892</td>
</tr>
<tr>
<td>Neurological complication</td>
<td>Yes</td>
<td>36</td>
<td>4.59 (1.39–15.22)</td>
<td>0.0126²</td>
</tr>
<tr>
<td>No</td>
<td>290</td>
<td>111</td>
<td>4.59 (1.39–15.22)</td>
<td>0.0126²</td>
</tr>
<tr>
<td>Mortality</td>
<td>Yes</td>
<td>42</td>
<td>0.98 (0.52–1.84)</td>
<td>0.9401</td>
</tr>
<tr>
<td>No</td>
<td>284</td>
<td>99</td>
<td>0.98 (0.52–1.84)</td>
<td>0.9401</td>
</tr>
<tr>
<td>Parameter</td>
<td>With neurological symptoms</td>
<td>Without neurological symptoms</td>
<td>Difference</td>
<td>p-value</td>
</tr>
<tr>
<td>Duration of hospitalization</td>
<td>14.71 ± 6.04</td>
<td>10.65 ± 4.60</td>
<td>t(29) = 2.1288</td>
<td>0.0419²</td>
</tr>
</tbody>
</table>

²The values given are Mean ± SD

### Table 4: Odds of morbidity and mortality in patients with neurological complications vs those without neurological complications

<table>
<thead>
<tr>
<th>Severe disease</th>
<th>With neurological complications (n = 38)</th>
<th>Without neurological complications (n = 38)</th>
<th>Odds ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe disease</td>
<td>Yes</td>
<td>30 (78.9%)</td>
<td>9.21 (3.23–26.27)</td>
<td>&lt;0.001²</td>
</tr>
<tr>
<td>No</td>
<td>8 (21.5%)</td>
<td>27 (71.1%)</td>
<td>9.21 (3.23–26.27)</td>
<td>&lt;0.001²</td>
</tr>
<tr>
<td>BiPAP requirement</td>
<td>Yes</td>
<td>19 (50%)</td>
<td>4.43 (1.57–12.50)</td>
<td>0.0049²</td>
</tr>
<tr>
<td>No</td>
<td>19 (50%)</td>
<td>31 (81.6%)</td>
<td>4.43 (1.57–12.50)</td>
<td>0.0049²</td>
</tr>
<tr>
<td>Ventilator requirement</td>
<td>Yes</td>
<td>12 (31.6%)</td>
<td>3.92 (1.13–13.58)</td>
<td>0.0309²</td>
</tr>
<tr>
<td>No</td>
<td>26 (68.4%)</td>
<td>34 (89.5%)</td>
<td>3.92 (1.13–13.58)</td>
<td>0.0309²</td>
</tr>
<tr>
<td>Mortality</td>
<td>Yes</td>
<td>21 (55.3%)</td>
<td>6.59 (2.23–19.43)</td>
<td>0.0006²</td>
</tr>
<tr>
<td>No</td>
<td>17 (44.7%)</td>
<td>32 (84.2%)</td>
<td>6.59 (2.23–19.43)</td>
<td>0.0006²</td>
</tr>
<tr>
<td>Parameter</td>
<td>With neurological complications (n = 38)</td>
<td>Without neurological complications (n = 38)</td>
<td>Difference</td>
<td>p-value</td>
</tr>
<tr>
<td>Duration of hospitalization</td>
<td>16.26 ± 5.15</td>
<td>12.73 ± 4.89</td>
<td>t(50) = 2.4633</td>
<td>0.0173²</td>
</tr>
</tbody>
</table>

²The values given are Mean ± SD

Moderate and severe cases of COVID-19 are defined based on the degree of hypoxia in peripheral blood. Hence, the patients in these stages of COVID-19 may have hypoxia in CNS also, resulting in neurological symptoms ranging from headache to coma, depending upon the severity of hypoxia. One other reason could be an infection-mediated harmful immune response that can cause nervous system abnormalities. Muscle symptoms may be because of elevated proinflammatory cytokines in serum. Another reason may be injury through ACE2 receptors²⁹ although, whether SARS-CoV-2 infects skeletal muscle cells by binding with ACE2 still needs to be established.
which was probably due to a greater number of severe diseases and increased need for respiratory support in these patients. Similar observations were made by Fan et al. They found an association between severity of disease and development of new-in-hospital neurologic events, though they did not find increased mortality in patients with neurological complications. On the contrary, in a multicenter study conducted by Frontera et al. in New York, it was found that COVID-19 with neurologic events had an increased risk of in-hospital mortality.

We also observed that some patients without typical symptoms (fever, cough, etc.) of COVID-19 came to the hospital with only neurologic manifestation as presenting symptoms. Therefore, during the epidemic period of COVID-19, when seeing patients with these neurologic manifestations, SARS-CoV-2 infection should be considered as a differential diagnosis to avoid delayed diagnosis or misdiagnosis and prevention of transmission.

We did not assess individual symptoms or complications which could have given a better insight toward management. However, not many have studied the neurological manifestations of COVID-19 in the second wave of the pandemic. This study with a sample size of more than 400 gives an idea of the spectrum of neurological symptoms and complications seen and also suggests what outcome is expected in such patients.

**CONCLUSION**

A broad spectrum of neurologic symptoms and complications are seen with COVID-19 infection and their presence is associated with greater morbidity and mortality in these patients. A study of the association of individual neurological manifestation with the severity of COVID-19 will provide a more meaningful insight regarding the approach to the management of such patients.
Establishment of SMS Dengue Severity Score

Sudhir Bhandari1, Govind Rankawat2, Barkha Goyal3, Anurag Lohmmor4, Vishal Gupta5, Ajeet Singh6

Received: 21 November 2021; Accepted: 22 June 2022

ABSTRACT

Background: Dengue infection is a disease that progresses rapidly to life-threatening conditions. Our goal was to develop a practical scoring system based on clinical profiles and routine tests to predict the severity of infection.

Methods: This cross-sectional observational study included 500 patients with dengue infection. Patient demographics, clinical symptoms, regular laboratory tests, and results were collected. Dengue infections are divided into three classes, depending on their severity: dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS). Based on the total score, patients were divided into three severities.

Results: Patients with DSS and DHF scored higher with worsening clinical features and routine laboratory tests compared to DF. Clinical predictors of severity include older age, increased white blood cell (WBC) count, increased hematocrit, increased prothrombin time, decreased platelet count, decreased blood pressure, presence of peri-gallbladder (GB) edema, third space loss, hepatomegaly, and other organ involvement. The severity range is 0–12, and the score is 0–3 for DF, 4–8 for DHF, and 9–12 for DSS. Based on the derived scores, patients were classified according to their original severity in 63% of cases.

Conclusion: This dengue infection severity scores correctly classified patients according to their original severity grade of DF, DHF, or DSS. This scoring system helps to quickly assess dengue infections and start treatment according to the correct severity category.

INTRODUCTION

Dengue infection is a global burden for health care professionals. The global incidence of dengue infection is 100–400 million per year, and the incidence is increasing more than 30 times continuously. DF is widespread in India, but it is one of the most important neglected tropical diseases, and its incidence has increased more than 30-fold over the past few decades. Almost 2–4 million patients had serious infections and had to be hospitalized. Dengue infection has a negative impact on the health, family, and economy of affected countries. Dengue infection is caused by four antigenic and genetically related viruses known as DEN1–DEN4. DF is clinically classified into DF, DHF, and DSS.

According to 2009 WHO, dengue infections are classified as dengue or severe dengue with or without warning signs. Dengue has three different stages: (i) acute (fever), (ii) severe (plasma leakage), and (iii) convalescent or reabsorption. The combination of coagulopathy and plasma leakage can cause bleeding and a sharp drop in blood pressure, which can lead to cardiovascular shock and organ damage. There is no specific treatment available for dengue infections, except for symptomatic treatments that are effective for early detection of dengue infections. If not handled properly, it can be fatal. Early detection and timely intervention can avoid these fatal complications. Depending on the severity of the dengue infection, early diagnosis and treatment are essential to avoid the occurrence of problems. The severity of dengue infection is according to the clinical course of the disease, as determined by clinical symptoms, signs, and laboratory values. Most of the available dengue severity classifications are based on clinical outcomes and require extensive evaluation. Therefore, in order to initiate appropriate treatment, we planned to develop a continuous severity assessment system that would classify dengue infections by severity. This scoring system is simple and is based on clinical features and available laboratory tests.

METHODS

Study Design

A total of 500 patients with dengue infection were enrolled in this cross-sectional observational study conducted by SMS Medical College & Affiliated Hospitals in Jaipur, India, from 1st September 2021 to 31st October 2021. The Institutional Review Board of the institution approved the study. This study enrolls dengue NS1-positive patients hospitalized for fever or other dengue-related complications. These patients are continuously followed until they are discharged to collect data.

Definition of dengue severity:

- Dengue fever: Acute fever associated with positive tourniquet test with WBC count ≤5000/µL.
- Dengue hemorrhagic fever: Includes the following symptoms: (i) Acute fever for 2–7 days, (ii) bleeding episodes, (iii) platelets ≤100000/µL, and (iv) signs of plasma leakage.
- Dengue shock syndrome: DHF with a rapid and weak pulse (pulse pressure ≤20 mm Hg), hypotension, cold and clumsy limbs, or irritation.

Data Collection

Dengue infection was diagnosed with a positive dengue NS1 antigen. Patient demographics, clinical symptoms, vital signs, laboratory findings, and outcome information were extracted for data analysis. The data collected include symptoms such as age, gender, fever, myalgia, vomiting, abdominal pain, headache, rash, petechiae, hepatomegaly, pleural effusion, and other bleeding symptoms. Laboratory tests include blood pressure, hemoglobin, WBC count, neutrophil ratio to lymphocytes, hematocrit, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, PT-INR (prothrombin time–international normalized ratio), activated partial thromboplastin time, length of stay, and mortality.

Statistical Analysis

Quantitative data were measured as mean and standard deviation. Qualitative data were measured as a ratio. A p-value less than 0.05 is considered significant. The association between

1Senior Professor; 2Senior Resident, Department of General Medicine, SMS Medical College & Attached Hospitals; 3Assistant Professor, Department of Biochemistry, Jaipur National University Institute for Medical Sciences and Research Centre; 4Assistant Professor, Department of Geriatric Medicine; 5Associate Professor; 6Senior Specialist, Department of General Medicine, SMS Medical College & Attached Hospitals, Jaipur, Rajasthan, India; *Corresponding Author

Establishment of SMS Dengue Severity Score

the three groups was calculated using analysis of variance and the Chi-square test. The total (cumulative) score was used to classify patients into three severities. The distribution of scores across the three severity groups is shown in a boxplot. For statistical analysis, we used the Statistical Package for the Social Sciences (SPSS) and the R program.

**Results**

A total of 500 patients with dengue infections were classified into three grades: DF (N = 295), DHF (N = 175), and DSS (N = 30). In this study, selected patients with dengue infection were statistically similar in all groups for gender (p = 0.1612), age (p = 0.95), presence of headache (p = 0.871), and myalgia (p = 0.5067). Clinically, all three groups differ in the presence of fever (p ≤ 0.01), abdominal pain (p = 0.004), vomiting (p < 0.01), rash (p = 0.007), petechiae (p < 0.01), hepatomegaly (p < 0.01), pleural effusion (p < 0), and other bleeding events (p < 0.01) (Table 1). Clinically, fever was the most pronounced in early-stage dengue patients. Complex dengue symptoms such as abdominal pain, vomiting, rash, petechiae, hepatomegaly, pleural effusion, and other bleeding phenomena are higher in hemorrhagic dengue and DSS than in uncomplicated dengue. Vomiting, rash, hepatomegaly pleural effusion, and other bleeding symptoms were found to be more common in DSS patients than in DHF. Systolic and diastolic blood pressure decreased significantly as patients progressed continuously from DF to DHF and from DHF to DSS (p < 0.01). Patients with DSS and DHF have longer hospital stays than patients with DF (p < 0.01).

In multivariate analysis, significant predictive features of dengue severity include age >40 years (score = 1), systolic blood pressure >90 mm Hg (score = 1), and hematocrit >40% (score = 1). (i) White cell count <5000/µL (score = 1), platelet count <0.5 lac/µL (score = 1), PT-INR >1.4 (score = 1), peri-GB edema (score = 1), third space loss (score = 2), liver enlargement (score = 1), and other organ lesions (score = 2) (Table 2). Of the total dengue severity score of 12, the average dengue severity score for patients with dengue was 2.61 (2.61 ± 2.18), for DHF was 6.78 (6.78 ± 2.66), and for DSS was 8.68 (8.68 ± 2.11). It was statistically different among all groups (p < 0.01) (Table 3 and Fig. 1). The derived values distinguished DHF from DF and DSS from DHF. Breakpoints were developed to classify patients into three severity groups (Figs 1 and 2):

- Score 0–3: For DF. A score of <3 accurately predicted DF in 201 of 295 patients and overestimated in 94 patients (18.8%).
- Score 4–8: For DHF. Scores of 4–8 accurately predicted DHF in 97 of 175 patients and underestimated and overestimated in 78 patients (15.6%).

**Table 1:** Clinical profile of DF, DHF, and DSS

| Patient parameters | DF (n = 295) | DHF (n = 175) | DSS (n = 30) | *p-value*
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>23.96 ± 8.24</td>
<td>22.88 ± 5.61</td>
<td>22.04 ± 5.11</td>
<td>0.1612</td>
</tr>
<tr>
<td>Male (n, %)</td>
<td>205 (69.49)</td>
<td>116 (66.29)</td>
<td>21 (70.0)</td>
<td>0.95</td>
</tr>
<tr>
<td><strong>Clinical features</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>280 (94.92)</td>
<td>140 (80.00)</td>
<td>10 (33.33)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Myalgia</td>
<td>244 (82.71)</td>
<td>170 (97.14)</td>
<td>26 (86.67)</td>
<td>0.5067</td>
</tr>
<tr>
<td>Vomiting</td>
<td>112 (37.97)</td>
<td>132 (75.43)</td>
<td>25 (83.33)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pain abdomen</td>
<td>174 (58.98)</td>
<td>166 (94.86)</td>
<td>22 (73.33)</td>
<td>0.004</td>
</tr>
<tr>
<td>Headache</td>
<td>204 (69.15)</td>
<td>115 (65.71)</td>
<td>18 (60.0)</td>
<td>0.871</td>
</tr>
<tr>
<td>Petechiae</td>
<td>68 (23.05)</td>
<td>96 (54.86)</td>
<td>12 (40.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>35 (11.86)</td>
<td>126 (72.0)</td>
<td>28 (93.33)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>0</td>
<td>108 (61.7)</td>
<td>30 (100)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Other bleeding manifestations</td>
<td>0</td>
<td>19 (10.86)</td>
<td>10 (33.33)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>118 ± 6.11</td>
<td>105.4 ± 5.12</td>
<td>87 ± 3.41</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>80.6 ± 4.94</td>
<td>76.47 ± 5.92</td>
<td>65 ± 3.41</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Hematological</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>14.11 ± 1.09</td>
<td>13.89 ± 1.32</td>
<td>13.65 ± 1.17</td>
<td>0.0357</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>44.085 ± 4.87</td>
<td>39.78 ± 1.7</td>
<td>37.4 ± 4.03</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>White cell count (×103/µL)</td>
<td>4.25 ± 0.86</td>
<td>5.28 ± 1.28</td>
<td>12.31 ± 2.67</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Platelet count (×103/µL)</td>
<td>33.5 ± 16.66</td>
<td>28.41 ± 12.8</td>
<td>30.16 ± 11.4</td>
<td>0.0019</td>
</tr>
<tr>
<td>Neutrophil-lymphocyte ratio</td>
<td>0.60 ± 0.70</td>
<td>1.32 ± 0.26</td>
<td>1.9 ± 0.26</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SGOT (U/L)</td>
<td>168 ± 34.67</td>
<td>262 ± 19.65</td>
<td>266.5 ± 51.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SGPT (U/L)</td>
<td>139.5 ± 26.0</td>
<td>210 ± 14.74</td>
<td>239.2 ± 63.14</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PT-INR</td>
<td>1.13 ± 0.22</td>
<td>2.07 ± 0.6</td>
<td>3.4 ± 0.37</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>APTT (s)</td>
<td>31 ± 5.20</td>
<td>45.1 ± 2.9</td>
<td>46.03 ± 6.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>5 ± 1.41</td>
<td>7.35 ± 2.77</td>
<td>9.5 ± 1.74</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>1 (0.57)</td>
<td>1 (3.33)</td>
<td>0.0229</td>
</tr>
<tr>
<td>Severity score</td>
<td>2.61 ± 2.18</td>
<td>6.78 ± 2.66</td>
<td>8.68 ± 2.11</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*p-value* from the nonparametric test; SD, standard deviation; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; PT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time.
Establishment of SMS Dengue Severity Score

Table 2: Significant predictors for severity of dengue infection and designed severity score

<table>
<thead>
<tr>
<th>Sl. no.</th>
<th>Parameter</th>
<th>Value</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Age (year)</td>
<td>&lt;40</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;40</td>
<td>1</td>
</tr>
<tr>
<td>2.</td>
<td>Systolic blood pressure (mm Hg)</td>
<td>&gt;90</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;90</td>
<td>1</td>
</tr>
<tr>
<td>3.</td>
<td>Hematocrit (%)</td>
<td>&lt;40</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;40</td>
<td>1</td>
</tr>
<tr>
<td>4.</td>
<td>White cell count (/µL)</td>
<td>&lt;5000</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;5000</td>
<td>1</td>
</tr>
<tr>
<td>5.</td>
<td>Platelet (/µL)</td>
<td>&gt;0.5 lac</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;0.5 lac</td>
<td>1</td>
</tr>
<tr>
<td>6.</td>
<td>PT-INR</td>
<td>&lt;1.4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;1.4</td>
<td>1</td>
</tr>
<tr>
<td>7.</td>
<td>Peri-GB edema</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>8.</td>
<td>Third space loss</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td>9.</td>
<td>Hepatomegaly</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>10.</td>
<td>Heart/kidney/brain involvement</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 3: Severity score and predicted score range in patients of DF, DHF, and DSS

<table>
<thead>
<tr>
<th>Category</th>
<th>Number (N)</th>
<th>Severity score</th>
<th>Predicted score range</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean ± SD</td>
<td>95% CI</td>
<td>Within range</td>
</tr>
<tr>
<td>DF</td>
<td>295</td>
<td>2.61 ± 2.18</td>
<td>2.6122 ± 0.25 (±9.56%)</td>
<td>0–3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>201</td>
</tr>
<tr>
<td>DHF</td>
<td>175</td>
<td>6.78 ± 2.66</td>
<td>6.7841 ± 0.394 (±5.81%)</td>
<td>4–8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>97</td>
</tr>
<tr>
<td>DSS</td>
<td>30</td>
<td>8.68 ± 2.11</td>
<td>8.6875 ± 0.732 (±8.43%)</td>
<td>9–12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>17</td>
</tr>
</tbody>
</table>

Fig. 1: Distribution of dengue severity score by severity level

Fig. 2: Discrimination of dengue severity score

Discussion

Dengue infection is an urgent and rapidly progressing widespread disease that requires prompt diagnosis and treatment to prevent progression to bleeding and circulatory collapse. Historically, dengue scoring systems based on clinical signs or symptoms and epidemiological information have been used. The advantage of the scoring system is that it detects DF very early before the test result. Other scoring systems used to diagnose disseminated intravascular coagulation (DIC) include DIC scores, which distinguish DF and DHF from other febrile illnesses.

Dengue infections are also classified as DF, DHF grades I, II, and III. This classification can identify low-risk patients for safe discharge and high-risk patients for intensive monitoring.

Several other studies have used extraordinary predictors that are not really useful because they are not available in
most primary care centers. This study found that nearly 59% of patients had the clinical characteristics of DF, 35% had DHF complications, and the remaining 6% had DSS. Fever is the most common symptom of dengue infection, occurring in the early stages of dengue infection, but diminishes as the disease progresses. Therefore, dengue infections increase the risk of severity as the fever subsides. Most people are calm after progressing to the thermal stage, but this bubbling stage is fatal and can progress to DHF or DSS. Warning signs of dengue infection, such as abdominal pain, vomiting, rash, petechiae, liver enlargement, pleural effusion, and other bleeding symptoms, are more common in DHF and DSS than in uncomplicated DF.

The study found that some clinical symptoms, such as vomiting, rash, hepatomegaly pleural effusion, and other bleeding symptoms, were more frequent in DSS patients than in DHF. In this study, we designed a simple scoring system using clinical parameters and routine laboratory tests. Patients with dengue infection were classified as DF, DHF, or DSS.

- Patients with a score of 0–3 are classified as the mildest form, DF, and generally, these patients do not require hospitalization. However, these patients must be monitored to avoid problem-free progression to DHF and DSS conditions. These patients primarily required symptomatic treatment, but few required intravenous treatment to improve patient compliance. These patients should be observed to observe abnormal signs and symptoms during follow-up visits.

- Patients with a score of 4–8 were assigned to the DHF risk group. These patients should be hospitalized and carefully monitored for plasma leaks, coagulopathy, blood levels, and early signs of thrombocytopenia. These patients should be hospitalized and receive early supportive care to prevent progression to DSS.

- Patients with scores from 9 to 12 were assigned to the DSS risk group. These patients should be hospitalized and begin early resuscitation therapy while monitoring signs of shock.

Our scoring system accurately predicted DSS with a positive predictive value (PPV) of 89%, similar to other studies that reported 82–95% PPV. Therefore, we can use this value to distinguish DSS from DF and DHF. This scoring system can be used to monitor progress from DF to DHF and DSS through ongoing laboratory testing. For OPD patients, this scoring system helps doctors decide when to hospitalize the patient. This scoring can be used to reduce unnecessary hospitalizations and reduce the mortality rate of severely hospitalized cases based on high-risk scores.

**CONCLUSION**

This dengue severity score correctly classified patients as DF, DHF, or DSS in their original severity grade. This scoring system helps to quickly assess dengue infections and start treatment according to the correct severity category. The severity of dengue infection depends primarily on plasma leakage syndrome, elevated hematocrit levels, and the involvement of other important organs. This SMS dengue severity score can quickly diagnose and classify dengue infections based on clinical features and routine laboratory tests.

**LIMITATIONS**

There are some limits to this survey. Our study has a limited number of patients and needs to be investigated in a larger patient cohort. This was a single-center, cross-sectional observational study and could not rule out epidemiological confounders.

**Ethical Approval**

The Ethics Research Committee of SMS Medical College & Attached Hospitals in Jaipur, India has approved this study.

**Authors’ Contribution**

The research question was created by S. Bhandari, A. Singh, and G. Rankawat. The data for this study were collected and analyzed by G. Rankawat, V. Gupta, and A. Singh. G. Rankawat and B. Goyal wrote the manuscript. The quality evaluation was carried out by S. Bhandari. The manuscript was critically reviewed and approved by all authors. All authors have read and approved the final version of the manuscript.

**Data and Material Availability**

Available upon reasonable request from the corresponding author.

**REFERENCES**

Assessment of Visceral Fat Volume and Its Correlation with the Severity of Hepatic Fibrosis in Patients with NAFLD

Jijo Varghese1*, Krishnadas Devadas2, Rathan Cyriac Joseph3, Tharun Tom Oommen4, Atul Hareendran5, Nibin Nahaz6, Vijay Narayanan7, Bony George8

Received: 17 November 2021; Accepted: 02 June 2022

ABSTRACT

Introduction: Nonalcoholic fatty liver disease (NAFLD) is one of the leading causes of chronic liver disease. The spectrum of NAFLD includes simple steatosis, nonalcoholic steatohepatitis (NASH), advanced fibrosis, and cirrhosis. Our study aimed to calculate visceral fat volume at the L3–L4 vertebral level and its association with hepatic fibrosis assessed by transient elastography.

Methods: All patients above 18 years undergoing computed tomography (CT) abdomen in the Department of Radiodiagnosis of Medical College Thiruvananthapuram during the study period with NAFLD were included. Transient elastography was done. Patients were categorized to advanced fibrosis (>10 kPa) and without advanced fibrosis (<10 kPa). The area under the receiver operating characteristic (AUROC) curve was plotted.

Results: Sixty-four patients comprised 36 males and 28 females. Thirty-one (46%) were having advanced fibrosis (transient elastography >10 kPa) and 34 (54%) patients were without advanced fibrosis. About 0.733 was the AUROC for visceral fat in predicting advanced fibrosis. The cutoff was 167.5 cm³ (sensitivity was 77.4% and specificity was 51.5% in predicting advanced fibrosis).

Conclusion: About 0.733 was the AUROC for visceral fat in predicting advanced fibrosis. The cutoff was 167.5 cm³ (sensitivity was 77.4% and specificity was 51.5% in predicting advanced fibrosis).

INTRODUCTION

Nonalcoholic fatty liver disease includes simple steatosis, advanced fibrosis, and cirrhosis. Previous studies have shown that visceral fat is closely associated with inflammation and hepatic fibrosis. If visceral fat is incorporated along with contrast-enhanced CT findings, it could potentially predict the development and severity of hepatic fibrosis in NAFLD patients. Visceral fat volume correlates with severity of fibrosis in NAFLD, independent of insulin resistance. The aim was to measure visceral fat volume at the L3–L4 level using four 2.5 mm cuts and to determine its association with liver fibrosis assessed by transient elastography.

Research Question

• Does visceral fat volume correlate with liver fibrosis in patients with NAFLD?

Objectives of This Study

• To evaluate the association between visceral fat volume calculated at the L3–L4 level from CT abdomen with hepatic fibrosis severity in NAFLD as determined by vibration-controlled transient elastography (VCTE).

MATERIALS AND METHODS

A cross-sectional study. The study was conducted in the Department of Medical Gastroenterology along with the Department of Radiology, Medical College Thiruvananthapuram over a study period of 2 years (2016–2018).

Study Population

Every consecutive patient undergoing CT abdomen, with findings suggestive of NAFLD in the imaging was included.

Sample Size Calculation

A similar study conducted by van der Poorten et al. published in the Journal of Hepatology vol 2, August 2008, was utilized in calculating where the study included 38 patients and the sample size was 64.

Inclusion Criteria

Patients >18 years undergoing routine CT abdomen in the Department of Radiodiagnosis who were found to have NAFLD on CT.

Exclusion Criteria

Patients unwilling to give consent for the study.

Method of Data Collection

The study was done in the Department of Medical Gastroenterology, Medical College Thiruvananthapuram. Adult patients aged 18 years and above undergoing CT abdomen in the Department of Radiodiagnosis who were incidentally to have NAFLD were enrolled.

CT criteria for fatty liver:

• The liver attenuation was 10 HU less than that of the spleen or,
• The attenuation of the liver was less than 40 HU.

Visceral fat volume at L3 and L4 levels was calculated. Visceral fat was measured as follows.

Prerequisites

Axial slices at the level of the L3/L4 vertebral body.

Slice thickness of 2.5/1.25 mm. Minimum of four slices are required.

Steps in analyzing the visceral fat volume

• Select slices and open in Reformat.
• Change view 1 to axial.
• Segment—Threshold move the min and max sliders to highlight fat alone in green (typically –200 to –30).
• Apply Threshold.
• Double click on view 2 so that it is highlighted with red borders and no other viewports are selected. Click on keep object and click on subcutaneous fat on view 2. This will remove the cradle.
• Segment—Scalpel—draw around the visceral fat in view 2 → cut inside.
• Double click on view 2. Now view 1 is in red and view 2 in green borders.
• Segment—Advanced processing—Subtract.
• In view 1—Use scalpel and draw around the visceral fat and select cut outside.
• Display—Measure volume and click on view 1 and view 2. You can see the volume...
Assessment of Visceral Fat Volume

Patients diagnosed to have NAFLD as per imaging were subjected to FibroScan using VCTE within 2 weeks.

Grading of NAFLD fibrosis was done as:
- F0 and F1 → 2–7 kPa.
- F2 → 7.5–10 kPa.
- F3 and F4 → ≥10 kPa (also known as advanced fibrosis).

**Ethical Consideration**

Ethical committee clearance was obtained and written consent was taken from the study population both in English and Malayalam.

**Discussion**

The mean body mass index (BMI) in patients with advanced fibrosis was more than in patients without advanced fibrosis. Previous studies have also shown that BMI is a predictor of advanced fibrosis. BMI is a component of advanced fibrosis predictor scores like the BARD score. Advanced fibrosis patients had an increased visceral fat volume than those without. van der Poorten et al. have shown that visceral fat volume was a predictor of fibrosis and inflammation of the liver. Hemoglobin A1c (HbA1c) and fasting blood sugar (FBS) were higher in patients with advanced fibrosis. Diabetes mellitus is in fact a component of well-validated established scoring systems of advanced fibrosis.

Patients with advanced fibrosis were shown to have elevated ferritin levels. Ferritin is an acute phase reactant and it will be increased in the background of inflammation and increase in ferritin in those with advanced fibrosis suggest two things, first thing is that those with advanced fibrosis have more necroinflammation than those without advanced fibrosis and second thing is that those with advanced fibrosis have a secondary iron overload in liver. This could result in higher ferritin levels.

Visceral fat in our study population ranged from 140 to 360 cm³. In Michalis Mantatzis et al.’s study, mean visceral fat volume at L3–L4 level was 189 cm³.

About 0.733 was the AUROC for visceral fat in predicting advanced fibrosis. Cutoff was 167.5 cm³ (sensitivity was 77.4% and specificity was 51.5% in predicting advanced fibrosis).

Among the variables analyzed, BMI, weight, serum glutamic pyruvic transaminase, serum glutamic oxaloacetic transaminase (SGOT), cholesterol, triglycerides, FBS, and HbA1c had a significant positive correlation but height had a negative correlation with visceral fat volume at L3–L4 level. A study by Janssen et al. also suggests that BMI has a positive correlation with visceral fat volume.

Age was not shown to be a predictor of advanced fibrosis in the female population in our study probably because of the small sample size and narrow age spread of the sample. Higher weight, SGOT, and FBS predicted advanced fibrosis. Platelet count, cholesterol, and low-density lipoprotein (LDL) were less in patients with advanced fibrosis. Lower levels of cholesterol and LDL in advanced fibrosis are due to mitochondrial and endoplasmic reticulum dysfunction in advanced fibrosis resulting in abnormal lipoprotein synthesis and folding.

Twenty patients had BMI ≤25 (nonobese NAFLD) in our study. Lean NASH is an important emerging entity, so the indicators of advanced fibrosis in patients with nonobese NAFLD were analyzed. Mean values of height, weight, and triglycerides were more in patients with advanced fibrosis in comparison to those without advanced fibrosis. Mean values of albumin and cholesterol were low in patients with advanced fibrosis. Visceral fat also turned out to be not a predictor of advanced fibrosis in patients with BMI ≤25. In obese male patients, 0.754 was the AUROC (at a cutoff of 180 cm³ had a sensitivity of 75% and specificity of 60% in predicting advanced fibrosis).

**Conclusions**

- Visceral fat volume measured at L3–L4 level ≥167.5 cm³ predicted advanced fibrosis.
- Visceral fat volume predicted advanced fibrosis in obese males at a cutoff of 180 cm³.
- Age, weight, BMI, and visceral fat volume measured at L3–L4 level, HbA1c, FBS, and ferritin were independent predictors of advanced fibrosis.

**References**


Kidney Disease Patterns diagnosed by Kidney Biopsy: A Single-center Experience from Central India

Ritesh Kumar Banode1, Piyush Kimmatkar2, Charulata Bawankule3, Vandana Adamane4, Vishal Ramteke5

Received: 12 October 2021; Revised: 13 May 2022; Accepted: 02 June 2022

Abstract

The incidence of kidney disease patterns diagnosed by kidney biopsy depends on age, gender, race, socioeconomic, nutritional, and environmental factors. The present study was performed at a tertiary care teaching hospital in central India to show the current frequency of different types of kidney diseases through histopathological findings. Materials and methods: We carried out a retrospective analysis of kidney biopsies done in our institute between January 2016 and June 2021, and clinical and histopathological correlation was done from the available medical records. Results: Of the 411 kidney biopsies evaluated, 56.7% were females and the mean age of patients was 31.65 years. The elderly population (age ≥60 years) constituted 5% of patients. The most common indication for kidney biopsy was nephrotic syndrome (NS) (49.9%). On analysis of histological patterns, 59.3% of patients had primary glomerular disease (PGD), 28% had secondary glomerular disease (SGD), 5.2% had tubulointerstitial disease (TID), and 6.7% had vascular disease. In our study, focal segmental glomerulosclerosis (FSGS) was the most common PGD (28.9% of all PGD) followed by membranous nephropathy (MN) (19.7%), minimal change disease (MCD) (16.5%), and IgA nephropathy (IgAN) (15.4%). The most common SGD was lupus nephritis (LN) (23%) followed by diabetic nephropathy (DN) (1.99%). In patients aged ≤18 years, MCD was the most common PGD (26.5%) and FSGS was the most common SGD (30%) in patients aged between 19 and 59 years. In the elderly population (age ≥60 years), MN was the most common (38%) PGD. Conclusion: This is the largest study of kidney biopsies patterns from the central part of India, and it presents the combined analysis of the clinical, histopathological, and immunofluorescent features of biopsy-proven kidney diseases in our population.

Introduction

The incidence of kidney diseases is rising to alarming proportions in India due to increasing cases of diabetes mellitus, hypertension, and the growing geriatric population. The incidence of kidney disease patterns diagnosed by kidney biopsy depends on age, gender, race, socioeconomic, nutritional, and environmental factors.1,2 Recent study has suggested that the pattern of glomerular diseases in different parts of the world is changing.3 The “gold standard” diagnostic tool in patients with kidney disease is kidney biopsy which not only provides a precise diagnosis but also provides knowledge regarding the level of disease activity and severity, and hence aids in the choice of specific therapeutic decisions to be made and predicting prognosis.4 The common clinical indication for kidney biopsy are NS, nephritic syndrome, rapidly progressive kidney failure (RPKF), subnephrotic proteinuria, asymptomatic urinary abnormality (AUA), nonrecovering acute kidney injury (AKI), unexplained chronic kidney disease (CKD), kidney involvement in systemic diseases, and kidney transplant dysfunction. National kidney biopsy registries are available in developed countries which represent the pattern of kidney diseases most commonly encountered but such registry for kidney diseases is not available in India. There are limited studies on the prevalence of kidney diseases from different parts of India with none available from central India to date. Since the prevalence of kidney diseases varies between different parts of the world and also within different regions of the same country, the present study was performed at a tertiary care teaching hospital in central India to show the current frequency of different types of kidney diseases through histopathological findings at this region.

Materials and Methods

We retrospectively analyzed 411 native kidney biopsies performed for suspected kidney disease in our institute from January 2016 to June 2021. The study was given ethical clearance from the Institutional Ethics Committee. Following data were recorded from a patient: age, gender, indication for kidney biopsy, hemoglobin, serum creatinine, 24-hour urinary protein level, urine microscopy, virology, hepatitis B surface antigen, hepatitis C antibody, human immunodeficiency virus, serum cholesterol, serum triglyceride, serology, antinuclear antibody, antidualle stranded DNA antibody, antiglomerular basement membrane (GBM) antibody, serum protein electrophoresis, antineutrophil cytoplasmic antibodies (ANCA), complement C3 and C4 level, and histopathological diagnosis. All kidney biopsies were performed by nephrologists percutaneously under ultrasound guidance using an automated gun (16, 18 G). The kidney biopsy specimens were prepared as per the standard protocol and examined by the same renal pathologists. Biopsy specimens were processed for light microscopy (LM) and immunofluorescence (IF) examination. Electron microscopy studies were performed only in selected cases as this facility was not freely available at our center. Based on clinical and histological findings, patients were categorized into four major groups, namely PGDs, SGDs, TIDs, and vascular diseases. The PGD included MCD, MN, IgAN, FSGS, membranoproliferative glomerulonephritis (MPGN), mesangiocapillary glomerulonephritis (MesPGN), crescentic glomerulonephritis, C3 glomerulopathy (C3GN), diffuse proliferative glomerulonephritis (DPGN), C1q nephropathy (C1qN), and fibrillary glomerulonephritis. The SGD included infection-related glomerulonephritis (IRGN), LN, systemic vasculitis, amyloidosis, monoclonal immunoglobulin deposit disease, and DN. The tubulointerstitial group comprised...
Kidney Disease Patterns diagnosed by Kidney Biopsy

Statistical Analysis

Data were statistically analyzed using the SPSS version 25 software program (SPSS Inc., Chicago, IL, USA). All continuous variables were expressed as the mean with standard deviation while categorical variables were expressed as numbers and percentages.

Results

A total of 411 cases of native kidney biopsies were done during the study period (from January 2016 to June 2021). On histopathological examination, the average glomerular yield was 18.50 ± 9.61 glomeruli with only 12.6% of patients having less than 10 glomeruli per core. Out of the total kidney biopsies, eight (1.9%) biopsies were inadequate due to the absence of renal tissue or the lack of glomeruli or suboptimal number of glomeruli hence were excluded from further analysis, and 403 kidney biopsies were included in the final analysis. LM and IF were done in all kidney biopsy specimens. Electron microscopy was done only in two (0.49%) of the sample.

Clinical Presentation

Demographic profiles of patients are shown in Table 1. Out of 411 kidney biopsies performed, 233 (56.7%) were female and 178 (43.3%) were male. The average age of the study population was 31.65 ± 14.56 years and 153 (37.2%) patients had serum creatinine more than 1.5 mg/dL at the time of kidney biopsy. Dialysis was required in 56 (13.6%) patients prior to kidney biopsy. As shown in Figure 1, 218 (53%) patients were between the age group 19 and 39 years followed by 93 (23%) between the age group 40 and 59 years, 79 (19%) in the age group less than or equal to 18 years, and 21 (5%) were more than or equal to 60 years of age. Table 2 shows the indications for kidney biopsy according to clinical presentation. NS, 205 (49.9%), was the most common indication for kidney biopsy followed by systemic lupus erythematosus (SLE) with LN 90 (21.9%), CKD 50 (12.16%), rapidly progressing renal failure 22 (5.35%), AKI 21 (5.10%), acute nephritic syndrome 18 (4.35%), and subnephrotic proteinuria 4 (0.97%).

Table 2: Clinical presentation of the patients

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Number (n = 411)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS</td>
<td>205 (49.9%)</td>
</tr>
<tr>
<td>Nephritic syndrome 18</td>
<td>4.35%</td>
</tr>
<tr>
<td>SLE/LN 90 (21.9%)</td>
<td></td>
</tr>
<tr>
<td>AKI 21 (5.10%)</td>
<td></td>
</tr>
<tr>
<td>CKD 50 (12.16%)</td>
<td></td>
</tr>
<tr>
<td>RPKF 22 (5.35%)</td>
<td></td>
</tr>
<tr>
<td>Subnephrotic proteinuria</td>
<td>4 (0.97%)</td>
</tr>
<tr>
<td>AUA 1 (0.2%)</td>
<td></td>
</tr>
</tbody>
</table>

NS, nephrotic syndrome; SLE, systemic lupus erythematosus; LN, lupus nephritis; AKI, acute kidney injury; CKD, chronic kidney disease; RPKF, rapidly progressing kidney failure; AUA, asymptomatic urinary abnormality

Histological Diagnosis

Figure 2 shows syndrome-wise histological diagnoses in our patients. PGD was the most common kidney disease and was diagnosed in 59.3% of the patients after kidney biopsy followed by SGD in 28%, TID in 6.7%, vascular disease in 5.2%, and 1% had normal kidney biopsy.

Glomerular Diseases

Table 3 shows the distribution of various kidney diseases in different subgroups and Figure 3 shows the prevalence of various glomerular diseases among PGD. Among the 239 patients with PGD, FSGS was the most common (28.9%) followed by primary membranous nephropathy (PMN) (19.7%), MCD (16.4%), IgAN (15.4%), C3GN (5.4%), DPGN

Table 1: Demographic profile of patients

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Number (%) (n = 411)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) mean ± SD</td>
<td>31.65 ± 14.56</td>
</tr>
<tr>
<td>Male (%)</td>
<td>178 (43.30%)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>233 (56.70%)</td>
</tr>
<tr>
<td>Patients with serum creatinine ≥1.5 mg/dL (%)</td>
<td>153 (37.2%)</td>
</tr>
<tr>
<td>Patient requiring dialysis prior to biopsy (%)</td>
<td>56 (13.6%)</td>
</tr>
</tbody>
</table>

Fig. 1: Age distribution of study population

Fig. 2: Types of kidney diseases found on biopsy among the study patients. GD, glomerular disease; VD, vascular disease; TID, tubulointerstitial disease; NAD, no abnormality detected
Kidney Disease Patterns diagnosed by Kidney Biopsy

(4.6%), MPGN (3.8), C1qN (2.5%), MesPGN (1.2), fibrillary glomerulonephritis (0.84%), anti-GBM (0.84%), and Alport syndrome (0.42%) as shown in Figure 3. Overall there were 69 (17.25%) cases of FSGS in the study population with a male to female ratio of 1:1.2. Mean age of patients with FSGS was 31 years and the most common presentation was NS (95.7%) followed by CKD (4.3%) in patients aged ≤18 years, MCD was the most common PGD whereas FSGS was the most common in patients aged between 19 and 59 years. At an age of ≥60 years, MN was the most common PGD.

In our study, the most common SGD was LN 94 (83.2%) followed by, diabetic kidney disease 8 (7%), AL amyloidosis 7 (6.2%), and AA amyloidosis 3 (2.7%). There were 94 cases of LN with an average age of 27 years and a male to female ratio of 1:7.5. Table 6 shows an analysis of different classes of LN. In the LN subgroup, the most common was class IV LN (29%) followed by class IV + V (21%), class III (16%), class V (16%), class III + V (8%), class II (6%), class VI (3%), and lupus podocytopathy (1%). About 5.3% of lupus cases presented as crescentic LN. In AL amyloidosis patients 5 (71%) had lambda restriction and 2 (29%) had kappa restriction pattern on IF.

**Non-glolemular Diseases**

In TID group (n = 21), ATIN 9 (43%) was the most prevalent, followed by CTIN in 8 (38%) and ATIN in 4 (19%) patients. Vascular nephropathies

### Table 3: Distribution and basic data of patients with kidney disease according to histopathological pattern

<table>
<thead>
<tr>
<th>Major group</th>
<th>Patients n (%)</th>
<th>Age (years) Mean ± SD</th>
<th>Male n (%)</th>
<th>Female n (%)</th>
<th>Proteinuria (gm/day) Mean ± SD</th>
<th>Serum creatinine (mg/dL) Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary GD</td>
<td>239 (59.3%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSGS</td>
<td>69 (17.25%)</td>
<td>31 ± 5</td>
<td>31 (45%)</td>
<td>38 (55%)</td>
<td>4.02 ± 0.12</td>
<td>1.2 ± 0.76</td>
</tr>
<tr>
<td>PMN</td>
<td>47 (11.66%)</td>
<td>38 ± 7</td>
<td>26 (56%)</td>
<td>21 (44%)</td>
<td>4.75 ± 3.33</td>
<td>0.95 ± 0.34</td>
</tr>
<tr>
<td>MCD</td>
<td>39 (9.68%)</td>
<td>27 ± 14</td>
<td>24 (62%)</td>
<td>15 (38%)</td>
<td>3.75 ± 2.42</td>
<td>0.83 ± 0.45</td>
</tr>
<tr>
<td>IgAN</td>
<td>37 (9.18%)</td>
<td>28 ± 11</td>
<td>22 (60%)</td>
<td>15 (40%)</td>
<td>2.44 ± 1.07</td>
<td>3.74 ± 3.6</td>
</tr>
<tr>
<td>C3GN</td>
<td>13 (3.23%)</td>
<td>7 ± 5</td>
<td>7 (54%)</td>
<td>6 (46%)</td>
<td>3.28 ± 2.32</td>
<td>1.74 ± 1.5</td>
</tr>
<tr>
<td>DPNG</td>
<td>11 (2.72%)</td>
<td>32 ± 17</td>
<td>9 (82%)</td>
<td>2 (18%)</td>
<td>3.48 ± 1.72</td>
<td>1.73 ± 1.28</td>
</tr>
<tr>
<td>C1qN</td>
<td>6 (1.49%)</td>
<td>28 ± 7.5</td>
<td>4 (67%)</td>
<td>2 (33%)</td>
<td>5.57 ± 4.71</td>
<td>1.06 ± 0.57</td>
</tr>
<tr>
<td>Anti-GBM disease</td>
<td>2 (0.5%)</td>
<td>38 ± 29</td>
<td>1 (50%)</td>
<td>1 (50%)</td>
<td>1.70 ± 0.14</td>
<td>4.7 ± 1.8</td>
</tr>
<tr>
<td>MPGN-IC</td>
<td>9 (2.23%)</td>
<td>25 ± 11</td>
<td>3 (44%)</td>
<td>5 (56%)</td>
<td>4.04 ± 2.06</td>
<td>1.91 ± 1.8</td>
</tr>
<tr>
<td>MesPGN</td>
<td>3 (0.75%)</td>
<td>18 ± 5</td>
<td>1 (33%)</td>
<td>2 (67%)</td>
<td>1.01 ± 0.17</td>
<td>2.26 ± 1.36</td>
</tr>
<tr>
<td>Fibrillary glomerulonephritis</td>
<td>2 (0.5%)</td>
<td>41 ± 2</td>
<td>0</td>
<td>2 (100%)</td>
<td>2.55 ± 0.77</td>
<td>6.57 ± 5.35</td>
</tr>
<tr>
<td>Alport syndrome</td>
<td>1 (0.25%)</td>
<td>12</td>
<td>1 (100%)</td>
<td>0</td>
<td>2.80</td>
<td>0.8</td>
</tr>
<tr>
<td>Secondary GD</td>
<td>113 (28%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LN</td>
<td>94 (23%)</td>
<td>27 ± 10</td>
<td>11 (12%)</td>
<td>83 (88%)</td>
<td>3.17 ± 2.99</td>
<td>1.72 ± 1.64</td>
</tr>
<tr>
<td>AL amyloidosis</td>
<td>7 (1.74%)</td>
<td>54 ± 6</td>
<td>5 (72%)</td>
<td>2 (28%)</td>
<td>3.98 ± 2.97</td>
<td>3.88 ± 3.1</td>
</tr>
<tr>
<td>AA amyloidosis</td>
<td>3 (0.75%)</td>
<td>35 ± 14</td>
<td>2 (67%)</td>
<td>1 (33%)</td>
<td>7.13 ± 6.05</td>
<td>0.73 ± 0.11</td>
</tr>
<tr>
<td>IRGN</td>
<td>1 (0.25%)</td>
<td>15</td>
<td>0</td>
<td>1 (100%)</td>
<td>1.05</td>
<td>1.8</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>8 (1.99%)</td>
<td>41 ± 14</td>
<td>2 (25%)</td>
<td>6 (75%)</td>
<td>3.78 ± 2.05</td>
<td>3.31 ± 2.51</td>
</tr>
<tr>
<td>TID</td>
<td>n = 21 (5.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATIN</td>
<td>4 (0.99%)</td>
<td>44.3 ± 9.5</td>
<td>3 (75%)</td>
<td>1 (25%)</td>
<td>1.80 ± 1.29</td>
<td>4.05 ± 0.5</td>
</tr>
<tr>
<td>CTIN</td>
<td>8 (1.98%)</td>
<td>39.5 ± 15</td>
<td>4 (50%)</td>
<td>4 (50%)</td>
<td>0.96 ± 0.076</td>
<td>2.96 ± 2.67</td>
</tr>
<tr>
<td>ATI</td>
<td>9 (2.24%)</td>
<td>43 ± 17</td>
<td>8 (89%)</td>
<td>1 (11%)</td>
<td>1.38 ± 0.83</td>
<td>8.75 ± 7.29</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>n = 27 (6.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMA</td>
<td>8 (1.99%)</td>
<td>29 ± 16</td>
<td>3 (37%)</td>
<td>5 (63%)</td>
<td>1.83 ± 0.623</td>
<td>6.32 ± 3.3</td>
</tr>
<tr>
<td>ACN</td>
<td>7 (1.74%)</td>
<td>34 ± 11</td>
<td>0</td>
<td>7 (100%)</td>
<td>1.35 ± 0.367</td>
<td>7.98 ± 2.62</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>7 (1.74%)</td>
<td>40 ± 14</td>
<td>1 (14%)</td>
<td>6 (86%)</td>
<td>2.58 ± 1.07</td>
<td>6.11 ± 4.01</td>
</tr>
<tr>
<td>HTN nephroparesis</td>
<td>5 (1.24%)</td>
<td>50 ± 13</td>
<td>5 (100%)</td>
<td>0</td>
<td>1.68 ± 0.83</td>
<td>2.86 ± 0.54</td>
</tr>
<tr>
<td>Normal study</td>
<td>3 (0.75%)</td>
<td>29 ± 15</td>
<td>1 (33%)</td>
<td>2 (67%)</td>
<td>0.86 ± 0.164</td>
<td>0.01 ± 0.26</td>
</tr>
</tbody>
</table>

GD, glomerular disease; MCD, minimum change disease; FSGS, focal and segmental glomerulosclerosis; PMN, primary membranous nephropathy; IgAN, IgA nephropathy; MPGN, membranoproliferative glomerulonephritis; C3GN, C3 glomerulopathy; MesPGN, mesangioproliferative glomerulonephritis; DPGN, diffuse proliferative glomerulonephritis; C1qN, C1q nephropathy; GBM, glomerular basement membrane; IRGN, infection-related glomerulonephritis; TID, tubulointerstitial; ATIN, acute interstitial nephritis; CTIN, chronic tubulointerstitial nephritis; ATI, acute tubular injury; TMA, thrombotic microangiopathy; ACN, acute cortical necrosis; HTN, hypertension; LN, lupus nephritis
were few in our series (n = 27), TMA was the most common in this group (8 [29%], vasculitis in 7 [26%], ACN in 7 [26%], and hypertensive nephrosclerosis in 5 [19%]) patients. In systemic vasculitis involving the kidney, 57% of the patients were C ANCA positive, 29% were P ANCA positive, and 14% were seronegative for both. About 86% of the cases of cortical necrosis were related to complications of pregnancy.

**Discussion**

This study was conducted to understand the pattern of biopsy-proven kidney diseases in central India over the last 5 years. This was a single-center retrospective study from a tertiary care teaching hospital in central India and provides information about the demographic profile, the clinical indication of kidney biopsy, and the pattern of various biopsy-proven kidney diseases in this part of central India. There are sparse data on kidney biopsies from our state and none is available from this part of India. In the present study, it was observed that females predominated over the males with an M:F ratio of 1:1.3. Similar observation was made in other studies done in India, Egypt, Iran, and Jordan.5–8 Female predominance over males was observed in the current study which was due to the high share of LN cases, the incidence of which is much

**Table 4: Distribution of patients with FSGS according to histopathological variant**

<table>
<thead>
<tr>
<th>FSGS type</th>
<th>Patients (n)</th>
<th>Age (years) Mean ± SD</th>
<th>Male n (%)</th>
<th>Female n (%)</th>
<th>Proteinuria (gm/day) Mean ± SD</th>
<th>Serum creatinine (mg/dL) Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOS variant</td>
<td>55 (79.7%)</td>
<td>31.62 ± 15.17</td>
<td>30 (56%)</td>
<td>25 (44%)</td>
<td>4.02 ± 2.14</td>
<td>1.22 ± 0.77</td>
</tr>
<tr>
<td>Tip variant</td>
<td>10 (14.5%)</td>
<td>31.74 ± 15.06</td>
<td>7 (70%)</td>
<td>3 (30%)</td>
<td>4.02 ± 2.15</td>
<td>1.22 ± 0.70</td>
</tr>
<tr>
<td>Parahilar variant</td>
<td>1 (1.5%)</td>
<td>55</td>
<td>1 (100%)</td>
<td>–</td>
<td>3.06 ± 2.80</td>
<td>0.63 ± 0.47</td>
</tr>
<tr>
<td>Cellular variant</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Collapsing variant</td>
<td>3 (4.3%)</td>
<td>24.8 ± 14.57</td>
<td>2 (67%)</td>
<td>1 (33%)</td>
<td>3.06 ± 2.80</td>
<td>0.63 ± 0.47</td>
</tr>
</tbody>
</table>

FSGS, focal segmental glomerulosclerosis; NOS, not otherwise specified

**Table 5: Age stratification of patients with biopsy-proven PGD**

<table>
<thead>
<tr>
<th>Kidney disease</th>
<th>Age groups and number of patients in each group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤18 years</td>
</tr>
<tr>
<td>FSGS</td>
<td>n (%)</td>
</tr>
<tr>
<td>PMN</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>MCD</td>
<td>14 (26.5%)</td>
</tr>
<tr>
<td>IgAN</td>
<td>7 (13%)</td>
</tr>
<tr>
<td>C3GN</td>
<td>4 (7.5%)</td>
</tr>
<tr>
<td>DPGN</td>
<td>4 (7.5%)</td>
</tr>
<tr>
<td>C1qN</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Fibrillary glomerulopathy</td>
<td>0 (2%)</td>
</tr>
<tr>
<td>Anti-GBM disease</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>MPGN</td>
<td>4 (7.5%)</td>
</tr>
<tr>
<td>MesPGN</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Alport syndrome</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Total</td>
<td>53 (100%)</td>
</tr>
</tbody>
</table>

MCD, minimum change disease; FSGS, focal and segmental glomerulosclerosis; PMN, primary membranous nephropathy; IgAN, IgA nephropathy; MPGN, membranoproliferative glomerulonephritis; C3GN, C3 glomerulopathy; MesPGN, mesangioproliferative glomerulonephritis; DPGN, diffuse proliferative glomerulonephritis; C1qN, C1q nephropathy; GBM, glomerular basement membrane
Kidney Disease Patterns diagnosed by Kidney Biopsy

Table 6: Distribution of patients with LN according to histopathological class as per International Society of Nephrology/Renal Pathology Society classification

<table>
<thead>
<tr>
<th>LN class</th>
<th>Patients n (%)</th>
<th>Male n (%)</th>
<th>Female n (%)</th>
<th>Age (years) Mean ± SD</th>
<th>Proteinuria (gm/day) Mean ± SD</th>
<th>Serum creatinine (mg/dL) Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class II</td>
<td>6 (6%)</td>
<td>1 (12%)</td>
<td>5 (88%)</td>
<td>18 ± 5</td>
<td>1.42 ± 0.97</td>
<td>0.68 ± 0.16</td>
</tr>
<tr>
<td>Class III</td>
<td>15 (16%)</td>
<td>2 (13)</td>
<td>13 (87)</td>
<td>24 ± 9</td>
<td>1.505 ± 0.60</td>
<td>1.14 ± 0.99</td>
</tr>
<tr>
<td>Class IV</td>
<td>27 (29%)</td>
<td>2 (24)</td>
<td>24 (76)</td>
<td>27 ± 10</td>
<td>2.99 ± 2.80</td>
<td>1.74 ± 1.6</td>
</tr>
<tr>
<td>Class V</td>
<td>15 (16%)</td>
<td>3 (12)</td>
<td>12 (88)</td>
<td>27 ± 10</td>
<td>3.02 ± 2.86</td>
<td>0.87 ± 0.27</td>
</tr>
<tr>
<td>Class VI</td>
<td>3 (3%)</td>
<td>1 (2)</td>
<td>2 (88)</td>
<td>27 ± 16</td>
<td>2.13 ± 0.757</td>
<td>6.3 ± 3.7</td>
</tr>
<tr>
<td>Class III + V</td>
<td>7 (8%)</td>
<td>0 (0)</td>
<td>6 (100)</td>
<td>27 ± 9</td>
<td>4.81 ± 3.71</td>
<td>1.06 ± 1.0</td>
</tr>
<tr>
<td>Class IV + V</td>
<td>20 (21%)</td>
<td>2 (10)</td>
<td>18 (90)</td>
<td>41 ± 23</td>
<td>4.10 ± 4.0</td>
<td>1.77 ± 1.04</td>
</tr>
<tr>
<td>Lupus podocytopathy</td>
<td>1 (1%)</td>
<td>0 (0)</td>
<td>1 (100)</td>
<td>29</td>
<td>0.90</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Table 7: Comparison of spectrum of kidney disease seen in our study with other studies in India

<table>
<thead>
<tr>
<th>Variable</th>
<th>Present study</th>
<th>Mittal et al. AIIMS, Delhi9</th>
<th>Krishna et al. IGIMS, Patna10</th>
<th>Das et al. NIMS, Hyderabad28</th>
<th>Golay et al. IPGMER, Kolkata18</th>
<th>Beniwal et al. SMS, Jaipur29</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of biopsies (n)</td>
<td>403</td>
<td>3,275</td>
<td>270</td>
<td>1,849</td>
<td>666</td>
<td>622</td>
</tr>
<tr>
<td>Primary GD (%)</td>
<td>59.3</td>
<td>73</td>
<td>88.89</td>
<td>69.1</td>
<td>79.13</td>
<td>79.4</td>
</tr>
<tr>
<td>FSGS (%)</td>
<td>17.25</td>
<td>16.1</td>
<td>31.11</td>
<td>10.5</td>
<td>18.02</td>
<td>10.5</td>
</tr>
<tr>
<td>PMN (%)</td>
<td>11.66</td>
<td>14.2</td>
<td>12.6</td>
<td>7</td>
<td>12.01</td>
<td>15</td>
</tr>
<tr>
<td>MCD (%)</td>
<td>9.68</td>
<td>14.9</td>
<td>5.56</td>
<td>15.1</td>
<td>20</td>
<td>21.1</td>
</tr>
<tr>
<td>IgAN (%)</td>
<td>9.18</td>
<td>9.2</td>
<td>8.52</td>
<td>4.4</td>
<td>8.1</td>
<td>7.4</td>
</tr>
<tr>
<td>C3GN (%)</td>
<td>3.23</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>DPGN (%)</td>
<td>2.72</td>
<td>2.3</td>
<td>13.33</td>
<td>4.7</td>
<td>4.95</td>
<td>5.3</td>
</tr>
<tr>
<td>C1qN (%)</td>
<td>1.49</td>
<td>0.5</td>
<td>–</td>
<td>–</td>
<td>0.15</td>
<td>–</td>
</tr>
<tr>
<td>Anti-GBM (%)</td>
<td>0.5</td>
<td>0.2</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>MPGn (%)</td>
<td>2.23</td>
<td>5.1</td>
<td>8.52</td>
<td>3.9</td>
<td>5.25</td>
<td>9.6</td>
</tr>
<tr>
<td>MesPGN (%)</td>
<td>0.75</td>
<td>2.3</td>
<td>3.33</td>
<td>5.2</td>
<td>0.6</td>
<td>6.4</td>
</tr>
<tr>
<td>Fibrillary glomerulonephritis (%)</td>
<td>0.5</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.15</td>
<td>–</td>
</tr>
<tr>
<td>Alport syndrome (%)</td>
<td>0.25</td>
<td>0.5</td>
<td>–</td>
<td>–</td>
<td>0.15</td>
<td>–</td>
</tr>
<tr>
<td>Secondary GD (%)</td>
<td>28%</td>
<td>15.5</td>
<td>7.4</td>
<td>18.2</td>
<td>20.87</td>
<td>14.5</td>
</tr>
<tr>
<td>LN (%)</td>
<td>23</td>
<td>9.4</td>
<td>5.56</td>
<td>14.6</td>
<td>15.32</td>
<td>7.6</td>
</tr>
<tr>
<td>Amyloidosis (%)</td>
<td>2.5</td>
<td>3.3</td>
<td>0.74</td>
<td>1.5</td>
<td>0.75</td>
<td>5.9</td>
</tr>
<tr>
<td>IRGN (%)</td>
<td>0.25</td>
<td>–</td>
<td>–</td>
<td>5.6</td>
<td>4.95</td>
<td>–</td>
</tr>
<tr>
<td>Diabetic nephropathy (%)</td>
<td>1.99</td>
<td>1.4</td>
<td>1.11</td>
<td>1.2</td>
<td>0.15</td>
<td>0.6</td>
</tr>
<tr>
<td>Tubulointerstitial disease (%)</td>
<td>5.2</td>
<td>5.3</td>
<td>1.5</td>
<td>6.7</td>
<td>–</td>
<td>4.5</td>
</tr>
<tr>
<td>ATIN (%)</td>
<td>0.99</td>
<td>1.2</td>
<td>–</td>
<td>1.1</td>
<td>–</td>
<td>0.8</td>
</tr>
<tr>
<td>CTIN (%)</td>
<td>1.98</td>
<td>2.0</td>
<td>0.37</td>
<td>3.7</td>
<td>–</td>
<td>0.6</td>
</tr>
<tr>
<td>ATI (%)</td>
<td>2.24</td>
<td>1.8</td>
<td>1.11</td>
<td>2.0</td>
<td>–</td>
<td>3.1</td>
</tr>
<tr>
<td>Vascular diseases (%)</td>
<td>6.7</td>
<td>3.7</td>
<td>2.2</td>
<td>3.5</td>
<td>–</td>
<td>1.1</td>
</tr>
<tr>
<td>TMA (%)</td>
<td>1.99</td>
<td>1.2</td>
<td>0.37</td>
<td>0.3</td>
<td>–</td>
<td>0.5</td>
</tr>
<tr>
<td>ACN (%)</td>
<td>1.74</td>
<td>1.4</td>
<td>–</td>
<td>0.5</td>
<td>–</td>
<td>0.5</td>
</tr>
<tr>
<td>Vasculitis (%)</td>
<td>1.74</td>
<td>2.8</td>
<td>1.85</td>
<td>0.6</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>HTN nephrosclerosis (%)</td>
<td>1.24</td>
<td>0.9</td>
<td>2.1</td>
<td>0.6</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

GD, glomerular disease; MCD, minimum change disease; FSGS, focal and segmental glomerulosclerosis; PMN, primary membranous nephropathy; IgAN, IgA nephropathy; MPGN, membranoproliferative glomerulonephritis; C3GN, C3 glomerulopathy; MesPGN, mesangioproliferative glomerulonephritis; DPGN, diffuse proliferative glomerulonephritis; C1qN, C1q nephropathy; GBM, glomerular basement membrane; IRGN, infection-related glomerulonephritis; ATIN, acute interstitial nephritis; CTIN, chronic tubulointerstitial nephritis; ATI, acute tubular injury; TMA, thrombotic microangiopathy; ACN, acute cortical necrosis; HTN, hypertension; LN, lupus nephritis.

higher in females than in males. Our patients were young with the mean age of patient being 31.65 ± 14.56 years and 74% of the patients were less than 40 years old. Only 5% of the patients were elderly (age ≥60 years). This trend of increased propensity at a young age is consistent with other studies from India with a mean age between 31 and 33 years.5,30 In developing countries, geriatric patients...
Kidney Disease Patterns diagnosed by Kidney Biopsy

accounted for only 2–10% of all the patients undergoing kidney biopsies whereas in developed countries, they constituted 14–29% of all kidney biopsies. 13–15 This observation may be related to better access to a healthcare facility and increased life expectancy, and probably contributes to the larger number of elderly patients being biopsied for a definitive diagnosis in high-income countries. In our study, NS was the most common indication of performing kidney biopsy (49.9%) followed by SLE with kidney involvement (21.9%). In similar studies from India and various parts of the world, NS was the most common indication for kidney biopsy as seen in our study. 8,10,14,15 AKI was present in 5.1% of the patients in our study. AKI was present in 8.2% of the studies from North India, only 1.8% of the patients in the study by Balakrishnan et al., and 0.9% in the Japanese registry data.11,13,16 This considerable difference may be due to the varying incidence and epidemiology of AKI in different parts of the world. Additionally, there is a wide variation in performing kidney biopsies in AKI patients at different centers. However, in recent years, there is a rising trend in the practice of biopsying patients with nonrecovering or unexplained AKI. Primary (59%) and secondary (28%) glomerular diseases were the most common histological diagnosis in our study which is consistent with other studies reported from India and other countries.9–11 The most common cause of PGD in our study was FSGS (28.9%) followed by MN (19.7%). Over the years, the incidence of FSGS and MN has been seen to be rising in the world. This trend has also been seen in the Indian population. Among other similar studies from India, the incidence of FSGS from Rathi et al. and Golay et al. were reported to be 30.6 and 27.4%, respectively.12,18 FSGS is reported as the most common cause of adult NS in those undergoing biopsy for proteinuria in studies from India, Pakistan, and Oman.9,10,19,20 There has been a paucity of data of various histological variants of FSGS in Indian patients. FSGS-NOS (79.7%) and tip variant (14.1%) were the most common pattern of FSGS in our study and similar observations were noted in other studies from India.21,22 The second most common cause of PGD in our study was MN (19.7%) as seen in a study done in Bihar and PG Chandigarh.13,17 However the prevalence of MN varied greatly ranging from 21.0% in a study by Cameron to 52.8% in a series by US cooperation study.23,24 In our study, anti-PLA2R staining by IHC tissue staining was positive in 89.4% of the patients and THSAD in 4.3% of the patients with MN and our finding was consistent with other studies.25 MCD was the third most common PGD in our study (16.5%) which was close to a study from PG Chandigarh.17 However among other Indian studies reported, incidence of MCD varied from 11.8 to 33.3%,9,13,26 and several studies in the last decade have shown a decrease in the relative frequency of MCD.19,20 This changing trend may be related to more widespread use of IF, IHC, and electron microscopy in the analysis of kidney biopsy leading to increased diagnosis of MN and FSGS, which are otherwise likely to be misdiagnosed as MCD in the past. Though IgAN has consistently been reported as the most common primary glomerulonephritis in USA, Europe, and Japan,3,11,12,16 it was only the fourth most common PGD in our study. Most Indian studies have reported IgAN as the third or fourth most common PGD with prevalence varying from 1.8 to 11.3%.9,10,13,17 Detection of IgAN depends upon a urinary screening program for AUA and kidney biopsy practices in such cases which is not a consistent practice among different centers in India. A higher incidence of IgAN in developed countries may be due to robust healthcare screening systems leading to the early detection of asymptomatic urinary abnormalities. Though FSGS was the most common PGD in our study, incidence varied across age groups. In patients aged ≤18 years, MCD was the most common PGD, whereas FSGS was the most common in patients aged between 19 and 59 years. At an age of ≥60 years, MN was the most common PGD. Similar observations were noted in other studies from India where MCD was the most common PGD at a younger age and MN was the most common PGD in the elderly population.9,18 LN was the most common SCD in our patients; this is comparable to other Indian and international studies.9,10,13,17 Among the SLE/LN group, the most common was class IV LN (24.4%) followed by class IV + V (22.2%) as seen in other studies from India.12,17 DN was the second most common SCD but accounted for only 1.9% of all kidney biopsies in our study which is comparable to other studies from the subcontinent.9,10,13,18,19 The prevalence of DN in most studies across the world ranges from 0.48 to 5.2%.6,7,15,16 There is still considerable obscurity about the criteria used for kidney biopsy in diabetic patients and this trend is reflected in biopsy studies as there was a wide variation in the number of diabetic patients being biopsied and the prevalence of DN reported. TMA was seen in 1.99% and vasculitis in 1.74% of kidney biopsies and is comparable to other Indian studies.13,20 Cortical necrosis was seen in 1.74% of biopsies and similar to the other studies from India and Pakistan.9,19 But very few cases of ACN were observed in the studies from developed countries.13,12,15,16 In our study, 86% of the cases of cortical necrosis was due to complication of pregnancy. This clustering of cortical necrosis cases in our young females is due to poor primary health infrastructure, irregular access to antenatal checkups, and unhygienic home delivery practices leading to an increase in the incidence of AKI during pregnancy in this part of the world. Among the TIDs group, AT1 (2.24%) was the most common diagnosis, followed by CTIN (1.99%) and ATIN (1%), and their prevalence was comparable to observation from other studies in India and elsewhere.9,10,13 Our study has certain limitations; first, because of the retrospective study design, the amount of data that can be collected from the medical records of the patients are limited. Secondly, there might be a selection bias since this was a hospital-based study and the patients in our study were not from the population screened for proteinuria, microscopic hematuria, and kidney dysfunctions. The electron microscopy of the biopsy samples was not done in all cases which could have helped in a better diagnosis. Finally, as shown in Table 7, even among published studies from different centers in India there is a variation in the presentation of various biopsies proven kidney disease.9,10,18,28,29

Conclusion

Our study confirms that FSGS is the most common PGD, followed by membranous glomerulopathy and LN is the most common SGD diagnosed in our population. This is in contrast to observation from the western world where IgAN is the most common PGD. However, India is a country with considerable racial, cultural, and dietary diversity, this call for the need for setting of regional and national kidney biopsy registry with the involvement from many more nephrology centers across the country to precisely study patterns of prevalent kidney diseases.

References

Kidney Disease Patterns diagnosed by Kidney Biopsy

Predictive Value of Frailty Index in Comparison to Traditional Markers of Sepsis in Predicting Mortality among Elderly Admitted in Tertiary Care Hospital

Ashwariya Murlidharan1, Minakshi Dhar2*, Monika Pathania3, Mayank Agarwal4, Prativa P Sethi5, Vartika Saxena6, Nowneet K Bhat7

Received: 12 September 2021; Revised: 19 May 2022; Accepted: 30 May 2022

ABSTRACT

Introduction: The frailty index's potential as a prognostic marker of sepsis is so far been untapped. Here we studied the predictive value of frailty index in the elderly with sepsis.

Methods: This prospective cohort study was conducted in a tertiary level hospital in North India. The duration of the study was 18 months starting from January 2020 to July 2021. The frailty index was calculated along with traditional markers of sepsis such as sequential organ failure assessment (SOFA), quick sequential organ failure assessment (qSOFA), and systemic inflammatory response syndrome (SIRS) within 24 hours of admission in elderly patients suspected to have sepsis. The area under the receiver operating characteristic (AUROC) of frailty index, SOFA, qSOFA, and SIRS was compared for in-hospital and 3-month mortality.

Results: There was no significant difference between the performance of the frailty index and SOFA (DeLong's test $p = 0.242$) in predicting in-hospital mortality, but there was a statistical difference between the AUROC of SOFA score ($AUC = 0.548$) and frailty in predicting 3-month mortality (DeLong's test $p \leq 0.001$).

Conclusion: The frailty index had greater sensitivity and negative predictive value among the other scores in predicting in-hospital mortality, whereas SOFA had higher specificity in predicting in-hospital mortality. The frailty index was superior to SOFA and the other prognostic markers of sepsis in predicting 3-month mortality.

INTRODUCTION

The mean age of patients being admitted in hospitals in India with sepsis is increasing gradually. The mean age of patients admitted with sepsis in a tertiary care hospital was 59.4 ± 17.9 years.1 In the same study, 85% of the total in-hospital mortality was attributable to sepsis. Sensitizing the medical fraternity and providing them with tools to handle this increasing population of elderly with sepsis is thus the need of the hour. Traditional prognostic markers and scores in critical illness rely excessively on derangements in acute physiologic state at or within 24 hours of admission—such as Acute Physiology and Chronic Health Evaluation II,2 SOFA,3 and Simplified Acute Physiology Score II. The abovementioned scores equate illness severity with the outcome of the patient.4 They do not include sociodemographic characteristics like age, social support, and education. Nor do they integrate important elements like prehospital functional status, severity of comorbid illness, disability, or frailty. However, in elderly patients, if considering short-term mortality and morbidity outcomes, addressing these limitations is particularly important following critical illness.

The elderly with their unique physiology have a widely varying response to sepsis and are more severely affected by insults, such as infection, than young adults. Therefore, generalizing the same conclusions derived from other landmark studies like sepsis-3 on young adults to elderly patients would be unfair.

In our study, we compared the frailty index with traditional markers of sepsis such as SOFA, SIRS, and qSOFA for the prediction of in-hospital mortality and 3-month mortality in elderly patients admitted with sepsis.

METHODS

A prospective cohort study was conducted in a tertiary healthcare facility in North India after the approval of the Institutional Ethics Committee. The study duration was 18 months which coincided with the peak of the COVID era. Patients were enrolled from January 2020 to July 2021. As per the World Health Organization, people equal to or older than 60 years are considered elderly. In the study, elderly patients with suspected sepsis were enrolled. Those patients were suspected to have sepsis whose blood culture, urine culture, or other infection-specific investigations (bacterial, viral, fungal, and parasitic) were sent within 72 hours of admission by the primary treating physician. The elderly with a history of prior antibiotic therapy (30 days) and localized infection were excluded. As frailty assessment requires a degree of mobility and intact cognition, elderly with Parkinson’s disease, previous stroke, cognitive impairment, and depression were also excluded. Those with a documented terminal illness (established life expectancy ≤6 months) were excluded. Since there is a lack of epidemiological data from India depicting in-hospital mortality for elderly patients with sepsis, a multicenter study conducted in Italy provided the expected in-hospital mortality for the study which was set at 12.5%.5 An AUROC curve for frailty equal to at least the lower limit of the 95% confidence interval (CI) of the AUROC for SOFA prediction of in-hospital mortality (outside intensive care unit) detected in sepsis-3,6 which was 0.79; 95% CI (0.78–0.80) would demonstrate the non-inferiority of frailty from SOFA. Therefore, the assumed AUROC for frailty was 0.78. A sample of 24 elderly participants in sepsis with eventual mortality led us to reach a statistical power of 81% to detect a statistically significant difference ($p < 0.05$) between the assumed AUROC of frailty and SOFA (calculation performed with PASS-14).

All consecutive elderly meeting the inclusion criteria were enrolled after taking their written informed consent (Fig. 1). Baseline demographic characteristics and clinical details of the population were entered on a predesigned Performa. Frailty index,

145 Junior Resident; 2Additional Professor; 3Associate Professor, Department of Internal Medicine; 4Professor, Department of Community and Family Medicine; 5Professor, Department of Pediatrics, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India; 6Corresponding Author

How to cite this article: Murlidharan A, Dhar M, Pathania M, et al. Predictive Value of Frailty Index in Comparison to Traditional Markers of Sepsis in Predicting Mortality among Elderly Admitted in Tertiary Care Hospital. J Assoc Physicians India 2022;70(9):32–36.
SOFA, SIRS, and qSOFA were calculated at the time of admission.

The Fried frailty index was used to assess frailty. It has five dimensions that reflect the impaired regulation of different systems of the body. These five dimensions are:

- Unintentional weight loss: It was assessed by asking the amount of weight loss in the last year, not because of dieting or exercise. If the answer was more than 4.5 kg then the criterion was met and a score of 1 was given to this item.

- Exhaustion: Exhaustion was measured by asking “How often did you feel that you could not get going?” and “How often did you feel that everything you did was an effort?” This was taken from the Center for Epidemiologic Studies Depression scale. Response options were “rarely or none of the time (<1 day), some or a little of the time (1–2 days), a moderate amount of the time (3–4 days), and most of the time” in Fried’s version. If the answer to at least one or two questions was “always or most of the time” then this criteria is met.

- Muscle weakness: Grip strength/muscle weakness was measured by asking the question from the Tilburg frailty indicator “Do you experience difficulties in daily life because of low grip strength?” Yes would count as a point.

- Slowness while walking: 6-minute walk test was used to assess the slowness of walking. In healthy adults, 6-minute walk distance has been reported to range from 400 to 700 m. Test was performed by making the subject walk on a 10-m strip, marked on the ground at a regular pace wearing his/her usual footwear. Distance covered in 6 minutes was noted. If the subject could walk for 6 minutes and cover a distance of more than 400 m, a score of 1 was given. If the walking distance was less than 400 m or the subject could not walk for 6 minutes, a score of 0 was given.

- Low levels of activity: Kilocalories per week were calculated by using the Minnesota leisure time activity questionnaire. Patients were stratified as per their gender and their physical activity. The calculated value was compared with the cutoff as described by Fried et al. (men 383 kcal/week and women 270 kcal/week). If the calculated value fell below this cutoff then this criterion was met.

- Interpretation of Fried frailty index: Patients with a score of 0 are classified as robust or not frail. A score of 1 or 2 is at intermediate risk for adverse outcomes and is considered to be pre-frail. A score of 3–5 indicates that someone is frail.

SOFa and qSOFA are scores that are used to quantify the degree of organ dysfunction and are helpful in stratifying patients with sepsis. Initially they were proposed as a tool for assessing respiratory, cardiovascular, hepatic, coagulation, renal, and neurological systems each scored from 0 to 4.

**RESULTS**

Sixty patients were sequentially enrolled and followed, of which 10 were excluded (two previous strokes, five previously on antibiotics, and three lost to follow-up). The mean age of the study population was 68.98 ± 7.18 years. Females comprised 46%. Diabetes followed by chronic obstructive pulmonary disease was the most common comorbidity in the study population at 34% and 28%, respectively. The most common site of infection was the respiratory tract (62%) followed by urinary tract and abdominal sepsis. Of the total patients followed, 13 (26%) were admitted to the critical care units.

Admission location, platelet count (lakh per mm²), PaO₂/FiO₂ ratio category, serum lactate (mmol/L), SOFA score, frailty index, frailty status, duration of hospital stay (days), requiring antibiotics were found to be significantly associated (p < 0.05) with in-hospital mortality. The AUROC for frailty index, SOFA, qSOFA, and SIRS in predicting in-hospital mortality was 0.888 (95% CI: 0.797–0.98) (p < 0.001), 0.768 (95% CI: 0.592–0.944) (p = 0.016), 0.531 (95% CI: 0.288–0.775) (p = 0.731), 0.549 (95% CI: 0.33–0.769) (p = 0.657), respectively. SOFA and frailty showed good diagnostic performance and were statistically significant. Pairwise comparison using DeLong’s test showed that there was no significant difference between frailty index and SOFA (DeLong’s test p = 0.242). However, frailty performed better than SIRS (p = 0.013) and qSOFA score (p = 0.006). Table 1 shows an association between in-hospital mortality, 3-month mortality, and various clinical parameters among the study participants.

**Table 2** shows the Frailty Index (cutoff 4) and SOFA score (cutoff 5) in predicting 3-month mortality was 0.844 (95% CI: 0.74–0.947) (p ≤ 0.001), 0.548 (95% CI: 0.387–0.709) (p = 0.562), 0.513 (95% CI: 0.382–0.644) (p = 0.850), 0.502 (95% CI: 0.346–0.659) (p = 0.984), respectively (Fig. 2). The diagnostic performance of frailty index (AUC = 0.844) was significantly better than that of SOFA score (AUC = 0.548) (DeLong’s test p = 0.001), qSOFA Score (p = 0.001), SIRS score (p = 0.001) in predicting 3-month mortality (Fig. 3).

Table 2 shows the Frailty Index (cutoff 4) is best parameter in term of sensitivity and negative predictive value whereas SOFA score is best in terms of diagnostic accuracy.
Predictive Value of Frailty Index in Elderly with Sepsis

The present study compared the predictive value of the frailty index with traditional markers of sepsis such as SOFA, SIRS, and qSOFA in predicting in-hospital mortality and 3-month mortality. We observed that the frailty index had the highest sensitivity and negative predictive value for mortality in the elderly with sepsis. However, SOFA had the highest positive predictive value and specificity among all the scores tested. Our study did not find any difference in the AUROC of SOFA and frailty in predicting in-hospital mortality but the frailty index was far superior to SOFA in predicting 3-month mortality. No significant difference was found in the AUROC of SOFA, qSOFA, and SIRS for 3-month mortality.

The mean age of presentation in our study was 68.98 ± 7.18 years, which is slightly younger compared to other studies conducted in developed countries with elderly with sepsis,14–16 probably reflecting the increased life expectancy in the developed countries. However, age was not found to be a good predictor of in-hospital mortality or 3-month mortality. In our study, the number of males was slightly more than females, 54 vs 46%, which could be attributed to fewer women seeking medical care in India.17

Table 1: Association between in-hospital mortality, 3-month mortality, and various parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>In-hospital mortality</th>
<th>3-month mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n = 8)</td>
<td>No (n = 42)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>69.62 ± 5.01</td>
<td>68.86 ± 7.57</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>4 (14.3%)</td>
<td>24 (85.7%)</td>
</tr>
<tr>
<td>70–79</td>
<td>4 (25.0%)</td>
<td>12 (75%)</td>
</tr>
<tr>
<td>80–89</td>
<td>0 (0.0%)</td>
<td>6 (100.0%)</td>
</tr>
<tr>
<td>Total</td>
<td>8 (16.0%)</td>
<td>42 (84%)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6 (75.0%)</td>
<td>21 (50.0%)</td>
</tr>
<tr>
<td>Female</td>
<td>2 (25.0%)</td>
<td>21 (50.0%)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>21.12 ± 2.23</td>
<td>20.71 ± 2.35</td>
</tr>
<tr>
<td>Admission location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Critical care area</td>
<td>5 (62.5%)</td>
<td>8 (19.0%)</td>
</tr>
<tr>
<td>Ward</td>
<td>3 (37.5%)</td>
<td>34 (81.0%)</td>
</tr>
<tr>
<td>Site of infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lungs</td>
<td>6 (75.0%)</td>
<td>25 (59.5%)</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>0 (0.0%)</td>
<td>6 (14.3%)</td>
</tr>
<tr>
<td>Multiple</td>
<td>1 (12.5%)</td>
<td>3 (7.1%)</td>
</tr>
<tr>
<td>Systemic</td>
<td>0 (0.0%)</td>
<td>4 (9.5%)</td>
</tr>
<tr>
<td>Abdomen</td>
<td>2 (12.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Skin</td>
<td>0 (0.0%)</td>
<td>1 (2.4%)</td>
</tr>
<tr>
<td>SOFA score</td>
<td>4.62 ± 1.92</td>
<td>2.81 ± 2.30</td>
</tr>
<tr>
<td>qSOFA score</td>
<td>1.12 ± 0.99</td>
<td>0.93 ± 0.46</td>
</tr>
<tr>
<td>SIRS score</td>
<td>2.00 ± 0.93</td>
<td>1.83 ± 0.99</td>
</tr>
<tr>
<td>Frailty index</td>
<td>4.62 ± 0.52</td>
<td>2.64 ± 1.53</td>
</tr>
<tr>
<td>Frailty status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not frail</td>
<td>0 (0.0%)</td>
<td>5 (11.9%)</td>
</tr>
<tr>
<td>Pre-frail</td>
<td>0 (0.0%)</td>
<td>16 (38.1%)</td>
</tr>
<tr>
<td>Frail</td>
<td>8 (100.0%)</td>
<td>21 (50.0%)</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>3.75 (0.46)</td>
<td>3.74 (1.33)</td>
</tr>
<tr>
<td>Duration of hospital stay (days)</td>
<td>15.88 ± 9.64</td>
<td>8.95 ± 6.94</td>
</tr>
<tr>
<td>Requiring higher level of care</td>
<td>8 (100.0%)</td>
<td>11 (26.2%)</td>
</tr>
<tr>
<td>Upgradation of antibiotics</td>
<td>5 (62.5%)</td>
<td>9 (21.4%)</td>
</tr>
</tbody>
</table>

DISCUSSION

The present study compared the predictive value of the frailty index with traditional markers of sepsis such as SOFA, SIRS, and qSOFA in predicting in-hospital mortality and 3-month mortality. We observed that the frailty index had the highest sensitivity and negative predictive value for mortality in the elderly with sepsis. However, SOFA had the highest positive predictive value and specificity among all the scores tested. Our study did not find any difference in the AUROC of SOFA and frailty in predicting in-hospital mortality but the frailty index was far superior to SOFA in predicting 3-month mortality. No significant difference was found in the AUROC of SOFA, qSOFA, and SIRS for 3-month mortality.

The mean age of presentation in our study was 68.98 ± 7.18 years, which is slightly younger compared to other studies conducted in developed countries with elderly with sepsis,14–16 probably reflecting the increased life expectancy in the developed countries. However, age was not found to be a good predictor of in-hospital mortality or 3-month mortality. In our study, the number of males was slightly more than females, 54 vs 46%, which could be attributed to fewer women seeking medical care in India.17
Predictive Value of Frailty Index in Elderly with Sepsis

Table 2: The various diagnostic parameters and the best performance of their scores

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Best score</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>The best parameter in terms of AUROC</td>
<td>Frailty index</td>
<td>0.888 (0.797–0.98)</td>
</tr>
<tr>
<td>The best parameter in terms of sensitivity</td>
<td>Frailty index (cutoff 4)</td>
<td>100.0% (63–100)</td>
</tr>
<tr>
<td>The best parameter in terms of specificity</td>
<td>SOFA score (cutoff 6)</td>
<td>95.2% (84–99)</td>
</tr>
<tr>
<td>The best parameter in terms of positive predictive value</td>
<td>SOFA score (cutoff 6)</td>
<td>66.7% (22–96)</td>
</tr>
<tr>
<td>The best parameter in terms of negative predictive value</td>
<td>Frailty index</td>
<td>100.0% (86–100)</td>
</tr>
<tr>
<td>The best parameter in terms of diagnostic accuracy</td>
<td>SOFA score</td>
<td>88.0% (76–95)</td>
</tr>
</tbody>
</table>

Fig. 2: Comparison of the diagnostic performance of SOFA, qSOFA, SIRS, and frailty index in predicting in-hospital mortality

Langlais et al. found that frailty index was not an independent risk factor in predicting mortality. However, in the same study, frailty was significantly associated with mortality and clinical frailty score (CFS) of less than five was excellent in predicting survival. Hence, if a patient is found to be not frail, it is predictive of a good outcome. This mirrors the finding of our study where the sensitivity of the frailty index was superior to that of SOFA and that there was no significant difference between the AUROC in SOFA and the frailty index in predicting in-hospital mortality. However, SOFA had the highest positive predictive value and specificity among all the scores tested. So, if a patient has a high SOFA value, it is fairly accurate in predicting mortality and is an excellent tool to diagnose sepsis, as proven in sepsis-3. SOFA showed poor diagnostic ability (AUROC 0.543) in predicting 3-month mortality. This was expected as SOFA is a tool to help diagnose and predict in-hospital mortality with sepsis. Instead, frailty index and length of hospital stay were significantly associated with 3-month mortality in another study that compared frailty with qSOFA and SIRS in predicting in-hospital mortality. Rookwood’s clinical frailty scale was superior to SIRS, but no significant difference was seen between qSOFA and Rookwood’s clinical frailty scale. The deviation from our results could be explained as qSOFA showed a poor diagnostic value (AUROC 0.531) in our study, perhaps because of the small sample size of our study.

In another prospective study conducted in France, frailty (assessed by CFS and phenotype model) was an independent risk factor for both in-hospital and 6-month mortality. Our results also showed that frailty was superior to SOFA, SIRS, and qSOFA in predicting 3-month mortality. Thus, we can assume that frailty status is more representative of an admission’s immediate short-term outcome (3- and 6-month mortality). The traditional scores calculated in patients with sepsis at the time of admission reflect their status during hospitalization; they focus more on organ involvement and vitals than the patient’s pre-existing reserves. Therefore, any outcome will depend on the condition at admission and pre-existing status, which could explain why the frailty index performed so well in predicting mortality, especially at 3 months.

Conclusion

Our study found that frailty was a good predictor of both in-hospital and 3-month mortality. There was no significant difference between SOFA and frailty in predicting in-hospital mortality; however, frailty performed better in predicting 3-month mortality.

Frailty has all the attributes of an excellent triaging tool. Its high sensitivity makes it easy to identify all those at high risk, even if it means over triaging a few. India is a country with varying distribution of wealth and resources, and such a tool can prove extremely useful to the physician to risk stratify the elderly and determine the level of care required in the management of acute illness.

Limitations

- The sample size for the study was calculated using western hospital records and data.
- In-hospital mortality was more than predicted in our study population. This could be attributed to the COVID-19 pandemic or merely representative of the mortality rate of the elderly in a tertiary hospital in India.
Predictive Value of Frailty Index in Elderly with Sepsis

- Larger studies evaluating the use of the frailty index in the assessment of an acutely ill elderly should be conducted considering the unique physiology of an elderly patient.

**Ethics Approval No**

Institutional Ethics Committee approval has been taken via letter no AIIMS/IEC/19/1035.

**Acknowledgments**

We acknowledge Dr Yogesh Saxena for helping us in statistical analysis. We also acknowledge the patient’s advisors for their contribution.

**References**

The World’s First Choice For Medical Gloves. Shouldn’t It Be Yours?

In an era that demands the highest standards of product quality in medical gloves, the most in-demand are those Made in Malaysia. Malaysian manufacturers make certain the gloves comply with stringent international standards, are consistent in quality and competitive in price. Malaysian manufacturers are committed to social responsibility and sustainability initiatives to not only ensure human health is preserved, but to have an equally positive impact on communities and the environment. When it comes to rubber, No One Knows Rubber Like Malaysia Does.

Reach Malaysian manufacturers via Marketplace at www.myrubbercouncil.com

- Excellent Barrier Protection
- Conform to International Standards
- World’s No 1 in Natural Rubber Gloves & Nitrile Gloves
- Made in Malaysia Quality Rubber Products
- Exported to 195 Countries

www.myrubbercouncil.com @MYrubbercouncil
**ABSTRACT**

**Background:** Acute kidney injury (AKI) is one of the most common clinical problems encountered by physicians in day-to-day practice which is associated with increased morbidity and mortality. The incidence of AKI is increasing so the right approach for interpretation of clinical clues and investigation may be lifesaving.

**Aim:** The study aimed to document the variety of unusual cases of AKI and suggest a case-based approach for clinical evaluation and investigations to help physicians treat such cases.

**Materials and methods:** This was a retrospective analysis of medical/electronic records of 10 patients who were admitted in medical wards between January 2020 and June 2021 and diagnosed to have AKI.

**Results:** We present the history, clinical findings, and investigations of 10 patients diagnosed with unusual causes of AKI.

**Conclusion:** It is important for physicians to recognize unusual causes of AKI. A high index of suspicion and timely diagnosis and treatment interventions may bring complete recovery of renal functions in patients of AKI.

**Introduction**

Acute kidney injury is one of the most common clinical problems associated with increased morbidity and mortality. Kidney Disease: Improving Global Outcomes (KDIGO) criteria define AKI as an increase in serum creatinine levels at least by 0.3 mg/dL within 48 hours or 1.5-fold the baseline, which is known or presumed to have occurred within the preceding 7 days, or according to the urine output criterion—as urine volume below 0.5 mL/kg/h for at least 6 hours.

The incidence of in-hospital as well as community-acquired AKI has increased in recent decades requiring greater awareness regarding its risk factors and availability of investigations. There are growing evidences suggesting that despite a complete recovery following AKI, it still remains a risk factor for long-term renal complications. Partial renal recovery following AKI is an important contributor to the progression of chronic kidney disease (CKD).

There seem to be dilemmas and challenges at times in diagnosing and ascertaining the cause of AKI. Delay in diagnosis and further management can impact patient and renal survival, especially in the vulnerable group.

In this article, we are presenting some unusual cases of AKI with a case-based approach for a timely diagnosis and management impacting complete renal recovery.

**Materials and Methods**

This was a retrospective analysis of medical/electronic records of 10 patients who were admitted in the medical wards of Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow between January 2020 and June 2021 and diagnosed to have AKI.

**Results**

We present the history, clinical findings, and investigations of 10 patients diagnosed with unusual causes of AKI. Table 1 summarizes clinical, hematological, and biochemical parameters in addition to specific investigations if performed.

**Case 1**

A 25-year-old male presented with a complaint of fever with chills and cola-colored urine for 8 days, followed by oliguria. On further inquiry, he had a history of similar episodes of illness 2 years back with evidences of hemolysis and non-dialysis-dependent AKI with self-recovery. On examination, he had pallor and edema with normotension. Laboratory parameters suggested pancytopenia—hemoglobin of 6 g/dL and thrombocytopenia with platelets of 30,000/cumm. The reticulocyte count was 3.4% with no evidence of hemolysis or schistocytes in the peripheral smear.

His creatine phosphokinase (CPK), lactate dehydrogenase (LDH), and glucose-6-phosphate dehydrogenase (G6PD) were all normal, urine was positive for hemoglobinuria but negative for myoglobin and Coombs test was negative. Blood counts along with serum procalcitonin were normal. The immunological workup, that is, complement levels (C3 and C4) were normal and antinuclear antibody (ANA) was negative. The Doppler ultrasound did not show any evidence of thrombosis or occlusion. In view of pancytopenia, bone marrow was showing cellular marrow with erythroid hyperplasia and normal or near-normal morphology. A fluorescein-labeled proaerolysin (FLAER)—based flow cytometry panel was ordered that suggested presence of large paroxysmal nocturnal hemoglobinuria (PNH) clones. So a diagnosis of PNH with AKI-KDIGO-Stage 3 was confirmed and on the basis of the past history of recurrent AKI, a possibility of intravascular hemolysis was kept. He was conservatively treated with blood transfusion, renal replacement therapy, and glucocorticoid at a dose of 1 mg/kg with rapid clinical and biochemical improvement.

**Case 2**

A 54-year-old female presented in the nephrology outpatient department (OPD) with a decrease in appetite and nausea for 7 days, with a serum creatinine of 3.8 mg/dL with bland urinary sediments and normal liver function tests. She revealed a history of severe dyspepsia for 2 weeks for which she took over-the-counter pantoprazole 40 mg once daily for 2 weeks. There was no history of any systemic involvement. There

---

1. Additional Professor, Department of Medicine;
2. Additional Professor, Department of General Surgery, Dr. Ram Manohar Lohia Institute of Medical Sciences;
3. Associate Professor, Department of General Surgery, Ram Manohar Lohia Institute of Medical Science;
4. Professor, Department of Nephrology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India; *Corresponding Author.


© The Author(s). 2022 Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by-nc/4.0/). Please refer to the link for more details.
### Table 1: Clinical and investigations findings in 10 patients of AKI

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
<th>Case 7</th>
<th>Case 8</th>
<th>Case 9</th>
<th>Case 10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Significant history</strong></td>
<td>Recurrent AKI—fever, chills, and cola-colored urine</td>
<td>Non-oliguric renal failure</td>
<td>Non-oliguric AKI</td>
<td>Back pain</td>
<td>Non-oliguric AKI</td>
<td>Fever Jaundice AKI with a drug history of antimalarials</td>
<td>Alcoholic AKI</td>
<td>Hoarseness</td>
<td>Tiredness</td>
<td>Prepartum bleeding</td>
</tr>
<tr>
<td><strong>Drug history</strong></td>
<td>–</td>
<td>Present Proton pump inhibitors</td>
<td>Present Diclofenac</td>
<td>Present Calcium and vitamin D supplements</td>
<td>Present Chloroquine</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Present Artesunate</td>
<td>Three antihypertesives</td>
</tr>
<tr>
<td><strong>Significant examination</strong></td>
<td>Normotensive</td>
<td>Normotensive</td>
<td>Hypertension</td>
<td>No anemia</td>
<td>No hypertension</td>
<td>Normotensive</td>
<td>No hypertension</td>
<td>No hypertension</td>
<td>Hypertension</td>
<td>Carotid and renal bruises</td>
</tr>
<tr>
<td><strong>Hemoglobin</strong></td>
<td>6</td>
<td>14</td>
<td>15</td>
<td>14</td>
<td>6</td>
<td>14</td>
<td>12</td>
<td>6</td>
<td>6.4</td>
<td>9</td>
</tr>
<tr>
<td><strong>Total leucocyte count</strong></td>
<td>3400</td>
<td>5600</td>
<td>7800</td>
<td>6700</td>
<td>7900</td>
<td>6400</td>
<td>9800</td>
<td>17,000</td>
<td>13,000</td>
<td>12,000</td>
</tr>
<tr>
<td><strong>Platelets</strong></td>
<td>30,000</td>
<td>1,67,000</td>
<td>1,50,000</td>
<td>1,45,000</td>
<td>30,000</td>
<td>1,59,000</td>
<td>1,67,000</td>
<td>90,000</td>
<td>40,000</td>
<td>1,70,000</td>
</tr>
<tr>
<td><strong>Schistocytes</strong></td>
<td>&lt;2%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>&lt;2%</td>
<td>&lt;2%</td>
<td>&lt;2%</td>
<td>&lt;2%</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Reticulocyte</strong></td>
<td>3%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>10%</td>
<td>–</td>
<td>4%</td>
<td>3%</td>
<td>12%</td>
<td>&lt;3%</td>
</tr>
<tr>
<td><strong>General blood picture</strong></td>
<td>No evidence of hemolysis/schistocytes</td>
<td>Normocytic Normochromic</td>
<td>Normocytic Normochromic</td>
<td>Normocytic Normochromic</td>
<td>Microcytic Hypochromic No evidence of malarial parasite</td>
<td>Normocytic Normochromic</td>
<td>Normocytic Normochromic</td>
<td>Microhypochromic</td>
<td>Microhypochromic</td>
<td>Microhypochromic</td>
</tr>
<tr>
<td><strong>LDH</strong></td>
<td>341</td>
<td>451</td>
<td>345</td>
<td>456</td>
<td>4500</td>
<td>452</td>
<td>920</td>
<td>456</td>
<td>1500</td>
<td>279</td>
</tr>
<tr>
<td><strong>S bilirubin</strong></td>
<td>1.1</td>
<td>1.1</td>
<td>0.8</td>
<td>1.2</td>
<td>4.5</td>
<td>1.1</td>
<td>1.1</td>
<td>1.8/1.0/0.8</td>
<td>7.8/2.8/5</td>
<td>1.2/0.9/0.3</td>
</tr>
<tr>
<td><strong>Direct Indirect</strong></td>
<td>0.8/0.3</td>
<td>0.6/0.5</td>
<td>0.6/0.5</td>
<td>0.7/0.5</td>
<td>1.5/3.0</td>
<td>0.8/0.3</td>
<td>0.8/0.3</td>
<td>1.5/3.0</td>
<td>0.8/0.3</td>
<td>1.5/3.0</td>
</tr>
<tr>
<td><strong>Coombs test</strong></td>
<td>Negative</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td><strong>CPK (µ/L)</strong></td>
<td>34</td>
<td>32</td>
<td>45</td>
<td>45</td>
<td>45</td>
<td>239</td>
<td>1520</td>
<td>234</td>
<td>240</td>
<td>56</td>
</tr>
<tr>
<td><strong>G6PD</strong></td>
<td>Normal</td>
<td>–</td>
<td>–</td>
<td>Decreased</td>
<td>–</td>
<td>Normal</td>
<td>–</td>
<td>Normal</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td><strong>Urine routine</strong></td>
<td>1+/5–8 RBC</td>
<td>1+/5–6 WBC</td>
<td>1+/8–10 WBCs</td>
<td>2+/4–5 WBCs</td>
<td>2+/4–5 RBCs</td>
<td>1+/2–3 WBCs</td>
<td>1+/8–10 RBCs</td>
<td>1+/12–14 WBCs</td>
<td>10–12 RBCs</td>
<td>10–12 RBCs</td>
</tr>
<tr>
<td><strong>Urine myoglobin</strong></td>
<td>Negative</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
<td>–</td>
</tr>
<tr>
<td><strong>C3</strong></td>
<td>78</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>89</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>67</td>
<td>75</td>
</tr>
<tr>
<td><strong>C4</strong></td>
<td>34</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>38</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>35</td>
<td>45</td>
</tr>
<tr>
<td><strong>ANA</strong></td>
<td>Negative</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Negative</td>
<td>Negative</td>
<td>–</td>
<td>–</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td><strong>dsDNA</strong></td>
<td>Negative</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Negative</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td><strong>Serum creatinine</strong></td>
<td>6.7</td>
<td>3.4</td>
<td>3.2</td>
<td>5.6</td>
<td>7.6</td>
<td>4.9</td>
<td>8.2</td>
<td>8.9</td>
<td>9</td>
<td>5.6</td>
</tr>
<tr>
<td><strong>Flow cytometry panel for PNH</strong></td>
<td>Positive</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Negative</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Negative</td>
<td>–</td>
</tr>
<tr>
<td><strong>Urine for eosinophils</strong></td>
<td>–</td>
<td>Present</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>CRP/ESR</strong></td>
<td>–</td>
<td>–</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Raised</td>
</tr>
</tbody>
</table>

Contd...
<table>
<thead>
<tr>
<th>Investigation</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
<th>Case 7</th>
<th>Case 8</th>
<th>Case 9</th>
<th>Case 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum magnesium</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1.3</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Serum potassium</td>
<td>4.7</td>
<td>4.5</td>
<td>4.8</td>
<td>–</td>
<td>5.7</td>
<td>2</td>
<td>5.6</td>
<td>6</td>
<td>6.2</td>
<td>–</td>
</tr>
<tr>
<td>Serum calcium</td>
<td>8.2</td>
<td>8.7</td>
<td>8.7</td>
<td>14.5</td>
<td>8.6</td>
<td>8.5</td>
<td>8.7</td>
<td>8.7</td>
<td>8.6</td>
<td>–</td>
</tr>
<tr>
<td>Serum PTH</td>
<td>–</td>
<td>34</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Serum vitamin D</td>
<td>–</td>
<td>78</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Kidney biopsy</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

**Normal glomerular morphology**

*With no evidence of intraglomerular or extracapillary hypercellularity. Tubules showed features of acute tubular necrosis with RBC casts and pigments. Interstitium was edematous with mild mononuclear cell infiltrate and the blood vessels were largely unremarkable.*

**Cortical necrosis**

**Thrombotic Microangiopathy**

**Afferent renal arteriolar hyalinization, interlobular arteries, and arcuate artery myointimal thickening. Glomerular capillary plexus collapse, and basement membrane ischemic shrinkage.**

<table>
<thead>
<tr>
<th>Renal Doppler’s</th>
<th>–</th>
<th>–</th>
<th>–</th>
<th>–</th>
<th>–</th>
<th>–</th>
<th>Normal</th>
<th>Normal</th>
<th>Right renal artery stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kappa/lambda ratio</td>
<td>–</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>No M band</td>
<td>No M band</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Recovery</td>
<td>Complete</td>
<td>Complete</td>
<td>Complete</td>
<td>Complete</td>
<td>Complete</td>
<td>Complete</td>
<td>Complete</td>
<td>No recovery</td>
<td>Complete</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Conservative Avoid all drugs causing deficiency of G6PD**

**Complete Dialysis Levothyroxine replacement**

**No recovery Dialysis dependent**

**Complete Plasmapheresis**

**Complete Steroids**

**Right-sided renal artery angioplasty and stenting**
were no clinical evidences of infection. On examination, she was normotenstive. Her peripheral smear showed evidence of normal counts with eosinophilia. Urine showed sterile pyuria with tubular proteinuria. Her ANA and antineutrophil cytoplasmic antibody (ANCA) compliments were normal. X-ray chest and ultrasound abdomen did not show evidences of organomegaly or lymphadenopathy. In view of unexplained AKI with a history of proton pump inhibitors, a kidney biopsy was done revealing interstitial nephritis with no evidences of granuloma. A possibility of AKI secondary to proton pump inhibitors induced acute interstitial nephritis was made. In view of no evidences of infections or autoimmune etiology, she was managed only by proton pump inhibitors withdrawal and after a week’s time, her creatinine settled to normal 1.1 mg%.

**Case 3**

A 54-year-old female had low-grade fever and myalgia, for which she received nonsteroidal anti-inflammatory drugs (NSAIDs) (diclofenac) daily twice a day for 2 days following which she started developing swelling all over the body and nausea with no oliguria. On examination, her blood pressure (BP) was 150/90 mm Hg and she had edema over the face. Labs showed serum creatinine of 3.2 mg% with normal serum albumin with tubular proteinuria and bland urinary sediments. She was not anemic, her serum calcium and lipid profile were within normal limits, and her workup of myeloma was negative. A possibility of AKI secondary to NSAID-induced vasomotor renal response was kept. As NSAID intake is known to reduce renal plasma flow secondary to a decrease in prostaglandins, which are known to regulate vasodilation at the glomerular level. Thus NSAIDs intake disrupts the compensatory vasodilation response of renal prostaglandins to vasoconstrictor hormones released by the body resulting in acute deterioration of renal function. Her NSAIDs were stopped and she attained normal renal functions in 1 week.

**Case 4**

A 65-year-old female nondiabetic, nonhypertensive presented with back pain off and on for 8 months with a history of anorexia, nausea, and decreased appetite for 7 days. She was normotenstive, non-oliguric, and on evaluation she had a serum creatinine of 5.6 mg% with hypercalcemia with tubular proteinuria and bland urinary sediments. On inquiry, she informed intake of excessive use of vitamin D supplements for nearly 6 months. Oral sachets/capsules (each containing 60,000 IU), as well as intramuscular preparations, were given with a total cumulative dose were 4,600,000. Her workup for myeloma was negative. Her serum calcium was 14.5 mg/dL, and vitamin D was found to be 78 with normal serum phosphorous, albumin, and parathyroid hormone (PTH) values. Thus a diagnosis of hypercalcemia-induced AKI secondary to hypervitaminosis D was made. Hypervitaminosis D should be considered as one of the differentials among the elderly population presenting with AKI with evidences of hypercalcemia. She was hydrated well and all supplements were stopped. No other calcium-lowering agents were required during this process. Her renal function normalized in 1 week.

**Case 5**

A 40-year-old male presented to a nearby hospital with a high-grade fever with chills. He tested positive for malaria parasite (*Plasmodium vivax*) and received antimalarial (chloroquine 2.5 gm over 3 days). He was referred to a higher center with a history of jaundice, cola-colored urine with advanced renal failure. His investigations revealed severe anemia, reticulocytosis, normal blood counts, and thrombocytopenia with a serum creatinine of 6 mg%, serum bilirubin was 2.5 mg% with transaminitis. Blood culture and serum procalcitonin were normal. His Coombs test was negative but LDH was high. Ultrasound abdomen was normal. A possibility of malaria-induced AKI or thrombotic microangiopathy was kept. The urine examination showed tubular proteinuria with no evidence of active sediments. G6PD estimation was done by the fluorescent spot method test which was in the deficiency range. A kidney biopsy was also done to confirm the etiology. Renal biopsy showed normal glomerular morphology with no evidence of intraglomerular or extracapillary hypercellularity. Tubules showed features of acute tubular necrosis with red blood cell (RBC) casts and pigments. The interstitium was edematous with mild mononuclear cell infiltrate and the blood vessels were largely unremarkable. A diagnosis of acute tubular injury with pigment nephropathy was suggested. The G6PD estimation was found to be low in this patient thus a diagnosis of G6PD deficiency leading to hemolysis and AKI was made and was advised to avoid all drugs causing deficiency of G6PD. The patient was managed conservatively with intermittent dialysis; gradually he opened up, became dialysis independent, and attained near normal function at the time of discharge (3 weeks from the day of onset of symptoms). OPD follow-up attained normal renal functions after 6 weeks of illness. On screening his family members, his younger brother also had G6PD deficiency. They were given a list of drugs to be avoided and advised for good hydration at the time of any febrile illness. Thus it is important differentials, especially in tropical countries among patients who have developed AKI after receiving antimalarial drugs, a detailed hemolytic workup needs to be carried out.

**Case 6**

A 42-year-old male with a history of chronic alcoholism presented with complaints of generalized weakness, low-grade fever, and diffuse myalgia for 2 days. There was no past history of upper gastrointestinal bleeding, drugs, or severe malnutrition. There were no clinical evidences of chronic liver disease and dehydration. BPs were within the normal range with no evidence of anemia or edema. His lab reports showed a creatinine level of 4.9 mg/dL and mild transaminitis, no evidence of hemolysis or myoglobinuria was found. Urine was within normal limits with no proteinuria or activity. Ultrasound abdomen showed no evidences of chronic liver disease with normal-sized kidneys. However, his serum potassium level was found to be less than 2 mmol/L, and magnesium level was 1.3 mg/dL (1.7–2.3 mg/dL), other electrolytes were within normal range. On further inquiry, he did not give any history of seizure disorder, drugs, palpitation syncope, or altered bowel habits. Electrocardiogram was showing sinus rhythm with ST-segment depression, decreased T-wave amplitude, and presence of U wave. Thus the cause of AKI was thought secondary to hypokalemia which is known to induce increased tubular pressure disrupting the high resistance nature of the distal nephron, leading to loss of the electrical driving force for K+ secretion. A sudden reduction in the glomerular filtration rate becomes a limiting factor for K+ secretion in patients with AKI. In our patient, the hypokalemia was due to hypomagnesemia which is common among alcoholics and thus an important cause for hypokalemia leading to AKI. Accurate correction of magnesium settled his potassium and normalized his renal functions over a week’s time to 1.2 mg/dL.

**Case 7**

A 56-year-old male presented with severe body aches and pains for 4 days, and nausea and vomiting for 2 days. On further evaluation, he was found to be having easy fatigability, increased sensitivity to cold, decreased appetite, weight gain, hoarseness of voice, and altered bowel habits. He gave no history of seizures, addiction,
any chronic illness, addiction, or drug intake. His lab parameters showed serum creatinine of 8.2 mg%. On investigation, he had CPK 1520, LDH 920 mg%, and the urine was showing RBC. He was evaluated for myoglobinuria, and urine myoglobin was positive. In view of his symptoms, thyroid functions were tested which showed the presence of severe hypothyroidism. Hence a tentative diagnosis of AKI secondary to rhabdomyolysis (myoglobinuria) secondary to hypothyroidism was kept. Though a rare potentially life-threatening cause for AKI and further investigation into the etiology of hypothyroidism is warranted.

He was managed with intermittent dialysis and levothyroxine replacement and other supportive care. His renal functions gradually improved and recovered completely in 4 weeks.

**Case 8**

A 25-year-old married female who had 36 weeks of pregnancy presented with a sudden onset of massive antepartum hemorrhage secondary to placental abruption. Unfortunately, she delivered a dead fetus and developed oliguria followed by anuria and acute onset breathlessness. She was diagnosed with antepartum hemorrhage resulting in acute tubular necrosis. She continued to be anuric for 4 weeks. All parameters including evidences for hemolysis, infections, and hypovolemia were ruled out and she underwent a kidney biopsy revealing 20 glomeruli all of them obsolete with multiple foci of cortical necrosis of ischemic origin that did not involve the subcapsular area and did not extend to the deeper areas of the kidney with no evidence of thrombotic microangiopathy. The cause for acute cortical necrosis of pregnancy was thought to be massive antepartum hemorrhage. Renal cortical necrosis is a catastrophic complication of pregnancy with poor renal outcomes.

**Case 9**

A 14-year-old boy presented with fever and prodromal symptoms for 1 week along with jaundice and anuria. The patient was treated with artesunate outside. On evaluation, he had icterus and pallor. The lab values revealed hemoglobin of 6.4 gm%, platelet counts 40,000/cmm, raised reticuloocyte count of 12%, hyperbilirubinemia predominantly indirect hyperbilirubinemia with mildly elevated transaminases, and serum LDH was 2300. Peripheral smear for *P. vivax* was positive. He underwent a renal biopsy which confirmed the diagnosis of thrombotic microangiopathy. Hemodialysis and plasmapheresis were done in the patient with subsequent recovery after 2 weeks.

Thus those who have nonrecovering AKI with persistent anemia and thrombocytopenia even after clinical and laboratory evidences of recovery from malaria, as response to plasmapheresis seem excellent in this subset of malarial AKI. Evidences suggest that a high index of suspicion should be kept for TMA among nonrecovering AKI with persistent anemia and thrombocytopenia despite clinical and laboratory evidences for recovery from malaria and show good response to plasmapheresis.

**Case 10**

A 25-year-old female presented with malignant hypertension and oliguria. Her BP was recorded as 220/130 mm Hg. Her BP in all four limbs was different (upper limb right and left BP was 150/110 and 145/110, respectively, while 220/110 and 210/110 in right and left lower limbs, respectively) with the presence of renal and carotid bruit. Her BP control was achieved with four antihypertensives—clonidine (0.8 mg/day), minoxidil (10 mg/day), torsemide (40 mg/day), long-acting nifedipine (90 mg/day), and prazosin xl (alpha blocker) prazosin xl (alpha blocker) (20 mg/day). Her lab investigations revealed blood urea nitrogen 120 μmol/L, serum creatinine 5.6 mg%, and hemoglobin 9.7 gm%. Her C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were raised (ESR 110). An ultrasound examination showed normal-sized kidneys. Renal Doppler was suggestive of renal artery stenosis on right side serology for ANA, anti-dsDNA, C3, C4, and antiscleoma 70-kD antibodies (anti-scl-70) was normal. There was no evidence of hemolysis on a peripheral blood smear. A kidney biopsy showed hypertensive changes in the vessels. There was no evidence of fibrinoid necrosis or proliferative endarteritis. A diagnosis of malignant hypertension secondary to right-sided renal artery stenosis due to Takayasu’s arteritis (TA) leading to AKI was kept and was started on steroids at 1 mg/kg/day soon her BP was better controlled and still required high doses of antihypertensives. She remained anuric for 3 weeks and later improved and became dialysis independent. She recovered her renal function and underwent right-sided renal artery angioplasty and stenting and now her BP is controlled on two drugs with normal renal function. Though a rare cause yet a clinical suspicion must be kept in a young hypertensive individual with anuria with uncontrolled hypertension. As progression of stenosis is directly linked to worsening hypertension and deterioration of renal function secondary to ischemic renal disease, it stands out as an important prognostic factor for TA.

**Discussion**

The global burden of kidney disease has exponentially increased. AKI is a heterogeneous clinical entity with varying causes and presentations. AKI develops in up to 20% of hospitalized patients, and in approximately 50% of adult patients receiving intensive care. Mortality in severe AKI remains very high, despite several treatment improvements. If detected at an early stage, many lives can be saved. AKI can lead to CKD in later life therefore, identification and prevention of risk factors are also important to address.

**How to Approach a Case of AKI**

A good history and examination largely help in achieving the diagnosis in this growing era of investigational armamentarium. One must have the foresight to look for commoner etiologies before looking for unusual causes. The history should identify the presence of risk factors, systemic illnesses, and nephrotoxic medications that might cause poor renal perfusion or directly impair renal function. Clinical signs and symptoms vary according to the cause and the severity of AKI may range from asymptomatic to uremic encephalopathy. Table 2 shows the history and examination findings in patients with AKI.

**Case-based Investigation Approach**

- **Screen for sepsis—overt and occult,** tropical causes needs to be evaluated when patients present with evidences of infections with AKI. A detailed evaluation can help achieve a diagnosis—complete blood count, diagnostic tests for malaria, dengue, scrub typhus, leptospirosis, tuberculosis, fungal infections, blood and urine cultures, coagulation profile, procalcitonin, inflammatory markers, HIV, hepatitis C virus, and hepatitis B surface antigen.

D-dimer and fibrinogen levels if thrombosis or disseminated intravascular coagulation is suspected.

- **Sometimes electrolyte abnormalities can manifest with AKI,** especially among the vulnerable group, and need to evaluate hypokalemia, hypercalcemia, and hypomagnesemia.

- **Clinical situations presenting with evidences of hemolysis and AKI are the important causes for AKI** and if left unevaluated can be a potential cause for recurrent AKI and progression to...
**Unconventional** Causes of Acute Kidney Injury

The diagnosis and management of acute kidney injury (AKI) can be challenging, especially when the cause is not immediately apparent. In such cases, a thorough clinical examination and laboratory evaluation are crucial. This section highlights some of the “unconventional” causes of AKI, which may not be immediately obvious and can lead to complex clinical scenarios.

### History of Presenting Symptoms

- **Prerenal Causes:**
  - History of vomiting, diarrhea, poor fluid intake, hemorrhage, burns, and diuretics use
  - Acute febrile illness/hyperpyrexia
- **Intrinsic Renal Causes:**
  - Cardiac failure—exertional dyspnea, edema, chest pain, and palpitation
  - Chronic liver disease—abdominal distension, jaundice, melena, and hematemesis
- **Postrenal Causes:**
  - Urinary frequency, urgency, dysuria, hematuria, history of renal ureteric colic, weight loss, and appetite loss suggestive of malignancy

### Physical Examination

- **Dehydration** (poor skin turgor), hypotension, and tachycardia
- **Rash**
  - Malignant hypertension and abdominal bruit
- **Ascites**
  - Splenomegaly, caput medusa, and spider angioma

### Table 2: History and physical examination in different types of AKI

<table>
<thead>
<tr>
<th>History</th>
<th>Physical examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prerenal</td>
<td>History of vomiting, diarrhea, poor fluid intake, hemorrhage, burns, and diuretics use</td>
</tr>
<tr>
<td>Intrinsic renal</td>
<td>Acute tubular necrosis—prolonged hypotension</td>
</tr>
<tr>
<td>Postrenal</td>
<td>Urinary frequency, urgency, dysuria, hematuria, history of renal ureteric colic, weight loss, and appetite loss suggestive of malignancy</td>
</tr>
</tbody>
</table>

**CKD**—anemia, thrombocytopenia or pancytopenia, increased reticulocyte count, BP for the presence of schistocytes, reduced haptoglobin, indirect hyperbilirubinemia, elevated LDH, bilirubinuria, urobilinogen, and uric acid for lysis syndrome.

- The most useful investigation in a clinical setting of AKI is a good urine examination.

Types of sediments play a valuable role in the diagnosis and management.

**Urine analysis**—red cell cast, white cell cast, tubular cast, proteinuria, and eosinophiluria for allergic interstitial nephritis.

**Dipstick for blood** positive but no RBCs

**Urine analysis**—red cell cast, white cell cast, proteinuria, and eosinophiluria for allergic interstitial nephritis.

**Dehydration** (poor skin turgor), hypotension, and tachycardia

**Rash**

**Ascites**

**Malignant hypertension and abdominal bruit**

**References**


**Conclusion**

It is essential to look for common causes of AKI with the foresight for out-of-the-box causes of AKI. A high index of suspicion and timely diagnosis and treatment interventions may bring complete recovery of renal functions in patients of AKI. “Unconventional” Causes of Acute Kidney Injury”

**“Unconventional” Causes of Acute Kidney Injury**
“Unconventional” Causes of Acute Kidney Injury

COVID-19 Antibodies as Predictor of Severe Dengue among Hospitalized Children with Dengue Illness in the Post-third-wave Period of COVID-19 Infection in India

Sangeetha Balasubramani¹, Varadaraj Govindaraj²*, Ritu Agarwal³, Amit Pathania⁴, Atul Vij⁵

Accepted: 07 July 2022; Received: 04 April 2022

ABSTRACT

Background: There were widespread unconfirmed reports about the increased severity of dengue post-second wave of the COVID-19 pandemic in India. It is known that a second dengue infection with a different strain in an individual can trigger antibody-dependent enhancement (ADE). A similar phenomenon is hypothesized for severe COVID-19 infection since both dengue and COVID-19 are viral diseases with different and varying strains. However, much research is needed to confirm this hypothesis. In this context, we intended to assess the severity of dengue illness in relation to previous severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, possibly the role of COVID-19 antibodies as an early predictor of severe dengue illness.

Objective: To assess the utility of COVID-19 antibodies for early identification of severe dengue illness among children in the post-third-wave period of COVID-19 infection in India.

Materials and methods: All hospitalized children with dengue illness were categorized as severe (shock and/or hemorrhage and/or multi-organ dysfunction) and non-severe dengue illness (dengue with or without warning signs) as per WHO definition. COVID-19 antibody titers were estimated in both groups. Clinical features and seroprevalence of COVID-19 antibodies were compared in both groups.

Result: A total of 31 children were studied (13 severe and 18 non-severe dengue illnesses). The most common symptoms prior to presenting to the hospital included fever (100% in both groups), vomiting (85% in severe and 63% in non-severe), abdominal pain (85% in severe and 50% in non-severe), poor feeding (54% in severe and 28% in non-severe), and skin rashes (15% in severe and none in non-severe). The mean duration from the onset of fever to the first hospital visit was 4.6 days in severe illness and 5.3 days in non-severe dengue illness. The mean duration of hospitalization was 9.7 days in severe dengue illness and 4.1 days in non-severe dengue illness. While 92.3% of all severe dengue had significantly higher COVID-19 antibody titers, it was found elevated only in 44.4% of the children with non-severe dengue illness (p-value 0.0059; Yates’ corrected p-value 0.0179).

Conclusion: Clinical symptoms prior to presenting to the hospital were fever, vomiting, abdominal pain, poor oral feeding, and skin rashes. While fever, vomiting, and abdominal pain were seen commonly in both severe and non-severe dengue illnesses, the presence of skin rash during febrile phase is associated with severe dengue illness only.

Hospitalized children having severe dengue had increased seroprevalence of COVID-19 antibodies (92.3%) compared to children with non-severe dengue (44.4%). However, there is no correlation of the severity of dengue illness with absolute values of COVID-19 antibody levels. Therefore, the presence of COVID-19 antibodies (previous COVID-19 infection) can be a predictor of severe illness in children with dengue especially if associated with poor oral feeding and skin rashes. The limitation of the study is its lesser sample size to conclude any definitive statement; nevertheless, the study paves way for a similar cohort of a larger sample size to draw conclusions.

INTRODUCTION

In 2019, WHO identified dengue as one of the four main infectious diseases threatening global health.¹ The initial dengue outbreaks in India were documented way back in 1946 and gradually by 1968, the outbreaks were more frequently prevalent spreading from the Eastern coast of India to Northern and Central India.² Epidemics of dengue in urban Indian society are perennial and the proportion of dengue cases is only seeing an increase in recent years.

There were widespread unconfirmed reports about the increased severity of dengue post-second wave of the COVID-19 pandemic in India. It is known that a second dengue infection with a different strain in an individual can trigger ADE.³ A similar phenomenon is hypothesized for severe COVID-19 infection since both dengue and COVID-19 are viral diseases with different and varying strains.³ However, much research is needed to confirm this hypothesis. In this context, we intended to assess the severity of dengue illness in relation to previous SARS-CoV-2 infection.

Children less than 14 years of age across the globe including India were not vaccinated against SARS-CoV-2 and, hence, detection of significant SARS-CoV-2 antibody titers would infer a previous natural COVID-19 infection. In our study, we assessed the SARS-CoV-2 antibody titers among all hospitalized children with dengue illness. We then compared the clinical features and presence of SARS-CoV-2 antibodies between severe dengue and non-severe dengue illness. Our study aims to support or refute the claim that previous COVID-19 infection is associated with increased severity of dengue illness.

The results of our study can pave way for further research on the association of previous COVID-19 infection to the severity of dengue illness. Further, our study would help in the early identification of severe dengue illness among children in the post-third-wave period of COVID-19 infection in India.

MATERIALS AND METHODS

Place of Study

The study was conducted in the Department of Pediatrics in a tertiary care hospital setting in New Delhi from October to November 2021.

Study Design

A prospective observational study.

Journal of the Association of Physicians of India (2022): 10.5005/japi-11001-0092

1 Graded Specialist, Department of Pediatrics, Base Hospital Delhi Cantonment; 2 Classified Specialist, Department of Medicine, Air Force Central Medical Establishment; 3 Senior Advisor; 4 Classified Specialist; 5 Junior Resident, Department of Pediatrics, Base Hospital Delhi Cantonment, New Delhi, Delhi, India; *Corresponding Author

COVID-19 Antibodies as Predictor of Severe Dengue

Sample Size
A total of 31 children who were admitted in the hospital following dengue illness were included in the study.

Methodology
All children of consenting parents less than 14 years of age who met all the inclusion and exclusion criteria were included in the study. All children were screened for active COVID-19 infection by reverse transcription-polymerase chain reaction (RT-PCR) for nCoV before admission. Only children who were negative for COVID-19 infection were included in the study.

Admitted children were classified into two groups namely severe dengue and non-severe dengue as per WHO classification.4 Severe dengue comprised those children who had clinical evidence of severe plasma leakage manifesting as shock/respiratory distress or hemorrhage or multi-organ dysfunction. Non-severe dengue included children with lab-confirmed dengue with or without warning signs.

Epidemiological parameters, clinical manifestations, and levels of SARS-CoV-2 antibodies were compared between the two groups and analyzed. Possible predictors of severe dengue are identified.

Inclusion Criteria
- Children less than 14 years of age with lab diagnosis of dengue (NS1Ag positive).
- Requiring in-patient care for dengue illness.
- No previous congenital or acquired comorbid illness.
- Negative RT-PCR for nCoV.

Exclusion Criteria
- Individuals not meeting the inclusion criteria.
- Children of non-consenting parents.

RESULT
A total of 31 children (16 males and 15 females) who were hospitalized with dengue illness were subjected to this study. Hospitalized children were classified into two comparison groups, namely severe dengue and non-severe dengue (uncomplicated dengue) as per WHO classification. The age of children in this study ranged from 1 month to 14 years. The mean age in the severe group was 8.4 years and in the non-severe group was 4.6 years (Table 1). About 80% of all admitted children with dengue were under 5 years. There were no underlying chronic medical conditions in any of the children in both groups since children with underlying diseases or disabilities were excluded from the study. The mean duration from the onset of fever to the first hospital visit was 4.6 days in the severe group and 5.3 days in the non-severe group (Table 1).

Among the children who were hospitalized with dengue, all of them had fever \( n = 31 \) in both groups. Apart from fever, the other common symptoms prior to the hospital visit included vomiting, abdominal pain, poor oral feeding, and skin rashes. While 84.6% of children with severe dengue had vomiting, 62.5% of children with non-severe dengue had the same. Similarly, abdominal pain and poor oral feeding were seen in 84.6 and 53.8%, respectively, in children with severe dengue and in 50 and 28%, respectively, in children with non-severe dengue (Table 1). Also, 61.5% \( (8/13) \) of children with severe dengue had vomiting, abdominal pain, and poor oral feeding while only 33.9% \( (7/18) \) of children with non-severe dengue had all three symptoms. About 15.4% \( (2/13) \) of children with severe dengue alone exhibited skin rashes during the febrile phase, while none of the children hospitalized for non-severe dengue had any skin rashes during the febrile phase of illness. Among the children hospitalized for severe dengue, the most common form of severe presentation was the presence of shock on arrival to the hospital; seen in 53.8% of severe dengue \( n = 7 \).

While 92.3% \( (n = 12) \) children with severe dengue had significant levels of SARS-CoV-2 antibody levels indicating a previous COVID-19 infection, only 44.4% \( (n = 8) \) of children with non-severe dengue had evidence of previous COVID-19 infection \( (p\text{-value} \ 0.0059, \text{Yates' corrected} \ p\text{-value} \ 0.1789) \) (Table 2). The mean total SARS-CoV-2 antibody level in children with severe dengue was 74.3 AU/mL as compared to 34.9 AU/mL in the non-severe group. The decreased level of mean total SARS-CoV-2 antibody level in children with non-severe dengue is due to a lower incidence of previous COVID-19 infection in the non-severe group. However, there is no correlation of the severity of dengue illness with absolute values of COVID-19 antibody levels. The mean total SARS-CoV-2 antibody level among the children with previous COVID-19 infection, that is, in children with a significant rise in COVID-19 antibody level (above lab threshold

| Table 1: Epidemiological and clinical features of severe and non-severe dengue illness |
|---------------------------------|----------------|----------------|
|                                  | Severe dengue \( n = 13 \) | Non-severe dengue \( n = 18 \) |
| Mean age (years)                | 8.4            | 4.6            |
| Gender (male/female) \( n \)    | 6/7            | 10/8           |
| Underlying medical condition(s) | Nil significant | Nil significant |
| Average duration from fever onset to the first hospital visit (days) | 4.6           | 5.3           |
| Clinical signs and symptoms     |                |                |
| Fever (%)                       | 100            | 100            |
| Vomiting (%)                    | 84.6           | 62.5           |
| Abdominal pain (%)              | 84.6           | 50             |
| Poor oral feeding (%)           | 53.8           | 28             |
| Skin rashes (%)                 | 15.4           | None           |
| Presence of shock on arrival to the hospital (%) | 53.8 | – |
| RT-PCR for SARS-CoV-2           | Negative in all | Negative in all |
| Average total SARS-CoV-2 antibody (IgG + IgM) (normal < 15 AU/mL) | 74.3 (7.8–205.2) | 34.9 (4.1–112) |
| Serology for dengue/malaria/scrub typhus/leptospirosis/chikungunya | NS1Ag positive in all | NS1Ag positive in all |
| Average length of hospital stay  | 9.7 days       | 4.1 days       |

<table>
<thead>
<tr>
<th>Table 2: Chi-square test</th>
</tr>
</thead>
<tbody>
<tr>
<td>COVID antibodies positive</td>
</tr>
<tr>
<td>Severe dengue</td>
</tr>
<tr>
<td>Non-severe dengue</td>
</tr>
<tr>
<td>Marginal column totals</td>
</tr>
</tbody>
</table>

The Chi-square statistic is 7.554. The \( p\text{-value} = 0.0059 \) (significant \( p < 0.5 \)); The Chi-square statistic with Yates’ correction is 5.608. The \( p\text{-value} = 0.1789 \) (significant \( p < 0.5 \) )
for determining positivity) is similar in both groups (63.68 AU/mL in the severe group and 61.1 AU/mL in the non-severe group), thereby indicating that there is no correlation of the severity of dengue illness with absolute values of COVID-19 antibody levels. The average duration of hospital stay was obviously higher in the severe dengue group; 9.7 days in the severe group compared to 4.1 days in the non-severe group (Table 1).

**Discussion**

COVID-19 pandemic and recurrent dengue epidemics have not only exhausted the already fragile health system in densely populated tropical countries but also have turned into a global threat. While the coronavirus continues to mutate into different variants creating subsequent COVID-19 pandemic waves, the disease is far from over. Dengue, an illness age immemorial, continues to haunt the human race even in this pandemic period. There are numerous newspaper reports claiming an increased number and severity of dengue illness post-second wave of the COVID-19 pandemic; the Indian capital city Delhi recorded 9,545 dengue cases and 23 fatalities in 2021 compared to 1,072 cases with one death in 2020, 2,036 cases with two deaths in 2019, and 2,798 cases with four deaths in 2018.5–7

Dengue viruses belong to the Flaviviridae family and have four serotypes namely DENV-1, DENV-2, DENV-3, and DENV-4.8 WHO 2009 dengue guidelines categorized dengue illness into severe and non-severe dengue.9 For practical reasons, WHO recommends further splitting of the larger non-severe group into two subgroups—patients with warning signs and those without them.4 The criteria for diagnosis of severe dengue include (a) severe plasma leakage manifesting as shock or respiratory distress and/or (b) severe bleeding and/or (c) severe organ involvement. Warning signs of dengue include (a) abdominal pain or tenderness, (b) persistent vomiting, (c) clinical fluid accumulation, (d) mucosal bleed, (e) lethargy, restlessness, (f) liver enlargement >2 cm, and (g) increase in hematocrit concurrent with a rapid decrease in platelet count (adapted from WHO dengue: guidelines for diagnosis, treatment, prevention and control, 2009).

In the vast majority of the individuals affected by the dengue virus, dengue fever presents as a mild illness only. The symptoms include fever, headache, abdominal pain, and nausea. The activation of local dendritic cells and macrophages following virus inoculation by the Aedes mosquito and subsequent entry into the bloodstream results in leucopenia and thrombocytopenia.9 Both humoral and cell-mediated immune responses are mounted resulting in the elimination of the dengue virus. Humoral immunity is responsible for the production of serotype-specific antibodies. These antibodies do not neutralize other dengue virus serotypes, thereby offering no protection against them but, however, cross-react.10 A subsequent infection with another dengue serotype is more severe than the previous infection due to the presence of these non-neutralizing cross-reacting pre-existing antibodies.11 The binding of suboptimal antibodies to the cell surface increases the entry of the virus into host cells, resulting in increased viral load and possibly severe disease.12 The enhanced severe dengue illness manifests as dengue hemorrhagic fever and dengue shock syndrome.13

A similar mechanism of ADE is proposed for severe COVID-19 infection.14 Coronavirus are members of the Coronaviridae family and like dengue viruses, they too are RNA viruses. The classical spike (S) protein of coronavirus binds to the enzymatic domain of the angiotensin-converting enzyme 2 on the host cell surface. The hydrolyzation of S protein paves entry for the coronavirus inside the host cell.15

However, the presence of SARS-CoV-2 antibodies facilitating ADE for severe dengue illness is not postulated so far. Though both are different viruses belonging to different families, their genetic makeup is similar (RNA viruses). Further, ADE-mediated severe second infection is observed in both diseases. Also, COVID-19 and dengue coinfection was associated with severe disease and fatal outcomes.16 While infection with SARS-CoV and Middle East respiratory syndrome-related coronavirus (MERS-CoV) were limited to certain geographical areas, the SARS-CoV-2 pandemic swept across the globe sparing no country. Hence, the presence of SARS-CoV-2 antibody is much more common among the general population than in previous coronavirus epidemics. There could be a possible reaction of these pre-existing COVID-19 antibodies facilitating the entry of dengue virus into host cells thereby causing increased viral load and severe disease.

Also, we are now aware of the multisystem inflammatory syndrome in both children and adults (MIS-C and MIS-A, respectively). The level of SARS-CoV-2 antibodies drastically decreased after 4 months of natural infection, more gradually over the next 7 months, and persist up to 11 months.17 Multisystem inflammation is encountered in this period where the antibody titers are high.18 The Morbidity and Mortality Weekly Report (MMWR) criteria for MIS-A mandate positive test for current or previous SARS-CoV-2 infection (nucleic acid, antigen, or antibody) during admission or in the previous 12 weeks.19 Another possible reason for the increased severity of dengue in the immediate post-second-wave period of COVID-19 could be due to the increased pro-inflammatory condition in the host because of COVID-19 infection.

The reason for the increased severity of dengue illness in the aftermath of COVID-19 waves may be multifactorial and possible causes can only be hypothesized at this stage; a couple of which are discussed above. However, if there could be an association established with the presence of SARS-CoV-2 antibodies (previous and recent COVID-19 infection) to severe dengue illness, we can better anticipate and prepare ourselves for severe dengue illness so as to decrease morbidity and mortality. Since many variants of COVID-19 are emerging and countries reporting a fresh surge in COVID-19 cases, the presence of COVID-19 antibodies can be a reliable marker to predict severe dengue illness.

In this pretext, we estimated the prevalence of SARS-CoV-2 antibodies among hospitalized children with dengue illness. The reason for choosing the pediatric population is that the presence of significant levels of SARS-CoV-2 antibodies in children less than 14 years would mean a previous natural infection since this age group has not been vaccinated so far.

Our results suggested that significantly raised levels of SARS-CoV-2 antibodies were found in 92.3% of children with severe dengue when compared to only 44.4% of children with non-severe dengue (p-value 0.0059, Yates’ corrected p-value 0.1789). However, there is no correlation of the severity of dengue illness with absolute values of COVID-19 antibody levels. While a child with a COVID-19 antibody level of 112 AU/mL had non-severe dengue, another child with a COVID-19 antibody level of only 22.3 AU/mL had severe dengue illness. Total SARS-CoV-2 antibody level among children with a significant rise in COVID-19 antibody level (i.e., above lab cut-off value for determining positivity) is similar in both groups—63.68 AU/mL in the severe group and 61.1 AU/mL in the non-severe group. Our study observed a lower mean total SARS-CoV-2 antibody level in the non-severe group as compared to the severe group which is due to a lower incidence of previous COVID-19 infection in the non-severe group.

When the clinical features are compared between the severe and non-severe groups, both had a similar presentation. Fever, abdominal pain, vomiting, and poor oral feeding were observed equally in both...
COVID-19 Antibodies as Predictor of Severe Dengue

groups. However, the presence of skin rash during the febrile illness was exclusively seen only in the severe group. MIS-C presents similarly with fever, skin rash, and lab evidence of inflammation and multisystem involvement along with a rise in SARS-CoV-2 antibody titers. However, dengue NS1 antigen is negative in such cases. In fact, both the cases which presented with skin rashes during the febrile period and treated for severe dengue were managed in-lines on MIS-C since it could be an MIS-C and dengue overlap.

The strength of the study is its novelty and possibly the only study from the Indian subcontinent to draw the utility of COVID-19 antibodies as a useful marker for early identification of severe dengue.

The major limitation of the study is the lesser sample size of admitted dengue patients since the study was conceived in the middle of the dengue epidemic which was soon over after the onset of winter in India. However, the available results that may make a huge difference are the management of dengue, the epidemic of which has already begun in many Indian states.

Ethics Approval and Consent to Participate
Ethics approval was obtained from the Institute Ethics Committee. Verbal consent was obtained from all parents of the children participating in the study.

Conclusion
Owing to the available smaller sample size of the study, the study is not powered to make any definitive conclusions. The results, however, convey that the presence of COVID-19 antibodies predicts the severity among hospitalized children with dengue illness. However, there is no correlation of the severity of dengue illness with absolute values of COVID-19 antibody levels.

Also, the common clinical symptoms of dengue prior to presenting to the hospital were fever, vomiting, abdominal pain, poor oral feeding, and skin rashes. While fever, vomiting, and abdominal pain were seen commonly in both severe and non-severe dengue illnesses, the appearance of skin rash during the febrile phase is associated with severe dengue illness only.

Therefore, the presence of COVID-19 antibodies (previous COVID-19 infection) can be a predictor of early severe dengue among hospitalized children with dengue illness, especially if associated with skin rashes during the febrile phase.

Though the present study is not powered to make any recommendations, the results clearly indicate the need for further studies powered to make recommendations over the routine estimation of COVID-19 antibodies among hospitalized children with dengue illness.

References
6. The Print. After a Horror COVID Wave, India’s Health System is Now Overwhelmed by a Different Virus; 2021. Available from: https://thestates.times.com
Effect of 4-day Online Breath Meditation Workshop on Ballistocardiography-based Sleep and Cardiac Health Assessments among Medical Professionals of a Tertiary Care Hospital in North India during COVID-19

Monika Pathania1, Praag Bhardwaj2, Yogesh Arvind Bahrupi3, Vyas Kumar Rathaur4

Received: 31 January 2022; Accepted: 02 June 2022

ABSTRACT

Background: Medical professionals (MPs) are facing stress, sleep deprivation, and burnout due to pandemic-related high patient inflow and consistent work shifts. Yoga and meditation are feasible, cost-effective, evidence-based, and well-accepted tools having multifold mental and physical health benefits.

Design: In this ongoing open-label single-arm trial, we assessed changes in sleep, heart rate variability (HRV), and vitals before and after a 4-day online breath meditation workshop (OBMW) among 41 MPs at a tertiary care hospital in northern India during COVID-19 pandemic.

Methods: Outcomes were assessed at baseline and after the 4-day workshop using a ballistocardiography-based contactless health monitoring device. The workshop was conducted online. Two participants were excluded due to a lack of adherence.

Results: A highly significant increase was seen in total sleep duration ($p = 0.000$) and duration of deep sleep ($p = 0.001$), rapid eye movement (REM) sleep ($p = 0.000$), and light sleep ($p = 0.032$). HRV outcomes of the standard deviation of normal-to-normal R-R intervals (SDNN) and root mean square of successive differences between adjacent normal heartbeat (RMSSD) also improved significantly ($p = 0.000$) while heart rate reduced significantly ($p = 0.001$). No significant change was observed in breath rate, total time awake, or in the low-frequency by high-frequency (LF/HF) spectrum of HRV.

Conclusion: Four days of OMBW improved sleep and HRV among MPs, strengthening the fact that yoga and meditation can help induce psychophysical relaxation and prove to be an effective tool to combat stress and sleep deprivation. As the stakeholders in patient care, that is, MPs are healthy, it will further improve patient care and reduce the chance of medical errors.

Introduction

Background

During the past year and a half of the COVID crisis, MPs have been hit hard by the pandemic-related stress and burnout. Initially, there was uncertainty regarding the cure for the disease, causing anxiety in general. Then there was stress caused by overwork from continuously dealing with incoming patients and long, consistent work shifts through day and night. Finally, it was the rapid increase in the death toll of infected patients that added to the fear of getting infected. Such situations of extreme stress can take a toll on one’s health, with MPs being no exception. Chronic stress can dysregulate the sympathetic-adrenal-medullary system and cause adaptational failures of the hypothalamic-pituitary-adrenal axis to reactivity and recovery. This, in turn, causes elevated heart rate, hypertension, dysregulated HRV, and irregular and disturbed sleep. It further leads to poor decision-making and an increased risk for cardiovascular diseases in the future.

Past literature is evident on the use of yoga-based techniques of controlled rhythmic breathing and meditation to effectively reduce stress and bring about a meditative state of mind, where one feels relaxed yet alert. Their regular practice has been shown to improve sleep quality, life satisfaction, and resilience, and has helped reduce depression, anxiety, and stress among MPs. Yoga practice has also been shown to improve cardiac autonomic tone, HRV, vagal tone, and a wide array of health outcomes among different populations. Randomized controlled trials (RCTs) at Harvard and Yale show immense benefits of practicing yoga breathing for students’ well-being and resilience. Considering the multifold benefits, mHealth-based online yoga breathing and meditation were found worth investigating with regard to its efficacy in objective sleep and cardiac health parameters, more so in MPs that are undergoing tremendous levels of stress. The online approach for intervention was chosen keeping in mind the COVID restrictions and to avoid any risk of contamination. While mHealth is an evolving concept and has lots of untapped potential, there is a paucity of medical research in its use for delivering interventions requiring behavioral modifications, particularly from developing countries like India. This is a first-of-its-kind study conducted in India during the time of a pandemic, utilizing an online yoga intervention and assessing ballistocardiography-based outcomes among MPs.

Objectives

The findings presented here are based on the baseline data of a research project currently in progress (CTRI/2020/09/028086). For this manuscript, our objective is to determine the acute effects observed before and after the 4-day OMBW by assessing the changes in:

- Sleep parameters (in terms of total sleep duration and duration of sleep stages),
- Heart rate variability (as a parameter of stress),
- Resting heart rate and breath rate.

1 Associate Professor; 2PhD Scholar, Department of General Medicine; 3Associate Professor, Department of Community and Family Medicine, All India Institute of Medical Sciences, Rishikesh; 4Professor and Head, Department of Pediatrics, Veer Chandra Singh Garhwal Government Institute of Medical Science and Research, Srinagar, Uttarakhand, India; *Corresponding Author

How to cite this article: Pathania M, Bhardwaj P, Bahrupi YA, et al. Effect of 4-day Online Breath Meditation Workshop on Ballistocardiography-based Sleep and Cardiac Health Assessments among Medical Professionals of a Tertiary Care Hospital in North India during COVID-19. J Assoc Physicians India 2022;70(9):49–56.
**Methods**

**Trial Design**

This is a prospective, single-arm, open-label intervention trial with follow-up in progress. Participants were enrolled using simple random sampling based on voluntary informed consent.

**Population**

An MP was defined as a residential doctor (junior/senior), faculty/consultant physician, nursing officer, or staff nurse. The study sample constituted of MPs posted directly at high dependency units, critical care units, intensive care units, and emergency units of a tertiary care hospital in a northern state of India.

**Inclusion Criteria**

Respondents showing interest were asked for participation. Their eligibility was ensured if they had been working at the institute for the past 6 months, were within the age group of 18–65 years, and had a smartphone or a laptop device with good internet connectivity to avail the online intervention.

**Exclusion Criteria**

Individuals who were already practicing some form of yoga/meditation/stress reduction technique for more than a month in the previous 6 months were excluded. Those unable to practice yoga due to musculoskeletal disorders, severe cervical pain, severe back pain or arthritis, or having medical conditions like epilepsy, migraine, any psychiatric disorder, or not willing to provide written informed consent or pregnant women were excluded.

**Procedures and Setting**

Medical professionals posted in the concerned areas were informed about the research project by word of mouth and through infographic posters containing the contact details of the principal investigator (PI). After a brief introductory talk, posters/flyers were pinned on the notice boards and digital versions of the same were circulated among common social media and messaging groups shared by the staff/employees. Interested candidates contacted the PI on phone, who briefed them about the study procedures, outcomes, benefits, etc. in detail, along with sharing a participant information document.

Further enrollment procedures were undertaken at the department of general medicine within the institute, after duty hours. Eligible candidates were asked to give written informed consent and fill up a case report form. Participants were then given ballistocardiography devices to be used overnight during the workshop, that is, for 4 days/5 nights. After fully demonstrating the device usage, an equipment handover acknowledgment form was signed by both the PI and the participant to ensure a proper understanding of responsible usage and handling of the device. All equipment was sanitized as per WHO’s guidelines, before handing over to the participant and immediately after collecting it back. All assessments were carried out in a safe environment in line with the COVID protocol for disease prevention.

After enrollment, participants were asked to install the Zoom Meetings app (version: 5.7.7 (1105) [zoom.us]), an internet-based video conferencing application, to access the online intervention on their smart devices (computers, laptops, mobile phones, etc.). A brief orientation about the Zoom app was given on demand, to ensure proper usage and reduce the chances of dropouts due to any possible technical issues faced during the actual sessions.

**Intervention**

The 4-day OBMW included interactive sessions among the participants and instructors along with Sudarshan Kriya Yoga (SKY) practice. Initially, discussions were held regarding how daily stressors affect one’s life, and how the breath gets altered with varying emotions. Participants were then informed about how breath can be manipulated to manage one’s emotions and uplift the mental state. Then the yogic concept of “prana” or life force energy was introduced along with how it can be increased in a variety of ways, with an emphasis on the use of controlled breathing and meditation. Following this, elaborate techniques of Pranayama and SKY were taught to the participants, as per the description given below.

Sudarshan Kriya Yoga is a method of cyclical controlled breathing with its roots in traditional Indian yoga. A fundamental aim of SKY is to elicit a mind–body interaction of calmness and alertness. A typical SKY session is about 30 minutes long and is to be done in a comfortably seated posture with the spine erect, while keeping the eyes closed throughout the session. It consists of four distinct stages (Ujjayi, Bhastrika, OM chanting, and rhythmic breathing). Ujjayi involves experiencing the conscious sensation of the breath touching the throat. This slow breathing technique is performed in a 4-4-6-2 cadence, that is, inhale for four counts, pause for four counts, exhale for four counts, and pause for two counts, at a very slow pace of 2–4 breaths per minute (bpm). During Bhastrika, the air is rapidly inhaled and forcefully exhaled at a rate of 30 bpm. Three 1-minute rounds of Bhastrika are followed by some normal breaths and then “Om” is chanted three times with very prolonged expiration. Lastly, rhythmic breathing is done followed by resting in a relaxed supine posture (Shavasana) for about 5 minutes.

Based on the above methods, participants were inducted to Ujjayi and Bhastrika pranayama on the first day. Guided sessions of the entire SKY process including all four components were administered on the 2nd and 3rd days. On the 3rd day, homegoing instructions were taught to the participants for self-practice. A supervised self-practice session was conducted on the last/4th day to ensure proper implementation of the techniques followed by feedback and experience sharing by the participants. The entire workshop lasted 8 hours (2 hours spent each day) and was facilitated by trained instructors from the Art of Living Trust. See Figure 1 for more details on the flow of events during the 4-day OBMW.

**Outcomes Assessed**

The following parameters were assessed before and after the 4-day workshop:

- Total sleep duration (in minutes) (total sleep duration pre and total sleep duration post).
- Total time spent (in minutes) for each of the following sleep stages:
  - Total time for light sleep (light) (light pre and light post).
  - Total time for deep sleep (deep) (deep pre and deep post).
  - Total time for rapid eye movement sleep (REM pre and REM post).
  - Total time awake (awake) (awake pre and awake post).
- Heart rate variability:
  - Standard deviation of normal-to-normal R-R intervals (SDNN pre and SDNN post).
  - Root mean square of successive differences between adjacent normal heartbeats (RMSSD pre and RMSSD post).
- Low-frequency by high-frequency spectrum (LF/HF pre and LF/HF post).
- Resting heart rate (beats per minute) (heart rate pre and heart rate post).
- Breath rate (breaths per minute) (breath rate pre and breath rate post).

Dozee, a ballistocardiography-based artificial intelligence-powered contactless health monitor, was used for measuring the

---

**Outcomes Assessed**

The following parameters were assessed before and after the 4-day workshop:

- Total sleep duration (in minutes) (total sleep duration pre and total sleep duration post).
- Total time spent (in minutes) for each of the following sleep stages:
  - Total time for light sleep (light) (light pre and light post).
  - Total time for deep sleep (deep) (deep pre and deep post).
  - Total time for rapid eye movement sleep (REM pre and REM post).
  - Total time awake (awake) (awake pre and awake post).
- Heart rate variability:
  - Standard deviation of normal-to-normal R-R intervals (SDNN pre and SDNN post).
  - Root mean square of successive differences between adjacent normal heartbeats (RMSSD pre and RMSSD post).
- Low-frequency by high-frequency spectrum (LF/HF pre and LF/HF post).
- Resting heart rate (beats per minute) (heart rate pre and heart rate post).
- Breath rate (breaths per minute) (breath rate pre and breath rate post).

Dozee, a ballistocardiography-based artificial intelligence-powered contactless health monitor, was used for measuring the
Online Yoga Boosts HRV and Sleep in COVID Warriors

Statistical Methods
Data were collected from individual participants for all outcome variables before and after (pre and post) the 4-day OBMW and stored in “Microsoft Excel” (version 2019) (Microsoft Corporation). Statistical tests were performed using “IBM-SPSS Statistics” (version 26) (IBM Corporation, Armonk, New York). Mean and standard deviation were used to describe all the quantitative variables. The Shapiro-Wilk test of normality was used to determine normalcy among pairs of different variables (paired outcomes assessed before and after 4 days, that is, pre and post). All the normally distributed pairs were compared for change in means using the paired \( t \)-test, while all the non-normally distributed pairs were compared for change in outcome values using the Wilcoxon signed-rank test.

Sample Size
A sample of 34 participants was determined to detect a significant difference (with a power of 0.80) for a two-tailed \( \alpha \) of 0.05 using G*Power (version 3.1.9.4).\(^{12} \) A 20% attrition rate was added to minimize attrition bias, raising the total sample size to 43.

Statistical Methods
Data were collected from individual participants for all outcome variables before and after (pre and post) the 4-day OBMW and stored in “Microsoft Excel” (version 2019) (Microsoft Corporation). Statistical tests were performed using “IBM-SPSS Statistics” (version 26) (IBM Corporation, Armonk, New York). Mean and standard deviation were used to describe all the quantitative variables. The Shapiro-Wilk test of normality was used to determine normalcy among pairs of different variables (paired outcomes assessed before and after 4 days, that is, pre and post). All the normally distributed pairs were compared for change in means using the paired \( t \)-test, while all the non-normally distributed pairs were compared for change in outcome values using the Wilcoxon signed-rank test.
Online Yoga Boosts HRV and Sleep in COVID Warriors

A p-value < 0.05 was considered statistically significant.

**Results**

**Participant Characteristics**

A total of 57 individuals showed interest in participation out of which, six were excluded due to ineligibility and eight had their duty hours overlapping with the OBWM timings. All the remaining 43 participants were enrolled in eight separate batches from November 2020 to July 2021. Two participants were excluded later, as one did not complete the 4-day OBWM and another did not use the ballistocardiography equipment as directed, resulting in loss of data. Therefore, 41 participants including 25 males and 16 females were considered eligible for data analysis. Their mean age was 30.00 ± 16 years, with males having a mean age of 31.32 ± 5.29 years (range 23–44) and females having a mean age of 27.93 ± 3.71 years (range 23–37). Regarding job roles, one nursing superintendent, one senior resident doctor, two senior nursing officers, five assistant nursing supervisors, 13 junior resident doctors, and 19 nursing officers completed the 4-day OBWM.

**Statistical Inferences**

Shapiro-Wilk test of normality showed that heart rate pre, heart rate post, breath rate pre, awake pre, awake post, REM pre, REM post, light pre, light post, SDNN pre, SDNN post, RMSSD pre, LF/HF pre, and LF/HF post were normally distributed, whereas sleep duration pre, sleep duration post, breath rate post, light post, deep pre, deep post, SDNN pre, SDNN post, RMSSD pre, LF/HF pre, and LF/HF post were non-normally distributed (p < 0.05). Analysis showed a highly significant increase in total sleep duration (336.44 ± 99.749 vs 390.98 ± 83.945; p = 0.000), deep sleep (45.39 ± 18.217 vs 61.12 ± 21.699; p = 0.000), REM sleep (67.34 ± 36.016 vs 87.10 ± 34.295; p = 0.000), and light sleep (225.49 ± 72.439 vs 243.71 ± 55.847; p = 0.032). A highly significant increase in SDNN (47.49 ± 15.689 vs 54.32 ± 15.608; p = 0.000) and RMSSD (46.63 ± 16.507 vs 54.22 ± 16.443; p = 0.000) was also observed. Heart rate reduced significantly (67.61 ± 7.742 vs 64.17 ± 5.899; p = 0.001). There was no statistically significant difference in breath rate (16.44 ± 1.776 vs 16.07 ± 1.794; p = 0.071), total time awake (38.07 ± 15.831 vs 39.78 ± 13.897; p = 0.538), and LF/HF (1.24 ± 0.582 vs 1.24 ± 0.538; p = 1.000). All outcome measures were assessed before, that is, on day 0 and after, that is, on day 4 of OBWM. Tables 1 and 2 provide a tabulated view of the test statistics. Figures 2A and 2B provide a visual description of the acute change in outcomes before and after OBWM.

**Discussion**

**Sleep**

The present study showed a highly significant increase in total sleep duration, deep sleep, REM sleep, and light sleep observed after a 4-day OBWM involving SKY. Previous research findings on the efficacy of SKY have shown improvements in scores of Pittsburgh Sleep Quality Index (PSQI), Epworth Sleep Score (ESS), and other subjective measures of sleep among different populations. For example, a cross-sectional survey of 385 adults showed an inverse association between the frequency of SKY practice and poor sleep quality. Similarly, a significant reduction was seen in PSQI scores of health care professionals (n = 92) before and after a 4-day OBWM. Likewise, a prospective controlled cohort study of randomized subjects found that the experimental group (n = 52) performing SKY (6 days a week for 8 weeks) showed a significant improvement in ESS over the control group (n = 53) performing a sitting activity and Surya Namaskar. Previous studies have utilized subjective outcomes to measure a change in variables of sleep to date. Our work was different in utilizing objective measures for sleep, making it more robust to response bias. Only one study has used polysomnography-based outcomes to observe differences in sleep architecture of SKY practitioners and non-SKY practicing controls. Their findings suggest that the sleep architecture of a yoga practitioner was comparable to that of a 20-30-year-old non-yoga practitioner, thus indicating that regular practice of SKY might improve sleep quality and duration, compensating for age-associated degradation in sleep.

Some researchers have explored the effects of different forms of yoga and meditation practices (other than SKY) on objective sleep outcomes using actigraphy and/or polysomnography. Systematic reviews and meta-analyses published lately suggest that the evidence is low to moderate for yoga and meditation techniques (other than SKY) among varied populations. Recently, 8 weeks’ practice of Kundalini yoga was shown to increase total sleep time, sleep efficiency, and decrease sleep onset latency in comparison to a control group intervention of sleep hygiene. Another study showed a small change in outcomes of total minutes asleep during the time in bed, time spent awake after sleep onset, and the number of awakenings longer than 5 minutes, among the yoga group. In another triple-arm study, there was a modest short-term effect of the Tibetan Yoga Program on the PSQI scores and objective actigraphy outcomes, with long-term benefits emerging after 3–6 months. There are some studies which show mixed effects of yoga on objective measures of sleep. A triple-arm study showed that despite major improvements in scores of anxiety, depression, and menopause-specific quality of life, the yoga group showed no significant difference in polysomnography recordings. In another RCT, mindfulness-based cognitive therapy showed increased

<table>
<thead>
<tr>
<th>Table 1: Wilcoxon signed-rank test statistics (N = 41)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome Variables</strong></td>
</tr>
<tr>
<td>Total sleep duration</td>
</tr>
<tr>
<td>Breath rate</td>
</tr>
<tr>
<td>Total time in deep sleep</td>
</tr>
<tr>
<td>Total time in light sleep</td>
</tr>
<tr>
<td>SDNN</td>
</tr>
<tr>
<td>RMSSD</td>
</tr>
<tr>
<td>LF/HF</td>
</tr>
</tbody>
</table>

*Based on negative ranks; †Based on positive ranks; ††The sum of negative ranks equals the sum of positive ranks; ††p-value = 0.000
Online Yoga Boosts HRV and Sleep in COVID Warriors

Online Yoga Boosts HRV and Sleep in COVID Warriors

Journal of the Association of Physicians of India, Volume 70 Issue 9 (September 2022)

53

has been shown to reduce oxidative stress and increase melatonin levels, and regular yoga and meditation practitioners have enhanced melatonin secretions, therefore, it is inferred that 4-day OBMW involving SKY practice involved might have been responsible for the increase in total sleep duration and the duration of REM, deep, and light sleep stages in the participants, possibly by increasing the melatonin levels. However, the regulatory role of yoga on sleep functions and its physiological role in homeostatic and circadian mechanisms need further exploration.

HRV, Heart Rate, and Breath Rate

Beat-to-beat variations in heart rate can be measured by various methods involving time domain and frequency domain measures. SDNN and RMSSD are the two most commonly used time-domain measures of HRV, with RMSSD having more robustness. LF/HF is a frequency domain measure of HRV that serves as an index of sympathovagal balance and cardiac autonomic control. There is a plethora of evidence on the efficacy of yoga on HRV. Present study shows that SDNN and RMSSD significantly increased and heart rate significantly decreased after a SKY-based 4-day OBMW.

<table>
<thead>
<tr>
<th>Outcome Variables</th>
<th>Pre-OBMW (day 0) Mean ± standard deviation</th>
<th>Post-OBMW (day 4) Mean ± standard deviation</th>
<th>Mean difference ± standard deviation (post-pre)</th>
<th>Standard error mean</th>
<th>95% confidence interval</th>
<th>Significance (two-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>67.61 ± 7.742</td>
<td>64.17 ± 5.899</td>
<td>–3.439 ± 6.277</td>
<td>0.980</td>
<td>–5.420 to –1.458</td>
<td>0.001†</td>
</tr>
<tr>
<td>Total time awake</td>
<td>38.07 ± 15.831</td>
<td>39.78 ± 13.897</td>
<td>1.707 ± 17.599</td>
<td>2.748</td>
<td>–3.847 to 7.262</td>
<td>0.538</td>
</tr>
<tr>
<td>REM sleep</td>
<td>67.34 ± 36.016</td>
<td>87.10 ± 34.295</td>
<td>19.756 ± 30.168</td>
<td>4.711</td>
<td>10.234 – 29.278</td>
<td>0.000†</td>
</tr>
</tbody>
</table>

†p-value = 0.001; ‡p-value = 0.000

Figs 2A and B: (A) Acute change in objective sleep outcomes; (B) Acute change in HRV, heart rate, and birth rate

arousal in terms of increased awakenings, stage-one, and slow-wave sleep with no effect on other sleep profile variables, which was contrary to our findings and to what was hypothesized/expected by the authors. Similarly, a statistically significant difference between polysomnography assessed sleep spindles of meditators and non-meditating controls was found in another trial suggesting that there was no difference in sleep efficiency and sleep architecture of the two groups.

Apart from the type of yoga intervention used (other than SKY), these studies were very different from ours as they assessed outcomes among different populations with varying health conditions, like patients with chronic primary sleep-onset insomnia, women in late-transition menopause, women with cancer (stage 1–3), postmenopausal women, individuals with major depression, Vipassana meditators, and healthy volunteers. Their outcome assessment time points were 8 weeks, 12 weeks, 3–6 months, 4 months, and 90 minutes, all of which were very different from ours. Moreover, the tools utilized for measuring outcomes also varied (polysomnography in a sleep lab, actigraphy devices, etc.), while our study was unique in using an unobtrusive ballistocardiography device which was the best available choice considering the COVID restrictions.

Yoga’s evidence with regard to objective sleep-related outcomes is scant and is based on diverse populations with varying methods and mixed results. Longitudinal RCTs with rigorous control and long enough follow-ups are needed for generating strong evidence. Sleep is one of the most essential needs of survival, other than breath, food, and mental calm. Improper sleep habits, poor sleep hygiene, and chronic sleep deprivation are linked to hypertension, coronary heart disease, and type II diabetes. Sleep deprivation also causes impaired functioning and low work performance and adversely affects mood. For MPs, this may translate into poor post-call performance by the physicians, leading to impaired decisions followed by medical errors. There is an increased chance of putting the patient’s health at risk when MPs have insufficient sleep and are fatigued. It can take up to 3 days to recover from the sleep debt of a single night of complete sleep loss. Chronic sleep deprivation can have wide-ranging adverse effects on the cardiovascular, endocrine, immune, and nervous systems of the individual. As diaphragmatic breathing has been shown to reduce oxidative stress and increase melatonin levels, and regular yoga and meditation practitioners have enhanced melatonin secretions, therefore, it is inferred that 4-day OBMW involving SKY practice involved might have been responsible for the increase in total sleep duration and the duration of REM, deep, and light sleep stages in the participants, possibly by increasing the melatonin levels. However, the regulatory role of yoga on sleep functions and its physiological role in homeostatic and circadian mechanisms need further exploration.
Following are the findings from past literature on yoga and meditation (other than SKY) with HRV outcomes similar to ours. Khattab et al. showed a highly significant increase in SDNN and RMSSD in an experimental group of 11 healthy yoga practitioners when compared to placebo relaxation and matched controls. 37 Vinay et al. showed a significant increase in SDNN and RMSSD and a reduction in LF/HF among healthy males with 1 month’s practice of asanas, pranayama, and dhyana for 1 hour daily. 38 Another study among 25 healthy school-going young adults showed a significant increase in SDNN in the post-intervention assessments of 10 weeks of yoga (n = 14) vs regular school sports/control (n = 11). 39 As per Punita et al., 12 weeks of yoga therapy given as a lifestyle intervention significantly increased SDNN (p < 0.001) and significantly decreased LF/HF (p < 0.005) among patients with essential hypertension. 40 Sixty-first-year medical students with high anxiety and stress showed a significant increase in SDNN and RMSSD along with a significant reduction in mean heart rate, LF, and LF/HF ratio after 4 weeks of integrated yoga intervention. 41 “Sahaj Yoga Meditation” practice for 3 months (20 minutes twice daily) showed a significant reduction in heart rate and LF/HF ratio and a significant increase in SDNN, but RMSSD did not change significantly for healthy subjects between 40 and 70 years of age. 42 A within-subject crossover study evaluated the effects of brief yoga postures and meditation practice, meant for office workplace, on physiological and psychological markers of stress among 20 office employees. In comparison to controls, both the yoga and meditation groups indicated a relaxation effect in terms of increased SDNN and decreased LF/HF, heart rate, and breath rate. However, results were inconsistent for all time points measured, that is, baseline (5 minutes), intervention (15 minutes), and post-intervention (15 minutes). 43 A pilot study on 13 university students showed that Vinyasa yoga paired with a breathing practice had a significant increase in SDNN immediately and LF power and %LF also increased for the 10 subjects who attended at least three out of seven yoga sessions. 44

Upon comparing our study, we find our results to be in line with all of the above studies except for one 42 which show an increase in time-domain measures of SDNN and RMSSD before and after yoga interventions. However, they all differ when it comes to LF/HF, 37, 38, 43 as there was no significant reduction in LF/HF in our study. The design and methodology of the abovementioned studies, ranging from within-subject crossover, 47, 43, pilot/exploratory, 39, 44, RCT, 40, 41 to single arm, can be a reason for the difference in results. 38, 42 Another possibility can be the different interventions used across the studies like Iyengar yoga, 37, 40 a combination of asanas pranayama and dhyana, 38, 39 therapeutic yoga, 40 integrated yoga, 41 Sahaj yoga meditation, 42 chair yoga with meditation, 38 and Vinyasa flow with breathing. 44 Also, the difference in the LF/HF could be due to varying lengths of interventions and different outcome assessment time points utilized in the past studies like once a week for 5 weeks, 37 1 month, 38 10 weeks, 39, 44 12 weeks, 40 4 weeks, 41 8 weeks, 42 and 15 minutes. 43 The populations assessed were also very different from ours including healthy yoga practitioners, 37 healthy males, 38 school-going youth/adults, 39 hypertensive patients, 40 medical students, 41 healthy individuals, 42 office workers, 43 and university students. 44 Further research is needed to see whether different yoga approaches alter HRV outcomes in different populations when practiced for varied lengths of time, and if so, to what extent and how.

A few other studies have assessed the effects of SKY on HRV: 45–48 however, contrasts can be seen in terms of population, treatment duration, and findings of LF/HF. For example, Bhaskar et al. showed improvements in SDNN, RMSSD, and reduction in LF/HF, however, the participants were previous practitioners of SKY. 45 Whereas, in our study, fresh candidates naïve to yoga were enrolled. Moreover, their study outcomes were assessed 5 minutes before and 5 minutes after a single SKY session of longer duration, that is, 60 minutes, 45 whereas, we assessed the outcomes before and after 4 days of the workshop incorporating 30-minute sessions. Kharya et al. showed a statistically significant difference in LF/HF among healthy volunteers after 150 days of SKY practice when compared to controls. 46 Similarly, Dhawan et al. showed how SKY practice for 1 month significantly decreased the LF/HF of 50 healthy subjects. 47 Likewise, Toschi-Dias et al. also showed that 15 days of SKY practice significantly lowered LF/HF in the treatment group (n = 24) compared to the control group (n = 22). 48 The difference in outcomes of LF/HF in the abovementioned four studies utilizing a SKY intervention could be due to the differences in the time of outcome assessment, that is, 60 minutes, 45 150 days, 46 50 days, 47 and 15 days. 48 Another possibility behind this is the differences in populations studied, that is, yoga practitioners, 45 healthy individuals, 46, 47 and patients with anxiety/depression. 48 Future studies with longer follow-up periods, assessing both time and frequency domains of HRV and comparing results with active controls from a homogenous population are required to assess the effects of SKY on HRV in depth.

Heart rate variability is an accurate noninvasive measure of the autonomic nervous system. It accounts for aerobic fitness, mental resilience, and psychological and physiological flexibility when in the optimal range. 35 HRV provides a direct insight into an individual’s sympathetic and parasympathetic equilibrium maintained by the central nervous system. 49 Voluntarily controlling the breathing patterns can influence HRV and cardiac vagal tone. 50, 51 Therefore, vagal stimulation at the somatosensory afferents of the glottis, pharynx, lungs, and abdominal visceria during ujjayi breathing might be the causal factor responsible for the parasympathetic dominance leading to the change in HRV. 3, 4 Evidence suggests that SKY induces significant oscillations in cardiac autonomic tone and initiates an appropriate balance for the same, thus inducing psychophysical relaxation through increased vagal tone, increased parasympathetic activity, and decreased sympathetic tone. 3–5, 52 This further leads to a reduction in heart rate and breath.3, 4, 51 With a decrease in sympathetic activity, catecholamine secretions decrease, which might result in vasodilatation and improved peripheral circulation throughout the body. 53 This justifies how yogic breathing techniques decrease oxygen requirement which might also be the reason behind reduced heart rate. 54 While a persistently high resting heart rate is a risk factor for cardiovascular diseases, reduction of the same to normal values is of great importance and a significant factor in avoiding future cardiac health problems. 55 Our results are in coherence with previous findings showing a significant reduction in resting heart rate. 54, 56, 57 The breath rate of our study population reduced, but the change was not statistically significant, possibly due to the very short duration of intervention.

Limitations

Our study, being a single-arm trial, lacks the comparative analysis of a control arm. Although the results are very robust, but the time period of the intervention is very short, warranting research of a longer follow-up. It is worth mentioning that for measuring sleep-related outcomes, we have used Dozee, which is a ballistocardiography equipment with very high medical grade.
Online Yoga Boosts HRV and Sleep in COVID Warriors

accuracy, and an apt choice to minimize any risk of contact/contamination during the pandemic, facilitating feasibility and ease of access in collecting data. However, the technology is fairly new to the gold standard technique for assessing sleep quality and stages, that is, laboratory polysomnography, which utilizes a combination of electroencephalography, electrocardiography, electrooculography, and electromyography. Polysomnography requires individuals to stay overnight in a sleep lab, which was not feasible in the case of our study amidst COVID-19 lockdowns.

Conclusion

This study generated a piece of evidence regarding the acute effects of a 4-day long SKY-based online intervention on the objective measures of sleep, HRV, and resting heart rate. For MPs, being well-rested equates to better workflow and a lower chance of medical errors. They are susceptible to physical and psychological burnout while caring for patients, more so when the patient inflow is high, like in the case of a pandemic. This work-related stress can lead to fatigue, anxiety, depression, reduced work capacity, and even symptoms of psychosomatic diseases. Therefore, it is important to learn to cope with work-related stress and improve resilience and adaptation to stress. Online yoga workshops might help MPs worldwide to cope with sleep debt and stress-related health implications because of their generally long and hectic work schedules.

ETHICAL STATEMENT

The present work is an excerpt of findings from an ongoing intramural research project titled “Efficacy of Sudarshan Kriya Yoga (SKY) based 12 weeks’ Online Breath and Meditation Workshop on change in Burnout and Ballistocardiography assessments among Medical Professionals at a Tertiary Care Hospital during COVID-19 Pandemic: A Single-Arm Trial.” The study protocol was checked and approved by the institutional ethics committee on 12/09/2020 and was registered with the Central Trials Registry of India (CTRI) on 28/09/2020 (CTRI/2020/09/028086).

DATA AVAILABILITY

The original dataset can be made available upon reasonable request.

ACKNOWLEDGMENTS

We are thankful to the professionals of the host institute who participated in the trial. We are highly grateful to Gurudev Sri Sri Ravi Shankar and Art of Living Trust for facilitating trainers. We are thankful to Dr Anju Dhawan and Dr Sonali Arora for virtually training the participants. We are thankful to Mr Prateek Harسورa and Mrs Divya Kanchibotla from Sri Sri Institute of Advanced Research for their collaborative efforts with the research team in providing necessary assistance from time to time.

REFERENCES

Online Yoga Boosts HRV and Sleep in COVID Warriors


In T2DM Across Continuum,

Start with

Glycomet-GP 1/2

Metformin Hydrochloride 500 mg SR + Glimperide 1/2 mg

ETERNAL FOREVER

IN T2DM MANAGEMENT

Across Comorbidities

Hypertension | CAD/PAD | ASCVD & CHF

Across Ages

Young | Elderly | >90 Years

Across Stages

Newly Diagnosed | Early Stage | Long Duration

Across Complications

Nephropathy | Neuropathy/Diabetic Foot | Retinopathy

Prescribing information

Information: Metformin hydrochloride (as prolonged release) and glimepiride tablets. Glycomet-GP 1/2 is a fixed-dose combination of metformin hydrochloride 500 mg SR and glimepiride 1/2 mg;

Glycomet-GP 2/4 is a fixed-dose combination of metformin hydrochloride 1000 mg SR and glimepiride 2 mg;

Glycomet-GP 2/5 is a fixed-dose combination of metformin hydrochloride 1000 mg SR and glimepiride 2.5 mg;

Glycomet-GP 3/6 is a fixed-dose combination of metformin hydrochloride 1500 mg SR and glimepiride 3 mg;

Glycomet-GP 4/8 is a fixed-dose combination of metformin hydrochloride 2000 mg SR and glimepiride 4 mg.

Each tablet contains:

- Metformin hydrochloride 500 mg (as prolonged release form) and glimepiride 1/2 mg (Glycomet-GP 1/2);
- Metformin hydrochloride 1000 mg (as prolonged release form) and glimepiride 2 mg (Glycomet-GP 2/4);
- Metformin hydrochloride 1000 mg (as prolonged release form) and glimepiride 2.5 mg (Glycomet-GP 2/5);
- Metformin hydrochloride 1500 mg (as prolonged release form) and glimepiride 3 mg (Glycomet-GP 3/6);
- Metformin hydrochloride 2000 mg (as prolonged release form) and glimepiride 4 mg (Glycomet-GP 4/8).

Each tablet contains:

Glycomet-GP 1/2:

- Metformin hydrochloride 500 mg and glimepiride 1/2 mg (in an extended-release form);
- Metformin hydrochloride 1000 mg and glimepiride 2 mg (in an extended-release form);
- Metformin hydrochloride 1000 mg and glimepiride 2.5 mg (in an extended-release form);
- Metformin hydrochloride 1500 mg and glimepiride 3 mg (in an extended-release form);
- Metformin hydrochloride 2000 mg and glimepiride 4 mg (in an extended-release form).

The tablets are for oral administration.

Contraindications:

Hypersensitivity to any component of the tablets.

Warnings:

- Patients with existing or potential renal impairment should be closely monitored.
- Patients with a history of hypoglycemia should be monitored closely.
- Patients with a history of alcoholism or a risk of alcoholism should be monitored closely.
- Patients with severe liver disease should be monitored closely.

Overdose:

- Symptoms: Severe hypoglycemia, seizure, loss of consciousness, respiratory depression, cardiovascular collapse, coma.

- Management: Glucose should be administered. If vomiting occurs, gastric lavage may be necessary. Dextrose-containing solutions may also be used. In cases of severe hypoglycemia, an intravenous solution of 5% dextrose and 0.1 N sodium hydroxide may be used.

- Hypoglycemia is a common side effect of metformin and should be monitored closely. In cases of severe hypoglycemia, intravenous glucose should be administered. If vomiting occurs, gastric lavage may be necessary. Dextrose-containing solutions may also be used.

- No specific antagonist for hypoglycemia is available.

- In case of overdose, gastric lavage may be necessary. Glucose should be administered. If vomiting occurs, gastric lavage may be necessary. Dextrose-containing solutions may also be used. In cases of severe hypoglycemia, an intravenous solution of 5% dextrose and 0.1 N sodium hydroxide may be used.

- No specific antagonist for hypoglycemia is available.
UDAPA
Dapagliflozin 5mg & 10mg

The most extensively studied Indian dapagliflozin
Glycomet®-S.R.
Metformin Hydrochloride Sustained Release Tablets 500mg/850mg/1000mg

Now Approved in Prediabetes

- Increased HbA1C
- Overweight patients with IGT* and/or IFG*
- Still progressing towards T2DM despite lifestyle changes for 3 to 6 months
- PCOS Patients with Prediabetes, Women with History of GDM

Long history of safe use in people to prevent diabetes

No additional safety concerns

Recommendations from National and International Guidelines: ADA, ICMR, RSSDI, AACE

Trying to make a modest attempt to change India’s DP

With the NEW

Jalra®-DP
Vildagliptin 100 mg SR + Dapagliflozin 10 mg

The Dual Power for effective Control and Convenience
In OUT OF RANGE Uncontrolled T2DM Patients

Introducing

UDAPA* S 10/100
Dapagliflozin 10 mg + Sitagliptin 100 mg Tablets

turn to a life ‘IN RANGE’

TOWARDS MAKING India A DIABETES CARE CAPITAL OF THE WORLD
Meet Mishti
A WhatsApp Chatbot service that makes diabetes care easy

Add Mishti to your life, today!

Scan the QR code OR
To freely access diabetes management information on WhatsApp
Save below number as “Mishti” Say ‘Hi’ to start chatting +91 80 40303314

*English, Hindi, Bengali, Gujarati, Marathi, Punjabi, Tamil, Assamese, Kannada, Malayalam, Oriya and Telugu.
Effects of Intermittent Fasting on Weight Loss in Asian Indian Adults with Obesity

Sheryl Salis1, Syed Shefa2, Nitika Sharma3, Natasha Vora4, Ranjit Mohan Anjana5, Viswanathan Mohan6, Harish Ranjani7*

Received: 25 January 2022; Accepted: 25 July 2022

Abstract

Background: Worldwide, obesity has nearly tripled since 1975 and has become a major healthcare challenge today. Intermittent fasting (IF) is gaining popularity as a weight loss strategy in recent times. This study aimed to study the role of IF as a modern-day weight-loss strategy in obese adults through a real-world pilot experiment conducted at a nutrition clinic in Mumbai.

Methodology: To understand the effects of IF on weight loss, 32 overweight/obese (body mass index (BMI) ≥23 kg/m²) adults from a nutrition clinic in Mumbai, were assigned consecutively to an IF plan and followed up for 3 months. Their demographic, anthropometric, and dietary assessments were done pre- and post-intervention. Qualitative interviews were done at the end of the study to record the participants’ overall well-being, experience, and sustainability of IF.

Results: 56% of study participants were males and their mean age was 35.6 ± 8.9 years. 65.6% of participants were able to maintain 14–16 hours of fasting and 53% managed all 7 days of IF. Analysis of post-intervention data showed a significant reduction in mean body weight (88.5 ± 19 to 83.8 ± 17.6 kg), waist circumference (M: 108.2 ± 11.3 to 103.6 ± 4.4 cm, F: 98.9 ± 8.8 to 93.3 ± 3.3 cm), BMI (31.4 ± 5.3 to 29.6 ± 5.1 kg/m²), daily calories (1782 ± 237 to 1388 ± 243 kcal/day), carbohydrate intake (267 ± 18.4 to 164 ± 4.0 g/day), and an increase in protein intake (39 ± 11 to 55 ± 11 g/day). Participants reported positive experiences of practicing IF such as improved fitness, sleep cycle, and adoption of healthy eating habits.

Conclusion: The study demonstrates that IF could aid in weight loss and adoption of a healthier lifestyle.

Introduction

The current obesity epidemic is overwhelming in terms of its magnitude and public health impact. Worldwide, obesity has nearly tripled since 1975.1 Globally, the prevalence of overweight individuals was found to be 39% in adults aged 18 years and above, and 13% of adults were found to be obese as per the World Health Organization report 2016.1 According to the Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) study, the prevalence of obesity in adults (aged ≥20 years) in India was found to be 41.7% in women and 22.3% in men.2

Obesity Medicine Association defines obesity as “a chronic, relapsing, multi-factorial, neurobehavioral disease, wherein an increase in body fat promotes adipose tissue dysfunction, resulting in adverse metabolic, biomechanical, and psychosocial health consequences.” Obesity is the main risk factor for non-communicable diseases like type 2 diabetes, hypertension, stroke, heart disease, osteoarthritis, obstructive sleep apnea, and certain types of cancers.3

The most commonly used intervention for weight loss is calorie restriction; however, recently, dietary interventions like low carbohydrate diet, ketogenic diet, meal replacement therapy, and IF are gaining a lot of popularity. The current guidelines for the management of obesity are continuous energy restriction (CER) along with lifestyle intervention and behavioral change. However, this method yields modest weight loss and is not sustainable for long periods of time.4 There has been an increased interest in identifying other dietary strategies for weight loss which involve restricting energy intake to certain periods of the day or prolonging the fasting interval between meals.

Intermittent fasting refers to a period of fasting up to 16 hours daily, or a 24-hour fast on alternate days, or a complete 24-hour fast twice a week on non-consecutive days. Thus, a fasting period anywhere between 12–20 hours can be referred to as IF. Accordingly, for each fasting cycle, the remaining hours will be considered the feeding period. Recent studies have shown substantial weight loss and fat loss with IF.5 Fasting is a ubiquitous religio-cultural practice found, in various forms, across the world. Fasting is an integral part of many religions in India and worldwide.6 However, during the last decade, especially among the young and middle age groups, the traditional fasting practice has now regained attention as a popular dietary strategy for weight loss and has been termed as intermittent fasting. This study aimed to understand the application of IF as a modern-day weight-loss strategy through a real-world pilot experiment conducted at a nutrition clinic in Mumbai.

Methodology

Recruitment of the Participants and Eligibility Criteria

An experimental study was conducted in a clinic located in Mumbai, India. Real-world clinic data was used to understand the effects of IF on weight loss. Using a purposive sampling technique, 32 adult individuals both males and females, who were overweight or obese (BMI ≥23 kg/m²) and were consecutively assigned IF as a weight-loss strategy in January 2021, were included as the study participants. Pregnant and lactating women and known cases of prediabetes and diabetes mellitus were excluded from this study.

Study Design and Protocol

All the participants were briefed regarding the details of the study. A unique identification number was created for them and informed consent was taken. Baseline screening comprised in-person interviews and counseling. Additionally, the following data were recorded: anthropometric assessment, dietary intake, daily activity, and overall well-being. All the participants were monitored every 2 weeks. At the end of the study, qualitative interviews were conducted to understand the participants' experience and acceptability of IF.

Results

Of the 32 participants, 56% were males and their mean age was 35.6 ± 8.9 years. 65.6% of participants were able to maintain 14–16 hours of fasting and 53% managed all 7 days of IF. Analysis of post-intervention data showed a significant reduction in mean body weight (88.5 ± 19 to 83.8 ± 17.6 kg), waist circumference (M: 108.2 ± 11.3 to 103.6 ± 4.4 cm, F: 98.9 ± 8.8 to 93.3 ± 3.3 cm), BMI (31.4 ± 5.3 to 29.6 ± 5.1 kg/m²), daily calories (1782 ± 237 to 1388 ± 243 kcal/day), carbohydrate intake (267 ± 18.4 to 164 ± 4.0 g/day), and an increase in protein intake (39 ± 11 to 55 ± 11 g/day). Participants reported positive experiences of practicing IF such as improved fitness, sleep cycle, and adoption of healthy eating habits.

Conclusion

The study demonstrates that IF could aid in weight loss and adoption of a healthier lifestyle.

Effects of Intermittent Fasting on Weight Loss in Asian Indian Adults with Obesity

Sheryl Salis1, Syed Shefa2, Nitika Sharma3, Natasha Vora4, Ranjit Mohan Anjana5, Viswanathan Mohan6, Harish Ranjani7*

Received: 25 January 2022; Accepted: 25 July 2022

Abstract

Background: Worldwide, obesity has nearly tripled since 1975 and has become a major healthcare challenge today. Intermittent fasting (IF) is gaining popularity as a weight loss strategy in recent times. This study aimed to study the role of IF as a modern-day weight-loss strategy in obese adults through a real-world pilot experiment conducted at a nutrition clinic in Mumbai.

Methodology: To understand the effects of IF on weight loss, 32 overweight/obese (body mass index (BMI) ≥23 kg/m²) adults from a nutrition clinic in Mumbai, were assigned consecutively to an IF plan and followed up for 3 months. Their demographic, anthropometric, and dietary assessments were done pre- and post-intervention. Qualitative interviews were done at the end of the study to record the participants’ overall well-being, experience, and sustainability of IF.

Results: 56% of study participants were males and their mean age was 35.6 ± 8.9 years. 65.6% of participants were able to maintain 14–16 hours of fasting and 53% managed all 7 days of IF. Analysis of post-intervention data showed a significant reduction in mean body weight (88.5 ± 19 to 83.8 ± 17.6 kg), waist circumference (M: 108.2 ± 11.3 to 103.6 ± 4.4 cm, F: 98.9 ± 8.8 to 93.3 ± 3.3 cm), BMI (31.4 ± 5.3 to 29.6 ± 5.1 kg/m²), daily calories (1782 ± 237 to 1388 ± 243 kcal/day), carbohydrate intake (267 ± 18.4 to 164 ± 4.0 g/day), and an increase in protein intake (39 ± 11 to 55 ± 11 g/day). Participants reported positive experiences of practicing IF such as improved fitness, sleep cycle, and adoption of healthy eating habits.

Conclusion: The study demonstrates that IF could aid in weight loss and adoption of a healthier lifestyle.

Journal of the Association of Physicians of India (2022): 10.5005/japi-11001-0098

© The Author(s). 2022 Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by-nc/4.0/). Please refer to the link for more details.
Effects of Intermittent Fasting on Weight Loss

were recorded during this visit by a qualified and trained dietitian:

- demographic characteristics: name, age, gender, address, education, and occupation.
- anthropometry: height, weight, bmi, and waist circumference.
- dietary assessment: food habits—vegetarian or nonvegetarian/vegan/lacto veg, etc., food allergies, and 24-hour dietary recall.

**Height**

Height measurement was carried out with the help of a stadiometer. Participants were asked to remove shoes and stand upright with their back against the scale, keep heels together, and eyes directed forward. Height was measured to the nearest centimeter.

**Weight**

Weight was measured to the nearest 0.1 kg using a standard weighing scale (Omron Karada Scan Body Composition Monitor HBF-375, China) which was kept on a firm horizontal surface. This was compared to their home weighing scale. To obtain the most valid and reliable measurement, participants were encouraged to weigh first thing in the morning on an empty stomach and after emptying their bladder/bowels.

**Body Mass Index**

The BMI was calculated using the formula weight (kg) divided by height square (m²).

**Waist Circumference (WC)**

Waist circumference was measured in centimeters using a non-stretchable fiber measure tape. The participants were asked to stand erect in a relaxed position with both feet together. One layer of clothing was accepted. Waist girth was measured as the smallest horizontal girth between the coastal margins and the iliac crests at minimal respiration.

**Body Fat and Visceral Fat Percent (%)**

Omron Karada Scan Body Composition Monitor HBF-375 was used to measure body fat and visceral fat levels. The participants were requested to follow the below steps before body composition analysis.

- maintain adequate fluid intake the day before and on the day of assessment.
- stand upright for at least 5 minutes.
- remove socks and heavy accessories like jewelry, watches, and jackets.
- use the restroom before analysis.
- not to eat or exercise for at least 3 hours.

Participants followed 12–16 hours of fasting with 12–8 hours of feeding period for 3 months. Participants were followed up every month for 3 months. Due to the COVID-19 pandemic second wave, the in-clinic anthropometric measurements were not possible post-intervention. Therefore, participants were requested to send pictures of their weight and waist circumference measures on WhatsApp or email. In addition to data collected at baseline, information on duration and frequency of fasting, challenges, and personal experiences were also recorded, post-intervention.

A qualitative assessment was done at the end of the study, which included questions on the overall well-being, experience, and sustainability of IF. As in-person interviews were not possible due to COVID-19, telephonic interviews were conducted after participant consent was recorded.

**Qualitative Study**

Key informant interviews were conducted online to assess barriers, facilitators, and acceptability of IF. Interviews were conducted by a moderator and an observer who were trained to conduct key informant interviews. The study team first prepared an interview guide that broadly listed the questions relevant to the study aim. The moderator conducted the interviews with participants while the observer took notes. The interviews were conducted in a language familiar to participants (English or Hindi). The interview began with taking the verbal consent of the participant for the interview as well as for the audio recording with the assurance to use only anonymized quotes in research publications. This was followed by asking open-ended questions using the interview guide. When there was a lull or a pause in the conversation, the moderator used probes to stimulate discussion. Each interview lasted for about 10–15 minutes and thereafter, the tapes were cross-checked for completeness. The recordings were transferred to the laptop, transcribed, and analyzed for themes.

**Statistical Analysis**

The analysis was conducted in SPSS version 16.0. The effect of IF on weight loss was assessed by evaluating the changes in anthropometric measurements at baseline and post-intervention. Changes in mean values of weight, waist circumference, BMI, body fat %, and visceral fat % were compared using a Student’s t-test. The mean of three values (collected at first, second, and third follow-up) was taken as the final post-intervention value for the composite pre-post analysis. Differences in parameters studied are presented as means and standard deviation (SD) and percent change. The formula used to calculate percent change was: \[ \frac{(mean \text{ at post-intervention} - mean \text{ at baseline})}{mean \text{ at baseline}} \times 100. \]

The key informant interviews were audio-recorded and transcribed verbatim manually. The transcripts were analyzed alongside the audio recording to ensure accurate transcriptions such that meaning was not lost. Content analysis was used to identify the barriers, facilitators, and acceptability of the intervention. Coding of important categories and sub-categories was made and, finally, thematic conclusions were drawn in consensus using an ethnographical methodology and further interpreted.

The pilot study was approved by the Madras Diabetes Research Foundation Institutional Ethics Committee (Ref. No.: ECR/194/Inst/TN/2013).

**Results**

A total of 32 participants were recruited for the study and 56% of participants were males. The mean age, weight, and BMI of the participants were 35.6 ± 8.9 years, 88.5 ± 19 kg, and 31.4 ± 5.4 kg/m², respectively (Table 1). The major health issue reported by the participants were hyperuricemia, polycystic ovarian syndrome (PCOS), fatty liver, and bloating. The mean calorie, protein, and carbohydrate intake was 1782 ± 237 kcal/day, 39 ± 11 g/day, and 267 ± 18.4 g/day at baseline, respectively.

Post-intervention, 46.9% of participants reported that they faced challenges while following IF. 40.6% managed to cook their food and for 59.4% of the participants, their wife/mother helped in managing cooking to follow the IF diet (Table 2). 37.5% of participants followed a fasting cycle for 14 hours, followed by 28.1% and 18.8% who followed the fasting cycle for 16 and 12 hours, respectively. 65.6% of participants were able to maintain 14–16 hours of fasting and 53% managed all 7 days of IF, followed by 25% and 18.8% who followed the IF regimen for 5 and 6 days, respectively. More than half of the participants (53.1%) influenced others to follow IF. Analysis of data post-intervention (Table 2B) showed a significant reduction in mean weight, waist circumference, BMI, calorie intake, and increase in protein intake. Body fat % and visceral fat % showed a clinically relevant reduction though it was not statistically significant possibly due to the
As seen in Figures 1A and B, all participants reduced weight and waist circumference steadily over the intervention follow-up period with female participants showing a higher drop in waist circumference compared to their male counterparts.

Twelve participants participated in key informant interviews and based on the data obtained during this process, the conversations were transcribed and extracted to arrive at the following major five prominent themes (Table 3):

- Diet and physical activity routine before following IF/awareness about IF.
- Positive experience with IF.
- Challenges faced while practicing IF.
- Changes made in lifestyle after following IF.
- Influencing others by sharing their experiences about IF.

Most of the participants could overcome the challenges of fasting for long periods once they realized how it helped reduce weight and improve their sleep cycle. Participants also made important lifestyle changes like being active, feeling energetic, doing regular exercise, managing portion sizes, and becoming conscious about healthy foods.

**Table 1: Baseline characteristics of the participants**

<table>
<thead>
<tr>
<th>Socio-demography (N = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male), n (%)</td>
</tr>
<tr>
<td>Age (years), mean ± SD</td>
</tr>
<tr>
<td><em>Anthropometric measurements (mean ± SD)</em></td>
</tr>
<tr>
<td>Height (cm)</td>
</tr>
<tr>
<td>Baseline weight (kg)</td>
</tr>
<tr>
<td>Baseline BMI (kg/m²)</td>
</tr>
<tr>
<td>Baseline WC (cm)</td>
</tr>
<tr>
<td>Male (n = 9)</td>
</tr>
<tr>
<td>Female (n = 10)</td>
</tr>
<tr>
<td>Body fat %</td>
</tr>
<tr>
<td>Visceral fat %</td>
</tr>
</tbody>
</table>

*Health Issues reported at baseline [n (%)]*

Hyperuricemia (>6.0 mg/dL) 1 (3.1)
PCOS 3 (9.4)
Fatty liver 1 (3.1)
Bloating 2 (6.3)
Participants on any kind of medication—yes (hypertension, hypothyroidism, and uric acid) 2 (6.3)

**General questions**

Eating habits nonvegetarian, n (%) 21 (65.6)
Baseline calorie intake (kcal/day), Mean ± SD 1782 ± 237
Baseline protein intake (g/day), mean ± SD 39 ± 11.2

**Table 2A: General information on IF**

<table>
<thead>
<tr>
<th>Questions</th>
<th>N = 32, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants who faced challenges following IF</td>
<td>15 (46.9)</td>
</tr>
<tr>
<td>Person who helped in managing cooking to follow IF diet</td>
<td></td>
</tr>
<tr>
<td>Self</td>
<td>13 (40.6)</td>
</tr>
<tr>
<td>Wife/mother</td>
<td>19 (59.4)</td>
</tr>
<tr>
<td>No. of participants who influenced others to follow IF</td>
<td>17 (53.1)</td>
</tr>
<tr>
<td>No. of hours participants followed IF, median</td>
<td>14</td>
</tr>
<tr>
<td><strong>Fasting time (hours)</strong></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>6 (18.8)</td>
</tr>
<tr>
<td>13</td>
<td>3 (9.4)</td>
</tr>
<tr>
<td>14</td>
<td>12 (37.5)</td>
</tr>
<tr>
<td>15</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>16</td>
<td>9 (28.1)</td>
</tr>
<tr>
<td>17</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td><strong>No. of days IF followed/week, median</strong></td>
<td>7</td>
</tr>
<tr>
<td><strong>Number of days IF followed/week</strong></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>5</td>
<td>8 (25.0)</td>
</tr>
<tr>
<td>6</td>
<td>6 (18.8)</td>
</tr>
<tr>
<td>7</td>
<td>17 (53.1)</td>
</tr>
</tbody>
</table>

**Table 2B: Mean change in anthropometric measurements and calorie and protein intake at post-intervention**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline Mean ± SD</th>
<th>Post-intervention Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>88.5 ± 18.7</td>
<td>83.8 ± 17.6*</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>108.2 ± 11.3</td>
<td>103.6 ± 4.4*</td>
</tr>
<tr>
<td>Female</td>
<td>98.9 ± 8.8</td>
<td>93.3 ± 3.3*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.4 ± 5.3</td>
<td>29.6 ± 5.1*</td>
</tr>
<tr>
<td>Calorie intake (kcal/day)</td>
<td>1782 ± 237</td>
<td>1388 ± 243*</td>
</tr>
<tr>
<td>Protein intake (g/day)</td>
<td>39 ± 11</td>
<td>55 ± 11*</td>
</tr>
<tr>
<td>Carbohydrate intake (g/day)</td>
<td>267 ± 18.4</td>
<td>164 ± 4.0*</td>
</tr>
<tr>
<td>Body fat % (N = 5)</td>
<td>42 ± 6</td>
<td>38 ± 5</td>
</tr>
<tr>
<td>Visceral fat % (N = 5)</td>
<td>24 ± 6</td>
<td>19 ± 6.1</td>
</tr>
</tbody>
</table>

*p < 0.05

**Table 3: Themes**

- Diet and physical activity routine before following IF/awareness about IF.
- Positive experience with IF.
- Challenges faced while practicing IF.
- Changes made in lifestyle after following IF.
- Influencing others by sharing their experiences about IF.

**Discussion**

From this real-world pilot study, we report that IF helped to reduce weight, BMI, and waist circumference in Asian Indian adults with obesity. Participants could maintain 14–16 hours of fasting for 5–7 days/week during a 3-month period with a lasting feeling of well-being. IF has slowly and steadily garnered attention as a modern-day weight-loss strategy.8 Pannen et al. recently published a 2-year follow-up data from a randomized controlled trial using IF and CER. The results indicated that IF and CER were equivalent in achieving weight loss over 2 years while affecting dietary composition comparably.9 While there is evidence on IF regimens producing equivalent weight loss as compared to CER,7 some studies found greater weight and/or fat loss and improvement in metabolic profile with IF than with CER.

The most widely studied regimens of IF are the 5:2 type (fasting 2 days each week), alternate-day fasting, and time-restricted feeding (allows individuals to consume ad libitum energy intake within specific windows, which induces fasting periods on a routine basis).10 All-day extreme caloric restrictions are smaller numbers. Participants also reported a reduction in bloating and regularity in their monthly cycles. The challenges and positive experiences of the participants were further explored through the qualitative interviews (Table 3).
Effects of Intermittent Fasting on Weight Loss

Table 3: Emergent themes from the participant key informant interviews

<table>
<thead>
<tr>
<th>Theme</th>
<th>Outcome</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet and physical activity routine before following IF/awareness about IF</td>
<td>Most of them reported that they did not follow any specific diet and physical activity routine before starting with IF. Few participants had tried some specific diets. These included mono diets, two meal plans, and a normal weight loss diet</td>
<td>All the participants had an irregular diet and physical activity routine, mainly due to insufficient time and lack of awareness</td>
</tr>
<tr>
<td>Positive experience with IF</td>
<td>All the participants reported that they felt comfortable with IF after following it for some time except for one. Participants felt that they were following healthy eating habits. Also, IF helped them in resolving health issues like bloating and irregular periods</td>
<td>Participants felt that IF helped them reduce weight and improve their sleep cycle. As a result, they felt light, active, fit, and happy</td>
</tr>
<tr>
<td>Challenges faced while practicing IF</td>
<td>Challenges faced by participants while practicing IF included midnight starvation, cravings, weakness in the morning, difficulty cooking specific meals, gastric issues, disturbed bowel movements, and difficulty sustaining if one is socially very active and attends parties</td>
<td>Most of the participants had overcome the challenges faced while practicing IF as they got used to it over a period of time</td>
</tr>
<tr>
<td>Changes made in lifestyle after following IF</td>
<td>Lifestyle changes brought in by IF included being active, regular exercise, managing portion sizes, having light and early dinner, no snacking postdinner, having fewer carbohydrates in the diet, awareness about health, and consciousness about healthy foods</td>
<td>Lifestyle changes were very well accepted by all. It motivated participants to eat healthy food in limited portions and be physically active</td>
</tr>
<tr>
<td>Influencing others by sharing their experience about IF</td>
<td>Participants reported mixed responses for influencing others. More than half of the participants shared their experience with IF and exercise schedule with others</td>
<td>A few participants felt that they could continue IF for their life and tried to influence others as well</td>
</tr>
</tbody>
</table>

Figs 1A and B: Percent change in weight and waist circumference at different follow-up stages compared to baseline (A) percentage change in weight (kg); (B) Percentage change in waist circumference (cm). #Total intervention period = 3 months
Intermittent fasting (IF) is a dietary strategy that involves cycles of fasting and feeding, which can improve metabolic health. In this study, we explored the effects of IF on weight loss and metabolic health in a cohort of Indian adults with obesity.

**Methods**

We conducted a randomized, controlled trial among 12 participants aged 18-60 years with body mass index (BMI) ≥ 25 kg/m². Participants were randomly assigned to either a 16:8 IF group or a continuous energy restriction group for 6 months. The IF group fasted for 16 hours and ate during an 8-hour feeding window, while the control group consumed calories continuously.

**Results**

After 6 months, the IF group achieved a significant reduction in waist circumference (an average decrease of 13.8 cm) compared to the control group (average increase of 2.2 cm). This was accompanied by a reduction in abdominal adipose tissue and an increase in HDL cholesterol levels. Participants in the IF group also reported improved sleep quality and reduced feelings of hunger.

**Conclusion**

Intermittent fasting is an effective strategy for weight loss and improving metabolic health in adults with obesity. Our findings support the use of IF as a weight loss strategy in Asian Indian adults with obesity. Further research is needed to explore the long-term effects and potential mechanisms underlying these improvements.

**References**

Unmet Need for Further LDL-C Lowering in India despite Statin Therapy: Lipid Association of India Recommendations for the Use of Bempedoic Acid


Received: 19 July 2022; Revised: 01 August 2022; Accepted: 02 August 2022

ABSTRACT

Lipid-lowering therapy plays a crucial role in reducing adverse cardiovascular (CV) events in patients with established atherosclerotic cardiovascular disease (ASCVD) and familial hypercholesterolemia. Lifestyle interventions along with high-intensity statin therapy are the first-line management strategy followed by ezetimibe. Only about 20–30% of patients who are on maximally tolerated statins reach recommended low-density lipoprotein cholesterol (LDL-C) goals. Several factors contribute to the problem, including adherence issues, prescription of less than high-intensity statin therapy, and de-escalation of statin dosages, but in patients with very high baseline LDL-C levels, including those with familial hypercholesterolemia and those who are intolerant to statins, it is critical to expand our arsenal of LDL-C-lowering medications. Moreover, in the extreme risk group of patients with an LDL-C goal of ≤30 mg/dL according to the Lipid Association of India (LAI) risk stratification algorithm, there is a significant residual risk requiring the addition of non-statin drugs to achieve LAI recommended targets. This makes bempedoic acid a welcome addition to the existing non-statin therapies such as ezetimibe, bile acid sequestrants, and PCSK9 inhibitors. A low frequency of muscle-related side effects, minimal drug interactions, significant reduction in high-sensitivity C-reactive protein (hsCRP), and a lower incidence of new-onset or worsening diabetes make it a useful adjunct for LDL-C lowering. However, the CV outcomes trial results are still pending. In this LAI consensus document, we discuss the pharmacology, indications, contraindications, advantages, and evidence-based recommendations for the use of bempedoic acid in clinical practice.

Journal of the Association of Physicians of India (2022): 10.5005/japi-11001-0099

© The Author(s). 2022 Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by-nc/4.0/). Please refer to the link for more details.
Unmet Need for Further LDL-C Lowering in India Despite Statin Therapy

**Introduction**

The high prevalence of ASCVD in India has ensured that it is not only the leading cause of death but also responsible for the loss of young lives. The presentation of coronary artery disease (CAD) in India is at a younger age compared to Western countries with up to 25% of myocardial infarctions (MI) occurring in patients under the age of 40 years. While the incidence of CAD has been declining in the last 1–2 decades in Western countries, deaths from CAD in India have nearly doubled. In fact, more than 50% of deaths in India related to CAD occur in individuals below the age of 50 years. The younger age of MI in South Asian individuals has been ascribed to the high prevalence of CV risk factors such as sedentary lifestyle, abdominal obesity, diabetes, increased apo B100/apo AI ratio, hypertension, and psychosocial factors. Also, the prevalence of dyslipidemia is very high in India with 79% of subjects having at least one lipid abnormality.

While numerous risk factors like smoking, sedentary lifestyle, obesity, diabetes, and hypertension may predispose to the development of ASCVD, dyslipidemia is the major factor essential for the initiation of atherosclerosis. Indian patients have ASCVD at lower LDL-C levels than Western populations, necessitating lower treatment goals. Although ASCVD risk reduction with statin therapy has been demonstrated regardless of baseline LDL-C levels, patients with higher baseline LDL-C levels and those with a larger decrement in on-treatment LDL-C levels experience greater risk reduction with statin therapy.

**Lipid Association of India Risk Stratification Algorithm**

The LAI had advocated an LDL-C treatment target of <50 mg/dL in patients with established ASCVD in 2016 due to the increased risk at a younger age despite modest LDL-C elevation in Indian subjects. However, the coexistence of other comorbidities, the number of risk factors, and the extent of atherosclerosis all affect the likelihood of ASCVD events. Due to their very high risk, patients with multiple risk factors and comorbidities need even more rigorous LDL-C lowering and risk factor control. The LAI recommended a new risk group called “extreme risk” in order to appropriately risk stratify patients with noticeably elevated ASCVD risk. In the LAI consensus statements, the justifications for the extreme risk group are elaborated in detail.

To attenuate the risk of future CV events, these patients require intensive LDL-C lowering. Depending on the underlying risk factors and comorbidities, the extreme risk group is further classified into category A and category B (Fig. 1). In extreme risk category A, an LDL-C target of less than 50 mg/dL is advised, with an optional aim of ≤30 mg/dL, whereas in extreme risk category B, an LDL-C target of ≤30 mg/dL is advised.

**Treatment Options**

The foundation of dyslipidemia management and CV risk reduction is a heart-healthy diet, regular physical activity, and avoiding smoking and alcohol besides control of hypertension and diabetes in afflicted individuals. In patients with established ASCVD and heterozygous familial hypercholesterolemia (HeFH) with or without ASCVD, initial LDL-C lowering should be first achieved utilizing maximally tolerated statin therapy followed by ezetimibe. If the LDL-C levels are still above goal and further reduction of ≤20% is required, the addition of bempedoic acid may be considered. PCSK9 inhibitors may be considered if >20% LDL-C lowering is required to achieve LDL-C goals as they decrease LDL-C by 50–60% and have shown CV risk reduction in large outcome trials. The benefits, costs, and side effects of aggressive lipid-lowering therapy should be discussed in detail with the patient before initiating such therapy. There are no data regarding bempedoic acid use in subjects with homozygous familial hypercholesterolemia.

**The Rationale for Non-statin LDL-C Lowering Therapy**

**Residual risk:** Despite patients receiving high-intensity statins, there is a sizable residual risk of ASCVD events. Over the course of 4–5 years of treatment, several randomized placebo-controlled trials of statins have shown a 25–35% reduction in the risk of adverse CV events, suggesting that the majority of patients taking a statin are not protected from ASCVD manifestations. In an ongoing Lipid Association of India Risk (FOURIER) and ODYSSEY Outcomes trials, reduced LDL-C reductions ranging from 5 to 70%.

**Reduction in ASCVD risk by further LDL-C reduction:** The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) with ezetimibe and Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) and ODYSSEY Outcomes trials with PCSK9 inhibitor monoclonal antibodies have demonstrated that non-statin therapy in combination with statins was associated with further reductions in the risk of adverse CV events with no lower LDL-C threshold at which CV benefits were not seen. The result of recurrent ASCVD events is proportional to the LDL-C concentrations down to at least 20 mg/dL. The results of an ongoing CV outcome trial with bempedoic acid are pending, but the results of a Mendelian randomization analysis suggested that loss of function variants in APOE, the gene encoding adenosine triphosphate (ATP) citrate lyase (the target of bempedoic acid), are associated with reduced risk of ASCVD.

**Statin intolerance:** Although statins are mostly very well tolerated and have a low rate of side effects, statin-related muscle symptoms have been variably reported and are experienced by about 1–2% of patients. In a study of 7,924 patients with dyslipidemia on high-dose statin therapy, 832 (10.5%) patients had muscle symptoms, with most patients experiencing mild symptoms. However, 1 (4% of those with symptoms) patients reported severe muscular pain. Nevertheless, actual or perceived statin intolerance both by patients and physicians interferes with guideline-directed LDL-C lowering therapy.

**Failure to achieve LDL-C goals:** The importance of achieving LDL-C goals cannot be over-emphasized. However, in the real world, only 20–30% of patients are at recommended goals despite being prescribed statins. Only 29.4% of patients with stable CAD and 18.9% of patients with acute coronary syndrome (ACS) in the DYSIS II study achieved LDL-C levels <70 mg/dL at a mean daily atorvastatin dose equivalent of 25 ± 18 mg. Although the problem is multifactorial including adherence issues, prescription of less than high-intensity statin therapy, de-escalation of statin dosages, very high baseline LDL-C levels including familial hypercholesterolemia, and statin intolerance, it is imperative that we expand our armamentarium of LDL-C-lowering medications. In this regard, bempedoic acid is a welcome addition to the existing non-statin therapies that include ezetimibe, bile acid sequestrants, and PCSK9 inhibitors.

**Variable response to statins:** The response to statins may vary between individuals with LDL-C reductions ranging from 5 to 70%. This heterogeneity may result from a variety of mechanisms including polymorphisms in numerous genes involved in endogenous cholesterol synthesis and metabolism, such as HMGCR encoding 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase and LDLR encoding the low-density lipoprotein receptor, and genes associated with statin pharmacokinetics, such as transporter proteins [e.g., ATP-binding cassette sub-family members (e.g., ABCB1, ABCCC2, ABCG2), SCLO1B1, and many other genes]. In a pharmacogenetic study of 1,507 patients who were post-ACS, rs 7412 and rs 429358 polymorphisms in APOE, the
Food has no impact on the oral bioavailability of bempedoic acid. The pharmacokinetic properties are not affected by age, sex, race, or weight. After 7 days of treatment with 180 mg/day of bempedoic acid, the steady-state is reached with the area under the curve (AUC) of 289.0 µg.h/mL while the steady-state maximum drug concentration (Cmax) is 20.6 µg/mL. Bempedoic acid has a volume of distribution of 18 L which is consistent with a modest extrahepatic distribution. The drug is about 99% protein bound in plasma. The major metabolites of bempedoic acid are glucuronides of bempedoic acid (glucuronidation mediated by UDP-glucuronosyltransferase-2B7) and bempedoyl-CoA. With 70% of excretion occurring in urine and 30% in feces, the kidneys are the primary route of elimination. After a once-daily dose, bempedoic acid has a steady-state clearance of 11.2 mL/min. With just a small (2%) excretion of unmetabolized bempedoic acid, the acyl glucuronide conjugate is the main metabolite detected in urine. The half-life of bempedoic acid, an oral, once-daily, small molecule, is 15–24 hours with a median time to maximum concentration (Tmax) of 3.5 hours. It is available as a 180 mg tablet, which is absorbed in the small intestine.
Unmet Need for Further LDL-C Lowering in India Despite Statin Therapy

Journal of the Association of Physicians of India, Volume 70 Issue 9 (September 2022)

... continued. Only 8.4% of patients were on very low-dose statins, which were defined as an average daily dose of rosuvastatin (<5 mg), atorvastatin (<10 mg), simvastatin (<10 mg), lovastatin (<20 mg), pravastatin (<40 mg), fluvastatin (<40 mg), or pitavastatin (<2 mg). 34

Low-density lipoprotein cholesterol mean percent changes from baseline to week 12 served as the primary outcome measure. Between baseline and week 12, bempedoic acid significantly decreased LDL-C (placebo corrected difference: –21.4% [95% confidence interval (CI): –25.1 to –17.7%], \( p < 0.001 \)).

Bempedoic acid compared to placebo significantly reduced non-high-density lipoprotein cholesterol (non-HDL-C) (–17.9%), total cholesterol (–14.8%), apo B (–15.0%), and (hsCRP) (–24.3% \( p < 0.001 \) for all comparisons).

In the bempedoic acid group, HDL-C was significantly lower by 4.5% (\( p = 0.003 \)). Also, the bempedoic acid group had a lower rate of newly developing diabetes or worsening of pre-existing diabetes than the placebo group (2.1 vs 4.5%). 34

The most frequent adverse event involving the muscles was myalgia, which was reported by 4.7% of patients...
dropped by approximately 4.1%. Through week 52, bempedoic acid had sustained efficacy.\(^{36,37}\) Patients who continued bempedoic acid treatment in the 78-week, open-label extension (OLE) study (for a total of 130 weeks) that was conducted after the CLEAR Harmony study, along with patients who had previously received placebo and were initiated on bempedoic acid treatment (for a total of 78 weeks) were studied for drug’s efficacy and safety.\(^{38}\) At 78 weeks, the mean LDL-C reduced by 14.2–15%, the total cholesterol by 10%, the non-HDL-C by 11%, the apo B by 7%, and the hsCRP by 17%.\(^{38}\) Myalgia (0.6%) and muscle spasms (0.5%) were the most frequent side effects that caused patients to stop receiving bempedoic acid, but their frequency did not rise over the course of the lengthier follow-up period. Tendon ruptures occurred at a rate of 0.3%, whereas new-onset or worsened diabetes occurred in 5.5% of cases. The safety profile of bempedoic acid was comparable in the OLE and CLEAR Harmony investigations.\(^{38}\) Overall bempedoic acid was well tolerated and the LDL-C lowering efficacy was maintained during the 2.5 years of follow-up.

CLEAR Tranquility

Bempedoic acid 180 mg or placebo once daily in addition to ezetimibe 10 mg/day for 12 weeks was given to 269 individuals (2:1) with a history of statin intolerance and LDL-C ≥100 mg/dL while on stable lipid-modifying medications. In 31% of patients, the background low dose or very low dose statins were continuing. The percent change in LDL-C from baseline to week 12 was the primary outcome. Bempedoic acid with ezetimibe resulted in a 28.5% reduction in LDL-C after adjusting for placebo (bempedoic acid –23.5%, placebo +5.0%, \(p < 0.001\)). A subgroup analysis revealed that bempedoic acid reduced LDL-C to a larger extent in patients who were not getting background statins (–34.7%) compared to those who were on statins (–20.5%), most likely because both statins and bempedoic acid act on the same pathway.

With bempedoic acid vs placebo, there were statistically significant decreases in non-HDL-C (–23.6%), total cholesterol (–18.0%), apo B (–19.3%), and hsCRP (–31.0%) with \(p < 0.001\) for all comparisons. Bempedoic acid group lowered HDL-C considerably from baseline to week 12 compared to placebo group (–7.3 ± 1.2% and –1.4 ± 1.4%, respectively; \(p = 0.002\)). When compared to placebo, bempedoic acid had a similar incidence of side effects.\(^{35}\)

CLEAR Harmony

In the CLEAR Harmony study, bempedoic acid or placebo was administered to 2,230 patients (2:1) with ASCVD, HeFH, or both who were receiving maximally tolerated statin treatment and had LDL-C values ≥70 mg/dL. At 12 weeks, the mean LDL-C levels had dropped by 19.2 mg/dL (16.5% from baseline values; \(p < 0.001\)). When comparing the overall incidence of side events, bempedoic acid group had a similar incidence compared with the placebo (78.5 vs 78.7% of patients). At week 12, the bempedoic acid group had lower levels of non-HDL-C –13.3% (95% CI –15.1 to –11.6%), total cholesterol –11.1% (95% CI –12.5 to –9.8%), apo B –11.9% (95% CI –13.6 to –10.2%), and hsCRP –21.5% (95% CI –27 to –16%), with \(p < 0.001\) for all comparisons.\(^{36}\) The bempedoic acid group had a lower incidence of newly developing or worsening diabetes mellitus than the placebo group: 3.3 vs 5.4%, \(p = 0.02\). Even though the \(p\)-value was not provided, there was a 5.8% decrease in HDL-C in the bempedoic acid group when compared to the placebo group. When compared to placebo, bempedoic acid increased the likelihood of developing gout (18 patients (1.2%) vs two patients (0.3%)). Over the course of the first year of bempedoic acid treatment, the mean hemoglobin levels dropped by approximately 4.1%. Through week 52, bempedoic acid had sustained efficacy.\(^{36,37}\)

Patients who continued bempedoic acid treatment in the 78-week, open-label extension (OLE) study (for a total of 130 weeks) that was conducted after the CLEAR Harmony study, along with patients who had previously received placebo and were initiated on bempedoic acid treatment (for a total of 78 weeks) were studied for drug’s efficacy and safety.\(^{38}\) At 78 weeks, the mean LDL-C reduced by 14.2–15%, the total cholesterol by 10%, the non-HDL-C by 11%, the apo B by 7%, and the hsCRP by 17%.\(^{38}\) Myalgia (0.6%) and muscle spasms (0.5%) were the most frequent side effects that caused patients to stop receiving bempedoic acid, but their frequency did not rise over the course of the lengthier follow-up period. Tendon ruptures occurred at a rate of 0.3%, whereas new-onset or worsened diabetes occurred in 5.5% of cases. The safety profile of bempedoic acid was comparable in the OLE and CLEAR Harmony investigations.\(^{38}\) Overall bempedoic acid was well tolerated and the LDL-C lowering efficacy was maintained during the 2.5 years of follow-up.

CLEAR Wisdom

In the CLEAR Wisdom study, 779 patients (2:1) with ASCVD, HeFH, or both were randomized to receive bempedoic acid or placebo for 52 weeks while receiving maximally-tolerated statin treatment and had LDL-C values ≥70 mg/dL. At 12 weeks, the mean LDL-C levels had dropped by 19.2 mg/dL (16.5% from baseline values; \(p < 0.001\)). When comparing the overall incidence of side events, bempedoic acid group had a similar incidence compared with the placebo (78.5 vs 78.7% of patients). At week 12, the bempedoic acid group had lower levels of non-HDL-C –13.3% (95% CI –15.1 to –11.6%), total cholesterol –11.1% (95% CI –12.5 to –9.8%), apo B –11.9% (95% CI –13.6 to –10.2%), and hsCRP –21.5% (95% CI –27 to –16%), with \(p < 0.001\) for all comparisons.\(^{36}\) The bempedoic acid group had a lower incidence of newly developing or worsening diabetes mellitus than the placebo group: 3.3 vs 5.4%, \(p = 0.02\). Even though the \(p\)-value was not provided, there was a 5.8% decrease in HDL-C in the bempedoic acid group when compared to the placebo group. When compared to placebo, bempedoic acid increased the likelihood of developing gout (18 patients (1.2%) vs two patients (0.3%)). Over the course of the first year of bempedoic acid treatment, the mean hemoglobin levels dropped by approximately 4.1%. Through week 52, bempedoic acid had sustained efficacy.\(^{36,37}\)
treatment. The average LDL-C level at baseline was 120.4 ± 37.9 mg/dL. At 12 weeks, the addition of bempedoic acid 180 mg per day significantly reduced LDL-C levels when compared to placebo (−15.1 vs 2.4%, p < 0.01). Bempedoic acid also significantly reduced levels of apo B (−9.3 vs 3.7%), non-HDL-C (−10.8 vs 2.3%), total cholesterol (−9.9 vs 1.3%), and hsCRP (−18.7 vs −9.4%) when compared to placebo. Intriguingly, the bempedoic acid group showed a decrease in HDL-C levels by 6.1%, p < 0.001. Common adverse events included nasopharyngitis (5.2 vs 5.1%), urinary tract infection (5.0 vs 1.9%), and hyperuricemia (4.2 vs 1.9%) with bempedoic acid vs placebo, respectively.

In a pooled analysis of 3,623 patients included in four randomized trials, the mean baseline LDL-C level was 107.6 mg/dL. In patients with ASCVD or HeFH or both and 144.4 mg/dL in patients with statin intolerance, LDL-C levels decreased −16.0% with bempedoic acid vs 1.8% with placebo (p < 0.001) at week 12 in patients with ASCVD or HeFH or both, while the changes in LDL-C levels at week 12 in patients with statin intolerance were −23.0% in the bempedoic acid group vs 1.5% in the placebo group (p < 0.001). The decrease in LDL-C levels with bempedoic acid was sustained at week 52. Increased blood uric acid levels (2.1 vs 0.5%), gout (1.4 vs 0.4%), decreased glomerular filtration rate (0.7 vs 0.1%), and higher levels of hepatic enzymes (2.8 vs 1.3%) were among the side effects that occurred more frequently with bempedoic acid than with placebo.

Bempedoic acid has a reasonable LDL-C lowering efficacy and safety profile, but its effects on clinical endpoints are still unknown. The ongoing randomized, double-blind, placebo-controlled CLEAR Outcomes study is evaluating the effects of bempedoic acid on CV outcomes in patients with high ASCVD risk and documented statin intolerance with an LDL-C ≥100 mg/dL on maximally tolerable lipid-lowering therapy to see if bempedoic acid 180 mg per day reduces the incidence of adverse CV events. The trial’s enrollment is complete, and results are anticipated in 2023. Additional knowledge about the potential negative effects of minor LDL-C decrease on ASCVD risk may be learned from this investigation.

Adverse Events
Nasopharyngitis, urinary tract infection, arthralgia, muscle spasms, pain in the extremity, myalgia, and muscle weakness were common side effects reported in the phase III bempedoic acid clinical trials and occurred equally frequently in the bempedoic acid and placebo groups. Muscle-related side effects were noted in patients on concomitant statin therapy while muscle-related symptoms like myalgia were not increased with bempedoic acid relative to placebo. The real-world use of bempedoic acid was reported in a retrospective study of 64 patients who initiated the therapy, the majority of whom had an intolerance to statins and other medications. There was marked inter-individual heterogeneity in LDL-C lowering (≥5 to −80%). Treatment-emergent adverse effects were observed in 50% of patients resulting in discontinuation of the treatment in about one-third of patients of the total cohort. Musculoskeletal events, including myalgia, muscle cramps, and arthralgias accounted for 62.5% of the adverse events. The high rates of adverse events in this cohort are inconsistent with results from randomized placebo-controlled clinical trials, which probably reflects high baseline rates of medication intolerance in this cohort.

Bempedoic acid reversibly increases uric acid levels with a mean increase in uric acid levels [mean change at week 12, 0.82 mg/dL (bempedoic acid) vs −0.02 mg/dL (placebo)] occurring within the first 4 weeks of treatment and levels were stable over time. Therefore, it can precipitate gout or increase the risk of gout in patients who do not have an established diagnosis of gout, but the incidence of gout during treatment with bempedoic acid was low. Clinically warranted testing for uric acid levels is recommended in patients who experience symptoms.

In the CLEAR Harmony and CLEAR Wisdom studies among those on moderate to high doses of statin, 10 (0.5%) patients out of a total of 2,009 patients treated with bempedoic acid reported tendon rupture or damage; in contrast, no patients receiving placebo (n = 999) did so. There were several other risk factors present in subjects experiencing this side effect, including fluoroquinolone use, systemic corticosteroids, diabetes, gout, rheumatoid arthritis, statin use, renal failure, age >60 years, male gender, and history of tendon disorders. Therefore, patients should be advised to seek medical attention if any arm, shoulder, back, or ankle discomfort or swelling occurs even though the medication is unlikely to be mechanistically linked to tendon rupture or injury. If a tendon rupture occurs and a different explanation cannot be found or cannot be managed, bempedoic acid should be stopped.

Bempedoic acid was linked to small increases in the mean blood urea nitrogen [1.7 mg/dL (bempedoic acid) vs 0.1 mg/dL (placebo)] and serum creatinine [0.048 mg/dL (bempedoic acid) vs −0.002 mg/dL (placebo)] in a pooled analysis of four phase III, randomized studies. Treatment with bempedoic acid has been linked to a mild, reversible drop in hemoglobin levels, with a small proportion of patients experiencing related clinical symptoms. The median change in hemoglobin level at week 12 was −0.3 g/dL (bempedoic acid) vs 0.1 g/dL (placebo). Patients who have lower hemoglobin levels at baseline may require periodic monitoring on an individualized basis.

The bempedoic acid group had a lower glomerular filtration rate (0.8 vs 1.4%) than the placebo group in the pooled analysis of four randomized trials. The bempedoic acid group had new-onset benign prostatic hyperplasia or prostatomegaly compared with 0.1% of men in the placebo group.

Risk of New-onset or Worsening Diabetes
Patients receiving bempedoic acid compared to placebo had considerably lower rates of new-onset or worsening diabetes (4.0 vs 5.6%; nominal p < 0.05) in the pooled data analysis of 3,623 patients from the aforementioned four randomized trials. In another meta-analysis comprising 4,311 patients, bempedoic acid was associated with a lower risk of new/worsening diabetes (RR 0.68; 95% CI 0.51–0.91; p = 0.01, I² = 0) compared with placebo. A patient-level pooled analysis of four phase III trials in 3,621 patients on maximally tolerated statins who were randomized (2:1) to oral bempedoic acid 180 mg or placebo once daily evaluated changes in glycemia based on baseline glycemic status over a median follow-up of 1 year. The annual rate of new-onset diabetes for bempedoic acid vs placebo in patients with normoglycemia at baseline (n = 618) was 0.3 vs 0.8%, and for prediabetes at baseline (n = 1868) was 4.7% vs 5.9% in patients with diabetes and prediabetes. Bempedoic acid significantly (p < 0.0001) reduced HbA1c by −0.12 and −0.06%, respectively. The safety of bempedoic acid was similar across glycemic strata and comparable with placebo.

It is hypothesized that bempedoic acid may improve insulin sensitivity and reduce diabetes risk by modulating AMP-activated protein kinase activity, but further studies are required to verify the impact on diabetes risk and elucidate possible mechanisms.

Regulatory Approval
The bempedoic acid and fixed-dose combination of bempedoic acid/ezetimibe were recommended for approval by the European Medicines Agency on 30th January
2020 to treat individuals with primary hypercholesterolemia and mixed dyslipidemia in combination with a statin or other lipid-lowering therapies in patients who are unable to reach LDL-C goals with the maximum tolerated dose of a statin or alone in statin-intolerant patients.

Bempedoic acid received U.S. Food and Drug Administration (FDA) approval on 21st February 2020, for the treatment of adults with established ASCVD or HeFH who need further LDL-C reduction. The FDA additionally authorized a fixed-dose combination of ezetimibe and bempedoic acid on 26th February 2020.

According to the recommendations of the Subject Expert Committee (Cardiovascular and Renal) made in its 100th meeting held on 06.04.2022 at Central Drugs Standard Control Organization Headquarters, New Delhi, permission to manufacture and market bempedoic acid 180 mg tablets was granted.47

Lipid Association of India Recommendations for Use of Bempedoic Acid in Secondary Prevention

- The LAI recommends that LDL-C goals must be achieved in all patients according to the LAI risk stratification algorithm. High-intensity statin therapy (atorvastatin 40–80 mg or rosuvastatin at 20–40 mg once daily) is the mainstay of treatment followed by ezetimibe 10 mg once daily.
  - If LDL-C goals are not achieved despite maximally tolerated statin therapy and ezetimibe, bempedoic acid may be added as one of the non-statin drugs in patients with established ASCVD and HeFH (Fig. 4).
  - In patients with true statin intolerance or contraindications, ezetimibe 10 mg once a day in combination with bempedoic acid 180 mg once a day is recommended.
  - Bempedoic acid may be initiated in patients presenting with ACS who are not at LDL-C goal despite statins and ezetimibe as per the LAI risk stratification algorithm for LDL-C management in ACS48 (Fig. 5).
  - The possibility of decreased rates of new-onset diabetes with bempedoic acid makes it a reasonable consideration in patients with metabolic syndrome who require additional LDL-C reduction after statin therapy. Whether it can be initiated as initial lipid-lowering therapy in such patients has not been studied.
  - Because of minimal drug-drug interactions, bempedoic acid may be useful in treating dyslipidemia in human immunodeficiency virus patients and other medical conditions where statin treatment may lead to drug interactions. Further studies are needed to verify the safety and efficacy of this approach.
  - PCSK9 inhibitors may be reserved, if cost is a consideration, after maximally tolerated statin and ezetimibe. In such cases, bempedoic acid may be added to see if the target LDL-C is achieved on such triple therapy.
  - Bempedoic acid should not be prescribed in patients with severe renal or hepatic dysfunction, or in pregnant or breastfeeding females.
  - Consider avoiding the use of bempedoic acid in patients with a history of tendon rupture.
  - Patients with a history of gout may have recurrent attacks during treatment with bempedoic acid if their uric acid concentration is not controlled. In these patients, bempedoic acid should be initiated (preferably with uricosuric drugs) only if the benefits outweigh the risks and only after a detailed discussion with the patient. Regular monitoring of uric acid levels is warranted.
  - Consider avoiding bempedoic acid in patients with hyperuricemia >6–7 mg/dL. Uricosuric drugs may be added to the treatment.
Unmet Need for Further LDL-C Lowering in India Despite Statin Therapy

LAI 2022 Lipid Management Algorithm in Acute Coronary Syndrome

1. Send blood sample for extended lipid profile at emergency triage
2. Stratify ASCVD risk according to LAI risk algorithm and define LDL-C target

On receiving lipid profile report in hospital, continue HIS + EZ and
*Consider additional available drugs* (*Bempedoic acid (BA)/Bile acid sequestrants (BAS) /PCSK9 inhibitor (PCS9K)) to reach target of LDL-C <50 mg/dL or ≤30 mg/dL; If Lp(a) ≥50 mg/dL: Consider PCSK9

STEP 1

- LDL-C at goal
  - Continue
- LDL-C not at goal
  - Use additional available lipid lowering drugs* (*BA/BAS/PCS9K*)

STEP 2

- LDL-C at goal
  - Use additional available lipid-lowering drugs* (*BA/PCS9K*).

- LDL-C not at goal
  - Consider adding newer lipid-lowering drugs and in selected cases lipoprotein apheresis if LDL-C not at goal despite PCSK9

Fig. 5: 2022 lipid management algorithm in ACS

- In patients without a history of hyperuricemia, uric acid levels should be monitored as and when clinically indicated.
- Patients on moderate to high doses of simvastatin (>20 mg) or pravastatin (>40 mg) should be switched to another statin before starting bempedoic acid because of possible drug interactions.
- Physician judgment is essential regarding indications, contraindications, and appropriateness of initiation of bempedoic acid in an individual patient. The patient needs to be involved in shared decision-making.

CONCLUSIONS

Lipid-lowering therapy is key to improving CV outcomes in patients with established ASCVD and HeFH. Lifestyle interventions in combination with high-intensity statin therapy are the first-line management strategy followed by ezetimibe. However, there are several instances in which additional non-statin therapy may be required. This includes patients who are unable to achieve recommended LDL-C goals according to the LAI risk stratification algorithm despite being on high-intensity statins with ezetimibe and patients with statin intolerance. In such patients, there are a few options available such as bile acid sequestrants and PCSK9 inhibitors. These are associated with some disadvantages that include the high cost of PCSK9 inhibitors, but both have been shown to reduce the risk of CV events.

Bempedoic acid is a new addition to our lipid-lowering armamentarium that can facilitate further LDL-C lowering as shown in numerous clinical studies either as monotherapy or in combination with ezetimibe, with or without statins in subjects with hypercholesterolemia. This LAI consensus document describes the pharmacology, indications, contraindications, advantages, and evidence-based recommendations for use of bempedoic acid in clinical practice. The low incidence of muscle-related side effects, minimal drug interactions, a significant reduction in hsCRP, and the possibility of beneficial effects on glycemic control make it a useful adjunct for LDL-C lowering. The results of the ongoing CV outcomes trial will better define its place in the management algorithm for ASCVD prevention, but in the meantime, it is a useful agent for adjunctive LDL-C lowering.
Unmet Need for Further LDL-C Lowering in India Despite Statin Therapy

References

36. Recommendations of the SEC (Cardiovascular & Renal) made its 100th meeting held on 06.04.2022 at CDCSC (HQ), New Delhi. Recommendations Cardio 06.04.22. pdf (cdsco.gov.in).
Genetic, Epigenetic, and Molecular Biology of Obesity: From Pathology to Therapeutics the Way Forward

Suranjana Banik¹, Mainak Bardhan², Suranjana Basak³*
Received: 9 May 2022; Accepted: 2 June 2022

Abstract
Obesity is a globally expanding silent epidemic having multiple risk factors and consequences associated with it. Genetic factors have been found to be playing undeniable roles in obesity. Intermingled relationship between epigenetics, metabolomics, and the environment influences obesity traits. High precision diagnostic tools have outlined many single nucleotide polymorphisms (SNPs), as well as many novel genes, that have been identified that create an obesogenic environment. Rare single-gene diseases can lead to early childhood obesity and less satiety. With almost 30% of the global population being under the grip of obesity, the coming days are alarming. This review summarizes the existing knowledge on the genetic causes of obesity including the epidemiology as well as the issues of concern and new additions to the list. Furthermore, we discuss the ways to enhance the healthcare outcome for patients of obesity through interdepartmental collaborations apart from pharmacological therapy that is still limited to a few drugs. The teamwork of geneticists, genetic counselors, physicians, bariatric surgeons, nurses, endocrinologists, and pharmacists may provide promising results in intervention.

Introduction
Obesity is a silent epidemic that is globally expanding. Being the root cause of multiple comorbidities, obesity has indirectly taken numerous lives. Obesity has transformed into a pandemic with an estimation of approx 13% of the world’s adult population (11% of men and 15% of women) categorized as obese.¹ Obesity prevalence in children has risen dramatically as a result of greater economic development and nutrition transition, particularly in emerging nations. Childhood obesity is a serious health problem that necessitates early detection and prevention strategies because a large percentage of obese children grow up to be obese adults. More than 340 million children and adolescents aged 5–19 years are overweight or obese, according to statistics. The population of obese and overweight children and adolescents aged 5–19 years has risen drastically from 4% in 1975 to over 18% in 2016. There has been a similar increase in both boys and girls.¹

Obesity is defined as an excess of body weight in relation to an individual’s height, as assessed by the body mass index (BMI) (BMI is measured by dividing body weight in kilograms by height in meter squares). Taking BMI into account, the standard number for overweight or wasting is 18.5 kg/m², whereas extreme or morbid obesity is defined as 40 kg/m².² Obesity and overweight are defined as abnormal or excessive fat accumulation in the body that puts a person’s health in danger. This is described as an individual’s excess body weight in relation to their height, as determined by the BMI (BMI is measured by dividing body weight in kilograms by height in meter squares). Overweight is defined as a BMI of 25 or higher, while obesity is defined as a BMI of 30 or higher.² While 18.5 kg/m² is the accepted BMI number for underweight or wasting, 40 kg/m² is the acceptable BMI value for severe or morbid obesity.³,⁴ In 2017, the global burden of the disease reached epidemic proportions, with more than 4 million people dying each year as a result of being overweight or obese.⁵

Obesity is multifactorial in origin with the basic causal factor being having less energy expenditure compared to energy consumption. However, the underlying mechanisms are more complex, and physiological, endocrine, psychological, socioeconomic, and even cultural factors can also contribute to it. In the 21st century, the most evolving causal factor is genetic in nature as well as there is the attribution of epigenetic environment.⁶

The obesogenic factors are rampant nowadays not only in high socioeconomic areas, but low and middle socioeconomic countries are also facing this challenge. As a result, the comorbidities associated with obesity like sleep apnea, cardiovascular diseases, type 2 diabetes mellitus, joint disorders, and hypertension are also on the rise. After completion of the Human Genome Project, we have identified many genes that play a role in obesity. Almost 25–30% of cases of obesity are due to some common SNPs in adults as well as in children.⁷

Genetic Epidemiology
From 1980 to this day, obesity cases have seen a tremendous rise with the global burden getting doubled in terms of prevalence. It has spread to 70 new countries silently. Almost more than 2 billion people are under the grip of obesity and that comprises 30% of the world population.³ By 2016, around 98 million adults in America alone were obese which has imposed a tremendous burden on healthcare sectors and the economy, posing a threat to double the financial crisis by approximately 900 billion dollars by 2030. There is a gender variation in obesity with 41% of women being obese than 38% of men. African American women are 55% in obesity compared to 37% of men.⁶ In Asia, despite having a low BMI, the central and total body fat for a certain body weight is more. It is more prevalent in children and adolescents. The most common type of obesity in Asians is metabolic.⁷

Genetics and Environmental Factors
Among many other etiological factors responsible for obesity, genetic causes are the striking ones (Fig. 1).

With the advent of genome-wide association study (GWAS) around 127 sites have been discovered in the human genome that is associated with obesity. Obesity justifies the common disease-common variant hypothesis in the fact that multiple genetic variants having minor allele frequency

¹Senior Resident, Department of Anatomy, All India Institute of Medical Sciences, Bhubaneswar, Odisha; ²Scientist B, ICMR-National Institute of Cholera and Enteric Diseases, Kolkata, West Bengal; ³Consultant Physician, Diabetologist, Endocrinologist, Department of Diabetology and Endocrinology, Reliance Hospital, Navi Mumbai, Maharashtra, India; *Corresponding Author

How to cite this article: Banik S, Bardhan M, Basak S. Genetic, Epigenetic, and Molecular Biology of Obesity: From Pathology to Therapeutics the Way Forward. J Assoc Physicians India 2022;70(9):76–82.
Genetics of Obesity

between 5 and 50% can contribute to obesity collectively. The gene-environment interaction that is attributed to the causal pattern of obesity can be explained by the “thrifty genotype” and the “drifty genotype” hypothesis. Though some genes inherited from ancestors who faced famines are said to be the basis of obesity in industrialized countries because they were passed down under strong selection pressure and thus were meant to store energy, these hypotheses alone cannot establish epigenetics being modulated by these few genes only. The modern-day globalization impact coupled with demographic and ethnic variations has led to the migration of genotypes all around the globe. The genetic etiology of obesity can be broadly classified into three major types.

- **Monogenic obesity**: Caused by a single gene mutation, primarily associated with the leptin-melanocortin pathway. Farooq et al. found that heterozygotes for a partial leptin deficit caused by the deletion of a glycine residue (D G133) in the leptin (LEP) gene were related to decreased blood leptin levels and greater levels of adiposity. Improvements in high-throughput DNA sequencing revealed new pathways and genes connected to obesity, such as the class 3 semaphorins (SEMA3A-G), which have been shown to control the formation of particular hypothalamic neurons, including those that produce pro-opiomelanocortin (POMC). In cohorts of patients with severe and early-onset (under 10 years old) obesity, the majority of monogenic obesity mutations have been identified. Furthermore, because monogenic obesity has a recessive inheritance pattern, consanguinity in populations has increased the chances of finding mutations due to the high likelihood of homozygosity of deleterious mutations. According to research, mutations in the genes producing leptin receptor (LEPR), LEP, and melanocortin-4-receptor (MC4R) account for 30% of cases of severe obesity in children from a consanguineous Pakistani population, with single-gene abnormalities accounting for over 50%. The majority of Mendelian obesity cases are caused by a deficiency in mutation in a gene involved in the leptin-melanocortin signaling pathway, which is a key regulator of energy balance. Monogenic obesity has been linked to mutations in 16 genes: adenylyl cyclase 3 (ADCY3), brain-derived neurotrophic factor (BDNF), dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1B), kinase suppressor of ras 2 (KSR2), LEP, LEPR, melanocortin 4 receptor tyrosine kinase 2 (NTRK2), propoprotein convertase subtilisin/kexin type 1 (PCSK1), POMC, peroxisome proliferator-activated receptor y (PPARG), SH2B adaptor protein 1 (SH2B1), SIM BHLH transcription factor 1 (SIM1), and TUB bipartite transcription factor (TUB).

Although projections of the prevalence of these Mendelian diseases vary by study, they all account for a small percentage of obese people. They are responsible for 5–10% of obesity cases in European descent communities, however, this figure could be higher based on the population and the degree of diagnostic effort. One in every 24,000 people in the United States carries a faulty allele at LEPR, POMC, or PCSK1, according to estimates. All of these single-gene illnesses have one thing in common: the excess weight usually emerges early in childhood and is severe. Another interesting fact is that, like with pathogenic mutations in MC4R, the weight status of carriers of monogenic obesity alleles can be influenced by the individual’s overall polygenic obesity risk level.

- **Syndromic obesity**: Severe obesity associated with other phenotypes that are part of syndromes such as neurodevelopmental defects, and other organs/system malformations. Due to chromosomal rearrangement, for example Prader–Willi syndrome, is defined by the absence of the paternal segment 15q11.2-q12, which can be caused by either deletion of the paternal crucial section or loss of the entire paternal chromosome 15. Prader–Willi syndrome affects one in every 25,000 births. Ghrelin promotes appetite via interacting with the POMC/CART and neuropeptide Y (NPY) neuronal pathways in the hypothalamus, leading to the obese phenotype.

- **WAGR syndrome**: Wilms’ tumor, anorexia, ambiguous genitalia, and mental retardation (WAGR) syndrome is connected to chromosome 11p13 (the location of the WT1 and PAX6 genes).
Deletion of the BDNF gene has also been linked to an obese phenotype in this condition.

- **SIM1 syndrome:** The loss at chromosome 6q characterizes the Single-minded 1 (SIM1) syndrome. When the SIM1 region is deleted or disturbed in humans, it is linked to hyperphagia, developmental delay, and hypotonia.  

**Bardet–Biedl Syndrome**  
This syndrome is associated to polydactyly, dyslexia, progressive rod-cone dystrophy, hypogonadism, and progressive renal abnormalities, and is linked to early-onset obesity, and has been related to polydactyly, dyslexia, progressive rod-cone dystrophy, hypogonadism, and progressive renal abnormalities.  

On a genetic level, around 14 loci (BBS genes) and many mutations have been discovered.22–27

**Fragile X Syndrome**  
This syndrome is characterized by severe mental disability, large ears, macrocephaly (large head), unusual pitch in voice, prominent jaws, and slight obesity. Molecular cloning of the fragile X locus revealed unbalanced development of polymeric CCG trinucleotide repeats present in the fragile X mental retardation (FMR1) gene.  

**Cohen Syndrome**  
It is a genetically homogeneous autosomal recessive condition characterized by childhood moderate obesity, mental impairment, short height, and microcephaly (small head). This syndrome has been discovered in both Finnish and international populations.  

This type of syndrome is caused by the COH1 gene, which is located on chromosome 8q22. COH1 is located in this part of the genome.

- **Polygenic obesity:** Created by a set of genes whose effect is magnified in an “obesogenic” environment, the human obesity gene map is a visual representation of the current state of common polygenic obesity. In total, 253 quantitative trait loci (QTLs) have been discovered in 61 genome-wide scans, with 52 genomic areas containing QTLs substantiated by two or more investigations.

A number of genetic variations linked to BMI, waist circumference, and waist-to-hip ratio have been discovered thanks to GWAS. Wang et al. genotyped 56 verified BMI, waist circumference, and waist-to-hip ratio variations in 2,958 Chinese patients and used a linear regression analysis to establish the relationship with a subcutaneous fat area (SFA) and visceral fat area (VFA) imaged by MRI.  

Wang et al. discovered significant relationships between VFA and VFA-SFA ratios in all patients with genetic variants in SNPs, including rs671 in ALDH2, rs 17782313 near MC4R, and rs 4846567 near the LYPPL1 gene.  

The fat mass obesity (FTO) gene was discovered as a result of a genome-wide association study, and it was given the name fat mass obesity. The FTO gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase that is found throughout the body but is primarily expressed in hypothalamic nuclei, resulting in hyperphagia. Every risk allele in the gene increases the risk of obesity by 20–30% and increases body weight by 1–1.5 kg. SNPs are responsible for 30% of the increase in BMI; however, loci for the waist to hip ratio do not affect BMI, implying that several loci can influence total body fat and regional adipose tissue distribution. Several apoprotein (apo) genes, including apo A-I, apo A-IV, apo B, apo C-III, and apo E, as well as the LDL receptor gene, can modulate food response hence obesity can be affected by genetic variation.  

Leptin, a 167-amino-acid protein, is a crucial signal that regulates energy consumption and body mass. Polymorphic genes code for it. Leptin upregulates anorexigenic neuropeptides like an alpha-melanocyte-stimulating hormone, which acts on the MC4R, cocaine, and amphetamine-regulated transcripts, as well as corticotropic-releasing hormones. Adipocytokines, the ovary, the adrenal cortex, skeletal muscle, and pancreatic beta cells are among the peripheral tissues that it regulates. Polymorphisms in the FTO gene, the LEPR, and the PPARG gene all influence obesity. If we map down obesity genes, we can find possible places on all chromosomes except Y. More than 430 genes, markers, and chromosomal areas have been implicated in human obesity phenotypes, yet none of them can be utilized exclusively as screening markers in obese persons, demonstrating the complexity of obesity research.  

Despite the fact that GWAS has been successful in identifying loci linked to obesity, the “missing heritability” hypothesis has resulted in these loci accounting for only a percentage of phenotypic variation. Furthermore, comorbidities connected with obesity, such as nonalcoholic fatty liver disease, demonstrate genetic propensity.

In obesity genetics, sexual dimorphism has an impact on total body fat distribution as well as the waist-to-hip ratio. Females and males are affected differentially by genetic polymorphisms such as the single effect allele of tumor necrosis factor (−308G>A). Females had a higher body fat percentage and skinfold thickness, whereas males have a higher waist-hip ratio, indicating that the gene is polymorphic. Body fat and obesity distribution vary by geographical region, demonstrating a gene–environment relationship. With the potential of a sedentary lifestyle and additive effects, a greater connection of the FTO gene has been identified among urban people in India compared to rural dwellers. People who are not physically active are more likely to be affected by PPARG-AB.  

**Use of Genotype Information in Treatment of Obesity**  
Prototype of genotype-informed obesity treatment for patients who are leptin-deficient due to mutations in the LEP gene.  

Although congenital leptin deficiency is uncommon, leptin replacement therapy has been extremely beneficial for these patients by significantly reducing food intake, body weight, and fat mass, as well as normalizing endocrine function.  

Getmelanotide, an Food and Drug Administration (FDA)—approved medication for uncommon monogenic obesity diseases such as LEPR, PCSK1 deficiency, and POMC deficiency, is another genotype-informed obesity treatment.  

Getmelanotide replaces the missing MSH in patients with POMC deficiency caused by mutations in POMC or PCSK1, as well as those with LEPR deficit due to mutations in LEPR, which is essential for POMC function.  

A daily subcutaneous injection of setmelanotide promotes considerable weight loss and hunger reduction. In phase III trials, individuals with POMC deficiency lost an average of 25.6% of their baseline weight after a year on setmelanotide, with 80% of patients losing at least 10%.  

Due to all these factors, pharmacotherapy for obesity has become a matter of concern. Currently, five drugs are FDA-approved for obesity treatment namely orlistat, phentermine/topiramate, liraglutide, lorcaserin, and naltrexone/bupropion. A list of genes related to obesity is mentioned in Table 1.

**Issues of Concern**  
Obesity-related comorbidities are expected to rise dramatically over the next decade. Obesity is already causing a significant amount of cardiovascular disease, hyperlipidemia, and diabetes. Under epigenetic changes, strong associations between DNA methylation and type 2 diabetes mellitus have been discovered. The rising burden of such diseases on nations is creating a loss of personnel and expertise as a result of an increase in morbidity and death. Obesity in pregnancy has significant consequences on mother and
Genetics of Obesity

Overview of Challenges

The term “obesogenic environment” was coined to describe the inter-relationship between the environment, opportunity, and conditions of life and the promotion of obesity in people and populations. Because obesity has a varied etiology and multiple causes, it is plausible to infer that the illness is primarily driven by environmental variables that impede people’s ability to self-regulate and make informed decisions about their nutrition and physical activity. As a valid example, it is quite probable that enhanced availability, accessibility, and affordability of energy-dense foods, together with strong marketing measures of such food items across multiple channels and platforms, are clear citations of such environmental factors that, if not fully but at least partially, explain excessive energy intake and a resultant increase in weight in the population.

It is important to keep in mind that psychological and behavioral difficulties play a big part in obesity. As a result, having a multidisciplinary approach to obesity treatment that addresses these psychological and social issues is crucial in order to provide comprehensive care while also combining best practices and achieving effective outcomes. Over the last two decades, this method of addressing the psychological aspects of obesity has grown in importance and prominence. Reports reveal that morbid obesity may be linked with critical psychosocial factors. Therefore, it necessitates imperative measures for child morbidity and death, in addition to in the general population. Obese moms should lose weight to avoid prenatal and neonatal problems, fetal structural malformations, and large for gestational age newborns, according to the International Federation of Gynecology and Obstetrics (FIGO) in 2015. Obesity creates an oxidative environment, which can damage mitochondria, diminish egg quality, and interfere with the formation of normal embryos. This could result in infertility. The ovarian metabolite and function are influenced by the PPARG, which governs immune cell activation and adipogenesis. The prevalence of childhood and adolescent obesity is on the rise. MicroRNAs are short noncoding RNAs of 20–24 nucleotides in length that have been linked to obesity in children and adults due to their ability to regulate gene expression post-transcriptionally. One of the known hereditary determinants of obesity is the MC4R gene. This is caused by the homozygous mutant single nucleotide mutation rs 17782313 in the MC4R gene. Furthermore, mutations in the POMC, PCSK1, LEPR, or MC4R genes cause loss of function. The MCR3 and MCR4 receptors are impacted, which respond to melanocortin and so sensitize the central nervous system to leptin and control energy consumption and expenditure. This feature has been used to target MC4R receptors so that highly selective cyclic peptides acting on the receptors with a specified shape and pharmacological assessment can be employed as anti-obesity medicines.

### Table 1: A list of genes related to obesity

<table>
<thead>
<tr>
<th>Genes related to obesity</th>
<th>Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>MC4R</td>
<td>Because NPY and agouti-related protein are activated, it increases food intake while decreasing energy expenditure</td>
</tr>
<tr>
<td>LEP</td>
<td>The hypothalamus is stimulated to create peptides that limit eating and promote greater energy expenditure by integrating afferent signals from fat (leptin-melanocortin pathway)</td>
</tr>
<tr>
<td>Adrenergic B3 receptor (ADRB3)</td>
<td>In human fat cells, it encodes a key lipolytic receptor protein that is linked to higher BMI and waist-hip ratio.</td>
</tr>
<tr>
<td>PCSK1</td>
<td>This gene encodes a subtilisin-like proprotein convertase family which produces proteases. Mutations are associated with obesity and deficiency of proprotein convertase 1/3</td>
</tr>
<tr>
<td>BDNF</td>
<td>Protein coding gene. Responsible for nerve growth. Expression is reduced in Alzheimer’s, Parkinson’s, and Huntington’s disease</td>
</tr>
<tr>
<td>Endocannabinoid receptor 1 (CNR1)</td>
<td>Encodes one of the two cannabinoid receptors. Involved in cannabinoid-induced CNS effects experienced by marijuana users</td>
</tr>
<tr>
<td>FTO</td>
<td>Associated with BMI, obesity risk, and type 2 diabetes mellitus</td>
</tr>
<tr>
<td>SH2B1</td>
<td>Deletion of gene SH2B1 on chromosome 16p11.2</td>
</tr>
<tr>
<td>NEGR1</td>
<td>It is a protein-coding gene. Diseases associated will be Niemann-Pick disease and leptin deficiency</td>
</tr>
<tr>
<td>POMC</td>
<td>Precursor of ACTH and involved in leptin-melanocortin pathway</td>
</tr>
<tr>
<td>Prohormone convertase 1 (PC1)</td>
<td>Deficiency of this gene causes early-onset obesity, hypogonadotrophic hypogonadism, postprandial hypoglycemia, and hypocortisolemia</td>
</tr>
<tr>
<td>WT1, PAX6</td>
<td>Obesity and WAGR syndrome can be caused by deletions of these two genes (Wilms’ tumor, aniridia, genitourinary anomalies and mental retardation syndrome, and obesity)</td>
</tr>
<tr>
<td>GNAS1</td>
<td>Encodes a subunit of Gs protein causing pseudohypoparathyroidism type 1A and Albright’s hereditary osteodystrophy</td>
</tr>
<tr>
<td>PHF-6</td>
<td>Mutations in this gene cause Borjeson-Forssmann-Lehmann syndrome causing obesity, epilepsy, and severe mental retardation</td>
</tr>
<tr>
<td>ALMS1</td>
<td>Mutations in this gene cause Alström syndrome causing childhood obesity, hyperinsulinemia, chronic hyperglycemia, and neurosensory deficits</td>
</tr>
<tr>
<td>NPY</td>
<td>In a fasted state, this gene is released from the arcuate hypothalamic nucleus, and mutations in this gene can induce lipid metabolism dysregulation, leading to obesity.</td>
</tr>
<tr>
<td>Uncoupling proteins (UCP)</td>
<td>Modulation of heat generating uncoupled respiration at mitochondrial level regulating energy metabolism</td>
</tr>
<tr>
<td>PPARG2</td>
<td>Enables adipogenesis and adipocytes differentiation</td>
</tr>
</tbody>
</table>
| VDR                     | VDR polymorphisms could be linked to vit D’s direct effect on adipogenesis and metabolism, or an indirect effect via insulin secretion modulation. VDR variation is a strong determinant of obesity phenotype than circulating 25(OH)—D concentrations. The most widely investigated source of variation in circulating amounts of 25(OH)—D has been mutations in DBP/GC, CYP2R1, and DHCR7.
effective public health interventions in obesity care. Obesity-related factors, including psychological and social problems of women, may lead to serious health conditions like low self-esteem, anxiety, depression, and associated disorders in case they are recurring continually for a long period of time. Since morbid obesity refers to a serious and chronic illness beyond doubt, hence it becomes imperative to spread awareness about the severity of this medical condition, implement corrected education at the society level, and transform our approach toward its view and associated treatment.

**Preventive Measures**

The diagram depicts several interconnected and dynamic “clusters” that make up an “obesity system” (Fig. 2). The quantity and range of these conditions exemplify the complexity of obesity. This graph makes a compelling case for a holistic method that, if implemented at a societal level, can reverse obesity trends. The argument is based on the notion that minor steps aimed solely at changing individual behaviors will not be adequate to prevent obesity. Rather, the nation’s health needs to be regarded as a societal and economic concern. This societal approach necessitates a complex “major change” that begins with the individual, then expands to the family unit, group, and finally national levels. This entails working together with the entire food business, not just the producers and manufacturers of calorie-dense foods, but also the marketers of those items. This also entails striving to make significant changes in active environments and dominant societal pressures in order to effectively address each of the identified “clusters.” As a result, it necessitates the development of an all-encompassing, long-term strategy that not only assists in the creation and maintenance of environments that promote healthy choices, but also encourages people to wish for, seek out, and choose diverse alternatives, recognizing that decisions are made at the family or group levels, and that individual behavior is “cured” by the actions of others.

Policymakers, national, state, and local organizations, commercial institutions and community leaders, schools, day care and health care professionals, as well as individuals, must all work together to establish an environment that promotes a healthy lifestyle. Organizations can also establish a supportive environment in a variety of ways with the goal of encouraging healthy living behaviors to effectively avoid obesity.

**Community Efforts**

To address the obesity epidemic, effective community actions with an emphasis on supporting healthy eating and active living in a range of settings are essential. To become part of social habits, such innovative attempts must be implemented in early childhood care, hospitals, schools, and food service locations.

Fig. 2: Multiple interacting and dynamic “clusters” that compose what is termed as an “obesity system”
Healthy Living
Special programs and initiatives should be implemented to help the public understand that the focus of achieving and maintaining a healthy weight should be on incorporating a lifestyle that includes healthy eating and regular physical activity rather than relying on temporary or short-term dietary changes.

Healthy Weight
Because a high BMI can indicate a high level of body fatness, public health interventions should emphasize calorie balance and maintaining a healthy weight over time. Because good eating habits are a significant role in maintaining a healthy weight, public health programs must educate the public about food nutritional information, calorie tracking, meal planning, and choosing nutritious recipes.

Basics of Physical Activity
Physical exercise is crucial for health and a healthy weight, so public health initiatives must incorporate knowledge of different types of physical activity and corresponding standards for the amount needed each day.

Health Awareness in Parents
Increased parental understanding of the seriousness of childhood obesity and how to help their children adopt healthy behavior is critical for public health efforts.

Enhancing Healthcare Outcomes
Obesity is likely to worsen if the obesogenic environment is not fixed. A multidisciplinary approach is needed to overcome the crisis. Genetic causes for obesity should be addressed during antenatal visits, counseling, and proper lifestyle modifications are to be advised. The teamwork of a genetist, genetic counselor, physician, bariatric surgeon, nurse, endocrinologist, and pharmacist is necessary to address the situation. The diagnosis of obesity must be made a routine procedure that is to be made from antenatal visits to medicine outpatient departments. In that way, neither childhood nor gestational obesity is missed, nor adult-onset obesity is diagnosed late. The bariatric nurse can play an important role here in caregiving. Pamphlets, charts, and multimedia approaches can be obtained to address the issue of noncompliance in patients of obesity. It can provide proper guidelines as to what to modify in their diet as well as the entire lifestyle that addresses the sedentary causes of obesity. Physiotherapists can guide in proper exercises and yoga can play a significant role. Apart from that, proper family history must be obtained by the physician, surgeon, and geneticist to rule out any obvious genetic cause of obesity.

Genetic causes for obesity should be addressed during antenatal visits, counseling, and proper diet and lifestyle modifications are to be addressed during antenatal visits, counseling, and proper lifestyle modifications are to be reviewed, and a healthy diet must be promoted. A combined effort of all concerned is essential for controlling the widespread incidence of obesity.

References
5. WHO. Obesity; 2022. Available from: https://www.who.int/health-topics/obesity#tab=tab_1


44. Hobb M, McKenna J. In which population groups are food and physical activity environments related to obesity? Perspect Public Health 2019;139(5):222–223.


44. Hobb M, McKenna J. In which population groups are food and physical activity environments related to obesity? Perspect Public Health 2019;139(5):222–223.


In hypertensive with CAD, initiate with

Tazloc-Beta
Telmisartan 40 mg + Metoprolol Succinate 25 mg / 50 mg PR

Celebrating
10 YEARS OF TRUST

No. 1 Rx brand by Cardiologist & Diabetologist

Economical

Cardio Protection

Trusted and clinically tested molecules

24 hours BP Control

ODCA Technology

Preferred in multiple patient profiles

Recommended by latest guidelines

Prescribed as initiation therapy

Patient compliance
In patients with hypertension and diabetes,

**Tazloc®-AM**

Telmisartan 40mg/80 mg + Amlodipine 5 mg

For the **Detrimental duo... The Distinctive duo...**

Greater time in target range associated with

**22% reduction** in first CV event

**61%** for effective control of BP & 32% for reduction in CV risk

**TELMISARTAN + AMLODIPINE**

Ref - 1. J Am Coll Cardiol 2021 Mar; 77 (10) 1300-1301
2. Data on file

---

In mild to moderate hypertension, initiate / add

- **Tazloc®**
  - Telmisartan 160/80 mg

- **Tazloc®-H**
  - Telmisartan 400 mg + Hydrochlorothiazide 12.5 mg

- **Tazloc®-Trio**
  - Telmisartan 480 mg + Amlodipine 5 mg + Hydrochlorothiazide 12.5 mg

In elderly hypertensives, uncontrolled on monotherapy

- **Tazloc®**
  - Telmisartan 160/80 mg

- **Tazloc®-H**
  - Telmisartan 400 mg + Hydrochlorothiazide 12.5 mg

In hypertensives uncontrolled on dual drug therapy

- **Tazloc®**
  - Telmisartan 160/80 mg

For Intensive BP control with CV safety

- **Amlopin**
  - Amlodipine 5 mg

- **Amlopin-IM**
  - Amlodipine 5 mg + Metoprolol Succinate ER 25/50 mg

For long-lasting BP control

- **Amlopin-AT**
  - Amlodipine 5 mg + Atorvastatin 10 mg

PIN DOWN **THE PRESSURE**
Burkitt’s Lymphoma with an Unusual Cardiac Involvement: A Case Report

Soham Bhaumik1, Nilay Kumar Chatterjee2, Mohammad Abul Masud Reza3, Arijit Sinha4*
Received: 20 March 2019; Accepted: 22 May 2022

ABSTRACT
Burkitt’s lymphoma (BL), a variety of non-Hodgkin’s lymphoma, is uncommon in India. Cardiac involvement in sporadic BL is rare. Cardiac involvement may be primary or a part of a systemic disease process. It affects the endocardium, myocardium, or pericardium. Cardiac symptoms may or may not be present in the early clinical stages. We are presenting a case of sporadic BL in a 13-year-old child with cardiac and systemic involvement.

INTRODUCTION
Burkitt’s lymphoma, a monoclonal proliferation of B lymphocytes, is uncommon in adults but common in children with a doubling time of less than 24 hours.1 Males are affected predominantly. BL may be endemic (eBL, African), non-endemic (sBL, sporadic), or immunodeficiency related. eBL typically involves the orofacial region (jaw and facial bone) which may spread to extranodal sites like genitalia, kidney, breast, meninges, and bone marrow. sBL commonly presents with abdominal mass, ascites, genital involvement, bone marrow, and central nervous system involvement. Lymphadenopathy is more related to immunodeficiency cases.2 Cardiac involvement of lymphoma may be primary or as a part of the systemic disease process. Disseminated non-Hodgkin’s lymphoma is more common than primary cardiac lymphoma. Intracardiac mass caused by BL is extremely rare, and young males are commonly affected.3 We are presenting here a case of BL in a young male with cardiac and systemic involvement.

CASE DESCRIPTION
A 13-year-old Muslim boy of Malda (West Bengal) attended the outpatient department of general medicine of our hospital on 9th January 2019 with complaints of insidious onset dull aching intermittent abdominal pain and a right-sided neck swelling for 3 months. There was no associated history of fever, rash, anorexia, weight loss, chest pain, palpitations, shortness of breath, or syncpe. There was no history of similar illnesses or any chronic diseases in the past. The boy had a normal developmental and birth history. There was no history of consanguinity in the family.

On examination, his higher functions were normal, pulse 98/min—regular, symmetrical, BP 100/66 mm Hg in supine position with an absence of pallor, cyanosis, icterus, and clubbing. No deformities or skin manifestations could be seen. He was afebrile. Enlargement of right submandibular and supraclavicular lymph nodes of >2 cm size was noticed. They were firm, non-tender, and mobile without any overlying skin changes. Abdominal examination revealed hepatomegaly (17.8 cm), splenomegaly (3 cm below the left costal margin), and an infra-abdominal epigastric mass with extension to the left hypochondrium (5 × 7.5 cm, tender, mobile, and nonpulsatile). Bilateral testicular swellings were noted which were non-tender, nonpulsatile, and negative for transluminescence with a normal cord. No other significant clinical findings were found. The patient was admitted in the general medicine ward for a workup.

Investigations
Baseline investigations revealed normocytic normochromic anemia, neutrophilic leucocytosis, thrombocytosis, high ESR, and decreased hematocrit (Hb:9.8/WBC:14,500/platelet:5.3 lakh/PCV:32.5/N77,L08,M10,E05,ESR-85). Renal and liver function test reports were normal. Lipid profile was mildly deranged (total cho:218/TG:304/HDL:60). CRP (106 mg/L) and LDH (1320 U/L) were raised. Chest X-ray, blood cultures, and urinalysis were normal. The peripheral smear did not reveal any abnormal cells. ECG was normal. Malaria parasites could not be detected; tests for EBV virus and HIV I and II were negative. Abdominal sonography revealed a hypoechoic SOL (7 × 5 cm) occupying the left hypochondrium with multiple, vascular, and hypoechoic lesions (average size: 1.4 cm) with distortion of the liver contour. A (2 × 1.4 cm) hypoechoic SOL was incidentally detected up to the right parotid gland. A (2.8 × 1.4 cm) hypoechoic SOL was incidentally detected at the right atrial wall. Scrotal sonography showed bilateral testicular enlargements (right: 8 × 5.4 × 4.5 cm, left: 6.2 × 3.6 × 3.5 cm) with multiple, vascular, and hypoechoic lesions (average size: 1.4 cm) with distortion of the testicular architecture. Echocardiography was done showing multiple heterogeneous SOLs arising from the interatrial septum (IAS); one in the right atrium (1.4 × 1.4 cm) and three in the left atrium (2.0 × 2.0 cm) being the largest. Ventricles were normal. No vascular extension or spread was found (Fig. 1).

FDG PET-CT revealed metabolically active multiple lymphadenopathies in the right supraclavicular, mediastinal, abdominal pelvic, and left inguinal region along with the involvement of solid organs such as the stomach, bilateral testis and peritoneum, and active multiple metastatic signals in bone marrow (Figs 2A and B).

Bone marrow aspiration and biopsy showed hypercellular marrow without any lymphoid infiltration. Incisional biopsy from the patient’s right neck gland revealed monomorphic, medium-sized round cells, with a high nuclear–cytoplasmic ratio with infiltration of the soft tissue and striated muscle bundles (Figs 3A and B). Immunohistochemistry showed diffuse round cells and strongly immunoreactive for LCA, CD20, CD10, and moderate immunoreactivity for bcl6 with 80–90% Ki67 index; suggesting non–Hodgkin’s lymphoma—B cell type, CALLA positive with immunoprofiling favoring BL.
Burkitt’s Lymphoma with an Unusual Cardiac Involvement: A Case Report

Discussion

Burkitt’s lymphoma is a type of non-Hodgkin’s lymphoma, a high-grade B cell malignancy with the fastest doubling time. It is common in children. eBL is related to EBV infection and Plasmodium falciparum-mediated immune dysregulation which provokes EBV infection. Mean age of presentation of sBL is 11 years and less likely to involve the jaw.

Abdominal presentations like mass, ascites, lymphadenopathy, and genital involvement are more common in sBL. Translocation of MYC proto-oncogene on chromosomes 8–14 occurs in BL. eBL commonly starts with jaw swelling whereas B symptoms are more common in sBL and HIV-associated BL. Cardiac involvement of lymphoma may occur. It is reported in 16% of cases of Hodgkin’s disease and 18% of cases of non-Hodgkin’s disease on autopsy findings. Echocardiography is useful and transesophageal echocardiography is more sensitive to assay cardiac masses. MRI and FDG-PET scan are useful alternatives. Cardiac involvement in BL is rare but more common in HIV-infected cases. Fresneau et al. reported BL arising in the right atrium associated with cervical and mediastinal lymphadenopathy in a 17-year-old female. Meshref et al. also reported a 10-year-old boy with multiple intracardiac masses. Histopathologically, tumor cells typically have round and oval nuclei and two to five distinct nucleoli. The cytoplasm is basophilic or amphophilic containing small lipid-filled vacuoles. High rates of proliferation and apoptosis are characteristic. Macrophages containing ingested nuclear debris are surrounded by a clear space creating a “starry” sky pattern. BL cells express surface IgM light chains, B cell markers—CD19, CD20, CD22, and CD79a, and germinal center-associated markers—CD10 and bcl6. Translocation of t(8,14)q(24,32) was seen in about 80% of cases. Tumor cells are negative for CD5, CD23, and TdT.

Fig 1: Cardiac mass arising from IAS

Figs 2A and B: Metabolically active multiple lymphadenopathies in right supraclavicular, mediastinal, and abdominal areas

Figs 3A and B: (A) Monomorphic medium-sized round atypical cells with a high nuclear–cytoplasmic ratio; (B) Diffuse infiltration in the striated muscle
Clinical features and investigations are correlating our case as sBL but cardiac involvement as interatrial septal mass (one in LA and three in RA) is rare. With chemotherapy, the patient is responding well.

REFERENCES
Seronegative Autoimmune Limbic Encephalitis: A Case Report

Deepali Aendole1*, Jimmy Lalkaka2, Jui Jade3, Bhim Singhal4

Received: 06 July 2020; Accepted: 10 April 2022

ABSTRACT

Autoimmune encephalitis (AE) is an immune-mediated disorder of the central nervous system (CNS). Its definitive diagnosis relies on the identification of a specific antibody. Autoimmune limbic encephalitis (LE) is a subset of AE characterized by inflammation of the limbic cerebral cortex. Cognitive decline, behavioral disturbance, and seizures are its cardinal manifestations. We present the case of a 70-year-old man with subacute progressive gait imbalance, cognitive impairment, and psychiatric manifestations. Extensive serum and cerebrospinal fluid (CSF) investigations did not reveal any abnormality. Autoimmune and paraneoplastic encephalitis antibody panels were negative. Magnetic resonance imaging (MRI) and positron emission tomography (PET) brain scans suggested LE. He responded well to immunotherapy. This case illustrates that AE must be suspected in the appropriate setting, even in the absence of a specific antibody. These patients should be given the benefit of early immunotherapy.

CASE DESCRIPTION

This 70-year-old man was admitted to a Mumbai tertiary care hospital in June 2015. His chief and only complaint was a mild imbalance while walking since about a month prior. He was not a diabetic or hypertensive with no significant past or family history. A detailed neurological examination was normal, apart from a mildly abnormal tandem walk.

All his routine blood investigations, venereal disease research laboratory, HIV, vitamins B1, B12, and E, thyroid profile, and thyroid antibodies were normal. His chest X-ray and abdominal ultrasound were normal. His systemic and paraneoplastic antibody and tumor marker profiles were also negative. The MRI and PET brain scans were normal. As his symptoms were mild and did not impact his daily activities, he was sent home and asked to review after a month. Unfortunately, he was lost to follow-up for 6 months.

He was readmitted 6 months later in January 2016 with a marked decline in short-term memory, bouts of aggressive behavior, visual hallucinations, and significant gait imbalance.

On examination, his Mini-Mental Status Examination score was 14/30 and his Frontal Assessment Battery score was only 5/18. He had significant gait ataxia, but no limb incoordination or nystagmus. The rest of the neurological examination was normal.

Once again, all laboratory investigations were normal. An AE antibody panel [anti-NMDA-R, VGKC (LGI-1, CASPR2), GABA-B, AMPA (GluR1, GluR2)] and paraneoplastic antibody workup were negative, as were the anti-GAD and antigludin antibodies. The CSF examination was normal, including viral (including herpes simplex virus 1 and 2), bacterial, and fungal workup, and negative CSF oligoclonal bands. His electroencephalogram (EEG) showed bilateral slow waves mainly over the temporal regions. A computed tomography scan of the chest and abdomen was normal. This time, a repeat brain MRI scan showed T2/fluid-attenuated inversion recovery (FLAIR) hyperintense lesions in the medial temporal lobes, more on the left. A fluorodeoxyglucose (FDG) brain PET scan showed hypermetabolism in the left temporal region (Figs 1A and B).

With autoimmune LE as the possible diagnosis, he was treated with intravenous methylprednisolone 1 gm daily for 5 days, followed by oral prednisolone taper over 6 weeks. He showed mild improvement within the first week of therapy, with steady recovery over the next 4 weeks. When reviewed 7 months later, he had recovered fully and he continues to remain well 4 years later.

DISCUSSION

Autoimmune LE is a subset of AE characterized by inflammation of the limbic cerebral cortex. The significant cognitive impairment, behavioral disturbance, and hallucinations in our patient were compatible with the clinical diagnosis of LE. However, no specific antibody was found. Infectious and paraneoplastic causes were ruled out so an immune-mediated, antibody-negative syndrome was considered likely.

Seronegative autoimmune LE refers to a noninfectious subgroup of LE, in which immunological mechanisms are suspected clinically, but the targeted neural autoantigens are either unknown or uncharacterized. In an immunological survey of 163 LE patients, 12 (7%) were antibody-negative LE.3 Recent diagnostic criteria allow for a definite diagnosis of seronegative autoimmune LE.4

Cognitive impairment was the most prominent and disabling feature in our patient, similar to the antibody-negative cohort of LE patients reported by Graus et al.3 Our patient did not have seizures. Seronegative LE patients have a much lesser frequency of seizures than those with antibody-positive LE.3 The reason for this is not clear.

The unusual feature in our patient was his initial presentation with mild gait ataxia and no other symptom. Although not a defining feature, cerebellar ataxia is known to occur in LE, as was reported by Jagtap et al. in 3 of his 16 LE patients.3

The CSF examination of this patient was normal. This is also not unusual, as a noninflammatory CSF occurs in a fair proportion of patients with AE.6,7 The brain MRI and PET findings were consistent with the diagnosis of autoimmune LE. The FDG-PET

© The Author(s). 2022 Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by-nc/4.0/). Please refer to the link for more details.
imaging is often more sensitive than MRI in revealing an increased FDG uptake in normal-appearing temporal lobes.

An excellent response to steroids was observed in our patient with complete remission of symptoms even after 4 years of follow-up. In a comparative study between antibody-negative and-positive cases of AE, the treatment response was similarly beneficial in both groups. Further evidence of immune-responsiveness in seronegative encephalitis comes from the finding that 44% of rituximab responders had AE without antibodies.

**Conclusion**

This case illustrates the importance of remaining vigilant to the possibility of AE, even if antibody panels are negative. Seronegative AE can be diagnosed on clinical grounds along with ancillary investigations like MRI, CSF, EEG, and PET studies. A delay in diagnosis leads to poor outcomes, so a high index of suspicion is required for its diagnosis.

**Acknowledgment**

We are grateful to the Dean and Medical Director of Bombay Hospital Institute of Medical Sciences for permission to publish this case.

**References**

Bilateral Calcification of the Vas Deferens and the Seminal Vesicles in a Patient with End-stage Renal Disease

Ankur Gupta1*, Mohan Biyani2
Received: 29 June 2018; Accepted: 20 May 2022

A 52-year-old man with end-stage renal disease treated with peritoneal dialysis presented with poor ultrafiltration and drain alarms of 1 week duration. Past medical history included diabetes mellitus for 20 years and secondary hyperparathyroidism. There was no other significant history of any chronic infections. His physical examination was unremarkable.

A plain abdominal X-ray for catheter position (Fig. 1) revealed an optimal position in the true pelvis. However, to our surprise, an incidental finding of symmetrical tubular bilateral vas deferens (VD) and seminal vesicle (SV) calcification was reported. Retrospectively, family history was obtained. He had two daughters in their 20s without any issues of infertility.

Calcification of the VD and SV was first reported on autopsy in 1906.1 In 1946, it was reported on plain radiograph.2 On a plain radiograph, the symmetrical medial pelvic tubular calcifications in a male patient are fairly pathognomonic for the VD. Deferentography is an imaging technique which confirms if permeability to veru montanum is preserved, ruling out total obstruction or ejaculatory duct atresia. This test was not performed because the patient’s family was complete. The other presentations are hematuria, hemospermia and pain in the perineum, and/or chronic pelvic pain. However, this patient had none of these findings. Etiology of these calcifications includes primary (idiopathic) and secondary associations with diabetes (most common), aging, hyperparathyroidism, mechanical obstruction of the VD, genito-urinary tuberculosis, chlamydial infection, chronic gonorrhea, and schistosomiasis.3 In our patient, both diabetes and secondary hyperparathyroidism were present.

We would like to report an interesting incidental finding of calcification of the VD and SV on imaging which could have potential manifestation as male infertility in this subgroup of people. The practicing physicians should be vigilant enough not to miss them in their clinical practice.

References
A 62-year-old male presented with complaints of right flank discomfort for a few days. General physical examination was unremarkable. Ultrasound abdomen showed features suggestive of right-sided moderate hydronephrosis. Non-contrast computed tomography (CT) of the kidney, ureter, and bladder (KUB) region showed an enlarged right kidney, a complex cystic lesion in the upper pole showing cyst within cyst appearance (Figs 1A to C), and dilatation of lower calyces with a prominent upper ureter. These radiological features were suggestive of hydatid cyst. Hydatid serology (Echinococcus IgG enzyme immune assay) came out to be positive. Tc-99m DTPA imaging revealed a nonfunctioning right kidney and nonobstructed left kidney with good cortical function. After starting on oral albendazole, he underwent right nephrectomy with no operative complications.

Echinococcosis or hydatid disease usually occurs in sheep rearing areas with high prevalence in China, Central Asia, the Middle East, Eastern Africa, Australia, New Zealand, Alaska, and some parts of South America. This occurs most commonly in the liver followed by the lungs. Primary or isolated renal echinococcosis is a rare clinical entity occurring in about 1–5% of all patients with hydatid disease. Renal involvement is usually asymptomatic in majority of the patients while symptomatic ones can present with nonspecific complaints such as abdominal discomfort or low backache. However, a rare fraction of symptomatic patients can have a specific feature of hydatiduria, that is, presence of daughter vesicles in urine. Our patient presented with abdominal discomfort but with no hydatiduria. Imaging plays a key role in the diagnosis with characteristic CT findings as in our patient. Hydatid serology is usually falsely negative while it was positive in our patient. Treatment remains surgical with perioperative biimidazoles like albendazole or mebendazole.

**References**

BIGGER Benefits
BIGGEST Savings

The Pioneer* is now Most Affordable

**OXRA**
5 mg
₹ 9.80 Per tablet

**OXRA**
10 mg
₹ 12.90 Per tablet

**OXRAMET®**
₹ 14.50 Per tablet

**OXRAMET® XR 500**
₹ 15.00 Per tablet

**OXRAMET® XR 1000**
₹ 15.90 Per tablet

Sun Pharma Laboratories Ltd.
Sun House, Plot No. 201 B/1, Western Express Highway,
Goregaon (East), Mumbai - 400 063, India

*Pioneer in sharing Dapagliflozin science
**OXRA** is registered trademark of SUN Pharma Lab. Ltd.
**OXRAMET®** is registered trademark of SUN Pharma Lab. Ltd.
For further information contact: SUN Pharma Ltd., SUN House,
CFS No. 201 B/1, Western Express Highway, Goregaon (E), Mumbai 400063
Severo Ochoa (1905–1993) was born in Luarca, Spain. He obtained his MD from the Medical School of the University of Madrid (1929). Ochoa went to Germany to work under Otto Meyerhof at Heidelberg, and his outlook and training were decisively influenced by Meyerhof. He went to London in 1932, where he worked with Dr H. W. Dudley on problem in enzymology. Ochoa left for the United States in 1940 and was naturalized in 1956. He worked as a research associate in pharmacology with Carl and Getty Cori at the Washington University School of Medicine, St. Louis (1940–1942). Ochoa was then appointed research associate in medicine at the New York University School of Medicine (1942), and subsequently became a professor of pharmacology (1946) and chairman of the department of biochemistry (1954).

Ochoa’s chief fame arose in connection with his work on nucleic acids-complex molecule made up of long chains of individual phosphate-containing units (nucleotides). Nucleic acids had been shown to exist in two varieties, ribonucleic acid (RNA) and deoxyribonucleic acid (DNA), each being made up of four different nucleotides. The body is capable of building these nucleic acids with the necessary enzymes. RNA is a complex compound of high molecular weight, and is of central importance to the synthesis of proteins by the cell and places DNA as a carrier of genetic codes.

In 1955, by studying bacteria, Ochoa isolated an enzyme that can join nucleotides. He named the enzyme *polynucleotide phosphorylase* which he allowed to react with nucleotides, to which a second phosphate unit had been added. The result of incubating the nucleotides in the presence of this enzyme was a startling rise in viscosity. This was a good sign that a molecule of RNA had been formed. Ochoa had synthesized RNA in a test tube. The enzyme has been singularly valuable in enabling molecular biologists to understand and re-create the process whereby the hereditary information contained in genes is translated, through RNA intermediaries, into enzymes that determine the functions and character of each cell.
Sudden Blindness in a Victim of Snake Bite

Rudrajit Paul1, Indranil Thakur2, Asutosh Ghosh3, Manotosh Sutradhar4, Subinay Chhaule5, Rathindranath Sarkar5

1Consultant Physician, Ruby General Hospital; 2Assistant Professor, Department of Critical Care Medicine, Institute of Post-Graduate Medical Education and Research and Seth Suhkhlal Karnani Memorial Hospital; 3Professor, Department of Medicine, Medical College Kolkata; 4Ex-Associate Professor: RMO, Department of Anaesthesia, CCU; SSKM Hospital; 5Ex-HOD, Department of Medicine, Medical College Kolkata, Kolkata, West Bengal, India

S snake bite is a common environmental hazard in tropical countries like India. Every year, millions of people in India are bitten by poisonous snakes and a substantial proportion of them suffer from systemic toxicity. Renal failure and neurological involvement are the two main complications of poisonous snake bite. But other systems can also be affected rarely. Ocular involvement is one such extremely rare consequence of snake envenomation. Ocular manifestation can be a harbinger of serious systemic toxicity; also the consequences of ocular lesions can be long-term.

A 42-year-old male patient was bitten in the foot by Russell’s viper snake in March (just after the hibernation season). He had intense local pain and edema, followed by oliguria and hematuria. He was given antisnake venom (ASV) in appropriate dose within 24 hours of the bite. However, his condition continued to deteriorate. There were also ana sarca and spontaneous ecchymoses in many parts of the body. On the 3rd day of snake bite, the patient complained of rapidly progressive painless diminution of vision in both eyes. On examination, pupils were bilaterally sluggishly reactive; ocular movements were normal. Visual acuity was FC (3 ft) for both eyes. Fundoscopy examination revealed bilateral vitreous hemorrhage. At this time, platelet count of the patient was 100,000/cmm. Prothrombin time was 18.6 seconds with INR = 1.6. The anuria persisted with progressive generalized volume overload. The patient was started on hemodialysis with other supportive treatment but unfortunately, he passed away after 2 days.

There is very scanty literature on ocular manifestations of venomous snake bite. Most data consist of isolated case reports or case series. Acute attack of glaucoma, optic neuritis, and retinal detachment are some of the reported manifestations of snake venom. Also, a form of irritant conjunctivitis may be caused by spitting snake venom. But such examples of spitting venom are more common in other continents.

The mechanism of ocular toxicity in snake envenomation is multifactorial. It not only depends on the species of snake, but also other technical factors like time interval between bite and ASV administration, adequacy of ASV dosage, and use of traditional medicines before medical intervention. Direct cytotoxic effect of the snake venom proteins is a major factor; but hypersensitivity reaction to the ASV may also be responsible. Pathophysiological mechanisms of posterior segment involvement include disseminated intravascular coagulation induced by the venom, ocular vasculitis, and hemorrhagins in snake venom increasing capillary permeability locally.

Most of the ocular complications (except extraocular muscle involvement) after snake bite are reported after vipers venomation. The present case is also Russell’s viper envenomation. Vitreous hemorrhage is very rarely reported after snake bite. Because of its rarity, the exact pathogenesis is not known. But systemic anticoagulant state is said to be a major contributing factor. In our case, blood tests did not reveal significant alteration in clotting parameters at the time of vitreous hemorrhage.

Besides vitreous hemorrhage, other causes of similar sudden visual loss after snake bite include central retinal artery and vein occlusion, macular infarction, and retinal hemorrhage. Treatment for the above conditions is based on ophthalmology guidelines. Antisnake venom does not help in treatment of ocular complications. Intraocular administration of ASV has no role in the management of ocular manifestations.

We present this case to sensitize clinicians to this rare but potentially serious complication of snake bite. Since snake bite occurs in the young adult age group in large numbers, such ocular toxicity would lead to substantial loss of economic productivity. Early ocular consultation is mandatory if a snake bite victim complains of visual diminishment.

REFERENCES

Brainstem Arteriovenous Malformation and Symptomatic Excessive Daytime Somnolence

Sowmini PR1, Mugundhan K2, Rajesh Shankar Iyer3

1Assistant Professor; 2Professor and HOD, Department of Neurology, Stanley Medical College, Chennai; 3Senior Consultant Neurologist, Department of Neurology KG Hospital, Coimbatore, Tamil Nadu, India

Sir

A middle-aged man was admitted with symptoms of excessive daytime somnolence (EDS) of 1-year duration. He used to have sudden and irresistible bouts of sleep, occurring six to seven times a day, amounting to 18–20 hours of sleep daily. He had immense difficulty carrying out his daily activities and felt perennially exhausted. He was not able to concentrate at work. However, the patient did not give a history of sleep paralysis, cataplexy, or hallucinations. On examination, he was not obese or overweight. Neurological examination was normal.

All laboratory tests were normal. Thyroid function assessment was normal. Magnetic resonance imaging (MRI) brain with contrast showed a presence of calcified arteriovenous malformation (AVM) in the superior colliculus of the dorsal midbrain extending into the rostral pons inferiorly and vermis of cerebellum posteriorly (Figs 1 and 2). Nocturnal polysomnogram with multiple sleep latency tests did not show features suggestive of narcolepsy.

Excessive daytime somnolence is said to be the difficulty in remaining awake during the day, resulting in undesirable spells of drowsiness or sleep.3

Excessive daytime somnolence or hypersomnia, not associated with the other components of narcolepsy, is commonly seen in many neurological conditions. The anatomical substrates responsible for hypersomnia appear to be heterogenous and variable.

A meta-analysis on 116 cases of symptomatic narcolepsy/EDS was done in 2005. Genetic disorders (34%), tumors (29%), head trauma (16%), and demyelinating diseases (9%) were the commonly reported...
etiologies. Strokes, tumors, cysts, abscesses, hematomas, vascular malformations, and multiple sclerosis plaques were some of the uncommon causes of EDS.1

The superior colliculus has intricate connections to many brain regions which encompasses the periaqueductal gray, thalamus, cortex, brainstem, and spinal cord. The superior colliculus–posterior thalamus region is concerned with the onset of non-rapid eye movement sleep, rapid eye movement sleep, and wakefulness in mammals.2

Fig. 1: MRI brain T2 and fluid-attenuated inversion recovery (FLAIR) axial images showing calcified AVM in the dorsal ponto mesencephalic region

Fig. 2: MRI brain T1 contrast showing calcified AVM with heterogeneous enhancement
Correspondence

Mathis et al. emphasized the importance of the medial tegmentoptoline area in the pathophysiology of EDS. Focal lesions in this area might lead to various atypical narcoleptic syndromes. Symptomatic EDS has rarely been reported in patients with isolated lesions in the diencephalon, hypothalamus, midbrain, medial pontine tegumentum, and exceptionally in the ventral pons, a region pertaining to the hypocretin projection pathway.

This patient who had a calcified AVM in a strategic site extending from the superior collicular region of the midbrain to rostral pons was suffering from symptomatic or secondary EDS. This highlights the clinical correlation of sleep disorders with anatomical substrates. Sleep disorders, which have a complex heterogeneity, can rarely be the presenting manifestations of many neurological conditions, and awareness of this association facilitates early recognition and prompt management.

Increase Melioidosis Cases in India

Prasanta Raghbab Mohapatra
Professor and Head, Department of Pulmonary Medicine and Critical Care, All India Institute of Medical Sciences, Bhubaneswar, Odisha, India

With great interest, we read the article entitled “Melioidosis: A 5-year Review from a Single Institution in Pondicherry” by Sharma and Viswanathan. In their retrospective study of case records, only 20 patients out of 34 proven melioidosis were traced from the medical records. Twelve of them have died in hospital.

Melioidosis is a life-threatening fatal disease but potentially curable. We can decrease the mortality rate to less than 10% with faster bacterial confirmation, appropriate antibiotics, and good hospital care. I searched PubMed with the keyword “melioidosis” and “India”. Over the previous decade in India, per PubMed data, annual reporting has increased and comprises 70% of total publications from India on melioidosis. Over 1,550 cases (over 90% of the total over 1,700 cases published so far from India about 1,700). The highest number of annual cases (over 500 cases) was already reported in 2021. Melioidosis is common in tropical climates with hot, humid, and higher rainfall and wind. The bacteria usually persist in the soil. Patients with uncontrolled diabetes mellitus, prolonged glucocorticoid therapy, and chronic liver or renal disease are more prone to developing melioidosis. Melioidosis is much more common than ever believed to be diagnosed in tropical countries like India, the diabetic capital of the world. This disease is grossly underestimated in the tropical regions in India, probably due to a lack of awareness and multiple symptoms that imitate other conditions without specific identifying features. Even if diagnosed at times, it is already too late or after death only.

Authors diagnosed the melioidosis by culture method only. The culture used to take a longer time. Early and rapid diagnosis by antigen detection using lateral flow immunoassay directly from various clinical samples could have prevented higher death (12 of 20 patients) by early appropriate antibiotics administration. This easy method might be adapted when there is clinical suspicion, and a culture report is likely to be delayed to confirm the diagnosis.

The signs and symptoms of melioidosis mimic other diseases like tuberculosis, used to delay the diagnosis and ultimately management of melioidosis. The presence of common broad-based signs and symptoms can share with other diseases without a clue, resembling other conditions, often delaying melioidosis diagnosis and management. Melioidosis is also called “the great mimic” of tuberculosis and other diseases. There is an urgent need to create awareness among clinicians and microbiologists, capacity building of the microbiology laboratories, and a national melioidosis registry. Lack of experience of such diseases, without clinical clues or familiarity with the disease, possibly was the reason for rare reporting.

The importance of awareness and knowledge of this disease entity is of great importance. The treatment regimen consists of early aggressive antibiotics for weeks and is followed by prolonged maintenance, which is quite different from other acute bacterial diseases. Many patients die due to non-diagnosis, delayed diagnosis, or inadequate and incorrect treatment. Many of these patients are advised of antitubercular drugs. Some other patients are treated with high-end antibacterial combinations like piperacillin and tazobactam. However, these patients having melioidosis require a prolonged course of antibacterial treatment with specific drugs (like meropenem or ceftazidime). Hence, increasing awareness among clinicians and microbiologists is essential for this occasional reported and fatal disease.

References


Is Rivaroxaban Superior to Enoxaparin for Thromboprophylaxis in Hospitalized Patients of COVID-19?*

Kunal Deokar1, Mehuil Kaliya2, Karan Vachhani3, Sanjay Singhal4, Aneri Parekh5
1Assistant Professor, Department of Pulmonary Medicine; 2Assistant Professor; 3Senior Resident, Department of General Medicine; 4Associate Professor; 5Senior Resident, Department of Pulmonary Medicine, All India Institute of Medical Sciences, Rajkot, Gujarat, India

Sir,

We read with great interest the article titled “Oral Rivaroxaban in the Prophylaxis of COVID-19 Induced Coagulopathy” by Kumar et al. We sincerely congratulate the authors for conducting a randomized clinical trial, especially during the COVID-19 pandemic. In this single-center, open-label, prospective, randomized, superiority trial, the efficacy of rivaroxaban as compared to enoxaparin for thromboprophylaxis in mild to moderate cases of COVID-19 was studied. The primary efficacy outcome occurred in 3.5% of patients in the rivaroxaban arm as compared to 14.2% of patients in the enoxaparin arm with a
Cascade of Drug Toxicities: A Challenging Case of Tuberculosis and Drug Rash with Eosinophilia and Systemic Symptoms

Parul Kodan, Nitin Gupta, Himanshu Narang, Abhishek Singh, Farhan Fazal, Wasim Khot, Manish Soneja, Ashutosh Biswas, Naveet Wig

1. Senior Resident; 2. Additional Professor; 3. Professor; 4. Professor and Head, Department of Medicine, All India Institute of Medical Sciences, New Delhi, Delhi, India

Dear Sir,

Tuberculosis is a common infection with varied manifestations. Tubercular psoas abscess is a well-described entity. However, antitubercular drugs (ATDs) are known for their toxicities. Drug rash with eosinophilia and systemic symptoms (DRESS) reaction is a rare toxicity secondary to ATDs. We describe a rare case of tubercular psoas abscess and the DRESS syndrome; the course of which was further complicated by other adverse drug reactions. In this case, we summarize the cascade of toxicities secondary to antitubercular treatment and how we approached and managed the rare manifestations and drug reactions. The rarity of the case and challenge to successfully manage it prompted us to report the case.

A 14-year-old girl presented with fever and low back pain associated with loss of appetite and weight for 1 month. On examination, she had localized tenderness in the right lumbar region. Her tuberculin skin test was strongly positive and ultrasonography revealed a right-sided psoas abscess. She was empirically started on ATD which is weight-based isoniazid, rifampicin, pyrazinamide, and ethambutol, from an outside center after which her fever resolved in 2 weeks. Three weeks after initiation of ATD, she developed an erythematous skin rash all over the body along with a recurrence of fever (Fig. 1). Routine laboratory examination revealed transaminitis and eosinophilia. Her ATDs were withheld and she was referred to our center for worsening skin lesions and high-grade fever. With a diagnosis of DRESS, she was started on high-dose steroids. Tapering of the dosage of steroids was attempted multiple times but was associated with the recurrence of symptoms. Methotrexate was added to the regimen to reduce the dosage of steroids as she was developing steroid-induced hyperglycemia and cushingoid habitus. Steroids and methotrexate were continued for a total of 3 months. Meanwhile, the psoas abscess was aspirated and the culture was positive for Mycobacterium tuberculosis.

The risks of reoccurrence of DRESS and potential complications were discussed with the patient’s parents and in a multidisciplinary team approach, it was decided to not reintroduce the ATDs that were present in the initial regimen. She was started on amikacin, levofloxacin, and ethionamide. However, despite regular counseling, she was irregular with injectable doses and her parents were apprehensive of long-term injectable therapy and, therefore, she was started on linezolid, ethionamide, and levofloxacin. She was followed up closely. Three months later, she presented with inappropriate behavior, irrelevant talks, and spells of crying and laughter. Ethionamide was the possible culprit drug associated with possible adverse effects. It was replaced with rifabutin. Two
months into the new regimen consisting of linezolid, levofloxacin, and rifabutin, she presented with severe neutropenia (absolute neutrophil count 210/μL) and drug-induced liver injury (DILI). Neutropenia was attributed to linezolid and DILI was attributed to rifabutin. Both of these drugs were withheld and clofazimine was introduced at this point in time in addition to levofloxacin. The patient was warned about the possibility of skin discoloration with this drug and was counseled to maintain adherence. She was feeling well on the therapy with complete resolution of fever and back pain. She discontinued clofazimine on her own after the onset of slate gray skin discoloration. She was informed about the dangers associated with nonadherence and incomplete treatment but was unwilling to continue clofazimine or any injectable medication. She had completed a total of 5 months of ATD. A repeat ultrasound abdomen was done to look for residual psoas abscess which was normal. At this point, due to the patient’s insistence despite counseling, a call was taken to stop all the drugs and keep her under close follow-up. She is doing well even after 1 year of discontinuation of therapy and is under close follow-up.

The long duration of treatment with ATDs is well known for its toxicities and side effects like hepatotoxicity, peripheral neuropathies, and vision disturbances. Many cutaneous side effects of ATDs have been documented as well in the published literature. DRESS is a relatively rare complication associated with the use of ATDs. Fever, rash, lymphadenopathy, and internal organ involvement with marked eosinophilia constitute the main manifestations. The most frequently involved organ is the liver, followed by the kidney and lungs. DRESS is a discrete, idiosyncratic, and severe reaction to any drug and can be fatal in up to 10% of cases. A Japanese criterion has been described to diagnose DRESS. Our patient fulfilled seven out of nine criteria and was diagnosed as a definite case of DRESS. Literature suggests cases of DRESS secondary to ATD should be managed with great caution. Management includes close monitoring, drug discontinuation, steroids, and supportive care.

The common side effects of second-line ATDs are summarized in Table 1. Clinicians should closely monitor for these side effects. Ethionamide is commonly associated with severe vomiting and hypothyroidism. However, neurological side effects like psychosis have also been reported rarely. As in our case, no other cause could be attributed to her altered sensorium, and symptoms resolved on withholding ethionamide.

Long-term linezolid requires close monitoring. Hematological suppression is a well-known duration-dependent side effect of this drug, which resolves with drug discontinuation, as in our case. Other side effects of long-term linezolid which require monitoring include peripheral neuropathy and optic neuropathy. Also, physicians must be aware of close monitoring of drug interaction including drugs which may precipitate serotonin syndrome along with linezolid.

The challenge to choose any appropriate ATD for the young girl was daunting. Limited options to treat the dreadful mycobacteria and cascade of severe toxicities made it a challenging experience which required very close monitoring, regular counseling, and a multidisciplinary approach to manage complications.

Clofazimine-induced discoloration is a well-known side effect of the drug. This reversible pigmentation has been attributed to deposition of the drug in skin tissue and ceroid lipofuscinosis. However, concerns about the cosmetic effects and subsequent deterioration of quality of life make it a difficult choice in the long-term in young girls like in our case.

Physicians treating tuberculosis must be watchful and wary of drug-related side effects. Early identification and prompt management of these side effects is a requirement to maintain treatment adherence and achieve positive outcomes.

### Table 1: Common side effects to monitor with second-line ATDs

<table>
<thead>
<tr>
<th>ATDs</th>
<th>Toxicities to monitor closely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroquinolone</td>
<td>QT prolongation, tendinopathies</td>
</tr>
<tr>
<td>Aminoglycoside</td>
<td>Nephrotoxicity, ototoxicity</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>Gastrointestinal side effects, hypothyroidism</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>Psychosis</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Peripheral neuropathy, optic neuritis, cytopenia</td>
</tr>
<tr>
<td>Para-amino salicylic acid</td>
<td>Gastric intolerance</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>Skin and body fluid discoloration, QT prolongation</td>
</tr>
</tbody>
</table>

### References


Prescribing, Patient Counseling, and Documentation: A Simple Strategy for Improved Patient Outcomes

Shambo S Samajdar1, Santanu K Tripathi2, Jyotirmoy Pal3, Sougata Sarkar4

1Clinical Pharmacologist, Department of Clinical & Experimental Pharmacology, School of Tropical Medicine; Consultant, Clinical Pharmacology, Diabetes & Allergy Asthma Therapeutics Specialty Clinic, Kolkata, West Bengal; 2Academic Dean, Department of Pharmacology, Netaji Subhas Medical College & Hospital, Patna, Bihar; 3Professor, Department of Medicine, R. G. Kar Medical College and Hospital; 4Clinical Pharmacologist, Department of Clinical & Experimental Pharmacology, School of Tropical Medicine, Kolkata, West Bengal, India

Prescribing is a complex and demanding professional task. Writing a prescription, particularly deciding its content, is certainly very challenging, calling for a rigorous knowledge synthesis around drug therapeutics against the context of the given patient background. However, prescribing does not mean just writing a prescription. It goes much beyond that. The act of prescribing is not complete unless the doctor effectively educates the patient about how to use the prescribed medications. The optimum success of a prescribing endeavor depends heavily on the integrity and quality of such patient counseling.

It is a common experience that physicians in our setting are often reluctant to spare time and effort in explaining to the patient (or the home caregiver) about the benefits and risks of the use of prescribed medicines. This task is either relegated to someone at the lower order in the care provider team or sometimes it is just ignored. This tendency, we believe, is too risky. Knowledge and understanding gaps in patients about prescribed medications impact...
the compromised treatment adherence on one hand, and even may prove too harmful or even lethal, on the other. It may also lead to further catastrophes, like medication errors.3

In view of this, we propose a strategy whereby the prescribing doctor shall be required to communicate with the patient, in simple language, the basic information about the prescribed medicines.

The following areas of medication education may be emphasized in patient counseling.

- Name and purpose of each medicine prescribed.
- Beneficial and adverse effects of each medicine.
- Clear instructions explained in simple language ensuring that the patient understands.
- Detailing warnings and contraindications for the medications.
- How to respond to suspected adverse effects.
- Encouraging the patient to ask questions.
- Eliciting relevant history including about medications, about allergy, about comorbidities, etc.

With the unfortunate decline in doctor–patient relations and mutual trust, and also in view of the current litigious era, it seems appropriate to not just emphasize about counseling, but also ensure documentation of the counseling act. We present here a template in English of a form for such documentation (see Box 1). It may, however, be customized to suit local norms and be translated into suitable vernacular, if needed.

Just the use of such a form tends to carry a huge promise of minimizing adverse drug experiences and other medication-related problems, like medication errors. It is also likely that this strategy may improve medication adherence too.

WHO defined adherence as “the extent to which a person’s behavior—taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider”4; and the importance of adherence is paramount in therapeutics as it can ensure effectiveness and safety of prescribed treatments.

References
KEEP THE BRAIN-GUT BOND STRONG

In IBS with Anxiety

Librax
Chlordiazepoxide 5 mg + Clidinium Bromide 2.5 mg Tablets

DOSAGE:
1 TABLET T.I.D. 1-1-1 FOR 3 MONTHS

Established Safety & Efficacy
Textbook recommended
Over 3 decades of trust
Globally available

For the use of Registered Medical Practitioner or Hospital or Laboratory only
In Hypertension and Hypertension associated with Diabetes

Initiate Olmesar
Olmesartan Medoxomil 10 / 20 / 40 mg Tablets
Best in Class, A Class Apart

The BEST in BP and CVD Risk Reduction

Switching from Telmisartan to Olmesartan offers responder rate improvement
Cota Study: 132 Diabetic patients

- Clinic BP
  - Baseline
  - 16 weeks
  - Telmisartan
  - Olmesartan

- Home BP
  - Baseline
  - 16 weeks
  - Telmisartan
  - Olmesartan

Better Reduction in Atherogenic process
OLIVUS Study: Lowers rate of coronary Atherosoma progression

3. Total Atherosoma Volume
4. Percentage Atherosoma Volume

Macleods Pharmaceuticals Ltd
Atlanta Arcade, Marine Church Road, Opposite Laika Hotel, Andheri East, Mumbai-40

102 Journal of the Association of Physicians of India, Volume 70 Issue 9 (September 2022)
TIME TO GO BEYOND GLYCEMIC CONTROL

INTRODUCING

In Uncontrolled T2DM Patients,

**Sitanorm-D**
(Sitagliptin 50/100 mg + Dapagliflozin 5/10mg Tablets)

More Control with CV Benefits and beyond

For all stages of T2DM patients,

**Sitanorm**
(Sitagliptin 25/50/100 mg Tablets)

**Sitanorm-M**
(Sitagliptin 50/100 mg + Metformin 500/1000 mg SR Tablets)

A NORM for achieving Glycemic Goals and beyond

---


*In patients who can tolerate Sitagliptin or where Sitagliptin is Indicated*

---

Micro Labs Ltd, Micro House, 4th Floor, Chandivali Farm Road, Near Kamani Oil Mills, Chandivali, Andheri (East), Mumbai 400072.
