CONTENTS

Journal, Indian Academy of Clinical Medicine • Vol. 27, Number 3, July-September, 2026

Contains 80 pages from 161 to 240 (inclusive of all advertisements)

Original Articles

Angiographic Profile and Cardiovascular Risk Factors among Patients of NSTEMI Undergoing Percutaneous Coronary Intervention 166
Harshvardhan, MU Rabbani, Razeen Fatima, Amir Husain

Prognostic Value of Serum Triglyceride Glucose Index in Acute Heart Failure 171
Manjunath S, Pankaj Singhai, Anand Shenoy

Spirometric Indices in Adults with Type 2 Diabetes Mellitus: A Hospital-Based Comparative Cross-Sectional Study 178
Rahul Garg, Prashant Prakash, Mohd Abid, Piyush Tageja

Aetiological and Haematological Profile of Patients of Pancytopenia at a Tertiary Care Hospital in Northern India 186
Bishakha Swain, Ratnakar Sahoo, Vijay Kumar, Priyanka Verma

Review Articles

Approach to Adult-Onset Inborn Errors of Immunity: Defining the Enigma 193
Sarika Singh, Kamini

Active and Latent Tuberculosis Among Household Contacts of Pulmonary Tuberculosis Patients: Epidemiology, Determinants and Diagnostic Approaches: A Narrative Review 201
Kheta Ram Solanki, Ramakant Dixit, Ankur Gupta

Case Reports

Autoimmune Polyglandular Syndrome Type II Presenting as Seronegative Autoimmune Addison's Disease with Mixed Connective Tissue Disease 211
Amit Sharma, Deepak Jain, Divyajyoti Das, Manjri Garg, Shatakshi

Idiopathic Multicentric Castleman Disease Presenting as TAFRO Syndrome 215
Rajnish Singh, Shreyasee Patra, Brijesh Sharma, Madhubala Negi, Archana Mohan, Tanvi Suri, Shivanshu Gangwar

Severe Haemotoxic Viper Envenomation with Recurrent VICC, Transient Myocardial Injury, Dynamic Conduction Abnormalities, and Kounis Syndrome following Antivenom Therapy 220
Himanth Erappra, SK Singh, Varghese Koshy

Renal Transplant in a Case of EHPVO with Severe Pancytopenia 223
Kailash N Singh, Ankit Grover, Neerav Goyal, Sandeep Guleria

Unusual Presentation of Ovarian Serous Cystadenocarcinoma 225
Vinay Kumar, Rajat Jhamb, Rutu Karia, Nausheen Farha, Rimple khatri, Shrinath Nevanath

CONTENTS

Journal, Indian Academy of Clinical Medicine • Vol. 27, Number 3, July-September, 2026

Contains 80 pages from 161 to 240 (inclusive of all advertisements)

Case Reports	**Pancreatic Tuberculosis with Reversible Exocrine Insufficiency** *Vishwa Golyan, Abrar Hussain, Prabhat Kumar, Bhuvnesh Guglani*	228
	***Salmonella typhi* Liver Abscess in an Immunocompetent Adult** *Sudipta Ghosh, Gourab Bhaduri, Manoj Jain, Shelley Sharma Ganguly, Sujit Chaudhuri, Mrinmoy Pal, Sumeet Kumar*	231
	Hereditary Spherocytosis with Conjugated Hyperbilirubinaemia, Chronic Liver Disease and Portal Hypertension *Mukesh K Sarna, Manish Pahadia, Animesh Gaur, Shivam Bansal, Akash Aggarwal, Abheet Sonkhya, Nikhil Mehta, Sudha Sarna*	234
Pictorial CME	**Poly-Hill Sign and Popeye Arm in Facioscapulohumeral Muscular Dystrophy** *Devavrata Sahu, Karan Khatri, Ketan Bhatnagar, Jyoti Garg, Ashish Kumar Duggal*	238
Announcements	***Mrs Uma Bansal – Prof. B.C. Bansal Best Paper Award (Journal – 2026)***	185
	Advertisement Tariff of the Journal, Indian Academy of Clinical Medicine (JIACM)	192
	Regarding Updating the Address/Mobile No/E-mail ID	230
	Application Form for IACM Life Member/Fellow of the Association/Associate Member (PG Member)	240

The *JIACM* invites scientific and historical material of absorbing interest related to clinical medicine from all authors, whether or not Fellows or Members of the IACM. The editorials and articles do not represent the policy of the IACM unless this is specifically mentioned.

Self-addressed, sufficiently stamped envelopes must accompany all unsolicited manuscripts. Otherwise, material found unsuitable for publication will not be returned. The editor does not assume any responsibility for material submitted for publication.

The publication of an advertisement in this journal does not constitute an endorsement of the product by the Indian Association of Clinical Medicine, or by the Editor of the *Journal*. Advertisements carried in this journal are expected to conform to internationally accepted medical, ethical, and business standards.

Journal, Indian Academy of Clinical Medicine

EDITORIAL BOARD

Editor
Sumeet Singla (New Delhi)

Associate Editor
Vipin Mediratta (New Delhi)

Secretary
Amit Aggarwal (New Delhi)

Members
MPS Chawla (New Delhi)
DG Jain (New Delhi)
BB Rewari (New Delhi)
Smarajit Banik (Siliguri)

Ex-officio Members
MPS Chawla (New Delhi)
HK Aggarwal (Rohtak)
Suresh Kushwaha (Agra)

ADVISORY BOARD

AK Agarwal (Noida)
Sunita Aggarwal (New Delhi)
Navneet Agrawal (Gwalior)
KS Anand (New Delhi)
S Anuradha (New Delhi)
Dipanjan Bandyopadhyay (Kolkata)
Ashish Bhalla (Chandigarh)
Rohit Bhatia (New Delhi)
Pradip Bhaumik (Agartala)
Debasis Chakrabarti (Siliguri)
Shekhar Chakraborti (Siliguri)
Ashutosh Chaturvedi (Jaipur)
Nandini Chatterjee (Kolkata)
Kamal Chopra (New Delhi)
MK Daga (New Delhi)
Amit Das (Muzaffarpur)
Desh Deepak (New Delhi)
Saikat Dutta (Darjeeling)
RK Dhamija (New Delhi)
RM Dhamija (New Delhi)
Ajai Kumar Garg (Greater Noida)
Jyoti Garg (New Delhi)
Udas C Ghosh (Kolkata)
AK Gupta (Agra)
Subhash C Gupta (Agra)
R Handa (New Delhi)
BM Hegde (Mangalore)
Pulin Kumar Gupta (New Delhi)
Deepak Jain (Rohtak)
SK Jain (New Delhi)
VK Katyal (Rohtak)
Madhuchanda Kar (Kolkata)
VN Kaushal (Agra)
Rajesh Khadgawat (New Delhi)
Anil Kulshrestha (Ahemdabad)
Ajay Kumar (Patna)
Rajat Kumar (Canada)
BM Singh Lamba (New Delhi)
Ravi Keerthy M (Bangalore)
Manoranjan Mahapatra (N. Delhi)
Sanjiv Maheshwari (Ajmer)
Girish Mathur (Kota)
Alladi Mohan (Tirupati)
Sukumar Mukherjee (Kolkata)
G Narsimulu (Hyderabad)
MV Padma (New Delhi)
A Muruganathan (Tirupur)
Jyotirmoy Pal (Barrackpur)
V Palaniappen (Dindigul)
Jayanta Kumar Panda (Cuttack)
KK Pareek (Kota)
HS Pathak (Naihati)
Munish Prabhakar (Gurugram)
Anupam Prakash (New Delhi)
Prashant Prakash (Agra)
GD Ramchandani (Kota)
S Ramakrishnan (New Delhi)
Rakesh Sahay (Hyderabad)
Puneet Saxena (Jaipur)
Brijesh Sharma (New Delhi)
Ashok Shiromany (Agra)
RPS Sibia (Patiala)
G Sidhu (Ludhiana)
RK Singal (New Delhi)
Devender Prasad Singh (Bhagalpur)
Harpreet Singh (Rohtak)
MP Singh (Agra)
Rajnish Singh (New Delhi)
TP Singh (Agra)
Shyam Sunder (Varanasi)
SH Talib (Chhatrapati Sambhaji Nagar)
Ashok Taneja (Gurugram)
Nihal Thomas (Vellore)
Manjari Tripathi (New Delhi)
Sanjay Tyagi (New Delhi)
Rajesh Upadhyay (New Delhi)
GS Wander (Ludhiana)
Pushpa Yadav (New Delhi)

JOURNAL, INDIAN ACADEMY OF CLINICAL MEDICINE

is edited by

Dr. Sumeet Singla

for the

Indian Association of Clinical Medicine

Headquarters :

Post-Graduate Department of Medicine, Sarojini Naidu Medical College, Mahatma Gandhi Road, Agra - 282 002 (U.P.)

Editorial/Mailing Address

108 SFS Flats, Ashok Vihar, Phase-4, New Delhi - 110 052
Tel.: 9818143960

E-mail: iacmjournal@gmail.com

ISSN 0972-3560

RNI Regn. No. : DELENG/2000/1686

Indexed in Scopus, IndMED

Listed in UGC Approved List of Journals

"Bibliographic details of the journal available in ICMR-NIC's database – IndMED (http://indmed.nic.in). Full-text of articles (from 2000 onwards) available on medIND database (http://medind.nic.in)."

The statements and opinions contained in the articles of the
'Journal, Indian Academy of Clinical Medicine'
are solely those of the individual authors and contributors. The publisher and honorary editor disclaim any responsibility about the originality of contents. All the articles, however, are peer-reviewed.

The editor and publisher disclaim any responsibility or liability for the claims, if any, made by advertisers.

Papers which have been published in this *Journal* become the property of the *JIACM* and no part of this publication may be reproduced, or published in any form without the prior written permission of the editor.

Published by Dr. Sumeet Singla
for and on behalf of the Indian Association of Clinical Medicine
from 108 SFS Flats, Ashok Vihar, Phase-4, New Delhi - 110 052
and printed by him at Sumit Advertising, B-77, Ist Floor, Naraina Industrial Area, Phase-2, New Delhi - 110 028.

Indian Association of Clinical Medicine

Headquarters:
Post-Graduate Department of Medicine, Sarojini Naidu Medical College,
Mahatma Gandhi Road, Agra - 282 002 (U.P.)

Founder-President: MC Gupta (Agra)

GOVERNING BODY

President
BL Bhardwaj (Patiala)

President-Elect
HK Aggarwal (Rohtak)

Immediate Past-President
MPS Chawla (New Delhi)

Vice-Presidents
YB Agarwal (Agra)
DG Jain (Delhi)

Hony. General Secretary
Suresh Kushwaha (Agra)

Hony. Treasurer
MP Singh (Agra)

Hony. Editor, *JIACM*
Sumeet Singla (New Delhi)

Associate Editor, *JIACM*
Vipin Mediratta (New Delhi)

Members
DP Singh (Bhagalpur)
Anil Kulshrestha (Ahemdabad)
SPS Chauhan (Ferozabad)
Smarajit Banik (Siliguri)
Pradeep Agarwal (Jaipur)
Amit Das (Muzaffarpur)
Tarun Satija (Ludhiana)
Debasis Chakraborty (Siliguri)

Zonal Members

North Zone
Vikas Loomba (Ludhiana)

South Zone
V Chandrasekar (Warangal)

East Zone
Debaprasad Chakraborty (Agartala)

West Zone
Puneet Saxena (Jaipur)

Central Zone
Prashant Prakash (Agra)

Organising Secretary
(IACMCON-2026)
S Chandrasekhar (Chennai)

Organising Secretary
(IACMCON-2025)
Pritam Singh (Chandigarh)

Joint Secretaries
RPS Sibia (Chandigarh)
Ajeet Singh Chahar (Agra)
Amit Aggarwal (New Delhi)

ORIGINAL ARTICLE

JIACM 2026; 27 (3): 166-70

Angiographic Profile and Cardiovascular Risk Factors among Patients of NSTEMI Undergoing Percutaneous Coronary Intervention

Harshvardhan, MU Rabbani**, Razeen Fatima***, Amir Husain****

Abstract

Background: With the rising prevalence and mortality associated with coronary artery disease (CAD), especially in developing regions, there is a need for studies that provide insight into disease patterns. Non-ST-elevation myocardial infarction (NSTEMI) represents a significant subset of acute coronary syndrome (ACS), yet data regarding its angiographic profile in our region remain limited. The aim of the study was to evaluate the angiographic profile and assess the influence of cardiovascular risk factors on angiographic findings in NSTEMI patients undergoing Percutaneous Coronary Intervention (PCI).

Methods: This prospective observational study included 100 patients diagnosed with NSTEMI who underwent PCI at our institution between December 2018 and November 2020. Patients were evaluated for cardiovascular risk factors, angiographic profile, and the influence of these risk factors on angiographic findings.

Results: The mean age of presentation was 58.1 ± 11.1 years (males: 57 ± 11.0 years; females: 60.8 ± 11.3 years). Dyslipidaemia was the most common risk factor (49%). Single vessel disease (SVD) was the most common angiographic pattern (38%), followed by triple vessel disease (TVD, 29%) and double vessel disease (DVD, 27%). The left anterior descending (LAD) artery was the most frequently involved vessel. Patients with diabetes mellitus and hypertension showed a higher prevalence of multi-vessel disease (63.3% and 65.7%, respectively) compared to non-diabetics and non-hypertensives.

Conclusion: This study provides insight into the prevalence of cardiovascular risk factors and angiographic patterns in NSTEMI patients. It highlights the significant influence of risk factors on the severity and distribution of coronary artery disease.

Introduction

Cardiovascular diseases (CVD) are a leading cause of mortality worldwide, with a disproportionate burden in low- and middle-income countries such as India. Despite this, data regarding the prevalence and angiographic characteristics of coronary artery disease (CAD) in developing regions remain limited.

Rapid urbanisation and socio-economic changes have increased exposure to major cardiovascular risk factors, including diabetes mellitus, hypertension, smoking, and dyslipidaemia. Additionally, inadequate preventive strategies have contributed to the growing burden of CAD.

In India, CAD has reached epidemic proportions. Data from the Registrar General of India show an increase in mortality due to CAD from 17% (2001 - 2003) to 23% (2010 - 2013). The CREATE registry reported that 39% of acute coronary syndrome cases were NSTEMI, with a mortality rate of 3.7%, higher than in developed countries.

Furthermore, the utilisation of revascularisation procedures remains low. PCI rates in NSTEMI or unstable angina are approximately 7% in India compared to 25 - 37% in developed countries. Similarly, coronary artery bypass grafting (CABG) rates are significantly lower.

Despite the presence of numerous cardiac catheterisation centers, there is a lack of comprehensive data on the angiographic profile and associated risk factors in NSTEMI patients. Therefore, this study was carried out to evaluate the angiographic profile and assess the influence of cardiovascular risk factors on angiographic findings in NSTEMI patients undergoing PCI.

Material and Methods

This was a prospective, observational study conducted at a tertiary care centre in Northern India over a period of two years, including 100 patients diagnosed with NSTEMI who underwent PCI. The study was approved by the institutional ethics committee (D. No. 248/FM). Enrolment was done after informed consent from patients. The study was in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Inclusion Criteria

- Patients presenting with symptoms of acute coronary

**Assistant Professor, **Professor, Department of Cardiology, ***Assistant Professor, Department of Medicine, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh - 202 002, Uttar Pradesh.*
Corresponding Author: Dr Razeen Fatima, Assistant Professor, Department of Medicine, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh - 202 002, Uttar Pradesh. Tel: 8218790348, E-mail: razeenfatima@yahoo.co.in

syndrome

- ECG changes suggestive of NSTEMI
- Troponin I levels >99th percentile (as per the third universal definition of myocardial infarction)
- Patients providing informed consent

Exclusion Criteria

- ST-elevation myocardial infarction (STEMI)
- Chronic stable angina or unstable angina without MI
- Co-existing conditions such as sepsis or chronic kidney disease
- Patients not eligible for PCI

Definitions

- Significant CAD: ≥50% stenosis in major epicardial arteries
- Severity classification:
  - Mild: 20 - 49%
  - Moderate: 50 - 69%
  - Severe: 70 - 99%
  - Occluded: 100%
  - CTO: 100% occluded vessel that has existed for three or more months.

Risk Factors

- Hypertension: ≥140/90 mmHg or on treatment
- Diabetes Mellitus: FBS ≥126 mg/dL, PPBS ≥200 mg/dL, or HbA1c ≥6.5%
- Smoking: Current or within 1 year
- Dyslipidaemia: LDL ≥130 mg/dL, TG ≥150 mg/dL, or low HDL

Statistical Analysis

Data were analysed using SPSS version 25. Categorical variables were compared using the Chi-square test, and continuous variables using the Student's t-test. A p-value <0.05 was considered statistically significant.

Results

100 patients were recruited in the study. Out of 100 patients of NSTEMI, 77 were males and 23 were females. Mean age of females was 60.8 ± 11.3 years which was more than mean age of total patients (58.1 ± 11.1 years) and mean age of males which was 57 ± 11.0 years. Most common risk factor was dyslipidaemia (49) followed by smoking (37), hypertension (37) and diabetes (30) (Table I). SVD was most common (38) followed by TVD (29) and DVD (27). Most common vessel involved with maximum significant lesion was LAD (89) followed by RCA (68) and LCX (67) and left main (3). Total mild lesions were 91, moderate lesions were 22, severe lesions were 169 and total occlusions were 33. Chronic total occlusion (CTO) were 17, thrombotic lesions were 14 and calcified lesions were 7 (Table II).

Table I: Demographic characteristics of the patients

Demographic and risk factor profile	Number of patients
Mean age	58.1 ± 11.1 years
Males	77
Females	23
Diabetics	30
Hypertensives	37
Dyslipidaemia	49
Smokers	37
Previous Myocardial Infarction	9

Table II: Angiographic profile of NSTEMI patients

Coronary angiographic profile	Number of patients
SVD	38
DVD	27
TVD	29
LAD significant lesions	89
RCA significant lesions	68
LCX significant lesions	67

The relation between angiographic profile and major cardiovascular risk factors is shown in Table III. Severe coronary lesions were the most common finding across all risk factors, observed in 52.9% of diabetic patients, 53.0% of hypertensive patients, 43.3% of smokers, and 55.2% of patients with dyslipidaemia. Mild lesions were the next most frequent, whereas moderate lesions were relatively uncommon. Occluded lesions ranged from 7.5% in dyslipidaemia to 13.5% in diabetes mellitus.

With respect to the number of vessels involved, single vessel disease (SVD) was the most common pattern among smokers (60%) and patients with dyslipidaemia (46.8%). In contrast, diabetic and hypertensive patients showed a more even distribution of vessel involvement, with a relatively higher proportion of double vessel disease (DVD) and triple vessel disease (TVD).

Table III: Relation of angiographic profile with various risk factors

Angiographic Variable		Risk Factor			
		Diabetes mellitus	Hypertension	Smoker	Dyslipidaemia
Severity of Lesions	Mild	32 (30.8%)	42 (31.3%)	33 (34.0%)	49 (28.2%)
	Moderate	3 (2.9%)	10 (7.5%)	10 (10.3%)	16 (9.2%)
	Severe	55 (52.9%)	71 (53.0%)	42 (43.3%)	96 (55.2%)
	Occluded	14 (13.5%)	11 (8.2%)	12 (12.4%)	13 (7.5%)
	Total	104 (100%)	134 (100%)	97(100%)	174(100%)
No. of Vessels Involved	SVD	11 (36.7%)	12 (34.3%)	21 (60%)	22 (46.8%)
	DVD	9 (30.0%)	13 (37.1%)	10(28.6%)	12 (25.5%)
	TVD	10 (33.3%)	10 (28.6%)	4 (11.4%)	13 (27.7%)
	Total	30(100%)	35(100%)	35(100%)	57(100%)
No. of Significant Lesions	RCA	32 (43.8%)	27 (29.0%)	15(23.1%)	37 (29.6%)
	LAD	27 (37.0%)	37 (39.8%)	27(41.5%)	48 (38.4%)
	LCX	13 (17.8%)	28 (30.1%)	22 (33.9%)	40 (32%)
	LM	1 (1.4%)	1 (1.1%)	1 (1.5%)	0 (0%)
	Total	73(100%)	93(100%)	65(100%)	125(100%)
Characteristic Lesions	CTO	8 (50%)	5 (45.5%)	6 (46.2%)	9 (52.9%)
	Thrombus	6 (37.5%)	2 (18.2%)	6 (46.2%)	6 (35.3%)
	Calcified Lesion	2 (12.5%)	4 (36.4%)	1 (7.7%)	2 (11.8%)
	Total	16(100%)	11(100%)	13(100%)	17(100%)
Left main disease		03			
Mild lesions		91			
Moderate lesions		22			
Severe lesions		169			
Total occlusions		33			
Chronic total occlusions		17			
Thrombotic lesions		14			
Calcified lesions		7			

Analysis of significant coronary artery involvement showed that the left anterior descending artery (LAD) was the most frequently affected vessel in hypertensive (39.8%), smoking (41.5%), and dyslipidaemic patients (38.4%), whereas right coronary artery (RCA) involvement was most common among diabetic patients (43.8%). Involvement of the left circumflex artery (LCX) was moderate across groups, while left main (LM) artery involvement was rare.

Regarding characteristic lesion types, chronic total occlusion (CTO) was the most common finding across all risk factors, ranging from 45.5% in hypertension to 52.9% in dyslipidaemia. Thrombus formation was the second most frequent lesion type, while calcified lesions were comparatively less common, though relatively higher among hypertensive patients (36.4%).

Fig. 1 shows the distribution of number of vessels involved in diabetic and non-diabetic patients with NSTEMI undergoing PCI. Among diabetics, 33.3% (10/30) exhibited TVD, compared to 27.1% (19/70) of non-diabetics. DVD was present in 27% (n = 27) of all patients. In the diabetic subgroup, 30% (9/30) had DVD, while 25.7% (18/70) of non-diabetics showed two-vessel involvement. SVD was the most common finding at 38% (n = 38). It was seen in 36.7% (11/30) of diabetics and 38.6% (27/70) of non-diabetics. When analyzing Multi-Vessel Disease (MVD), defined as the presence of either DVD or TVD, a higher prevalence was noted in the diabetic group. 63.3% of

diabetic patients had MVD, compared to 52.8% of non-diabetic patients.

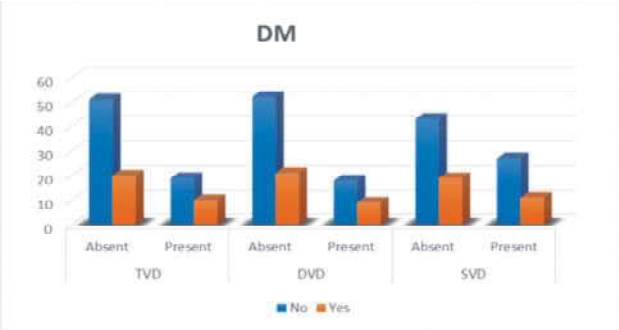


Fig. 1: *Distribution of number of vessels involved in diabetic and non-diabetic patients with NSTEMI undergoing PCI.*

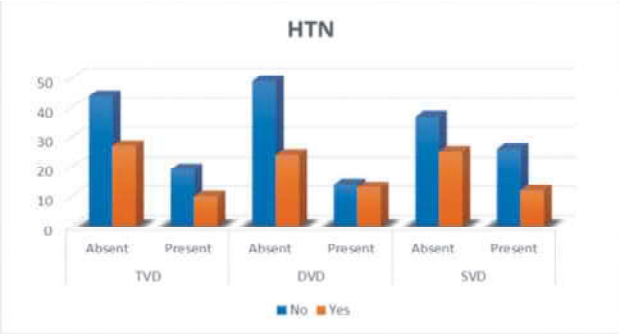


Fig. 2: *Relationship between hypertension and number of vessels involved in NSTEMI patients undergoing PCI.*

Similarly, hypertensive patients had a higher proportion of multi-vessel disease compared to non-hypertensive patients as shown in Fig. 2. TVD was present in 10 hypertensive patients (27.0%) compared to 19 non-hypertensive patients (30.1%) ($p > 0.05$). DVD was identified in 13 hypertensive patients (35.1%) and 14 non-hypertensive patients (22.2%). ($p > 0.05$). SVD was observed in 12 hypertensive patients (32.4%) and 26 non-hypertensive patients (41.2%) ($p > 0.05$). Hence 62.1% of hypertensive patients presented with MVD, whereas 52.3% of non-hypertensive patients exhibited involvement of two or more vessels.

In smokers, SVD was more common among smokers (60%) followed by DVD (28.6%) and TVD (11.4%) showing similarity with other studies. LAD had maximum number of total significant lesion in both group. Total occlusion was more (12.4%) as compared to non smokers (9.6%).

In dyslipidaemia subgroup, severe lesions were more common (55.2%) than in non dyslipidaemic (51.8%). SVD was most common in both dyslipidaemic and non dyslipidaemic (46.8%,34.0%) followed by TVD (27.7%,34.0%) and DVD (25.5%,31.9%). Maximum number of significant lesions were in LAD in both dyslipidaemic and non dyslipidaemic patients.

Discussion

The present study provides insight into the clinical and angiographic profile of patients with NSTEMI undergoing percutaneous coronary intervention (PCI) at our institute. The mean age of presentation was relatively young (58.1 ± 11.1 years), supporting the observation that cardiovascular disease occurs approximately a decade earlier in the Indian population compared to Western populations. Additionally, female patients presented at a later age, consistent with previously reported trends.

Dyslipidaemia emerged as the most common risk factor (49%) in our study population, although its prevalence was lower compared to the NCDR-ARG registry (63%). This difference may reflect regional, genetic, or lifestyle variations in the study population.

Single vessel disease (SVD) was the most common angiographic pattern (38%) among NSTEMI patients. Interestingly, triple vessel disease (TVD, 29%) was slightly more prevalent than double vessel disease (DVD, 27%), which differs from findings in some other studies. The left anterior descending (LAD) artery showed the highest number of significant lesions (n = 89), followed by the right coronary artery (RCA, n = 68) and left circumflex artery (LCX, n = 67), while left main involvement was relatively rare (n = 3).

The study highlights the strong influence of major cardiovascular risk factors on the severity and distribution of coronary artery disease (CAD). Severe coronary lesions were predominant across all risk groups, particularly among patients with dyslipidaemia, hypertension, and diabetes mellitus, suggesting that these metabolic and hemodynamic factors contribute to advanced atherosclerosis. Smoking was also associated with a high proportion of severe lesions, underscoring its role in accelerating coronary artery damage.

In terms of vessel involvement, SVD was most frequently observed among smokers and patients with dyslipidaemia, whereas diabetic and hypertensive patients demonstrated a higher prevalence of multi-vessel disease (DVD and TVD). This pattern reflects the diffuse nature of atherosclerosis in diabetes and long-standing hypertension, both of which promote endothelial dysfunction and vascular remodeling.

Analysis of individual vessel involvement revealed that the LAD artery was the most commonly affected vessel across most risk groups, consistent with its known anatomical and haemodynaemic susceptibility to atherosclerosis. However, in diabetic patients, the RCA showed slightly higher involvement, suggesting variability in plaque distribution

in this subgroup.

Chronic total occlusion (CTO) was the most common lesion characteristic (17%), indicating chronicity of advanced coronary artery disease in a significant proportion of patients. Thrombotic lesions (14%) were particularly common among smokers, likely due to smoking-induced hypercoagulability and endothelial injury. Calcified lesions (7%) were relatively less frequent but more commonly observed in hypertensive patients, possibly reflecting chronic vascular stress and long-standing disease.

A notable finding was the higher prevalence of multi-vessel disease among diabetic patients (63.3% *versus* 52.8%) and triple vessel disease (33.3% *versus* 27.1%) compared to non-diabetics. This aligns with the established understanding of diabetic macrovascular complications, where hyperglycaemia, insulin resistance, and oxidative stress contribute to diffuse and complex coronary lesions.

Similarly, hypertensive patients demonstrated greater multi-vessel involvement compared to non-hypertensives. Hypertension contributes to atherosclerosis through chronic mechanical stress, endothelial dysfunction, and activation of the renin – angiotensin – aldosterone system, leading to arterial remodeling and widespread plaque formation.

In contrast, smokers and patients with dyslipidaemia more commonly presented with SVD, consistent with existing literature. Smoking acts as a potent trigger for acute thrombosis, often leading to NSTEMI due to rupture of a single vulnerable plaque. However, the relatively higher rate of total occlusion in smokers (12.4%) highlights its aggressive pro-thrombotic effect.

A consistent finding across all subgroups was the predominant involvement of the LAD artery, reinforcing its critical role in coronary circulation and clinical outcomes. Regardless of the underlying risk factor, the LAD remains the most frequently affected vessel in NSTEMI-related atherosclerosis.

Conclusion

The present study provides valuable insight into the prevalence of cardiovascular risk factors and the angiographic profile of NSTEMI patients in our population. It highlights the significant influence of risk factors such as diabetes, hypertension, dyslipidaemia, and smoking on the pattern and severity of coronary artery disease.

Diabetes and hypertension were associated with more diffuse and multi-vessel involvement, whereas smoking and dyslipidaemia were more commonly associated with single vessel disease and thrombotic lesions. The LAD artery was the most frequently involved vessel across all subgroups.

These findings contribute to a better understanding of disease patterns in NSTEMI and may help in risk stratification and management planning. However, larger studies involving diverse geographic and socioeconomic populations are required to validate these findings and further strengthen the evidence base.

References

1. Thygesen K, Alpert JS, Jaffe AS *et al*. Third universal definition of myocardial infarction. *Circulation* 2012; 126 (16): 2020-35.
2. Tang EW, Wong CK, Herbison P. Global Registry of Acute Coronary Events (GRACE) hospital discharge risk score accurately predicts long-term mortality post acute coronary syndrome. *Am Heart J* 2007; 153 (1): 29-35.
3. Roe MT, Messenger JC, Weintraub WS *et al*. Treatments, trends, and outcomes of acute myocardial infarction and percutaneous coronary intervention. *J Am Coll Cardiol* 2010; 56 (4): 254-63.
4. Sharma R, Bhairappa S, Prasad SR. Clinical characteristics, angiographic profile and in-hospital mortality in acute coronary syndrome patients in South Indian population. *Heart India* 2014; 2 (3): 65.
5. Park HW, Yoon CH, Kang SH *et al*. Early- and late-term clinical outcomes and their predictors in patients with ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction. *Int J Cardiol* 2013; 169 (4): 254-61.

ORIGINAL ARTICLE

JIACM 2026; 27 (3): 171-77

Prognostic Value of Serum Triglyceride Glucose Index in Acute Heart Failure

Manjunath S, Pankaj Singhai**, Anand Shenoy****

Introduction

Admission with acute heart failure (AHF) carries high morbidity and in-hospital mortality, with nearly half of the patients rehospitalised within 6 months of discharge[1,2]. Clinical data and targeted treatment remain limited compared to chronic stable heart failure, as both represent distinct pathophysiological entities[3]. So far, established adverse prognostic indicators of AHF include blood urea nitrogen (BUN) levels >43 mg/dL, systolic blood pressure (SBP) <115 mmHg, serum creatinine >2.75mg/dL, and elevated cardiac biomarkers like natriuretic peptides and troponins[2,3].

Insulin resistance (IR) and associated reductions in downstream cardio-metabolic signaling are emerging as critical drivers of myocardial dysfunction and structural remodeling[4,5]. Hyperinsulinaemic-euglycaemic glucose clamp (HIEC) is the clinical gold standard for measuring insulin resistance[6], but its complexity and associated costs make it an impractical option. Alternative surrogate measures of insulin resistance include HOMA-IR, HOMA2-IR, QUICKI, and the serum triglyceride-glucose (TyG) index[7,8]. The TyG index is derived by a simple logarithmic formula: ln (Fasting blood glucose in mg/dL x Fasting serum triglycerides in mg/dL/2).

Emerging data suggest that the TyG index is an effective, low-cost surrogate marker for identifying insulin resistance, comparable or even superior to HOMA-IR in tracking insulin resistance-related conditions in diabetic and even in non-diabetic cohorts[12].

Longitudinal studies have indicated that elevated serum TyG levels are independently associated with an increased incidence of chronic heart failure[9,15]. However, its impact and prognostic influence during acute heart failure remain inadequately explored. This study was therefore designed to observe baseline Serum Triglyceride Glucose index (TyG) levels among consecutive patients admitted with AHF and evaluate its short-term, in-hospital prognostic significance alongside conventional clinical and bio-assay markers.

Material and Methods

Study Setting and Design

This study was designed as a single-center, prospective observational study in the Cardiac Care Unit (CCU) of Manipal Hospitals, Bangalore, India. The study period was 12 months following approval from the institutional scientific and ethics committees.

Study Population

Consecutive adult patients presenting with symptoms requiring admission for AHF were screened.

- **Inclusion Criteria:** Adult patients aged more than 18 years presenting with acute-onset breathlessness accompanied by clinical hallmarks of systemic/ pulmonary congestion (e.g., elevated jugular venous pressure, distended neck veins, severe bilateral pedal oedema, and basal crepitations) matching the structural definition of heart failure outlined by the ACC/AHA guidelines.
- **Exclusion Criteria:** AHF secondary to congenital, rheumatic and valvular heart diseases; advanced malignancy or ongoing chemotherapy regimens; active systemic sepsis, acute respiratory distress syndrome (ARDS), pulmonary embolism; liver cirrhosis; pancreatitis; pregnancy; and end-stage renal disease.

Data Collection and Laboratory Analysis

Comprehensive data of clinical presentation, detailed background history, demographic details, and physical examination was documented in a pre-defined proforma. Peripheral venous blood samples were drawn after an overnight fasting window (>10 hours) during the first morning of admission.

Laboratory and other investigation parameters were collected from the institutional electronic database.

**Senior Resident, Department of General Medicine, JSS Medical College, Mysuru - 571 134, Karnataka, **Senior Consultant and Head, Department of Internal Medicine, ***Senior Consultant, Department of Cardiology, Manipal Hospital, Old Airport Road, Bengaluru - 560 017, Karnataka.*

Corresponding Author: Dr Manjunath S, Senior Resident, Department of General Medicine, JSS Medical College, Mysuru - 571 134, Karnataka. Tel: 9738408496, E-mail: sripathymanjunathan561996@gmail.com

Study Outcomes

The primary outcomes tracked were: in-hospital mortality or clinical stability resulting in successful discharge. Secondary clinical endpoints included the specific requirement for and total duration of advanced organ supports, including intravenous inotropes, vasopressors, non-invasive ventilation (NIV), invasive mechanical ventilation (IMV), and intra-aortic balloon pump (IABP) counterpulsation.

Statistical Analysis

Sample size was calculated using Cochran's equation based on an expected historical in-hospital mortality rate of 13% for patients with AHF, yielding a target sample size of 148. Following exclusions and attrition of the sample, a final cohort of 140 patients was analysed. Continuous variables were expressed as Mean ± Standard Deviation (SD) or Median, while categorical variables were summarised as frequencies and relative percentages. Statistical significance was defined at a threshold of alpha = 0.05. Categorical parameters were assessed using Chi-Square and Fisher's Exact tests. Differences in non-parametric data were analysed using the Kruskal-Wallis test. Spearman-rank correlation matrices were constructed to evaluate variables against survival endpoints and explore inter-variable relationships. Receiver Operating Characteristic (ROC) curve analysis evaluated the area under the curve (AUC) and identified optimal biomarker cut-offs via Youden's index. Odds Ratios (OR) with corresponding 95% confidence intervals were derived to evaluate mortality risks. All statistics were computed using standard packages.

Results

Demographic and Clinical Baseline Profiles

A final cohort of 140 consecutive patients was successfully evaluated and consisted of 90 males (64%) and 50 females (36%). The overall mean age of the study group was 67 ± 11.4 years (range: 36 - 90 years), as shown in Fig. 1. Non-survivors were significantly older than survivors (73.6 ± 8.54 years *versus* 66.1 ± 11.45 years; p = 0.009). Patient gender demonstrated no significant prognostic relationship with in-hospital mortality (p = 1.0).

Cardio-metabolic comorbidities were highly prevalent across the cohort: 101 patients (72.1%) had type 2 diabetes mellitus with 33 (32.6%) using insulin therapy, 93 (66.4%) had systemic hypertension, 58 (41.4%) had established CAD, 51 (36.4%) had a history of chronic heart failure, and 23 (16.4%) had hypothyroidism. No statistically significant differences were observed in comorbidity distribution, insulin usage, or daily insulin doses between survivors and non-survivors.

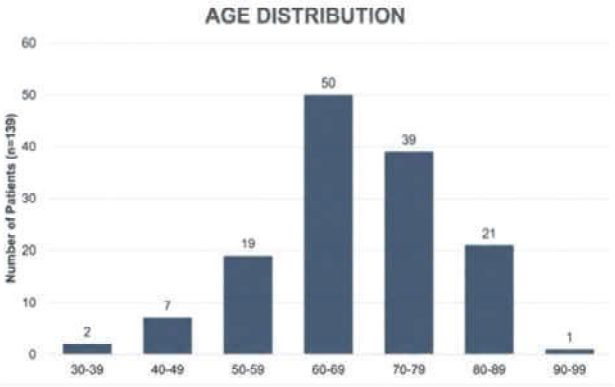


Fig. 1: *Age-wise distribution of the study population.*

Physical Examination, Admission Findings, and Echocardiography

Severe dyspnoea was highly prevalent, with 77 patients (55.0%) classified as NYHA functional class 4 at presentation. Physical examination revealed bilateral basal crackles in 133 patients (95.0%) and peripheral pitting oedema in 89 patients (63.6%). Haemodynamically, 36 patients (25.7%) presented with an SBP <115 mmHg. Mean qSOFA scores were significantly higher in non-survivors than in survivors (1.22 ± 0.43 *versus* 0.93 ± 0.52; p = 0.023).

On electrocardiography at admission, acute ischaemic ST-segment changes were identified in 36 cases (25.7%), predicting significantly increased odds of mortality (OR: 3.5, p = 0.019). Echocardiographic evaluation categorised 89 patients (63.6%) as HFrEF, 26 (18.6%) as HFmrEF, and 25 (17.9%) as HFpEF. The overall mean LVEF was 37% ± 10.4%, which did not differ significantly between survivors and non-survivors (p = 0.844). Left ventricular diastolic dysfunction was present in all 140 patients, with severe grade 3 LVDD identified in 52 individuals (37.1%).

Metabolic Profile Distributions and Biomarker Assay Performance

Difference in mean values of different parameters is shown in Table I and the Box and whisker's plot in Figs. 2 and 3. The mean TyG index for the entire study population was 9.12 ± 0.71. When applying a reference cut-off for insulin resistance (TyG of 8.8 based on previous study), 88 patients (62.9%) were categorised as insulin resistant. In this group, 12 deaths were recorded compared to 6 deaths in the low-TyG cohort, representing a statistically non-significant difference in in-hospital mortality rates (OR: 1.21, p = 0.799). Mean TyG values in subpopulations are shown in Table II. Segmented evaluations across diabetic, non-diabetic, active acute coronary syndrome, and chronic ischemic heart disease cohorts confirmed that a TyG threshold of 8.8 did not significantly alter diagnostic predictive accuracy.

Table I: Mean values of parameters (Survivors *versus* Non-Survivors).

Variables	Died (Mean ± SD)	Survived (Mean ± SD)	Total Pool (Mean ± SD)	p-Value (Two-Tailed)
Ejection Fraction (EF%)	37.2 ± 10.3	36.98 ± 10.4	37.0 ± 10.4	0.844
PASP (mmHg)	44.2 ± 13.8	42.7 ± 13.6	42.9 ± 13.6	0.660
Serum Creatinine (mg/dL)	1.64 ± 0.75	1.40 ± 0.89	1.43 ± 0.88	0.084
Blood Urea Nitrogen (mg/dL)	25.8 ± 14.8	22.3 ± 20.9	22.8 ± 20.2	0.188
Total Cholesterol (mg/dL)	143.6 ± 36.7	144.7 ± 41.7	144.6 ± 40.9	0.869
LDL Cholesterol (mg/dL)	82.7 ± 23.3	87.6 ± 36.6	87.0 ± 35.1	0.968
HDL Cholesterol (mg/dL)	39.5 ± 15.4	37.5 ± 9.8	37.8 ± 10.7	0.784
Fasting Blood Sugar (mg/dL)	192.6 ± 87.0	167.5 ± 83.3	170.7 ± 83.9	0.186
Serum Triglycerides (mg/dL)	132.0 ± 66.0	130.5 ± 62.1	130.7 ± 62.4	0.965
Fasting TyG Index	9.20 ± 0.80	9.10 ± 0.70	9.10 ± 0.70	0.413
HbA1c (%)	8.1±2.1	8.0 ± 2.0	8.0 ± 2.0	0.955
NT-proBNP (pg/mL)	11730 ± 9979	9641 ± 12852	9910 ± 12508	0.117
hs-Troponin I (pg/mL)	5284 ± 10926	3083 ± 15134	3366 ± 14647	**0.009**
AST (U/L)	90.4 ± 132.6	51.3 ± 164.6	56.29 ± 161.0	**0.004**
ALT (U/L)	90.7 ± 160.5	47.8 ± 148.2	53.3 ± 149.9	**0.008**
Serum Uric Acid (mg/dL)	6.8 ± 3.1	5.7 ± 2.3	5.87 ± 2.45	0.281

Note: Evaluated using Kruskal-Wallis non-parametric ANOVA variations.

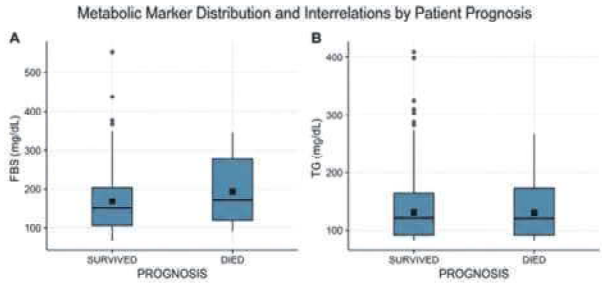


Fig. 2: *Box and whiskers plot showing mean FBS among survivors versus non-survivors.*

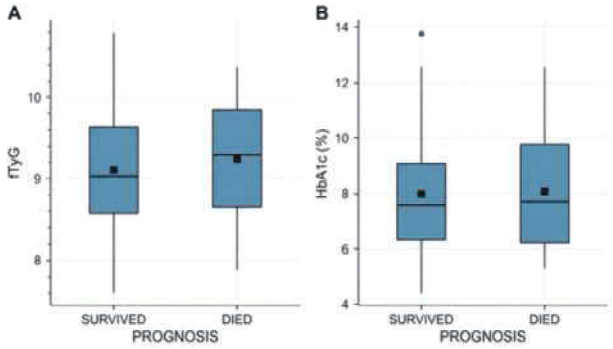


Fig. 3: *Box and whiskers plot showing mean TyG and HbA1c among survivors versus non-survivors.*

Aetiological Diagnoses and Mechanical Support Requirements

The dominant aetiology driving AHF was ischaemic heart disease (IHD), accounting for 113 cases (80.7%), followed by dilated cardiomyopathy (DCM; n = 10, 7.1%). Acute coronary syndromes (ACS) were present in 62 presentations (44.3%), consisting of 24 ST-elevation myocardial infarctions (STEMI), 36 non-ST-elevation myocardial infarctions (NSTEMI), and 2 unstable angina presentations. The presence of an active ACS event significantly increased overall in-hospital mortality (p = 0.046). Concurrently, 77 patients required emergency percutaneous coronary interventions (PCI) during hospital stay.

Duration of hospitalisation and requirements of organ support is shown in Table III. Advanced organ support was common: 83 patients (59.3%) required active intravenous inotropic infusions, 36 (25.7%) required vasopressors, 46 (32.9%) required non-invasive positive pressure ventilation (NIV), and 25 (17.9%) required invasive mechanical ventilation. No statistically significant differences were observed in the total duration or relative incidence of mechanical ventilation, vasopressor use, or inotropic support when partitioning the cohort using the baseline TyG index threshold of 8.8 or the ROC-derived threshold of 9.28.

Table II: Mean TyG values in subpopulations

Sub-Population	Died (Mean ± SD)	Survived (Mean ± SD)	Total (Mean ± SD)	p-Value
TyG in Diabetics	9.42 ± 0.71	9.27 ± 0.70	9.28 ± 0.70	0.438
TyG in Non-Diabetics	8.79 ± 0.82	8.69 ± 0.54	8.70 ± 0.57	0.850
TyG in ACS Patients	9.42 ± 0.83	9.20 ± 0.63	9.24 ± 0.67	0.269
TyG in Non-ACS Patients	8.89 ± 0.57	9.03 ± 0.75	9.02 ± 0.74	0.722
TyG in Ischemic Heart Disease	9.31 ± 0.78	9.16 ± 0.69	9.18 ± 0.70	0.390

Note: Evaluated using Kruskal-Wallis Test.

Table III: Duration of hospitalisation and requirement for organ support.

Component	Minimum (Days)	Maximum (Days)	Mean (Days)	Median (Days)	Standard Deviation
Total Hospitalisation	1	22	5.0	4	2.8
Intravenous Inotrope	0	8	1.2	1	1.4
Vasopressor Support	0	7	0.5	0	1.1
Invasive Mechanical Ventilation (IMV)	0	5	0.4	0	1.0
Non-Invasive Ventilation (NIV)	0	8	0.6	0	1.1
Intra-Aortic Balloon Pump (IABP)	0	4	0.1	0	0.5

Correlation Modeling and Discriminative ROC Curve Analysis

Table IV shows Spearman Rank-Order correlation of key parameters against in-hospital mortality. Only baseline qSOFA scores (rho = 0.193, p = 0.022), hs-Trop-I (rho = 0.221, p = 0.009), AST (rho = 0.245, p = 0.004), and ALT (rho = 0.226, p = 0.007) statistically correlated with in-hospital mortality. The TyG index did not correlate with clinical outcomes (rho = 0.069, p = 0.415).

Table IV: Spearman Rank-order correlation of key parameters against in-hospital mortality.

Parameter	Spearman's Rho (rho)	p-Value
TyG Index	0.069	0.415
NT-proBNP	0.133	0.188
qSOFA Score	0.193	0.022
hs-Trop-I	0.221	0.009
LVEF	0.017	0.845
AST	0.245	0.004
ALT	0.226	0.007
Serum Creatinine	0.147	0.084

Table V shows correlation between various study parameters. Within the study parameters, TyG index correlated with HbA1c (rho = 0.529, p <0.001), but showed no correlation with active markers of myocardial wall stretch (NT-proBNP) or baseline haemodynamic variables (LVEF and LVDD).

Mortality prediction by various parameters was analysed using the Receiver Operating Characteristic curve as shown in Fig. 4. Table VI shows ROC Curve Analysis for Mortality for various parameters. Table VII shows in-hospital mortality odds ratios for ROC-derived cut-off targets. Using the ROC-optimised TyG cut-off of 9.28, the resulting mortality risk calculation (OR: 1.86, p = 0.300) remained non-significant even when evaluated among subgroups. Conversely, risk ratios remained highly significant for elevated transaminases above their respective ROC cut-offs (ALT OR:

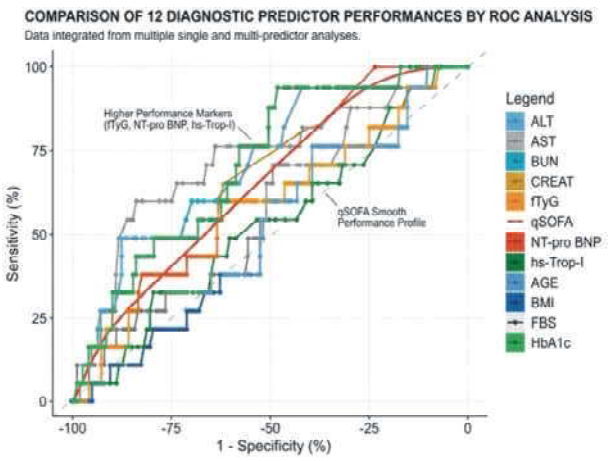


Fig. 4: *Composite ROC analysis comparing different biomarkers and clinical parameters.*

Table V: Comprehensive multi-variable matrix of inter-parameter correlation profiles.

Parameter	Metric	TyG	NT-proBNP	LVEF	AST	ALT	hs-Trop-I
NT-proBNP	rho	-0.072	–	–	–	–	–
	p	0.399	–	–	–	–	–
LVEF	rho	0.121	-0.303	–	–	–	–
	p	0.155	**<0.001**	–	–	–	–
AST	rho	-0.041	0.174	-0.169	–	–	–
	p	0.634	0.039	0.046	–	–	–
ALT	rho	-0.008	0.071	-0.227	0.832	–	–
	p	0.924	0.406	**0.007**	**<0.001**	–	–
hs-Troponin I	rho	0.120	0.330	-0.096	0.190	0.203	–
	p	0.158	**<0.001**	0.261	**0.025**	**0.016**	–
qSOFA Score	rho	-0.002	0.220	-0.095	0.171	0.107	0.165
	p	0.979	**0.009**	0.262	**0.044**	0.208	0.052
Serum Creatinine	rho	0.109	0.374	0.004	0.071	0.028	0.201
	p	0.199	**<0.001**	0.960	0.405	0.739	**0.017**
BUN	rho	0.056	0.401	-0.031	0.101	0.001	0.169
	p	0.509	**<0.001**	0.714	0.234	0.989	**0.045**
LVDD Grade	rho	-0.149	0.118	-0.372	0.014	0.019	-0.082
	p	0.078	0.166	**<0.001**	0.871	0.820	0.333
BMI	rho	-0.137	-0.096	0.057	0.035	-0.028	-0.028
	p	0.107	0.260	0.507	0.677	0.744	0.744
HbA1c	rho	0.529	-0.054	0.012	-0.062	-0.066	0.116
	p	**<0.001**	0.525	0.885	0.468	0.442	0.171
Serum Uric Acid	rho	-0.093	0.093	0.003	-0.070	-0.086	-0.071
	p	0.276	0.274	0.972	0.410	0.313	0.403

Table VI: Receiver operating characteristic curve analysis for mortality evaluation.

Tested Parameter	AUC	Youden Cut-off	Sensitivity (%)	Specificity (%)
AST	0.711	44	61.1	82.8
ALT	0.695	53	50.0	86.9
hs-Troponin I	0.691	74 pg/mL	94.4	43.4
Age	0.691	64 Years	94.4	34.4
qSOFA Score	0.629	2	100.0	17.2
Serum Creatinine	0.626	2.04 mg/dL	33.3	90.2
NT-proBNP	0.615	6440 pg/mL	72.2	55.7
BUN	0.596	29 mg/dL	38.9	82.8
Fasting Blood Sugar	0.563	101 mg/dL	100.0	21.3
TyG Index	0.560	9.28	61.1	59.8
LVDD Grade	0.543	2	100.0	10.7
LVEF (%)	0.514	41%	50.0	68.0
HbA1c (%)	0.504	9.7%	33.3	77.9
BMI (kg/m^2)	0.486	24.5	77.8	35.3

Table VII: In-hospital mortality odds ratios for ROC-derived cut-off targets.

Parameter	Died (n)	Survived (n)	Total	p-Value
TyG Index				0.300 (OR = 1.86)
<9.28	8	73	81	
≥9.28	10	49	59	
NT-proBNP (pg/mL)				0.080 (OR = 2.50)
<6440	6	68	74	
≥6440	12	54	66	
hs-Troponin I (pg/mL)				**0.009** (OR = 6.35)
<74	2	54	56	

≥74	16	68	84	
AST (U/L)				**<0.001** (OR = 6.37)
<44	8	102	110	
≥44	10	20	30	
ALT (U/L)				**<0.001** (OR = 6.60)
<53	9	106	115	
≥53	9	16	25	
Serum Creatinine (mg/dL)				**0.045** (OR = 3.50)
<2.04	13	110	123	
≥2.04	5	12	17	
BUN (mg/dL)				**0.020** (OR = 3.70)
<29	11	104	115	
≥29	7	18	25	
qSOFA Score				0.130 (OR = 2.60)
<2	14	110	124	
≥2	4	12	16	
LVEF (%)				0.590 (OR = 1.46)
<41%	11	85	96	
≥41%	7	37	44	

6.6, p <0.001; AST OR: 6.37, p <0.001) and hs-Trop-I levels exceeding 74 pg/mL (OR: 6.35, p = 0.009). Table VIII shows subgroup mortality signatures for ROC-Optimised TyG Cut-Off. Table IX shows organ support incidences predicted by ROC-Derived TyG Index cut-off. Requirements of organ support remained statistically insignificant even when ROC derived TyG cut-off was used for analysis.

Table VIII: Subgroup mortality signatures tracked by ROC-optimised TyG (9.28) cut-off.

Patient Subpopulation	Died (n)	Survived (n)	Total Subset Size	p-Value
Diabetic	13	88	101	0.560 (OR = 1.60)
– TyG <9.28	5	44	49	
– TyG ≥9.28	8	44	52	
Non-Diabetic	5	34	39	0.200 (OR = 3.90)
– TyG <9.28	3	29	32	
– TyG ≥9.28	2	5	7	
ACS	12	50	62	0.200 (OR = 2.30)
– TyG <9.28	4	27	31	
– TyG ≥9.28	8	23	31	
Non-ACS	6	72	84	1.000 (OR = 0.88)
– TyG <9.28	4	46	50	
– TyG ≥9.28	2	26	28	
Ischaemic Aetiology (IHD) Pool	16	97	113	0.400 (OR = 1.68)
– TyG <9.28	7	55	62	
– TyG ≥9.28	9	42	51	

Note: Evaluated via Fisher's Exact Test.

Table IX: Organ support incidences predicted by ROC-derived TyG index threshold (9.28).

Critical Care Intervention	Support Needed (Yes)	Support Not Needed (No)	p-Value
Intravenous Inotropes	83	57	-0.220 (OR = 0.60)
– TyG <9.28	52	29	
– TyG ≥9.28	31	28	
Vasopressors	36	104	0.300 (OR = 1.50)
– TyG <9.28	18	63	

Discussion

This prospective observational study sought to characterise the presence of metabolic insulin resistance in patients presenting with AHF using the TyG index, comparing its performance with conventional critical care biomarkers. Insulin resistance is known to accelerate coronary atherogenesis, promote macrovascular dysfunction, and induce subclinical myocardial fibrosis[13]. However, our data indicate that these metabolic indicators do not retain significant independent prognostic power during AHF.

Our study cohort had 72.1% prevalence of type 2 diabetes mellitus and an 80.7% prevalence of underlying ischaemic heart disease. These baseline rates are higher than those documented in national heart failure registers, such as the Trivandrum Heart Failure Registry (THFR; DM 55%, IHD 72%) or the National Heart Failure Registry (NHFR; DM 42.5%)[14,1]. This concentration of metabolic risk factors likely stems from our setting as a tertiary referral care facility and our deliberate exclusion of structural congenital or valvular rheumatic heart conditions.

Applying the baseline TyG index threshold of 8.8[12], nearly two-thirds (62.9%) of our AHF cohort showed insulin resistance whereas more than that had diabetes which is a known insulin resistant state. However, this categorisation failed to show a statistically significant correlation with in-hospital mortality or the length and intensity of active mechanical or pharmacological organ supports. Even when refining the index via ROC analysis to an optimized cut-off of 9.28, the resulting trend toward higher mortality remained statistically non-significant (OR: 1.86, p = 0.300).

This lack of acute predictive power contrasts with long-term follow-up registers but aligns with observations made

by other critical care registries. For instance, an evaluation of TyG performance in multi-systemic non-surgical intensive care cohorts found that while elevated TyG indices predicted adverse outcomes in isolated acute coronary syndromes, they showed an inverse relationship in decompensated heart failure presentations[10]. A key confounding factor in our patient cohort was the widespread use of baseline statin therapy (53%), which can alter serum triglyceride fractions independent of underlying peripheral insulin sensitivity. Furthermore, the short-term clinical course of AHF is dominated by immediate hemodynamic shifts, neurohormonal overactivation, and acute multi-organ congestion, which can mask the slower, chronic cellular effects of insulin signaling pathways.

In contrast to metabolic indices, biomarkers reflecting acute congestion, systemic hypoperfusion, and localised cellular stress demonstrated strong prognostic utility. The admission qSOFA score significantly correlated with higher in-hospital mortality, supporting the concept that acute heart failure shares clinical similarities with systemic critical illnesses like severe sepsis or ARDS regarding explosive onset and organ support requirements.

Notably, hepatic aminotransferases (AST and ALT) emerged as the strongest independent predictors of in-hospital mortality within our cohort[11]. Elevated AST (>44 U/L) and ALT (>53 U/L) levels were associated with a 6.3-fold and 6.6-fold increase in in-hospital mortality risk, respectively. This clinical finding highlights the severe impact of acute hepatic congestion and secondary systemic hypoperfusion (shock liver) as major drivers of early mortality in acute heart failure.

Conclusion

Although nearly two-thirds of patients presenting with AHF displayed features of systemic insulin resistance, the TyG index did not serve as a statistically reliable prognostic marker for in-hospital mortality or immediate organ support requirements during the acute phase of decompensation. Traditional markers of systemic strain, acute myocardial injury, and secondary hepatic congestion-specifically qSOFA, hs-Trop-I, AST, and ALT remained superior for early risk stratification. Further multi-center investigations are needed to determine whether surrogate markers of insulin resistance provide better utility for long-term tracking after initial haemodynamic stabilisation.

References

1. Huffman MD, Prabhakaran D. Heart failure: epidemiology and prevention in India. *Natl Med J India* 2010; 23 (5): 283-8.
2. Givertz MM, Mehra MR. Heart Failure: Pathophysiology and Diagnosis. In: Harrison's Principles of Internal Medicine. 21st ed. New York, NY: McGraw-Hill Education; 2022.
3. Desai AS, Mehra MR. Heart Failure: Management. In: Harrison's Principles of Internal Medicine. 21st ed. New York, NY: McGraw-Hill Education; 2022.
4. Aroor AR, Mandavia CH, Sowers JR. Insulin Resistance and Heart Failure: Molecular Mechanisms. *Heart Fail Clin* 2012; 8 (4): 609-17.
5. Riehle C, Abel ED. Insulin Signaling and Heart Failure. *Circ Res* 2016; 118 (7): 1151-69.
6. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* 1979; 237 (3): E214-223.
7. Du T, Yuan G, Zhang M. Clinical usefulness of lipid ratios, visceral adiposity indicators, and the triglycerides and glucose index as risk markers of insulin resistance. *Cardiovasc Diabetol* 2014; 13: 146.
8. Er LK, Wu S, Chou HH *et al*. Triglyceride Glucose-Body Mass Index Is a Simple and Clinically Useful Surrogate Marker for Insulin Resistance in Nondiabetic Individuals. *PLoS One* 2016; 11 (3): e0149731.
9. Zeng X, Han D, Zhou H *et al*. Triglyceride-Glucose Index and Homeostasis Model Assessment-Insulin Resistance in Young Adulthood and Risk of Incident Congestive Heart Failure in Midlife. *Front Cardiovasc Med* 2022; 9: 918440.
10. Huang R, Wang Z, Chen J *et al*. Prognostic value of triglyceride glucose (TyG) index in patients with acute decompensated heart failure. *Cardiovasc Diabetol* 2022; 21: 88.
11. Vakilian F, Rafighdoost AA, Rafighdoost AH. Liver Enzymes and Uric acid in Acute Heart Failure. *Res Cardiovasc Med* 2015; 4 (4): e22988.
12. Unger G, Benozzi SF, Perruzza F. Triglycerides and glucose index: a useful indicator of insulin resistance. *Endocrinol Nutr* 2014; 61 (10): 533-40.
13. Chiu TH, Tsai HJ, Chiou HYC. A high triglyceride-glucose index is associated with left ventricular dysfunction and atherosclerosis. *Int J Med Sci* 2021; 18 (4): 1051-7.
14. Harikrishnan S, Sanjay G, Anees T *et al*. Clinical presentation, management, in-hospital and 90-day outcomes of heart failure patients in Trivandrum, Kerala, India: the Trivandrum Heart Failure Registry. *Eur J Heart Fail* 2015; 17 (8): 794-800.
15. Guo W, Zhao L, Mo F *et al*. The prognostic value of the triglyceride glucose index in patients with chronic heart failure and type 2 diabetes: A retrospective cohort study. *Diabetes Res Clin Pract* 2021; 177: 108786.

ORIGINAL ARTICLE

JIACM 2026; 27 (3): 178-85

Spirometric Indices in Adults with Type 2 Diabetes Mellitus: A Hospital-Based Comparative Cross-Sectional Study

Rahul Garg, Prashant Prakash**, Mohd Abid***, Piyush Tageja*****

Abstract

***Background:** Type 2 diabetes mellitus (T2DM) may be associated with subclinical pulmonary dysfunction, but reported magnitudes vary widely, in part because studies differ in the reference equations and abnormality thresholds applied.*

***Material and Methods:** This hospital-based comparative cross-sectional study included 100 adults with T2DM and 100 age- and sex-matched controls at a tertiary care centre from March 2024 to May 2026. Participants were non-smokers aged 30 - 65 years without known cardiac or respiratory disease. Spirometry followed Indian Chest Society-National College of Chest Physicians (ICS-NCCP) and ATS/ERS standards. All indices – FVC, FEV1, FEV1/FVC, PEF and FEF25-75 – were referenced to a single published north Indian equation set, and abnormality was defined exclusively by the statistically derived lower limit of normal (LLN = predicted - 1.645* SEE). Fixed cut-offs were entirely omitted from definitions. Because total lung capacity was not measured, a low FVC with a preserved ratio was described as a low-volume spirometric pattern, not confirmed restriction. Comparisons used Welch's t-test, the chi-square test with an unconditional odds ratio, and Pearson correlations.*

***Results:** Adults with T2DM had lower FVC (2.52 ± 0.68 L versus 3.06 ± 0.72 L; mean difference -0.54 L; 95% CI -0.74 to -0.35) and FEV1 (2.11 ± 0.58 L versus 2.50 ± 0.61 L; -0.39 L; 95% CI -0.56 to -0.23). Expressed as per cent predicted, deficits were -17.1 percentage points for FVC (95% CI -20.2 to -13.9) and -16.8 for FEV1 (95% CI -21.1 to -12.6); p <0.001 for each. The FEV1/FVC ratio was marginally higher in the T2DM group (+1.6 percentage points; 95% CI +0.2 to +3.0; p = 0.023). Using the statistical LLN criteria, a low-volume pattern occurred in 56% of the T2DM group and 5% of controls (OR 24.18; 95% CI 9.06 to 64.57). No participant in either group exhibited an FEV1/FVC ratio below its LLN. Within the T2DM cohort, FVC and FEV1 correlated inversely with HbA1c and diabetes duration.*

***Conclusions:** Non-smoking adults with T2DM showed lower spirometric volumes with a preserved FEV1/FVC ratio and a frequent low-volume pattern. These cross-sectional findings are compatible with pulmonary involvement in T2DM but do not establish true restrictive ventilatory defects, which require lung-volume measurement.*

***Key words:** Type 2 diabetes mellitus, spirometry, forced vital capacity, lower limit of normal, reference equations.*

Introduction

Diabetes mellitus remains an expanding global health challenge. The International Diabetes Federation estimates that 589 million adults aged 20 - 79 years were living with diabetes in 2024, projected to reach 853 million by 2050[1]. Renal, retinal, neural and cardiovascular complications are thoroughly characterised; pulmonary involvement has received less attention[2,3].

The lung is plausibly susceptible to chronic hyperglycaemia. Non-enzymatic glycation can alter structural collagen and elastin, and microangiopathy can thicken the alveolar-capillary basement membrane[2-5]. These changes could reduce lung compliance, compromise elastic recoil, lower respiratory-muscle performance or impair gas transfer. Spirometry alone; however, cannot distinguish true restriction from submaximal inspiration, gas trapping, respiratory-muscle weakness or technical limitation; confirmation requires measurement of total lung capacity (TLC)[6].

Meta-analyses report modest reductions in FVC, FEV1 and expiratory flows in diabetes, typically with a preserved FEV1/FVC ratio[7-9]. Hospital-based series report larger deficits, with inconsistent associations with glycated haemoglobin (HbA1c) and diabetes duration[10-16]. Two major methodological choices plausibly contribute to this heterogeneity and are rarely made explicit. First, spirometers marketed in India commonly default to Caucasian reference equations; a study of 14,733 consecutive Indian spirometry records showed that Caucasian equations, and the widely used practice of 'ethnic discounting' by 10%, produce poor agreement with Indian equations and misclassify a substantial proportion of records[17]. Second, fixed thresholds (such as FVC <80%

**Professor, ***Post-Graduate Resident, Department of Medicine, FH Medical College and Hospital, Agra - 283 204, Uttar Pradesh, **Professor and Head, Department of Pulmonary Medicine, SN Medical College, Agra - 282 002, Uttar Pradesh, ****Senior Resident, Department of Medicine, Mahabodhi Medical College, Naknupa, Gaya - 824 211, Bihar.*

***Corresponding Author:** Dr Rahul Garg, Professor, Department of Medicine, FH Medical College and Hospital, Agra - 283 204, Uttar Pradesh. Tel:9012114542 , E-mail: gargrahul27@gmail.com*

predicted or FEV1/FVC <0.70) remain in common use despite a Grade 1A recommendation favouring statistically derived lower limit of normal (LLN) criteria[6]. Fixed numbers misalign with true statistical boundaries across different indices, generating compounding diagnostic distortion.

This study compared spirometric indices between adults with T2DM and frequency-matched controls, deriving every index from a single north Indian reference equation set and characterising clinical abnormality exclusively through statistically derived population-specific LLN thresholds, while examining unadjusted associations with HbA1c and diabetes duration.

Material and Methods

Study Design, Setting and Ethics

This hospital-based comparative cross-sectional study was conducted in the Department of General Medicine at a tertiary care centre from March 2024 to May 2026. The protocol was approved by the Institutional Ethics Committee (Approval number: FHMC/IEC/R.Cell/2024/32). All participants gave written informed consent.

Participants

Adults aged 30 - 65 years with T2DM were recruited by consecutive sampling; T2DM was diagnosed per American Diabetes Association criteria[18]. Controls without diabetes were recruited from the outpatient health check-up clinic and from patient attendants, and were frequency-matched to the T2DM cohort by age and sex. Absence of diabetes was verified by fasting plasma glucose <100 mg/dL and HbA1c <5.7%.

Exclusion criteria for all participants: current or past smoking; known asthma, chronic obstructive pulmonary disease, interstitial lung disease, or previous/active tuberculosis; ischaemic heart disease, valvular heart disease or heart failure; chest-wall or spinal deformity; neuromuscular disease; body mass index (BMI) >30 kg/m^2; occupational exposure to hazardous dust or fumes; pregnancy; acute respiratory tract infection within four weeks; or any contraindication to spirometry[6].

A target of 100 participants per group was set *a priori* for the primary outcome (FVC per cent predicted), to detect a minimum clinically important difference of 5 percentage points assuming SD 11%, two-sided alpha 0.05 and 80% power (requiring 76 per group), with allowance for 10% unusable or unrepeatable tests.

Participant Flow

Of 145 individuals with T2DM screened, 45 were excluded (BMI >30 kg/m^2, n = 23; former or current smoking, n = 12; asthma or tuberculosis, n = 10), leaving 100 enrolled. Of 130 potential controls, 30 were excluded (unrecognised dysglycaemia, n = 18; smoking history, n = 8; active respiratory symptoms, n = 4), leaving 100. All 200 participants completed testing with no missing data for primary or secondary outcomes.

Clinical and Laboratory Assessment

All participants underwent history and standardised examination. Height was measured to the nearest 1 mm on a calibrated stadiometer with the head in the Frankfort plane, as recommended[6]; weight was measured on a calibrated electronic scale; BMI was calculated as weight (kg) divided by height (m) squared. Fasting plasma glucose was measured by the glucose oxidase-peroxidase method and HbA1c by high-performance liquid chromatography. Diabetes duration was taken from the verified date of clinical diagnosis.

Spirometry

Spirometry was performed with an EasyOne Pro spirometer (ndd Medical Technologies, Zurich, Switzerland) running EasyOne Connect software, by a trained technician, with the participant seated, per ICS-NCCP and ATS/ERS standards[6,19]. Volume validation with a 3-L syringe was performed daily (acceptance ± 3.5%), with weekly linearity checks; a log of all validation data was maintained.

Pre-test restrictions: short-acting bronchodilators withheld 6 h, long-acting bronchodilators 24 h, caffeine-containing products 6 h, alcohol 4 h, large meals 2 h and vigorous exercise 30 min before testing[6]. Testing was pre-bronchodilator. At least three acceptable and two repeatable manoeuvres were obtained (largest two FVC and largest two FEV1 within 150 mL), to a maximum of eight attempts. The largest acceptable FVC and largest acceptable FEV1 were recorded, whether or not from the same manoeuvre[6]. All curves were visually inspected before numerical acceptance.

Reference Values and Definition of Abnormality

Manufacturer-supplied predicted values were not used. Instead, all raw values were exported and predicted values for every index - FVC, FEV1, FEV1/FVC, PEF and FEF25-75 – were computed offline from the equations of Chhabra *et al* for adults of north Indian origin, which were derived under the 2005 ATS/ERS standardisation protocol[20]. This preserves the requirement that all reported parameters derive from a single reference source[6]. For indices modelled on the natural-log scale, predicted values were obtained as exp(Ln-predicted + 1/2 SEE2) per the source appendix. The female

PEF equation is printed in the source table without an 'Ln' prefix; its coefficients and SEE are only interpretable on the log scale (the linear reading returns physiologically impossible values of ~1.6 L/s), and it was therefore treated as log-transformed, consistent with the corresponding male equation.

Abnormality was defined exclusively as an observed value below its lower limit of normal (LLN), calculated strictly as predicted - 1.645* SEE, using the SEE published for each specific equation[6,20]. Universal fixed per cent-predicted cut-offs were completely excluded to clear the methodology of mathematical categorisation bias. For log-transformed indices, LLN was computed in log space and back-transformed. In this cohort the LLN corresponded, on average, to 78.7% of predicted for FVC, 75.2% for FEV1, 73.9% for PEF and 59.9% for FEF25-75; the LLN for FEV1/FVC averaged 65.6% in absolute terms.

Spirometric configurations were categorised into physiological patterns based purely on these statistical LLN thresholds: low-volume pattern, FVC < LLN with FEV1/FVC > = LLN; low-ratio pattern, FEV1/FVC < LLN with FVC > = LLN; and combined pattern, both parameters falling below their respective LLN thresholds. Consistent with guideline wording, a low-volume pattern is reported as suggestive of a restrictive ventilatory defect and is not diagnostic of one[6]. FEV1, FVC and FEV1/FVC were pre-specified as the interpretive variables. PEF and FEF25-75 were pre-specified as exploratory and are reported for descriptive completeness only, since guidelines do not recommend FEF25-75 for clinical interpretation[6,21].

Statistical Analysis

Continuous variables were expressed as mean ± SD, categorical variables as counts and percentages. Standardised mean differences (SMD) assessed baseline balance. Because participants were frequency-matched rather than individually linked, independent (unconditional) methods were used throughout. Between-group mean differences were estimated by Welch's independent-samples t-test. Effect sizes are reported as Cohen's d from pooled SD. Pattern distributions determined by the LLN criteria were compared between groups using the chi-square test, and the risk of presenting a low-volume pattern was summarised as an unconditional odds ratio (OR) with a 95% CI. Pearson correlation coefficients (r) with Fisher z-transformed 95% CIs quantified within-group associations. Scatter plots display unadjusted least-squares trend lines for illustration; no regression models were fitted for inference. All tests were two-sided at alpha = 0.05. Analyses used SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). Reporting follows STROBE[22].

Results

Baseline Characteristics

The frequency-matched cohorts were balanced for age, sex, height and BMI (Table I). Mean age was 52.4 ± 8.6 years (T2DM) and 51.8 ± 8.9 years (controls); males comprised 58% of each group. Mean diabetes duration was 7.8 ± 4.5 years and mean HbA1c 8.4 ± 1.6%. Fasting glucose and HbA1c separated the groups as expected.

Table I: Baseline characteristics of adults with type 2 diabetes mellitus and age- and sex-matched controls.

Characteristic	T2DM (n = 100)	Controls (n = 100)	SMD
Age (years)	52.4 ± 8.6	51.8 ± 8.9	0.07
Male sex, n (%)	58 (58)	58 (58)	0.00
Height (cm)	162.7 ± 8.7	163.0 ± 8.3	0.04
Weight (kg)	65.6 ± 9.8	64.1 ± 9.2	0.16
BMI (kg/m2)	24.6 ± 2.7	24.2 ± 2.5	0.15
Fasting plasma glucose (mg/dL)	168.4 ± 42.6	88.7 ± 9.4	2.58
HbA1c (%)	8.4 ± 1.6	5.2 ± 0.4	2.74
Diabetes duration (years)	7.8 ± 4.5	–	–

Values are mean ± SD unless indicated. –, not applicable, An SMD below 0.10 indicates negligible imbalance.
BMI: body mass index; HbA1c: glycated haemoglobin; SMD: standardised mean difference.

Spirometric Indices

Absolute volumes and flows were lower in the T2DM group (Table II). FVC was reduced by 0.54 L (95% CI -0.74 to -0.35; d = -0.77) and FEV1 by 0.39 L (95% CI -0.56 to -0.23; d = -0.66). The observed FEV1/FVC ratio was marginally higher in the T2DM group (+1.63 percentage points; 95% CI +0.22 to +3.04; p = 0.023; d = +0.32).

Table II: Between-group differences in spirometric indices – absolute values.

Index	T2DM	Controls	Mean difference	95% CI	Cohen's d	p
FVC (L)	2.52 ± 0.68	3.06 ± 0.72	-0.54	-0.74 to -0.35	-0.77	**<0.001**
FEV1 (L)	2.11 ± 0.58	2.50 ± 0.61	-0.39	-0.56 to -0.23	-0.66	**<0.001**
FEV1/FVC (%)	83.8 ± 5.0	82.2 ± 5.1	+1.63	+0.22 to +3.04	+0.32	**0.023**
PEF (L/s)*	4.90 ± 1.52	6.40 ± 1.72	-1.50	-1.96 to -1.04	-0.92	**<0.001**
FEF25-75 (L/s)*	1.66 ± 0.42	1.92 ± 0.51	-0.26	-0.40 to -0.12	-0.56	**<0.001**

*Values are mean ± SD; n = 100 per group. Mean differences and 95% CIs from Welch's independent-samples t-test; Cohen's d calculated from the pooled SD. *Exploratory indices, not recommended for interpretation[6,21].*

Control-group means clustered near 100% of predicted for every volume and flow index (94.3-103.7%; Table III,

Fig. 1), showing the expected behaviour of a healthy reference group when a population-appropriate equation set is applied, and serving as an internal check that the reference source was correctly matched.

Table III: Between-group differences in volume and flow indices, expressed as per cent predicted (Chhabra *et al*)[20].

Index	T2DM	Controls	Mean difference	95% CI	Cohen's d	p
FVC (% predicted)	77.2 ± 12.4	94.3 ± 9.7	-17.06	-20.17 to -13.95	-1.53	**<0.001**
FEV1 (% predicted)	86.9 ± 17.2	103.7 ± 13.2	-16.84	-21.11 to -12.57	-1.10	**<0.001**
PEF (% predicted)*	78.4 ± 16.1	102.1 ± 13.6	-23.70	-27.85 to -19.56	-1.59	**<0.001**
FEF25-75 (% predicted)*	83.9 ± 11.8	96.4 ± 9.1	-12.51	-15.45 to -9.58	-1.19	**<0.001**

*Values are mean ± SD; n = 100 per group. *Exploratory indices. FEV1/FVC is not expressed as percent predicted: per ATS/ERS and ICS-NCCP the ratio is interpreted in absolute terms against its own LLN, and is reported in Table II[6,19].*

Spirometric Patterns

When applying the statistically derived LLN criteria, a low-volume pattern (FVC < LLN with a preserved FEV1/FVC >= LLN) occurred in 56 participants with T2DM (56%) versus 5 controls (5%). This configuration yielded an unadjusted odds ratio of 24.18 (95% CI 9.06 to 64.57; p <0.001) (Table IV). Notably, no participant in either the T2DM or control cohort exhibited an FEV1/FVC ratio below its corresponding LLN. Consequently, no low-ratio (obstructive) or combined spirometric patterns were found within the study population.

Table IV: Distribution of spirometric patterns by LLN criteria.

Pattern	T2DM (n = 100)	Controls (n = 100)
Normal	44 (44%)	95 (95%)
Low-volume (FVC <LLN with FEV1/FVC >= LLN)	56 (56%)	5 (5%)
Low-ratio (FEV1/FVC <LLN with FVC >= LLN)	0 (0%)	0 (0%)
Combined (both parameters <LLN)	0 (0%)	0 (0%)

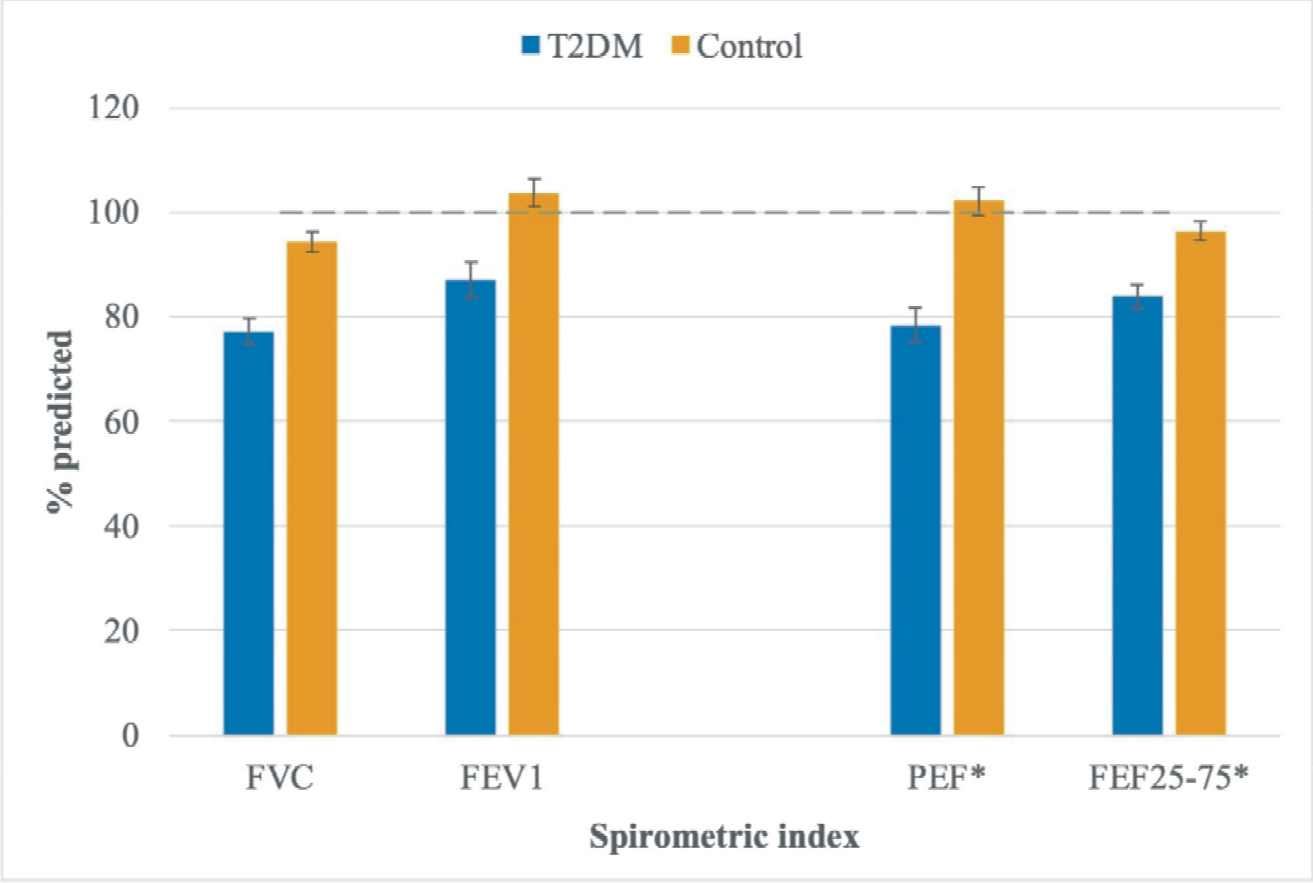


***Fig. 1:** Spirometric indices (per cent predicted) in adults with T2DM (n = 100) and age- and sex-matched controls (n = 100). Bars, group means; error bars, 95% CI. Dashed line marks 100% of predicted. All differences significant (p <0.001). *PEF and FEF25-75 are exploratory indices, shown separately and not recommended for clinical interpretation. FEV1/FVC is not shown, as the ratio is interpreted against its own LLN rather than as per cent predicted.*

*Values are n (%). LLN thresholds: FVC <predicted - 1.645 * SEE; ratio <predicted ratio - 1.645 * SEE. These categories describe spirometric configurations and do not confirm clinical restrictive or mixed ventilatory defects.*

Correlations with Metabolic Factors

Within the T2DM group, volumetric indices correlated inversely with glycaemic control and disease duration (Table V). FVC correlated inversely with HbA1c (r = -0.34; 95% CI -0.50 to -0.15; Fig. 2A) and with diabetes duration (r = -0.35; 95% CI -0.51 to -0.16; Fig. 2B); p < 0.001 for each. HbA1c and diabetes duration each accounted for approximately 12% of the variance in FVC per cent predicted (R^2 = 0.12 for both), indicating that most of the variation in lung volume in this cohort was not explained by either metabolic variable. FEV1 showed similar inverse correlations. The FEV1/FVC ratio showed no meaningful correlation with either parameter.

Table V: Correlations of spirometric indices with HbA1c and diabetes duration (T2DM group, n = 100).

Index	r vs HbA1c	95% CI	p	r vs duration	95% CI	p
FVC	-0.34	-0.50 to -0.15	**<0.001**	-0.35	-0.51 to -0.16	**<0.001**
FEV1	-0.38	-0.54 to -0.20	**<0.001**	-0.31	-0.48 to -0.12	**0.002**
FEV1/FVC	+0.08	-0.12 to +0.27	0.429	+0.06	-0.14 to +0.25	0.553
PEF*	-0.34	-0.50 to -0.15	**<0.001**	-0.28	-0.45 to -0.09	**0.005**
FEF25-75*	-0.30	-0.47 to -0.11	**0.002**	-0.24	-0.42 to -0.05	**0.016**

*Pearson r on per cent predicted. *Exploratory indices. HbA1c and duration were themselves correlated (r = 0.29), so these coefficients are not independent of one another. No adjustment was made for multiple comparisons; these are descriptive associations.*

Discussion

In this cohort, non-smoking adults with T2DM had lower FVC and FEV1 than age- and sex-matched controls, with a preserved – indeed marginally higher – FEV1/FVC ratio. Using the statistical LLN, a low-volume spirometric pattern was present in 56% of the T2DM group versus 5% of controls (OR 24.18), and no participant met LLN criteria for obstruction. Within the T2DM group, FVC and FEV1 correlated inversely with HbA1c and diabetes duration.

A defining feature of this study was that abnormality was judged only against population-specific LLN thresholds rather than fixed cut-offs[6]. Fixed limits such as FVC < 80% predicted or FEV1/FVC < 0.70 do not track the true lower boundary of the healthy range, which shifts with age, sex, height and the index itself, and so misclassify a variable proportion of records[17]. In this cohort the LLN averaged about 79% of predicted for FVC and 66% in absolute terms for the ratio, confirming that no single fixed number can represent the healthy boundary of every index at once. Anchoring the analysis to the LLN therefore makes the higher odds of a low-volume pattern in T2DM a departure from the population's own reference range rather than an artefact of an arbitrary threshold.

The direction of our findings matches the wider literature. Meta-analyses that together cover more than 140 studies report reduced FVC and FEV1 with a preserved FEV1/FVC ratio in diabetes[7-9], and cross-sectional case-control studies from Indian and other populations describe the same reduced-volume, ratio-preserved (restrictive-like) pattern[10,11,23,24]. Our low-volume pattern is therefore consistent with the dominant reading of the field, while

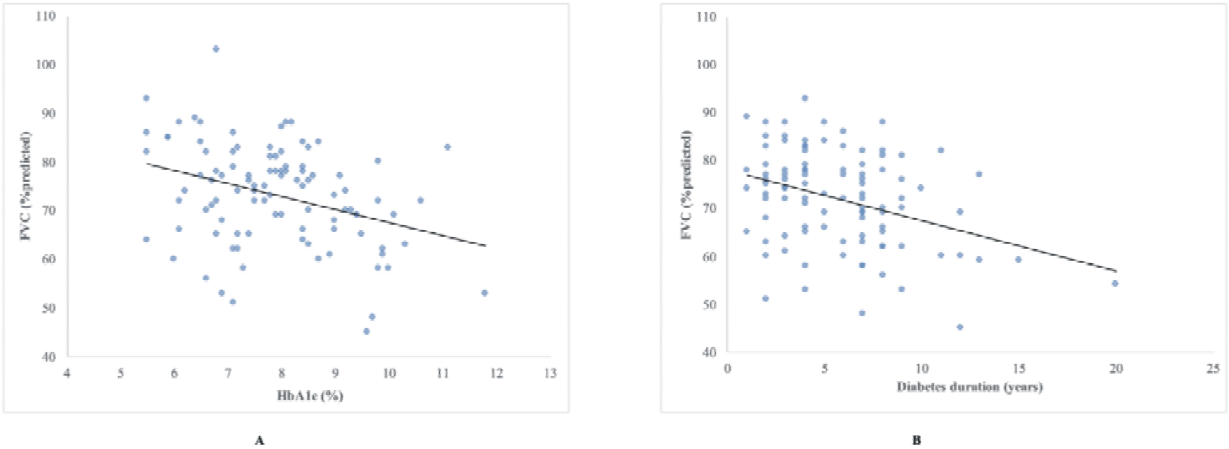


Fig. 2: *FVC (per cent predicted) plotted against HbA1c (panel A) and diabetes duration (panel B) in the T2DM group (n = 100). Each point represents one participant. Solid lines are ordinary least-squares fits shown for visual reference; inference is based on the Pearson correlation coefficients reported in Table V. Panel A, r = -0.34 (95% CI -0.50 to -0.15), R^2 = 0.12, p <0.001. Panel B, r = -0.35 (95% CI -0.51 to -0.16), R^2 = 0.12, p <0.001.*

the label 'restrictive' remains provisional without lung-volume measurement[6].

The magnitude of the deficit, and the frequency of the low-volume pattern, are at the higher end of what has been reported. Pooled meta-analytic FVC deficits are about -6.3 percentage points[7] and -9.21 percentage points[9], whereas we observed -17.1. A comparable Indian case-control study using a fixed 80%-predicted cut-off found a restrictive pattern in 54% of diabetic patients versus 10% of controls, giving roughly four-fold higher odds (OR 4.4)[23]; our low-volume pattern was similar in the diabetic group (56%) but rarer in controls (5%), giving a higher OR of 24.18. The similar case prevalence but lower control prevalence is consistent with a well-matched, non-smoking, non-obese control group referenced to a population-appropriate equation set, which keeps control means near 100% of predicted and prevents a reference mismatch from depressing both arms. Where Caucasian equations are applied to Indian participants, per cent-predicted values fall in both groups and the apparent prevalence of abnormality is inflated. We therefore report absolute values alongside per cent predicted so that others can re-reference our data.

Whether these deficits track glycaemic control and disease duration is the most divided question in this literature, and our data sit in the middle of it. We found modest inverse correlations of FVC and FEV1 with HbA1c and duration (Fig. 2). One group of studies reports significant negative correlations with poorer control or longer duration: the prospective Fremantle Diabetes Study and the ARIC cohort[14,15], and hospital studies in which FVC and FEV1 fell with rising HbA1c, sometimes strongly (for example, FEV1 versus HbA1c r = -0.74)[25], with lower FVC, FEV1 and PEF in poorly controlled patients[26], reduced volumes alongside raised inflammatory markers[12], and correlations with both HbA1c and duration[27]. Another group found no significant association with either variable[10,28]. Two large longitudinal cohorts add an important qualification: lung function in diabetes is lower but does not decline faster over time, and the deficit is already present before diabetes is diagnosed[16,29], which argues against a simple duration-dependent, glycation-driven process and raises the possibility of a shared antecedent such as insulin resistance. Because HbA1c and duration were themselves correlated in our data (r = 0.29) and our analyses are unadjusted, our coefficients should be read as descriptive associations, not as evidence of an independent dose-response.

No participant showed obstruction or a mixed pattern. This agrees with case-control studies reporting no obstructive component in non-smoking diabetic samples[23]. Where a mixed or obstructive picture has been described[27], it is most plausibly explained by the inclusion of smokers or by the use of fixed rather than LLN thresholds, both of which raise the apparent rate of obstruction.

Several mechanisms are proposed for lower lung volumes in diabetes: non-enzymatic glycation cross-linking collagen and elastin and degrading parenchymal elasticity, microangiopathic thickening of the alveolar-capillary basement membrane, low-grade systemic inflammation, respiratory-muscle weakness and autonomic neuropathy affecting chest-wall mechanics[2-5,30]. Because TLC and diffusing capacity (DLCO) were not measured, we cannot weight these pathways, and the low-volume pattern is also compatible with submaximal effort, which spirometry alone cannot exclude.

Spirometry may also understate pulmonary involvement in diabetes. Several studies that measured diffusing capacity found DLCO (or DLCO/VA) reduced, and falling with HbA1c, disease duration or microangiopathy, even when spirometric volumes were normal or near-normal[13,24,31,32]. Because we did not measure DLCO or TLC, our spirometry-based low-volume pattern probably captures only part of the picture, and normal spirometry in a diabetic patient should not be taken as reassurance. This is a further argument for adding DLCO, and ideally lung-volume measurement, to future assessment.

Interpretation of PEF and FEF25-75 requires particular restraint. ICS-NCCP guidelines carry a Grade 2A recommendation against reporting FEF25-75 and FEF75[6], and Quanjer *et al* showed they do not contribute to clinical decision making[21]. FEF25-75 is measured across a fraction of FVC, so any systematic reduction in FVC mechanically lowers it; its LLN in this cohort averaged only 60% of predicted, reflecting the very wide normal range that makes it unreliable. We therefore pre-specified both flow indices as exploratory. Their reduction here should not be read as independent evidence of small-airway disease; that would require oscillometry or high-resolution imaging. For the same reason, a low FVC with a preserved ratio cannot be called a restrictive ventilatory defect without plethysmographic confirmation of a reduced TLC[6].

Strengths and Limitations

Strengths include balanced group sizes, rigorous exclusion of smokers and obese participants, frequency-matching for age and sex, strict pre-test preparation, visual inspection of all curves, and the use of a single population-appropriate reference source for every index. Crucially, evaluating abnormality solely through an LLN-based classification removes the confounding effect of arbitrary fixed thresholds.

Limitations remain. The single-centre hospital-based design limits generalisability to community populations. The cross-

sectional design precludes inference about causal sequence or rate of decline. TLC and DLCO were not measured, so restriction is suggested rather than established. Bronchodilator reversibility testing was not performed; ICS-NCCP recommends it (Grade 1A) for anyone with suspected or demonstrated airflow obstruction, though no participant met LLN criteria for obstruction, so the omission is unlikely to affect these results. Analyses are unadjusted and remain open to residual confounding from physical activity, fat distribution, socio-economic status and medication. The reference equations of Chhabra *et al* were derived in Delhi; even within India, regional equations disagree, with north and south Indian equations discordant in 12.9% of records and north and west Indian equations in 22.1%[17,33], so a residual reference-population mismatch cannot be excluded. Finally, that equation set's FEV1/FVC model predicts somewhat lower ratios than its component FVC and FEV1 models imply, which raises FEV1 per cent predicted relative to FVC per cent predicted; this is a property of the reference source rather than of our cohort, and is a further argument for reporting absolute values.

Conclusion

In this hospital-based cohort, non-smoking adults with T2DM had lower FVC and FEV1 than matched controls, with a preserved FEV1/FVC ratio and an LLN-defined low-volume spirometric pattern in 56%, and these deficits tracked with diabetes duration and glycaemic control. When all indices are referenced to a single population-appropriate equation set and abnormality is defined exclusively by the statistically derived LLN, the signal persists with high clinical clarity. The findings are compatible with subclinical pulmonary involvement in diabetes but cannot confirm true restrictive ventilatory defects. Longitudinal studies incorporating TLC, DLCO and z-score interpretation are required to define the trajectory and clinical relevance of diabetic pneumopathy.

References

1. International Diabetes Federation. IDF Diabetes Atlas [Internet]. 11th ed. Brussels: International Diabetes Federation; 2025 [cited 2026 Jul 19]. Available from: https://diabetesatlas.org/
2. Pitocco D, Fuso L, Conte EG *et al*. The diabetic lung - a new target organ? *Rev Diabet Stud* 2012; 9 (1): 23-35.
3. Kopf S, Kumar V, Kender Z *et al*. Diabetic pneumopathy - a new diabetes-associated complication: mechanisms, consequences and treatment considerations. *Front Endocrinol (Lausanne)* 2021; 12: 765201.
4. Schuyler MR, Niewoehner DE, Inkley SR. Abnormal lung elasticity in juvenile diabetes mellitus. *Am Rev Respir Dis* 1976; 113 (1): 37-41.
5. Weynand B, Jonckheere A, Frans A. Diabetes mellitus induces a thickening of the pulmonary basal lamina. *Respiration* 1999; 66 (1): 14-9.
6. Aggarwal AN, Agarwal R, Dhooria S *et al*. Joint Indian Chest Society-National College of Chest Physicians (India) guidelines for spirometry. *Lung India* 2019; 36 (Suppl 1): S1-S35.
7. van den Borst B, Gosker HR, Zeegers MP. Pulmonary function in diabetes: a meta-analysis. *Chest* 2010; 138 (2): 393-406.
8. Klein OL, Krishnan JA, Glick S. Systematic review of the association between lung function and type 2 diabetes mellitus. *Diabet Med* 2010; 27 (9): 977-87.
9. Diez-Manglano J, Asin Samper U. Pulmonary function tests in type 2 diabetes: a meta-analysis. *ERJ Open Res* 2021; 7 (1): 00371-2020.
10. Shah SH, Sonawane P, Nahar P. Pulmonary function tests in type 2 diabetes mellitus and their association with glycaemic control and duration of the disease. *Lung India* 2013; 30 (2): 108-12.
11. Irfan M, Jabbar A, Haque AS. Pulmonary functions in patients with diabetes mellitus. *Lung India* 2011; 28 (2): 89-92.
12. Dennis RJ, Maldonado D, Rojas MX *et al*. Inadequate glucose control in type 2 diabetes is associated with impaired lung function and systemic inflammation: a cross-sectional study. *BMC Pulm Med* 2010; 10: 38.
13. Sinha S, Guleria R, Misra A. Pulmonary functions in patients with type 2 diabetes mellitus and correlation with anthropometry and microvascular complications. *Indian J Med Res* 2004; 119 (2): 66-71.
14. Davis WA, Knuiman M, Kendall P. Glycaemic exposure is associated with reduced pulmonary function in type 2 diabetes: the Fremantle Diabetes Study. *Diabetes Care* 2004; 27 (3): 752-7.
15. Yeh HC, Punjabi NM, Wang NY *et al*. Cross-sectional and prospective study of lung function in adults with type 2 diabetes: the Atherosclerosis Risk in Communities (ARIC) study. *Diabetes Care* 2008; 31 (4): 741-6.
16. Lange P, Parner J, Schnohr P. Copenhagen City Heart Study: longitudinal analysis of ventilatory capacity in diabetic and nondiabetic adults. *Eur Respir J* 2002; 20 (6): 1406-12.
17. Aggarwal AN, Gupta D, Behera D. Applicability of commonly used Caucasian prediction equations for spirometry interpretation in India. *Indian J Med Res* 2005; 122 (2): 153-64.
18. American Diabetes Association Professional Practice Committee. 2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes-2024. *Diabetes Care* 2024; 47 (Suppl 1): S20-S42.
19. Graham BL, Steenbruggen I, Miller MR *et al*. Standardisation of spirometry 2019 update: an official American Thoracic Society and European Respiratory Society technical statement. *Am J Respir Crit Care Med* 2019; 200 (8): e70-e88.
20. Chhabra SK, Kumar R, Gupta U. Prediction equations for spirometry in adults from northern India. *Indian J Chest Dis Allied Sci* 2014; 56 (4): 221-9.
21. Quanjer PH, Weiner DJ, Pretto JJ. Measurement of FEF25-75% and FEF75% does not contribute to clinical decision making. *Eur Respir J* 2014; 43 (4): 1051-8.
22. von Elm E, Altman DG, Egger M. STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007; 147 (8): 573-7.
23. Kapoor D, Kumar P, Ranjan A *et al*. Assessment of pulmonary function in patients with type 2 diabetes mellitus: a case-control study. *Int J Res Med Sci* 2015; 3: 207-13.
24. Anandhalakshmi S, Geethanjali S, Pavithra G. Alveolar gas exchange and pulmonary functions in patients with type II diabetes mellitus. *J Clin Diagn Res* 2013; 7 (9): 1874-7.
25. Vanidassane I, Malik R, Jain N. Study of pulmonary function tests in

type 2 diabetes mellitus and their correlation with glycaemic control and systemic inflammation. *Adv Respir Med* 2018; 86 (4): 172-8.

26. Kaur R, Uppal N, Uppal V. Impaired glycaemic control as a risk factor for reduced lung function in the Indian diabetic population. *Monaldi Arch Chest Dis [Internet]*. 2025. [cited 2026]; 95 (3).
27. Sharma A, Sharma A, Chauhan R. Spirometric lung functions in type 2 diabetes mellitus: a hospital-based study. *Cureus* 2023; 15 (5): e38919.
28. Khan MA, Sinha N. Assessment of lung functions by spirometry in diabetics with no respiratory complaints. *J Assoc Physicians India* 2022; 70 (11): 11-2.
29. Litonjua AA, Lazarus R, Sparrow D. Lung function in type 2 diabetes: the Normative Aging Study. *Respir Med* 2005; 99 (12): 1583-90.
30. Kolahian S, Leiss V, Nurnberg B. Diabetic lung disease: fact or fiction? *Rev Endocr Metab Disord* 2019; 20 (3): 303-19.
31. Guvener N, Tutuncu NB, Akcay S. Alveolar gas exchange in patients with type 2 diabetes mellitus. *Endocr J* 2003; 50 (6): 663-7.
32. Mori H, Okubo M, Okamura M *et al*. Abnormalities of pulmonary function in patients with non-insulin-dependent diabetes mellitus. *Intern Med* 1992; 31 (2): 189-93.
33. Chhabra SK. Regional variations in vital capacity in adult males in India: comparison of regression equations from four regions and impact on interpretation of spirometric data. *Indian J Chest Dis Allied Sci* 2009; 51 (1): 7-13.

ANNOUNCEMENT

Mrs. Uma Bansal - Prof. B.C. Bansal Best Paper Award (Journal -2026)

Best Original Article – "Evaluation of the Relation between Dialysis Vintage, Cognitive Functions and Functional Status in CKD Patients" – Dr. Shafin Rashad V, Dr. Senthilkumar, Dr. A Venkatesh, Dr. A Jayaprakash, Dr. Shree Sruthi E, Dr. Andrew JS, Dr. Niranjan Yadav – Department of Renal Dialysis Technology, Vinayak Mission's Research Foundation – Deemed to be University, Salem - 636 308, (Tamil Nadu).

Best Review Article – "The Role of Nutrition in Rheumatic Disease – A Global Perspective As Easy AS A, B, Ghee?" – Dr. Dominik Baluch, Dr. Elena Nikiphorou, Dr. Elena Phillippou – King's College London, London, UK.

Best Case Report – "Idiopathic Multicentric Castleman Disease Presenting as TAFRO Syndrome: A Diagnostic Enigma" – Dr. Rajnish Singh, Dr. Shreyasee Patra, Dr. Brijesh Sharma, Dr. Madhubala Negi, Dr. Archana Mohan, Dr. Tanvi Suri, Dr. Shivanshu Gangwar – Department of General Medicine, ABVIMS and Dr. Ram Manohar Lohia Hospital, Baba Kharak Singh Marg, New Delhi - 110 001.

ORIGINAL ARTICLE

JIACM 2026; 27 (3): 186-92

Aetiological and Haematological Profile of Patients of Pancytopenia at a Tertiary Care Hospital in Northern India

Bishakha Swain, Ratnakar Sahoo**, Vijay Kumar***, Priyanka Verma*****

Abstract

Background: Pancytopenia is characterised by simultaneous decrease in all the 3 cell lines: erythrocytes, leucocytes and platelets. Its aetiology is as variable as its presentation ranging from nutritional deficiencies to haematological malignancies. It may be completely treatable; however, in some cases, it requires extensive investigations for diagnosis and prolonged treatment. Our aim was to study the aetiological and haematological profile in patients of pancytopenia for early diagnosis, to avert catastrophic consequences by timely treatment.

Materials: This cross-sectional, observational study included 100 patients presenting with pancytopenia to the medical emergency and outpatient department of the Department of Medicine at ABVIMS and Dr. RML Hospital between November 2019 and March 2021.

Results: Mean age of patients was 37.92 ± 15.2 years with maximum number of patients (32%) in the age group of 21 - 30 years. 50 subjects were males and 50 were females. Megaloblastic anaemia (MA) accounted for 49% cases of pancytopenia. Other causes were infections (16%), hypersplenism (13%), drugs (6%), autoimmune disorders (5%), aplastic anaemia (AA) (4%), malignancy (3%), haemophagocytic lymphohistiocytosis (3%) and Sheehan syndrome (1%). 51% of patients had macrocytic anaemia, 35% had normocytic normochromic anaemia and 14% had dimorphic anaemia. The commonest bone marrow finding was hypercellularity with megaloblastic reaction and dyserythropoiesis (39.43%). Hypercellular, normocellular and hypocellular marrow were observed in 70.43%, 15.49% and 14.08% subjects, respectively.

Conclusion: This study elucidated causes and haematological profile of pancytopenia in Northern India. Megaloblastic anaemia was the most common aetiology in this study.

Key words: Pancytopenia, megaloblastic anaemia, bone marrow aspiration, peripheral blood smear, hypercellular bone marrow.

Introduction

Pancytopenia is not an illness but manifestation of an underlying disease. In simple language, it means lack of all cells (pan -all; cyte - cell; penia - poverty)[1]. It is characterised by decline in all three blood cell lines- erythrocytes, leucocytes and platelets[2]. Pancytopenia is encountered in daily clinical practice and is more common than realised due to its varied aetiology and variable presentation. Patients with pancytopenia present with symptoms of anaemia, leukopenia and thrombocytopenia, which if not diagnosed early, may be lethal. Pancytopenia is caused by failure of blood cell production, marrow suppression by drugs or infection, infiltration of bone marrow by malignant cells or fibrosis, ineffective erythropoiesis and dysplasia, peripheral sequestration of blood cells by overactive reticuloendothelial system, and immune or non-immune mediated increased destruction of blood cells[3]. Megaloblastic anaemia due to deficiency of vitamin B12/ folate, is a predominant cause of pancytopenia in India because of high prevalence of nutritional anaemia in the Indian subcontinent. Other causes include hypersplenism (congestive splenomegaly, chronic liver disease, malaria, and leishmaniasis), aplastic anaemia, myelodysplastic syndrome, subleukaemic leukaemias, military tuberculosis, multiple myeloma, paroxysmal nocturnal haemoglobinuria[3]. Genetic mutations and varied geographical distribution also affect the incidence and aetiology of pancytopenia. A careful examination of peripheral blood picture is the first step in the workup of pancytopenia and helps in planning relevant investigations. Bone marrow (BM) examination is a window to the diagnosis of pancytopenia as all blood cells are formed in it. It helps in the final diagnosis but may not always be conclusive. Having a knowledge of aetiology of pancytopenia is essential for prognosis and its management. Additional testing and clinical evaluation can be recommended when bone marrow studies are inconclusive[4]. This study was undertaken to evaluate the haematological parameters and aetiology of pancytopenia.

Assistant Professor, Department of Clinical Immunology and Rheumatology, KIMS Hospital, Bhubaneshwar - 751 024, Odisha, **Director Professor, Department of Medicine, ***Director Professor and Head, Department of Pathology, ABVIMS and Dr Ram Manohar Lohia Hospital, Baba Kharak Singh Marg, New Delhi - 110 001, ****Assistant Professor, Department of Medicine, UCMS and Guru Teg Bahadur Hospital, Dilshad Garden, Delhi - 110 095.

Corresponding Author: Dr Bishakha Swain, Assistant Professor, Department Clinical Immunology and Rheumatology, KIMS Hospital, Bhubaneshwar - 751 024, Odisha. Tel: 9730248779, E-mail: bshakha@gmail.com

Material and Methods

This was a cross-sectional, observational study conducted in the Department of Medicine at ABVIMS and Dr RML Hospital, New Delhi from November 2019 to March 2021 after obtaining permission from the institutional ethics committee. A total of 100 patients who presented to the outpatient and emergency department after taking proper informed consent were enrolled. The inclusion criteria were patients aged 18 years and above, having pancytopenia defined as haemoglobin level - below 9 g/dL, total leucocyte count - below 4000/mm^3, and platelet count - below 1,00,000/μL^3. Patients who were on chemotherapy, or had a history of radiotherapy and recent blood transfusion were excluded.

A thorough history, physical examination and relevant investigations were obtained and recorded. The investigations conducted were: Complete blood count (CBC), peripheral smear, reticulocyte count, serum vitamin B12 and folate levels, Serum Lactate Dehydrogenase (LDH) levels, kidney function test, liver function test, Anti-Nuclear Antibodies (ANA), Coomb's test, Human immunodeficiency virus- enzyme-linked immunosorbent assay (HIV ELISA), Anti Hepatitis C antibody, Hepatitis B surface Antigen (HBsAg), urinalysis, chest X-ray and electrocardiogram, ultrasound-abdomen. Patients were screened for Malaria, Dengue, Enteric fever, Chikungunya and Sepsis when suspected as per the clinical presentation. Special investigations were done when routine investigations were inconclusive. These included rk39 antigen, serum protein and immunofixation electrophoresis, spleno-portal axis doppler, Computed Tomography (CT) scan and Magnetic Resonance Imaging (MRI), Viral deoxyribonucleic Acid (DNA) Polymerase Chain Reaction (PCR) for Cytomegalovirus (CMV) and Epstein Barr Virus (EBV), Hormonal profile (Growth Hormone, Follicular Stimulating Hormone, Luteinizing Hormone, Thyroid Stimulating Hormone, FreeT3, FreeT4), procalcitonin levels, serum ferritin, serum fibrinogen and serum triglyceride level. Bone marrow aspiration and biopsy was done in 71 subjects.

Results

In this study, 50 patients were males and 50 were females. Mean age (years) of study subjects was 37.92 ± 15.2. Majority (32%) of patients belonged to age group 21 - 30 years and least patients were in the age group >70 years. Age-wise aetiological distribution is given in Table I.

49% patients had pancytopenia secondary to megaloblastic anaemia (MA) due to nutritional deficiency of vitamin B12 (28%) or both vitamin B12 and folate (21%). Other causes were: Infections (16%), hypersplenism (13%), drugs (6%), autoimmune disorders (5%), aplastic anaemia (4%), malignancy (3%), Haemophagocytic lymphohistiocytosis (HLH) (3%) and Sheehan syndrome (1%) (Fig. 1).

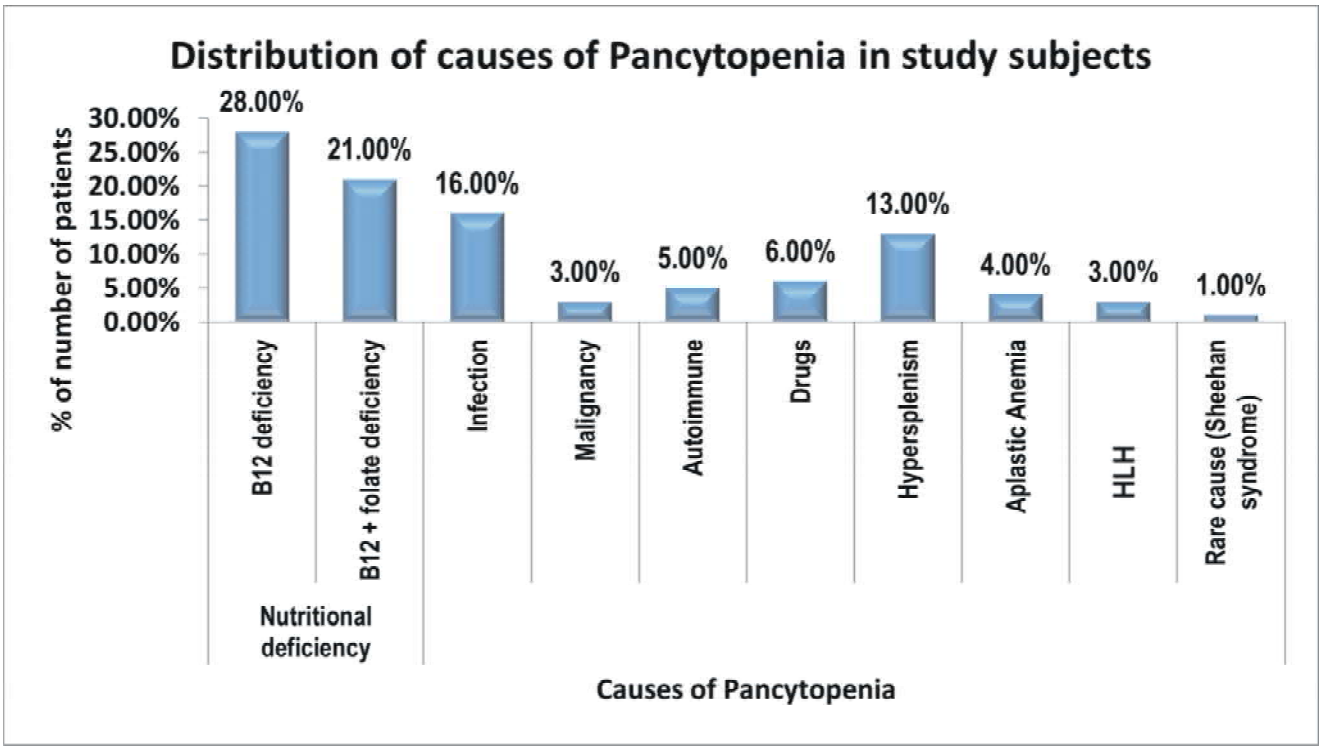


Fig. 1: *Distribution of causes of pancytopenia in study subjects.*

Table I: Age-wise distribution of aetiology of Pancytopenia.

Aetiology	<20 y	20 - 39 y	40 - 59 y	>60 y	Total
B12/folate deficiency	7	21	19	2	49
CLD/hypersplenism	0	5	6	2	13
Auto-immune	0	4	1	0	5
Drug Induced	0	5	1	0	6
Infections	1	12	3	0	16
Aplastic anaemia	0	0	2	2	4
Malignancy	0	0	1	2	3
Rarer diseases (HLH) (Sheehan syndrome)	1	2	 1		3 1
Total	9	49	34	8	100

Amongst B12 deficient individuals, dietary deficiency (89.29%) predominated followed by alcohol (7.14%) and 1 case was idiopathic (3.57%). The commonest cause of combined B12 and folate deficiency was dietary deficiency (66.67%) followed by alcohol use (23.81%) and malabsorption (Celiac disease) and idiopathic in only 1 out of 21 patients (4.76%). Thirty of the 49 subjects suffering from megaloblastic anaemia were vegetarian while 7 were vegans.

Out of 16 cases of infection, the commonest was malaria seen in 31.25% of patients (with infection) followed by disseminated tuberculosis (25%) and visceral leishmaniasis (12.5%). Cause of infection was HIV, CMV, EBV, sepsis (Klebsiella) and Dengue in only 1 out of 16 patients (6.25%) each.

Pancytopenia was attributable to hypersplenism in 13 cases. Chronic Liver Disease (CLD) was seen in majority (84.62%) whereas splenic abscess and portal hypertension (cause unidentified) caused hypersplenism in 1 patient (7.69%) each. The commonest cause of CLD was Alcoholic liver disease (7 cases), with 2 cases of Non-Alcoholic Fatty Liver Disease (NAFLD), one each of cryptogenic CLD and extrahepatic portal vein obstruction in a hepatitis B affected patient with CLD.

In the study, 6 patients were on myelotoxic drugs; 2 (33.33%) were taking Methotrexate (MTx). azathioprine, meropenem, carbimazole and cyclophosphamide were taken by only 1 out of 6 patients (16.67%) each. Haematological malignancies were seen in 3% cases; 1 patient each of Non-Hodgkin Lymphoma (NHL), Multiple Myeloma (MM) and Acute erythroid Leukaemia (AML-M6). Other causes of pancytopenia were aplastic anaemia seen in 4 patients, HLH in 3 (2 of which had tuberculosis and 1 remained unknown) and Sheehan syndrome in 1 patient.

Mean value of haemoglobin (g/dL), total leucocyte count (cells/mm^3), platelet count (/µL), packed cell volume (%) and corrected reticulocyte count (%) of study subjects was 5.53 ± 1.87, 2625.6 ± 824.86, 50100 ± 24174.24, 16.8 ± 5.57 and 1.73 ± 1.38, respectively.

Mean value of mean corpuscular volume (MCV) (fL), mean corpuscular haemoglobin (MCH) (pg) and mean corpuscular haemoglobin concentration (MCHC) (g/dL) of study subjects were 102.78 ± 16.6, 30 ± 2.12 and 33.73 ± 1.44 respectively.

In the present study, peripheral smear of 51% of patients was found to be macrocytic followed by normocytic normochromic (35%) and dimorphic (14%). Other features were hypersegmented neutrophils (35%) (Fig. 2), polychromatophils (14%), hemoparasite (5%), special features like rouleaux formation with lymphoplasmacytic forms (1%) and normocytic normochromic anaemia with 3 - 4% erythroblasts (1%).

71 patients were subjected to BM examination with variable findings (Fig. 4). 70.43% patients revealed a hypercellular marrow while normocellular and hypocellular marrow were observed in 15.49% and 14.08% patients respectively. 39.43% of patients had hypercellular marrow with megaloblastic reaction with dyserythropoiesis (MA) (Fig. 3), 18.30% had erythroid hyperplasia with normoblastic maturation with hypercellular marrow (Hypersplenism), 8.45% of patients had hypocellular marrow (drug induced pancytopenia), 7.04% of patients had normocellular marrow with normal maturation/mild dyserythropoiesis (autoimmune aetiology), 5.63% of patients had a hypocellular marrow replaced by fat (AA), 4.22% of patients had histiocytes and haemophagocytosis (HLH) (Fig. 5A), 5.63% of patients had normocellular marrow with granulomas and giant cells (disseminated Tuberculosis), mild dyserythropoiesis - 2.81% – was seen in patients with malaria without any haemoparasite and cellular marrow

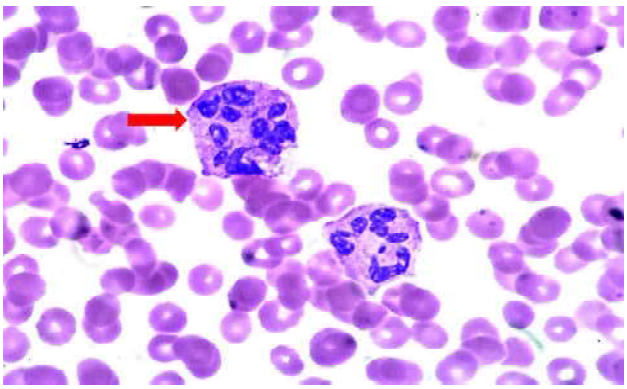


Fig. 2: *400X magnification. Leishman Stain. Megaloblastic anaemia. Peripheral Blood Smear showing hypersegmented neutrophils.*

with reactive changes was seen in 1.40 % patients (CMV infection). Specific findings were found in Visceral Leishmaniasis, i.e., LD bodies (2.81%) (Fig. 5B), Non-Hodgkin lymphoma- CD20 positive abnormal mononuclear cells (1.40%), AML M6- proerythroblasts witch block like PAS positivity (1.40%) and multiple myeloma CD 138 positive plasma cells (1.40%).

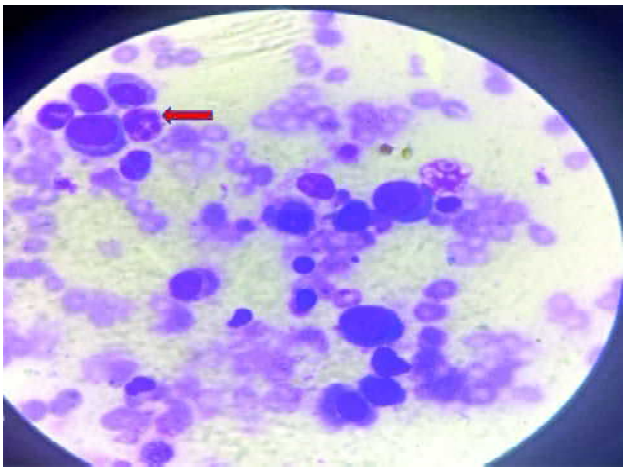


Fig. 3: *200X magnification. Giemsa stain. Bone marrow aspirate shows erythroid hyperplasia with megaloblasts (Red arrow).*

Aetiology	Bone marrow findings	Frequency (n %)
Megaloblastic anaemia	Hypercellular marrow with megaloblastic reaction with dyserythropoiesis	28 (39.43%)
Autoimmune	Normocellular marrow with normal maturation/mild dyserythropoiesis	5 (7.04%)
Drug induced	Hypocellular marrow	6 (8.45%)
Aplastic anaemia	Hypocellular marrow replaced by fat	4 (4.63%)
Haemophagocytic Lymphohistiocytosis	Histiocytes Haemophagocytosis	3 (4.22%)
Hypersplenism	Erythroid hyperplasia with normoblastic maturation	13 (18.30%)
Visceral leishmaniasis	Erythroid hyperplasia mild dyserythropoiesis/Leishmania Donovani (LD) bodies seen	2 (2.81%)
Disseminated tuberculosis	Normocellular with granulomas with langhans gaint cells	4 (5.63%)
Non Hodgkin's lymphoma	Abnormal mononuclear cells (CD 20 positive) with high NR ratio and opened up chromatin	1 (1.40%)
Multiple myeloma	Cellular with palsma cells (CD138 positive)	1 (1.40%)
Acute Myeloid Leukaemia	ME ratio 1:12/Erythroid hyperplasia/ >30% proerythropoiesis - No positivity	1 (1.40%)
Malaria	Mild dyserythropoiesis parasite	2 (2.81%)
Cyto megalovirous	Cellular Marrow with Reactive changes - No Inclusions	1 (1.40%)

Fig. 4: *Distribution of bone marrow findings of study subjects with corresponding aetiology.*

Discussion

Our study included 100 patients (50 males, 50 females) with a mean age of 37.92 ± 15.2 years. Most patients (32%) were in the 3rd decade. A study by Jain *et al*[5] showed a clear male predominance likely due to sociocultural factors unlike our study. Both studies; however, showed a predominance of younger adults presenting with pancytopenia. While the comparison study reported most cases in the 3rd and 4th decades, our study found the highest proportion (32%) in the 21 - 30 years age group, suggesting a slightly earlier peak age of presentation in our cohort.

The aetiological profile of pancytopenia demonstrated a distinct age-related pattern in our cohort. The majority of patients were between 20 and 59 years of age (83%), with 49% belonging to the 20 - 39-year age group. Vitamin B12/ folate deficiency was the predominant aetiology overall (49%) and remained the leading cause across the 20 - 39 and 40 - 59-year age groups, accounting for 42.8% and 38.8% of cases, respectively. This finding is consistent with a similar study where maximum number of megaloblastic anaemia cases were seen in the age group 41 - 50[6].

Another study by Dasgupta *et al*, reported aplastic anaemia predominated in younger patients, aged 5 - 35 years, whereas megaloblastic anaemia became relatively more prominent with increasing age and was the only reported cause among patients >65 years along with leishmaniasis unlike our study where majority of patients had Megaloblastic anaemia between ages of 20 - 59 years. None of our patients aged <40 years had aplastic anaemia. Four cases were seen in elderly[7].

Another study reported evenly distributed cases across age groups (11 - 20 and 21 - 30 years) together accounting for only 32% of cases, with a comparatively higher proportion in the paediatric (<10 years: 26%) and elderly (>60 years: 21%) populations). Megaloblastic anaemia, was the commonest aetiology (25%) followed by a broader spectrum of marrow-based and malignant disorders (aleukaemic leukaemia, hypoplastic/aplastic marrow, myelodysplastic syndrome, myelofibrosis, and hairy cell leukaemia) accounting for 37% of cases) and visceral leishmaniasis (11.8%)[8].

These differences reflect variations in geographical setting, referral patterns, patient characteristics and the relative prevalence of nutritional, infectious and marrow disorders between the cohorts. Our study excluded paediatric patients which could partially account for some differences among the studies.

In our study the majority of admitted patients were diagnosed with megaloblastic anaemia (49%) as the cause

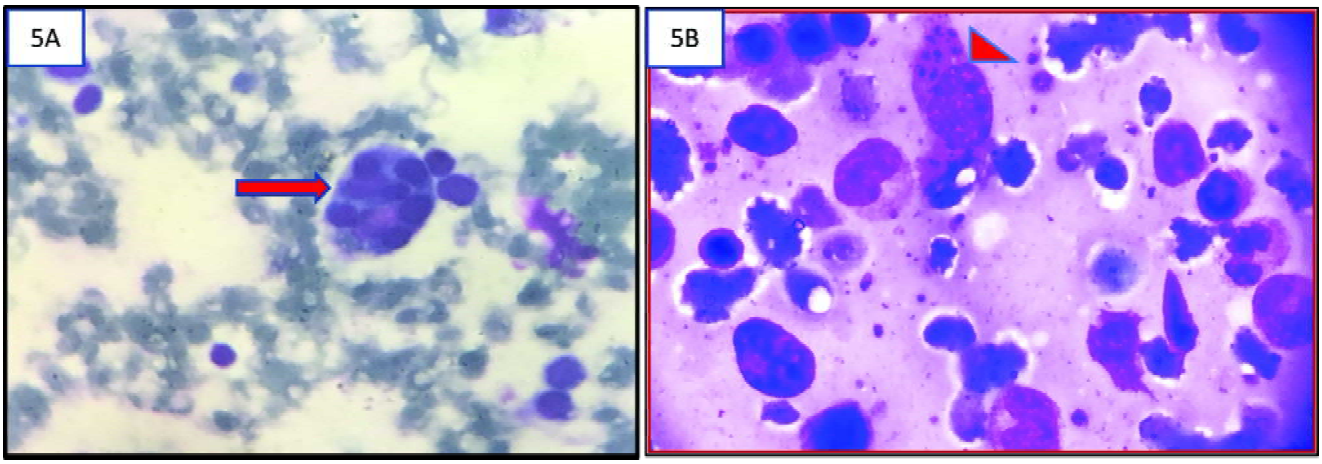


Fig. 5: *400X magnification. Giemsa stain. 5A) Haemophagocytic Lymphohistiocytosis. Histiocytic cells showing haemophagocytosis (Red arrow). 5B) Kala-azar. Bone marrow aspirate smear showing Leishmania Donovani (LD) bodies with amastigote forms (red arrow head) of the hemoparasite.*

of pancytopenia. The predominant cause for this was nutritional deficiency. This is similar to a study done by Kulkarni *et al*[9] wherein nutritional deficiency was the most common cause of pancytopenia. Rao *et al* [10] (74.04%), Dhooria *et al*[2] (29.5%) and Rohira *et al*[11] (50%) also report Megaloblastic anaemia as the commonest cause of pancytopenia in their studies. Dhooria *et al* showed that 55.9% pancytopenic subjects with Megaloblastic anaemia were vegetarians[2] while 61.2% were vegetarians in our study.

Viral infections are well documented causes of cytopenias and severe cases can also result in aplastic anaemia. In our study, infections were observed as the 2nd commonest cause of pancytopenia wherein malaria predominated (31.25%) followed by disseminated Tuberculosis (25%) and few cases of Visceral Leishmaniasis (12.50%). Viral illnesses with pancytopenia were observed in one case each (6.25%) of HIV, CMV, EBV, Dengue and 2 cases of hepatitis B.

Hypersplenism causes peripheral pooling or trapping and destruction of cells in an enlarged spleen resulting in cytopenias. It is also a frequent cause specially noted in alcoholic patients developing CLD with portal hypertension. In our study, hypersplenism (13%) was the third commonest cause of pancytopenia resulting from CLD (11% cases) and 1 case each of portal hypertension and splenic abscess. Dhooria *et al*[2] reported hypersplenism as the cause of pancytopenia in 4.5% cases in which hepatitis C and alcoholic CLD were the main causes.

Drug induced pancytopenia was observed in 6% cases. Maximum cases were caused by methotrexate followed by azathioprine. Similar finding was reported by Dhooria *et al*[2] where 21 patients (10.5%) were labelled as drug induced pancytopenia and methotrexate constituted 12 cases followed by azathioprine in 3 patients, combination of MTx and indigenous medication in 2 patients and 1 each of 6-Mercaptopurine, NSAIDS, Anti-retroviral therapy (ART) and combination of MTx and leflunomide.

In our study, only 3% cases constituted haematological malignancies with pancytopenia. Similar results were reported by Javalgi *et al*[12] where least common causes of pancytopenia were leukaemia (2.8%), myelofibrosis (0.9%), multiple myeloma (0.9%) and myelodysplastic syndrome (0.9%). Contrary to our study, Neha Sharma *et al*[13] (19%) and Dhooria *et al*[2] (14%) reported higher prevalence of malignancies causing pancytopenia.

Pancytopenia is seen as a frequent haematological involvement in various autoimmune diseases caused by defective hematopoiesis due to antibodies, infection/sepsis and immunosuppressant therapy. Our study reported only 5% cases of Systemic Lupus Erythematosus (SLE) which is comparable to Santra *et al*[14], where 3.7% cases of SLE caused pancytopenia out of 215 subjects.

Aplastic anaemia was seen in only 4% cases. This was corroborated by Jain *et al*[5] who reported 12 (4.8%) cases of hypoplastic/aplastic anaemia. But few studies[14,15,16] reported it as the commonest aetiology of pancytopenia.

HLH is a life-threatening disease characterised by uninhibited activation of immune cells. HLH could occur sporadically or genetically. The clinical presentation is typically triggered by infection, autoimmune conditions, or immunosuppression. HLH was established as a cause of pancytopenia by a comprehensive electronic literature search from January 1990 to July 2016 conducted by Gnanaraj *et al*[17]. We observed pancytopenia in 3 cases of HLH during this study.

One unusual cause of pancytopenia was a case of Sheehan syndrome who had presented with secondary

amenorrhoea which resolved after hormonal replacement; these findings are corroborated by a case report by Fatma *et al*[18] who observed the same in a Tunisian lady with post-partum pituitary apoplexy.

In our study, most cases were hypo-proliferative, with corrected reticulocyte count ranging from 0.2 - 6.8 %, the mean being 1.73 ± 1.38%. Many of these cases were related to megaloblastic anaemia with corrected reticulocyte count of patients <2% while a few were secondary to aplastic anaemia (corrected reticulocyte count <1%) and myelotoxic drugs. Reticulocyte count was raised in cases with hypersplenism and malaria. Priya *et al*[19] conducted a study to evaluate the role of Absolute Reticulocyte count (ARC) in patients of pancytopenia. They observed that ARC was severely reduced in aplastic anaemia whereas nutritional anaemias and myelodysplastic syndrome showed moderate decrease in ARC values. All marrow infiltrative disorders and systemic infections presented with high ARC.

In RBC indices, MCV revealed the widest variation with a range of 70 - 137.1 fL and mean of 102.78 ± 16.6 fL suggesting that most cases were macrocytic (51%). In the study conducted by Barik *et al*[20] MCV was increased in 49% cases. Dimorphic picture was seen in only 14% cases in our study. A study conducted by Rao *et al*[10] reported different features with predominant dimorphic anaemia (37.5%), followed by macrocytic anaemia (31.7%) and normocytic normochromic anaemia (15.3%).

Highest number of cases in our study had a hypercellular marrow (70.43%) with majority showing dyserythropoiesis and megaloblastic reaction (39.43%). Hypercellular bone marrow is indicative of infiltration by neoplasm, immune-dysregulation by inflammatory cells, dys-erythropoiesis by overwhelming infection and megaloblasts. Our study observed few cases (3%) of haematological malignancy. Visceral Leishmaniasis and HLH also revealed hypercellular bone marrow. Normocellular marrow was observed in 15.49% cases and hypocellular marrow in 14.08% cases. Special features observed were LD bodies in visceral leishmaniasis, giant cells and granulomas in disseminated Tuberculosis and haemophagocytes with histiocytosis in HLH. The bone marrow findings were reflective of the aetiology. A study conducted by Geetanjali *et al*[21] showed bone marrow hypocellularity in 18.7%, normocellularity in 32.8% and predominant hypercellularity in 48.5% with megaloblastic maturation in 23 cases (32.8%) which is akin to our study. In another comparable study by Javalgi *et al*[11] 68.8% cases had hypercellular marrow, followed by normocellular (15%) and hypocellular marrow (16.2%) and megaloblastic anaemia was found as the most common cause.

Pancytopenia was diagnosed in 29 patients without a bone marrow examination. Peripheral smear and CBC clinched the diagnoses in 24 patients. 20 patients had megaloblastic anaemia with a high MCV on CBC and hypersegmented neutrophils on peripheral smear, supplemented with vitamin B12 levels. Malaria led to pancytopenia in 3 cases with the peripheral smear showing schizonts of *plasmodium*. EBV DNA PCR and relative lymphocytosis diagnosed another case. Serology helped in diagnosing 2 cases (HIV Elisa, Dengue IgM). Ultrasound of the abdomen, hormonal profile and blood culture diagnosed hypersplenism (CLD), Sheehan syndrome and sepsis respectively.

It is notable that only 15 of the 100 patients needed bone marrow evaluation for a definitive diagnosis. These included disseminated TB (3), Aplastic anaemia (4), HLH (3), Leishmaniasis (2) and haematological malignancies (3).

The remaining 56 patients were diagnosed based on clinical history, examination, CBC and peripheral smear findings, along with serology and imaging. However, suggesting that bone marrow examination can be routinely avoided in the majority of patients with pancytopenia would be an oversimplification, given the possibility of underlying serious or unsuspected pathology. Moreover, diagnostic certainty is often easier to establish in retrospect.

Our study highlights that a thorough clinical history and examination, CBC, and peripheral smear remain the cornerstone of the initial evaluation of pancytopenia, guiding the need for further investigations, including bone marrow examination.

Limitations: The limitations of our study include the stringent definition of pancytopenia that may have resulted in under-representation of patients with early or milder cytopenias. Additionally, exclusion of patients with prior blood transfusion may have introduced selection bias, particularly in a tertiary-care setting, as pre-transfusion haematological parameters were not consistently available for retrospective assessment.

Conclusion

The aetiological profile of pancytopenia can be established with a thorough clinical history, physical examination and relevant haematological investigations. Early diagnosis of pancytopenia is pertinent as treatment varies with specific aetiology. In this study megaloblastic anaemia was found as the commonest cause followed by infections. Bone marrow examination was essential in few cases for diagnosis. Many cases of pancytopenia can be diagnosed without a bone marrow examination; however, for

confirmation the importance of a marrow examination cannot be underestimated.

References

1. Kar M, Ghosh A. Pancytopenia. *J Indian Acad Clin Med* 2002; 3 (1): 29-34.
2. Dhooria HP, Kaur S, Dhooria GS. Aetiological spectrum and clinical profile of patients admitted with pancytopenia. *J Adv Med Med Res* 2020; 32 (4): 56-65.
3. Garg AK, Agarwal AK, Sharma GD. Pancytopenia: Clinical approach. In: Bansode BR, editor. *Medicine Update.* 27th ed. New Delhi: Evangel Publishers; 2017; p. 450-54.
4. Weinzierl EP, Arber DA. The differential diagnosis and bone marrow evaluation of new-onset pancytopenia. *Am J Clin Pathol* 2013; 139 (1): 9-29.
5. Jain A, Naniwadekar M. An aetiological reappraisal of pancytopenia: Largest series reported to date from a single tertiary care teaching hospital. *BMC Hematol* 2013; 13 (1): 1-9.
6. Makheja KD, Maheshwari BK, Arain S. The common causes leading to pancytopenia in patients presenting to tertiary care hospital. *Pakistan J Med Sci* 2013; 29 (5): 1108.
7. Dasgupta S, Mandal PK, Chakrabarti S. Aetiology of Pancytopenia: An Observation from a Referral Medical Institution of Eastern Region of India. *J Lab Physicians* 2015; 7 (2): 90-5.
8. Chandra H, Gupta AK, Nath UK. Clinico-haematological study of pancytopenia: A single-center experience from north Himalayan region of India. *J Family Med Primary Care* 2019; 8 (12): 3944.
9. Kulkarni NS, Patil AS, Karchi SD. Study of pancytopenia in a tertiary care hospital in North Karnataka. *Int J Med Res Health Sci* 2017; 6 (3): 61-67.
10. Rao KS. Pancytopenia: A clinicohaematological study. *J Lab Physicians* 2011; 3 (1): 15-20.
11. Rohira N, Sawke GK, Sawke N. Pancytopenia associated megaloblastic anaemia: A clinicohaematological study in a tertiary care hospital. *Trop J Pathol Microbiol* 2019; 5 (2): 69-75.
12. Javalgi AP, Dombale VD. Clinicohaematological analysis of pancytopenia: A bone marrow study. *Natl J Lab Med* 2013; 2 (4): 12-7.
13. Sharma N, Bhatia PK, Kaul KK. A clinicohaematological study of pancytopenia: An experience of a tertiary care teaching hospital, Jammu, India. *Indian J Pathol Oncol* 2017; 4 (4): 632-7.
14. Santra G, Das BK. A cross-sectional study of the clinical profile and aetiological spectrum of pancytopenia in a tertiary care center. *Singapore Med J* 2010; 51 (10): 806-12.
15. Sitwat HA, Haque KA, Hussian G. Pancytopenia: Study for clinical features and aetiological pattern at tertiary care settings in Abbottabad. *Prof Med J* 2014; 21 (1): 60-5.
16. Rehmani TH, Arif M, Heraid S. Spectrum of pancytopenia. *Prof Med J* 2016; 23 (5): 620-6.
17. Gnanaraj J, Parnes A, Francis CW. Approach to pancytopenia: Diagnostic algorithm for clinical haematologists. *Blood Rev* 2018; 32 (5): 361-7.
18. Fatma M, Mouna E, Nabila R. Sheehan's syndrome with pancytopenia: A case report and review of the literature. *J Med Case Rep* 2011; 5 (1): 1-3.
19. Priya PP, Subhashree AR. Role of absolute reticulocyte count in evaluation of pancytopenia: A hospital-based study. *J Clin Diagn Res* 2014; 8 (8): FC01-FC03.
20. Barik S, Chandoke RK, Verma AK. A prospective clinicohaematological study in 100 cases of pancytopenia in capital city of India. *J Appl Haematol* 2014; 5 (2): 45-50.
21. Geetanjali N, Das S. Clinicohaematological profile and aetiological spectrum of pancytopenia: An institutional study. *Indian J Pathol Oncol* 2019; 6 (2): 302-8.

ADVERTISEMENT TARIFF

Journal, Indian Academy of Clinical Medicine

Advertisement Tariff effective January, 2020

Position	Single Issue	Consecutive Four Issues
(a) Back cover and Inside front cover	₹ 30,000/-	₹ 1,00,000/-
(b) Inside back cover	₹ 25,000/-	₹ 75,000/-
(c) Full page	₹ 20,000/-	₹ 60,000/-
(d) Half page	₹ 10,000/-	₹ 30,000/-

Note: Artworks/positives (processing)/art pulls of advertisements for Back cover, Inside front cover, Inside back cover and Full page should not exceed 28 cm (H) x 21 cm (W) – (for bleed); and 25 cm (H) x 18 cm (W) – (for non-bleed). For half page advertisements the artwork should not exceed 12 cm (H) x 18 cm (W).

Size of the Journal is 28 cm x 21 cm.

For advertisement assistance & queries, contact:
Mr. Yash Pal Satmukhi, Office Secretary, JIACM
Mobile: +91-9811107245

REVIEW ARTICLE

JIACM 2026; 27 (3): 193-200

Approach to Adult-Onset Inborn Errors of Immunity: Defining the Enigma

Sarika Singh, Kamini***

Introduction

Inborn errors of immunity (IEI), formerly known as Primary immunodeficiency Disorders (PIDs), are a diverse group of inherited disorders resulting from defects in the development or function of the immune system[1]. Advances in molecular genetics and immunology have significantly expanded the understanding of these conditions, leading to the identification of more than 500 distinct disorders caused by mutations in over 450 genes[2]. The term 'Inborn Errors of Immunity' was adopted by the International Union of Immunological Societies (IUIS) to reflect the broad spectrum of clinical manifestations beyond susceptibility to infections[3].

Traditionally, IEIs were considered rare disorders characterised primarily by recurrent, severe, or unusual infections. However, growing evidence has demonstrated that many patients also present with immune dysregulation, autoimmunity, autoinflammation, allergy, lymphoproliferation, and malignancy[2,4]. Consequently, the clinical spectrum of IEIs is much wider than previously recognised, often leading to delayed diagnosis and increased morbidity.

Early recognition and diagnosis of IEIs is crucial because timely interventions, including immunoglobulin replacement therapy, antimicrobial prophylaxis, hematopoietic stem cell transplantation, and targeted molecular therapies, can significantly improve patient outcomes and quality-of-life[3].

Prevalence

The prevalence of IEIs varies across regions worldwide and is influenced by factors such as genetic background, consanguinity, healthcare professionals' awareness, and the availability of diagnostic facilities. Improved awareness, newborn screening programs, advanced immunological testing, and next-generation sequencing technologies have contributed to a steady increase in the number of diagnosed cases worldwide.

Population-based registries from Europe and North America have reported prevalence rates ranging from approximately 2.7 to 11 cases per 100,000 population[5]. The prevalence documented in national registries varies according to diagnostic capabilities and reporting systems. France has reported a prevalence of approximately 11 per 100,000 population, while the United Kingdom and Germany reported 5.9 per 100,000 and 2.7 per 100,000 population, respectively[5,6]. Common Variable Immunodeficiency (CVID) represents the most frequently diagnosed IEI in adults, whereas severe combined immunodeficiency (SCID) and combined immunodeficiencies are more commonly identified in the pediatric population.

The true prevalence in India remains uncertain and is believed to be significantly underestimated because of limited awareness, inadequate diagnostic infrastructure, and restricted access to genetic testing. Data from tertiary care centers and the Indian Society for Primary Immunodeficiency (ISPID) registry suggest a steadily increasing number of diagnosed cases over the last decade. Predominantly, antibody deficiencies, combined immunodeficiencies, and phagocytic defects constitute the majority of reported cases. Compared with Western countries, India reports a relatively higher proportion of severe combined immunodeficiencies and autosomal recessive disorders, partly due to higher rates of consanguinity in certain regions. Recent estimates suggest that tens of thousands of patients with IEI may remain undiagnosed across the country[7].

Classification of Inborn Errors of Immunity (IEI)

The International Union of Immunological Societies (IUIS) classifies Inborn Errors of Immunity[3] into the following major categories:-

1. Immunodeficiencies Affecting Cellular and Humoral Immunity: These disorders involve defects in both T-cell and B-cell immunity, leading to severe susceptibility to infections. Examples: Severe Combined Immunodeficiency, MHC class II deficiency.
2. Combined Immunodeficiencies with Associated or Syndromic Features: These disorders are characterised

**Director Professor and Head, **Senior Resident, Department of Pathology, Maulana Azad Medical College, New Delhi - 110 002. Corresponding Author: Dr Sarika Singh, Director Professor and Head, Department of Pathology, Maulana Azad Medical College, New Delhi - 110 002. Tel: 9911182326, E-mail: sarikasingh97b@gmail.com*

by immunodeficiency accompanied by developmental abnormalities or syndromic manifestations. Examples: Wiskott-Aldrich syndrome, Ataxia-telangiectasia, DiGeorge syndrome, Hyper-IgE syndrome.

3. Predominantly Antibody Deficiencies: The most common group of IEIs, characterised by impaired antibody production. Examples: Common variable immunodeficiency (CVID), X-linked agammaglobulinemia, Selective IgA deficiency, Hyper-IgM syndrome.

4. Diseases of Immune Dysregulation: These disorders result from defects in immune tolerance and regulation, leading to autoimmunity and lymphoproliferation. Examples: Autoimmune Lymphoproliferative Syndrome (ALPS), Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked) IPEX syndrome, CTLA4 deficiency, and LRBA deficiency.

5. Congenital Defects of Phagocyte Number or Function: Characterised by impaired neutrophil production or function resulting in recurrent bacterial and fungal infections. Examples: Chronic Granulomatous Disease (CGD), Leukocyte Adhesion Deficiency (LAD), Severe Congenital Neutropenia.

6. Defects in Intrinsic and Innate Immunity: These disorders predispose individuals to specific pathogens because of defects in innate immune pathways. Examples: MyD88 deficiency, IRAK4 deficiency, Chronic Mucocutaneous Candidiasis.

7. Autoinflammatory Diseases: Characterised by recurrent episodes of sterile inflammation due to dysregulation of the innate immune system. Examples: Familial Mediterranean Fever (FMF).

8. Complement Deficiencies: Caused by defects in complement proteins, leading to recurrent infections and autoimmune diseases. Examples: C2 deficiency, C3 deficiency, Terminal complement component deficiencies (C5 - C9).

9. Bone Marrow Failure Syndromes: Characterised by defective hematopoiesis and variable immunodeficiency. Examples: Fanconi anaemia, Dyskeratosis congenita, Shwachman-Diamond syndrome.

10. Phenocopies of Inborn Errors of Immunity: Conditions that clinically resemble IEIs but result from acquired genetic alterations or autoantibodies. Examples: Autoantibodies against IFN-γ.

Genetic Mutations Associated with Major Subtypes of Inborn Errors of Immunity

1. Immunodeficiencies Affecting Cellular and Humoral Immunity	
Disease	**Gene Mutation**
X-linked SCID	IL2RG
ADA deficiency SCID	ADA
JAK3 deficiency	JAK3
RAG deficiency	RAG1, RAG2
MHC class ii deficiency	RFZANK, RFX5
2. Combined Immunodeficiencies with Associated or Syndromic Features	
Disease	**Gene Mutation**
Wiskott-Aldrich syndrome	WAS
Ataxia-telangiectasia	ATM
DiGeorge syndrome	22q11.2 deletion
Hyper-IgE syndrome	STAT3
3. Predominantly Antibody Deficiencies	
Disease	Gene Mutation
X-linked agammaglobulinemia	BTK
Common Variable Immunodeficiency	TNFRSF13B, NFKB1, NFKB2
Selective IgA deficiency	Multiple susceptibility loci (often sporadic)
Hyper-IgM syndrome	CD40LG, CD40, AICDA
4. Disease of Immune Dysregulation	
Disease	**Gene Mutation**
ALPS	FAS, FASLG
IPEX syndrome	FOXP3
CTLA4 deficiency	CTLA4
LRBA deficiency	LRBA
5. Congenital Defects of Phagocyte Number or Function	
Disease	**Gene Mutation**
Chronic Granulomatous Disease	CYBB, CYBA, NCF1
Leukocyte adhesion deficiency type i	ITGB2
Severe congenital neutropenia	ELANE, HAX1
6. Defects in Intrinsic and Innate Immunity	
Disease	**Gene Mutation**
MyD88 deficiency	MYD88
IRAL4 deficiency	IRAK4
Chronic mucocutaneous candidiasis	STAT1 GOF
7. Autoinflammatory Diseases	
Disease	**Gene mutation**

Familial Mediterranean Fever	MEFV
CAPS	NLRP3
TRAPS	TNFRSF1A
8. Complement Deficiencies	
Disease	**Gene mutation**
C2 deficiency	C2
C3 deficiency	C3
Terminal complement deficiency	C5 – C9
9. Bone Marrow Failure Syndromes	
Disease	**Gene mutation**
Fanconi anemia	FANCA, FANCC
Dyskeratosis congenita	DKC1, TERC, TERT
Shwachman-Diamond syndrome	SBDS
10. Phenocopies of Inborn Errors of Immunity	
Disease	**Gene mutation**
anti-il-6 autoantibody disease	Acquired autoantibodies

Infections Associated with Inborn Errors of Immunity and Warning Signs in Affected Patients

Inborn errors of immunity (IEI) are genetically determined disorders of immune development or immune function that classically predispose to recurrent, severe, persistent, unusual, or opportunistic infections. Although infection remains the most recognised presentation, many patients also have autoimmunity, allergy, lymphoproliferation, enteropathy, inflammation, or malignancy, so infectious and noninfectious clues should be interpreted together[3,8]. Characteristic Infection Patterns in Major IEI Subsets in Adults are shown in Table I.

Types of infections associated with IEI

1. Recurrent sinopulmonary bacterial infections

These are among the commonest infectious presentations of IEI. Typical infections include recurrent otitis media, sinusitis, bronchitis, and pneumonia, especially those caused by encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. This pattern is particularly characteristic of predominantly antibody deficiencies such as X-linked agammaglobulinaemia and common variable immunodeficiency, but it can also occur in combined immunodeficiencies[9].

2. Severe or recurrent skin and soft tissue infections

Patients with phagocyte defects and some combined immunodeficiencies may develop recurrent skin abscesses, cellulitis, furunculosis, osteomyelitis, or deep organ abscesses. *Staphylococcus aureus* is a common pathogen, and "cold" abscesses are a classic clue in autosomal dominant hyper-IgE syndrome[9].

3. Opportunistic fungal and protozoal infections

Opportunistic infections are a major warning clue for T-cell or combined immune defects. Important examples include *Pneumocystis jirovecii* pneumonia, mucocutaneous or invasive *Cryptosporidium parvum*, *Giardia lamblia*, and toxoplasmosis. *Candida* infection, *Aspergillosis*, *Cryptococcosis, Histoplasmosis*, and protozoal infections[9].

4. Viral infections that are severe, persistent, or extensive

Many IEI syndromes are associated with unusually severe or treatment-refractory viral disease. These include recurrent or disseminated herpes simplex virus, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, adenovirus, enterovirus, molluscum contagiosum, and extensive human papillomavirus-related warts. Extensive cutaneous viral infections are especially characteristic of disorders such as DOCK8 deficiency and related combined immunodeficiencies[9].

5. Gastrointestinal infections and chronic diarrhea

Persistent or recurrent diarrhoea is a common infectious presentation in IEI, particularly in combined immunodeficiencies and immune dysregulation syndromes. Bacterial, viral, fungal, and protozoal causes are all reported, including *Salmonella*, *Campylobacter*, pathogenic *E. coli*, rotavirus, adenovirus, *Candida*, *Giardia*, and *Cryptosporidium*. In some patients, chronic enteric infection may lead to malabsorption, failure to thrive, or sclerosing cholangitis, especially with cryptosporidiosis[9].

6. Mycobacterial and vaccine-related infections

Disseminated bacillus Calmette-Guerin (BCG) infection, BCG adenitis, or disease due to nontuberculous mycobacteria are important clues to specific IEI pathways, particularly defects affecting IFN-gamma/IL-12 signaling or severe T-cell impairment. Severe adverse events after live vaccines, including disseminated BCG disease, vaccine-associated paralytic polio, or chronic rotavirus infection, should immediately

raise suspicion of an underlying IEI[9].

7. Central nervous system and invasive infections

Some patients present with meningitis, meningoencephalitis, septicaemia, liver abscess, or deep-seated invasive infection. Recurrent deep infection, sepsis, or infection at unusual sites is more informative than simple frequency of common viral URTI episodes[9].

need for prolonged therapy.

- Recurrent pneumonia, especially more than one severe episode or repeated lower respiratory infections.
- Failure to thrive, poor weight gain, or growth failure in children.
- Recurrent deep skin or organ abscesses.
- Persistent thrush or fungal infection of skin or mucosa after infancy.

Table I: Characteristic Infection Patterns in Major IEI Subsets in Adults

IEI Subset	Typical Pathogens/Infections	Clinical Clues
Autoinflammatory Disorders	Usually not characterised by recurrent infections; occasional secondary infections	Recurrent sterile inflammation and fever episodes
Combined Immunodeficiency (CID)	Recurrent bacterial, viral, fungal, and opportunistic infections; *Pneumocystis jirovecii*, CMV, EBV, *Candida* spp.	Severe or recurrent infections involving multiple organ systems
Predominantly Antibody Deficiencies (CVID, XLA, Selective IgA deficiency)	*Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*; recurrent sinusitis, otitis, pneumonia; recurrent sinusitis, otitis, pneumonia	Recurrent sinopulmonary infections, bronchiectasis
Immune Dysregulation Disorders	EBV, CMV, recurrent respiratory infections	Autoimmunity, lymphoproliferation, cytopenias accompanying infections
Congenital Phagocytic Defects (CGD, LAD)	*Staphylococcus aureus, Serratia marcescens, Burkholderia cepacia*l *Aspergillus* spp., *Nocardia* spp.	Deep-seated abscesses, granulomas, poor wound healing
Defects in Intrinsic and Innate Immunity	Mycobacteria, HSV, VZV, HPV, invasive fungal infections	Severe infections with specific organisms despite otherwise normal immunity
Complement Deficiencies	*Neisseria meningitidis, Neisseria gonorrhoeae*	Recurrent meningococcal disease, septicaemia
Bone Marrow Failure Syndromes	Recurrent bacterial and fungal infections secondary to neutropenia	Cytopenias, marrow dysfunction
Phenocopies of IEI	Opportunistic infections resembling primary IEI	Autoantibodies or somatic mutations causing immune dysfunction
Combined Immunodeficiency with Syndromic Features (DiGeorge syndrome, AT, Hyper-IgE syndrome, WAS)	Recurrent bacterial, viral, and fungal infections depending on the underlying defect	Associated syndromic manifestations such as dysmorphism, eczema, ataxia, thrombocytopenia

Warning signs in patients with IEI

The traditional Jeffrey Modell warning signs remain useful as a screening framework, although recent evidence shows that they have higher specificity than sensitivity and may miss patients with predominantly noninfectious phenotypes. In practice, the most helpful warning signs are those that combine infectious severity with family history, treatment failure, or associated immune dysregulation.

Classical warning signs

- Multiple new ear infections within one year.
- Recurrent serious sinus infections within one year.
- Two or more months of antibiotics with little effect, or
- Need for intravenous antibiotics to clear infections.
- Two or more deep-seated infections, including septicaemia.
- Family history of IEI or early unexplained sibling deaths.

Additional warning signs beyond infection

Modern IEI recognition also requires attention to noninfectious clues. These include severe eczema, marked atopy, autoimmune cytopenias, lymphadenopathy, hepatosplenomegaly, granulomatous disease, chronic diarrhea, enteropathy, unexplained inflammation, and early-onset malignancy. Patients with these features may still have relatively few classic infections, so relying only on the old warning-sign lists can delay diagnosis[3].

The most suspicious pattern is not simply "frequent infection," because healthy children may also have repeated self-limited viral illnesses. More concerning features are severe infections, unusual organisms, opportunistic pathogens, poor response to standard antibiotics, repeated hospitalisations, infections at unusual sites, or infection combined with autoimmunity, eczema, lympho-proliferation, or growth failure. IEI should be considered at any age, since many antibody deficiencies and immune dysregulation syndromes present in adolescence or adulthood rather than infancy alone.

The infections associated with IEI span recurrent sinopulmonary bacterial disease, skin and deep abscess-forming infections, chronic gastrointestinal infection, severe viral disease, opportunistic fungal and protozoal infection, mycobacterial disease, and vaccine-related disseminated infection. Warning signs include recurrent severe infections, persistent thrush, deep abscesses, failure to thrive, need for intravenous antibiotics, and positive family history, but modern assessment must also include noninfectious red flags such as severe eczema, autoimmunity, enteropathy, and lymphoproliferation.

Approach to a patient with suspected IEI

A practical diagnostic approach begins with clinical suspicion. IEI should be considered in patients with recurrent, severe, unusual, or treatment-refractory infections; persistent thrush; skin or deep abscesses; failure to thrive; chronic diarrhoea; severe eczema or atopy; autoimmune cytopenias; unexplained lymphoproliferation; granulomatous inflammation; or a relevant family history. Suspicion should extend beyond children because many antibody deficiencies and immune dysregulation syndromes present in adolescence or adulthood[10].

A stepwise approach is useful:

1. Exclude secondary immunodeficiency caused by HIV or other infections, malnutrition, protein loss, malignancy, or immunosuppressive drugs.
2. Obtain baseline screening tests, including complete blood count with differential and peripheral smear, looking for lymphopenia, neutropenia, thrombocytopenia, abnormal leukocyte morphology, or syndromic haematologic clues.
3. Assess immune compartments with serum immunoglobulins (IgG, IgA, IgM), lymphocyte subset immunophenotyping by flow cytometry.
4. Use functional assays guided by phenotype, such as lymphocyte proliferation studies, neutrophil oxidative burst testing by DHR for chronic granulomatous disease, cytokine-response assays, and complement testing.
5. Proceed to molecular diagnosis using next-generation sequencing panels, whole-exome sequencing, or other genomic approaches, particularly in severe, syndromic, early-onset, familial, or diagnostically unresolved cases.
6. Refer early to a clinical immunologist because timely diagnosis changes outcomes, informs infection prophylaxis, immunoglobulin replacement, gene therapy options, and precision immunomodulation.

For severe combined immunodeficiency, urgency is critical because early diagnosis before major infection substantially improves outcome after haematopoietic stem cell transplantation. Newborn screening using T-cell receptor excision circles is an effective strategy for identifying many cases of SCID, though it does not detect all IEI. Diagnostic Approach to Suspected Inborn Errors of Immunity (IEI) in Adult shown in flowchart (Fig. 1).

Adult Patient with Suspected IEI

Clinical Assessment

- Recurrent, severe, unusual infections
- Autoimmunity
- Autoinflammation
- Lymphoproliferation
- Severe allergy/eczema
- Family history of IEI
- Early-onset malignancy

Initial Laboratory Evaluation

- CBC with differential count
- Peripheral smear
- Serum immunoglobulins (IgG, IgA, IgM, IgE)
- ESR/CRP
- HIV testing
- Basic biochemical profile (LFT. KFT, Total protein, A:G ratio, LDH, CRP)

Abnormal Findings?

Yes

Targeted Immunological Evaluation

- Lymphocyte subsets (CD3, CD4, CD8, CD19, CD16/56, CD7, CD57, CD45RA, CD45Ro, HLADR, CD25, CD24,CD38)

- Vaccine antibody responses
- Complement assays (CH50/AH50)
- Neutrophil oxidative burst (DHR)
- Functional immune assays

Phenotypic Classification

- Antibody deficiency
- Combined immunodeficiency
- Immune dysregulation
- Phagocytic defect
- Complement deficiency
- Innate immune defect

Genetic Evaluation

- Targeted gene panel
- Whole exome sequencing
- Whole genome sequencing

Definitive IEI Diagnosis

Management and Follow-up

- Immunoglobulin replacement
- Antimicrobial prophylaxis
- Targeted biologics
- Haematopoietic stem cell transplant
- Genetic counselling'

Fig. 1: *Diagnostic approach to suspected inborn errors of immunity (IEI) in adults.*

Although adult-onset severe combined immunodeficiency is uncommon, delayed diagnosis may lead to life-threatening opportunistic infections and hyperinflammatory complications. To highlight the diagnostic approach and pathological findings, we describe a representative case of disseminated cryptococcosis that revealed previously undiagnosed adult-onset SCID and was subsequently complicated by secondary haemophagocytic lymphohistiocytosis.

Case 1

A 42-year-old previously healthy male presented with a two-week history of persistent fever, generalised weakness, and progressive fatigue. He denied any history of recurrent infections, weight loss, chronic illness, immunosuppressive therapy, or prior hospitalisations. Physical examination revealed hepatosplenomegaly with bilateral sub-centimetric cervical lymphadenopathy. Initial laboratory investigations demonstrated pancytopenia with a haemoglobin level of 6.0 g/dL, total leukocyte count of 3.2 $\times$ 10 y/L, and a normocytic normochromic peripheral blood picture, while liver and renal function tests were within normal limits. In view of persistent fever and unexplained cytopenias, bone marrow aspiration and trephine biopsy were performed, revealing a hypocellular marrow with preserved trilineage haematopoiesis and numerous intracellular and extracellular fungal organisms, some exhibiting artefactual clearing. The fungal organisms stained positively with periodic acid-Schiff (PAS) and Gomori methenamine silver (GMS), while strong mucicarmine positivity confirmed the diagnosis of disseminated cryptococcosis. Fine-needle aspiration cytology from a neglected scrotal swelling also demonstrated abundant cryptococcal organisms, further supporting disseminated fungal infection (Fig. 2).

As disseminated cryptococcosis in an HIV-negative individual raised suspicion for an underlying immunodeficiency, further investigations were undertaken. Serological tests for HIV, hepatitis B and C, and autoimmune markers were negative, whereas serum immunoglobulin levels were markedly reduced. Flow cytometric immunophenotyping demonstrated profound lymphopenia with markedly reduced T-cells (342 cells/mm^3), B-cells (53 cells/mm^3), and NK cells (12 cells/mm^3), consistent with

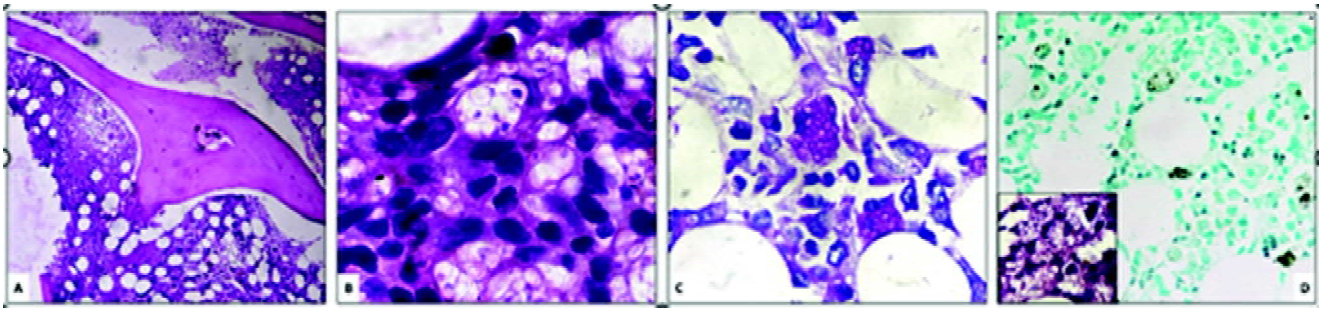


Fig. 2: *(A and B) Ante-mortem bone marrow biopsy demonstrating marrow involvement by Cryptococcus infection (100 x and 400 x, H and E). (C) Periodic acid–Schiff (PAS) stain highlighting fungal organisms (400 x) (D) Gomori methenamine silver (GMS) stain (200 x) demonstrating the fungal spores, with mucicarmine stain shown in the inset.*

severe combined immunodeficiency (SCID) or a late-onset combined immunodeficiency phenotype. The patient was treated with intravenous amphotericin B followed by high-dose fluconazole and broad-spectrum antibiotics; however, despite aggressive therapy, he developed progressive multiorgan dysfunction and succumbed to cardiac arrest. Post-mortem bone marrow examination revealed extensive hemophagocytosis with numerous CD68-positive histiocytes containing fungal organisms and engulfed haematopoietic cells. Retrospective review of laboratory investigations showed marked hyperferritinaemia (3,600 ng/mL) and hypertriglyceridaemia, fulfilling the diagnostic criteria for secondary haemophagocytic lymphohistiocytosis (HLH). This case illustrates a rare presentation of occult adult-onset SCID unmasked by disseminated cryptococcosis and complicated by fatal infection-associated HLH.

The following case highlight the diverse clinical spectrum of adult-onset inborn errors of immunity (IEI) presenting with visceral leishmaniasis. Owing to impaired cell-mediated immunity, patients with IEI are predisposed to severe, recurrent, or atypical infections, which may be the first manifestation of an underlying immune defect in adulthood.

Case 2

A 27-year-old previously undiagnosed male presented with fever, marked haepatosplenomegaly (liver 15.8 cm, spleen 19 cm), and bicytopenia with macrocytic anaemia (Hb 8 g/dL; MCV 100 fL) and leukopenia. Laboratory evaluation showed low ferritin (87.6 ng/mL) with normal platelet count on manual estimation. Bone marrow examination revealed a hypocellular marrow (approximately 50 - 60% cellularity for age) with trilineage haematopoiesis, prominent megaloblastic erythroid hyperplasia with dyserythropoietic changes, adequate megakaryopoiesis, increased histiocytes exhibiting haemophagocytosis, and no evidence of atypical cells, granulomas, or hematological malignancy. Bone marrow aspirate and imprint smears demonstrated both intracellular and extracellular amastigote forms of *Leishmania donovani*, confirming visceral leishmaniasis (Figure 3). The patient was advised vitamin B12/folate assessment along with specific evaluation and treatment for leishmaniasis. In view of the occurrence of disseminated visceral leishmaniasis in a young adult without an apparent secondary cause, an underlying inborn error of immunity (IEI) was considered. This case underscores that adult-onset IEI should be included in the differential diagnosis of visceral leishmaniasis presenting with cytopenias and haepatosplenomegaly, particularly after exclusion of haematological malignancy, as recognition of an underlying primary immunodeficiency has important implications for targeted immunological evaluation, genetic testing, management, and long-term follow-up.

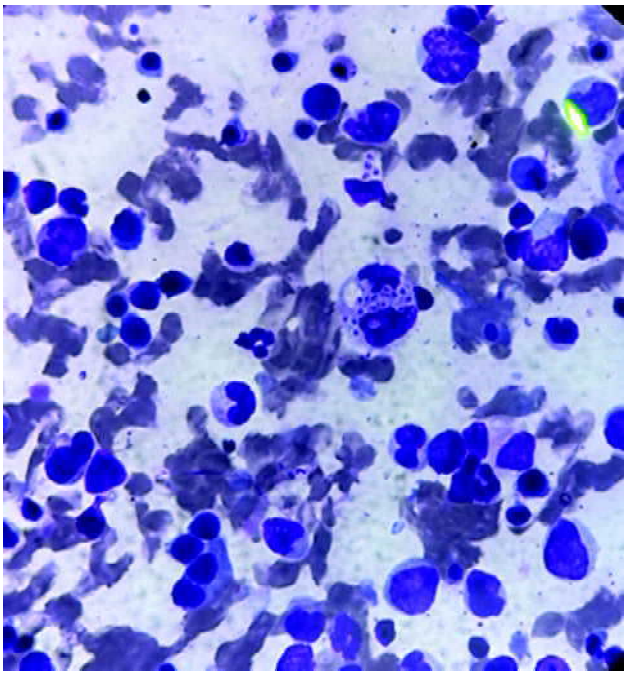


Fig. 3: *Bone marrow aspirate smears demonstrating amastigote forms of Leishmania donovani.*

Discussion

The modern IEI framework is no longer limited to recurrent infection syndromes. Instead, it encompasses disorders of host defence, immune regulation, inflammation, allergy, and predisposition to malignancy, linked by molecular defects in immune pathways. This broader view is especially relevant in adult medicine and pathology-based practice, where autoimmune, granulomatous, lymphoproliferative, or inflammatory presentations may precede recognition of an underlying IEI.

In the Indian context, under-recognition remains a major challenge. Expansion of national registries, improved access to flow cytometry and genomic testing, and greater clinician awareness are essential for defining the true epidemiology and improving patient outcomes.

The diagnostic evaluation of IEI is challenging because these disorders are clinically heterogeneous and may present at any age with infectious or non-infectious manifestations.

Although recurrent infections remain a major clue, many patients first come to attention because of autoimmunity,

severe eczema, enteropathy, lymphoproliferation, unexplained inflammation, or malignancy risk, which can delay recognition if clinicians rely too narrowly on classic warning signs. A major strength of the modern approach is the use of phenotype-directed testing. Careful characterisation of the infection pattern, age at onset, family history, vaccine reactions and associated immune dysregulations helps direct the initial laboratory panel and avoid indiscriminate testing. In this setting, basic investigations such as CBC, immunoglobulin levels, lymphocyte subsets, complement assays, and neutrophil oxidative burst testing remain highly valuable because they rapidly identify broad immune-compartment defects and help prioritize more specialised studies.

At the same time, laboratory diagnosis has clear limitations. Normal screening tests do not exclude IEI, especially in patients with subtle immune dysregulation, pathway-specific defects, or phenocopies, and the quality and standardisation of non-functional immunological assays can vary across laboratories. For this reason, functional assays and genomic testing have become increasingly important, particularly when the phenotype is severe, syndromic, early in onset, familial, or unexplained after first-line evaluation.

Genetic testing has transformed the field by moving diagnosis from broad clinical syndromes towards molecularly defined disease.

Overall, the most effective strategy is a tiered and multidisciplinary one that integrates clinical suspicion, screening immunology, targeted functional studies, and genetic confirmation. Such an approach improves diagnostic yield, reduces delay, and supports timely initiation of immunoglobulin replacement, antimicrobial prophylaxis, haematopoietic stem cell transplantation, or other targeted therapies.

Conclusion

Inborn errors of immunity are a rapidly expanding group of genetically determined disorders with diverse infectious and non-infectious manifestations. Current IUIS classifications recognize hundreds of genes and phenotypes, and clinical evaluation increasingly depends on integrating phenotype, immunologic testing, and genomic analysis. Western data suggest that IEI is more common than historically believed, while Indian prevalence remains incompletely defined because of underdiagnosis and limited registry capture. A structured, stepwise diagnostic approach is essential for early recognition, subtype definition, and institution of targeted therapy.

References

1. Mamede L, Sabà RC, Van Coillie S *et al*. Navigating disruption in the PID landscape: embracing opportunities and anticipating threats in the next ten years. *Front Immunol* 2025; 16: 1596971.
2. Thalhammer J, Kindle G, Nieters A *et al*. European Society for Immunodeficiencies Registry Working Party. Initial presenting manifestations in 16,486 patients with inborn errors of immunity include infections and noninfectious manifestations. *J Allergy Clin Immunol* 2021; 148 (5): 1332-41.
3. Tangye SG, Al-Herz W, Bousfiha A *et al*. Human Inborn Errors of Immunity: 2019 Update on the Classification from the International Union of Immunological Societies Expert Committee. *J Clin Immunol* 2020; 40 (1): 24-64.
4. Bousfiha A, Jeddane L, Picard C *et al*. Human Inborn Errors of Immunity: 2019 Update of the IUIS Phenotypical Classification. *J Clin Immunol* 2020; 40 (1): 66-81.
5. Gathmann B, Goldacker S, Klima M *et al*. The German national registry for primary immunodeficiencies (PID). *Clin Exp Immunol* 2013; 173 (2): 372-80.
6. Shillitoe B, Bangs C, Guzman D *et al*. The United Kingdom Primary Immune Deficiency (UKPID) registry 2012 to 2017. *Clin Exp Immunol* 2018; 192 (3): 284-91.
7. Jindal AK, Pilania RK, Rawat A. Primary Immunodeficiency Disorders in India-A Situational Review. *Front Immunol* 2017; 8: 714.
8. Subbarayan A, Colarusso G, Hughes SM *et al*. Clinical features that identify children with primary immunodeficiency diseases. *Paediatrics* 2011; 127 (5): 810-6.
9. George K, Govindaraj G. Infections in Inborn Errors of Immunity with Combined Immune Deficiency: A Review. *Pathogens* 2023; 12 (2): 272.
10. Devonshire AL, Makhija M. Approach to primary immunodeficiency. *Allergy Asthma Proc* 2019; 40 (6): 465-9.

REVIEW ARTICLE

JIACM 2026; 27 (3): 201-10

Active and Latent Tuberculosis Among Household Contacts of Pulmonary Tuberculosis Patients: Epidemiology, Determinants and Diagnostic Approaches: A Narrative Review

Kheta Ram Solanki, Ramakant Dixit**, Ankur Gupta****

Abstract

***Background:** Household contacts of pulmonary tuberculosis (TB) patients constitute a high-risk population for both active tuberculosis and latent tuberculosis infection (LTBI) because of prolonged and repeated exposure to infectious individuals. Understanding the burden, determinants, diagnostic approaches, and preventive strategies in this group is essential for effective tuberculosis control.*

***Objective:** To review the current evidence on the epidemiology, determinants, diagnosis, and prevention of active tuberculosis and LTBI among household contacts of pulmonary tuberculosis patients.*

***Methods:** A narrative review of published literature was conducted, focusing on studies evaluating the prevalence of active TB and LTBI, associated risk factors, diagnostic modalities, and preventive interventions among household contacts.*

***Results:** The prevalence of active tuberculosis among household contacts ranges from approximately 1% to 12%, while LTBI prevalence frequently exceeds 40% and may surpass 60% in high-burden settings. LTBI is considerably more common than active disease, representing a substantial reservoir for future tuberculosis cases. Evidence indicates that transmission and disease progression are influenced by a complex interaction of exposure-related and host-related factors. Prolonged exposure, smear positivity of the index case, overcrowding, and delayed diagnosis primarily influence infection acquisition, whereas progression to active disease is more strongly associated with age, diabetes mellitus, smoking, immune status, and nutritional status. Advances in molecular diagnostics, chest radiography, interferon-gamma release assays, and newer antigen-specific skin tests such as Cy-TB have improved opportunities for early detection. Recent studies also demonstrate that nutritional supplementation and tuberculosis preventive therapy can significantly reduce the risk of disease progression among household contacts.*

***Conclusion:** Household contacts represent a major reservoir of latent infection and a population at substantial risk of active tuberculosis. Effective tuberculosis control requires comprehensive household contact investigation integrating active case finding, LTBI screening, preventive therapy, nutritional support, and risk-factor modification. Strengthening these strategies will be essential for reducing transmission and accelerating progress toward tuberculosis elimination.*

***Key words:** Tuberculosis; latent tuberculosis infection; household contacts; contact investigation; risk factors; Cy-TB; tuberculosis preventive therapy; active case finding.*

Introduction

Tuberculosis (TB) remains a major global public health challenge and continues to be one of the leading causes of death from a single infectious agent. According to the World Health Organisation (WHO), an estimated 10.7 million people developed Tuberculosis worldwide in 2024, with India contributing the largest share of global burden. Despite significant advances in diagnosis, treatment, and prevention, Tuberculosis continues to impose substantial health, social, and economic consequences, particularly in low- and middle-income countries[1,2].

Transmission of *Mycobacterium tuberculosis* occurs primarily through inhalation of infectious aerosols generated by individuals with pulmonary TB. Consequently, household contacts of pulmonary TB patients represent one of the highest-risk populations for both TB infection and disease because of prolonged and repeated exposure within shared living environments. Factors such as overcrowding, poor ventilation, delayed diagnosis of the index case, and adverse socio-economic conditions further increase the risk of transmission within households[3].

Following exposure, individuals may develop either active TB or latent tuberculosis infection (LTBI). Active TB is associated with clinical disease, morbidity, mortality, and ongoing transmission, whereas LTBI represents a state of persistent immune sensitisation to *M. tuberculosis* without

Post-Gradute Resident, **Senior Professor and Former Head, ***Medical Officer, Department of Resipratory Medicine, JLN Medical College, Ajmer - 305 001, Rajasthan.

Corresponding Author: Dr Ramakant Dixit, Senior Professor and Former Head, Department of Resipratory Medicine, JLN Medical College, Ajmer - 305 001, Rajasthan. Tel: 9413040257, E-mail: dr.ramakantdixit@gmail.com

clinical evidence of disease. Although individuals with LTBI are asymptomatic and non-infectious, they constitute an important reservoir for future active TB. Household contacts consistently demonstrate substantially higher rates of both active TB and LTBI than the general population, making them a key target for TB control programmes[4,5].

The burden of TB among household contacts is influenced by a complex interaction of exposure-related, environmental, and host-related factors. Bacillary load of the index case, duration and intensity of exposure, crowding, ventilation, age, nutritional status, diabetes mellitus, HIV infection, smoking, and socio-economic conditions have all been implicated as determinants of infection and disease progression. While exposure-related factors primarily influence acquisition of infection, host-related factors appear to play a greater role in progression from latent infection to active disease[6-8].

Early identification of active TB and LTBI among household contacts has become a cornerstone of global TB control strategies. Systematic contact investigation, supported by advances in molecular diagnostics, interferon-gamma release assays (IGRAs), and newer antigen-specific skin tests such as Cy-TB, provides opportunities for earlier detection and preventive intervention[9,10].

Given the substantial burden of active TB and LTBI among household contacts, a comprehensive understanding of their epidemiology, determinants, diagnostic approaches, and preventive strategies is essential. This narrative review synthesizes current evidence on active and LTBI among household contacts of pulmonary TB patients, with particular emphasis on factors influencing transmission, disease progression, diagnosis, and prevention.

Methodology

A narrative review was conducted to evaluate the burden, determinants, diagnostic approaches, and preventive strategies related to active tuberculosis (TB) and latent tuberculosis infection (LTBI) among household contacts of pulmonary TB patients. Relevant English-language literature was identified through searches of PubMed, Scopus, Google Scholar, Embase, and the Cochrane Library.

The search strategy included combinations of Medical Subject Headings (MeSH) terms and keywords such as "tuberculosis", "latent tuberculosis infection", "household contacts", "contact investigation", "active tuberculosis", "risk factors", "Mantoux test", "interferon-gamma release assay", "Cy-TB", and "preventive therapy". Additional articles were identified through manual review of reference lists and relevant international guidelines.

Original research articles, systematic reviews, meta-analyses, randomised controlled trials, observational studies, and guidelines from organisations including the World Health Organisation (WHO) and the National Tuberculosis Elimination Programme (NTEP) were considered. Studies reporting data on active TB, LTBI, risk factors, diagnostic methods, or preventive interventions among household contacts were prioritized.

The evidence was synthesized thematically and organised into key domains including disease burden, determinants, diagnostic approaches, preventive therapy, and challenges in household contact investigation, with emphasis on areas of consensus, controversy, and future research needs.

Burden of Active Tuberculosis Among Household Contacts

Household contacts of pulmonary TB patients represent one of the highest-risk groups for active TB because of prolonged exposure to infectious aerosols within shared living environments. Numerous studies have demonstrated that systematic contact investigation identifies a substantial number of previously undiagnosed TB cases, emphasizing its importance in TB control programmes.

Evidence from systematic reviews and meta-analyses indicates that active TB among household contacts is not uncommon. Morrison *et al*[4] reported a pooled prevalence of 4.5% among close contacts in low- and middle-income countries, while Seid *et al*[11] reported a prevalence of 3.29% across sub-Saharan Africa. These findings suggest that approximately one in every 20 - 30 household contacts may have active disease, highlighting the value of routine contact investigation.

Considerable variation in prevalence has been reported across different settings. Daniel *et al*[12] observed an active TB prevalence of 2.72% among household contacts in Ethiopia, whereas studies from Brazil and other African countries have generally reported rates between 1% and 4%. In India, Singh *et al*[13] documented active TB in 6.9% of household contacts and demonstrated that new cases continued to emerge during follow-up, emphasizing the importance of longitudinal surveillance. Similarly, Chawla *et al*[14] reported tuberculosis in 12.1% of household contacts following active case finding, among the highest prevalence estimates reported in the literature.

The observed variability likely reflects differences in diagnostic methods, follow-up duration, infectiousness of index cases, HIV prevalence, nutritional status, socio-economic conditions, and household environmental factors. Studies incorporating active case finding, microbiological confirmation, and longitudinal follow-up generally report higher yields than cross-sectional or symptom-based screening approaches.

Despite these differences, a consistent finding across studies is that household contacts carry a substantially greater burden of active TB than the general population. This observation supports current WHO and national tuberculosis programme recommendations advocating systematic household contact investigation for early case detection and interruption of transmission. Overall, the available evidence demonstrates that active TB remains an important public health concern among household contacts and highlights the need for comprehensive screening, periodic follow-up, and targeted preventive interventions.

LTBI prevalence varies considerably across settings, ranging from approximately 20% to over 60%. In India, Sangma *et al*[15] reported an LTBI prevalence of 26.36%, while Praveen *et al*[16] observed a prevalence of 43.6% among contacts of sputum-positive pulmonary tuberculosis patients. Similarly, Barik *et al*[17] reported an LTBI prevalence of 20.4% using a combination of tuberculin skin testing and interferon-gamma release assays. Higher prevalence estimates have been reported from other regions, including Indonesia, where Karbito *et al*[18] documented LTBI in 63.8% of household contacts. Likewise, Moosazadeh *et al*[5] reported an LTBI prevalence of 42.8% and demonstrated that household contacts had a markedly higher risk of active TB than the general population.

Table I: Key studies reporting active tuberculosis among household contacts of pulmonary tuberculosis patients.

Study	Country	Study Design	Sample Size	Active TB Prevalence	Key Findings
Morrison *et al*[4]	Multiple LMICs	Systematic review and meta-analysis	Multiple studies	4.50%	Household contacts have substantially higher active TB burden than the general population
Seid *et al*[11]	Sub-Saharan Africa	Systematic review and meta-analysis	95 studies	3.29%	Confirmed significant burden of active TB among household contacts across Africa
Daniel *et al*[12]	Ethiopia	Cross-sectional	344 contacts	2.72%	Active case finding identified previously undiagnosed TB cases among contacts
Chawla *et al*[14]	India	Prospective observational	356 contacts	1.97%	Active contact investigation improved case detection
Singh *et al*[13]	India	Prospective cohort	548 contacts	6.90%	Demonstrated both co-prevalent and incident TB among household contacts
Pinto *et al*[31]	Brazil	National cohort study	420,854 contacts	2.12%	Household contacts had significantly elevated TB risk compared with the general population

LMICs: Low- and Middle-Income Countries.

Burden of Latent Tuberculosis Infection Among Household Contacts

Latent tuberculosis infection (LTBI) represents the largest reservoir of *Mycobacterium tuberculosis* infection worldwide and plays a central role in sustaining the TB epidemic. Although individuals with LTBI are asymptomatic and non-infectious, they remain at risk of progressing to active disease, particularly in the presence of immunosuppression or other risk factors. Consequently, identification and management of LTBI among household contacts have become key components of TB control strategies.

Household contacts experience substantially higher rates of latent infection than the general population because of prolonged exposure to infectious cases. Morrison *et al*[4] estimated that approximately 51.5% of household contacts in low- and middle-income countries have LTBI, indicating that more than half of exposed individuals acquire infection following close contact with an infectious case. This finding highlights the magnitude of the latent reservoir within households.

The wide variation in LTBI prevalence reflects differences in diagnostic methods, exposure intensity, index case infectiousness, household crowding, ventilation, socio-economic conditions, and background community transmission. Several studies have identified prolonged daily exposure, shared sleeping spaces, overcrowding, and diabetes mellitus as important predictors of LTBI acquisition. Karbito *et al*[18] demonstrated significantly higher infection rates among contacts exposed for more than five hours daily and among those living in overcrowded households, emphasizing the importance of exposure-related factors.

From a public health perspective, LTBI among household contacts presents both a challenge and an opportunity. While latent infection constitutes a major reservoir for future TB cases, it also provides an important target for preventive interventions. Systematic identification of LTBI through contact investigation, followed by appropriate TB preventive therapy, remains a cornerstone of the WHO End TB Strategy and national TB elimination programmes.

Overall, the available evidence demonstrates that LTBI is highly prevalent among household contacts and occurs far more frequently than active disease. The consistently elevated burden observed across diverse settings highlights the importance of routine contact investigation, accurate diagnostic approaches, and implementation of preventive strategies aimed at reducing future TB incidence.

whereas older adults may be at increased risk owing to immunosenescence and associated comorbidities. Adult contacts often demonstrate higher LTBI prevalence because of greater cumulative exposure.

Sex-related differences have been reported across studies. Acuña-Villaorduña *et al*[9] observed a higher

Table II: Key studies reporting latent tuberculosis infection among household contacts of pulmonary tuberculosis patients.

Study	Country	Study Design	Sample Size	LTBI Prevalence	Key Findings
Morrison *et al*[4]	Multiple LMICs	Systematic review and meta-analysis	Multiple studies	51.50%	More than half of household contacts had LTBI
Moosazadeh *et al*[5]	Iran	Systematic review and meta-analysis	Multiple studies	42.80%	Confirmed elevated LTBI burden among household contacts globally
Seid *et al*[11]	Ethiopia	Cross-sectional	668 contacts	42.80%	Demonstrated substantial LTBI prevalence in a high-burden setting
Sangma *et al*[15]	India	Cross-sectional	330 contacts	26.36%	Lower LTBI prevalence compared with many international studies
Praveen *et al*[16]	India	Cross-sectional	220 contacts	43.60%	Diabetes mellitus and exposure-related factors influenced LTBI risk
Barik *et al*[17]	India	Cross-sectional	235 contacts	20.40%	LTBI prevalence varied according to diagnostic modality used
Karbito *et al*[18]	Indonesia	Cross-sectional	138 contacts	63.80%	One of the highest LTBI prevalence rates reported; prolonged exposure and crowding were major determinants
Odera *et al*[32]	Kenya	Cross-sectional	175 contacts	55.70%	High LTBI burden among exposed household contacts

LMICs: Low- and Middle-Income Countries.

Determinants of Active and Latent Tuberculosis Among Household Contacts

The occurrence of active TB and LTBI among household contacts is influenced by a complex interaction of host-related, exposure-related, environmental, and socio-economic factors. While exposure to an infectious index case is a prerequisite for transmission, only a proportion of exposed individuals acquire infection, and an even smaller proportion subsequently progress to active disease. This variability reflects differences in susceptibility arising from demographic characteristics, nutritional status, comorbidities, living conditions, and intensity of exposure. Understanding these determinants is essential for identifying high-risk contacts, improving risk stratification, and designing targeted interventions for TB prevention and control.

(A) Host-Related Determinants

Several host-related factors influence susceptibility to TB infection and progression to active disease among household contacts. Age is an important determinant, although its effect differs for latent infection and active disease. Young children are particularly vulnerable to progression because of immature immune responses,

likelihood of LTBI among male contacts, while Velen *et al*[7] identified male sex as an independent predictor of active TB. Conversely, some studies have reported higher LTBI prevalence among female contacts, suggesting that gender-related differences may vary according to local socio-cultural and exposure patterns.

Comorbid conditions substantially increase TB risk. Diabetes mellitus has emerged as one of the strongest predictors of both LTBI and active disease among household contacts. Velen *et al*[7] reported more than a threefold increase in TB risk among diabetic contacts, while Praveen *et al*[16] similarly identified diabetes as an important determinant of LTBI. Other conditions including HIV infection, chronic kidney disease, and immunosuppressive states may also increase susceptibility to infection and disease progression.

Behavioural factors further contribute to risk. Smoking has been consistently associated with active TB among household contacts, with Velen *et al*[7] demonstrating a threefold increase in disease risk among current smokers. Household smoking exposure and excessive alcohol consumption have also been linked to increased TB risk through their adverse effects on respiratory defenses, immunity, and nutritional status.

Overall, age, sex, comorbidities, and behavioural factors significantly influence both acquisition of infection and progression to active disease. Identification of high-risk contacts based on these characteristics may improve the effectiveness of contact investigation and targeted preventive interventions.

(B) Exposure-Related Determinants

Exposure to an infectious TB patient is the fundamental prerequisite for transmission, and the intensity, duration, and proximity of exposure are among the strongest determinants of both LTBI and active TB among household contacts.

Duration of exposure has been consistently associated with increased infection risk. Acuña-Villaorduña *et al*[9] demonstrated a dose – response relationship between exposure duration and LTBI prevalence, with infection risk increasing significantly beyond 250 hours of exposure. Similarly, Karbito *et al*[18] reported nearly fivefold higher odds of LTBI among contacts exposed to index cases for more than five hours per day, highlighting the importance of prolonged exposure.

Physical proximity also plays a crucial role. Sharing a bedroom with an infectious patient has been associated with significantly higher LTBI prevalence, likely due to increased cumulative aerosol exposure. Acuña-Villaorduña *et al*[9] further reported that contacts sharing sleeping spaces with index cases had higher infection rates than other household members.

Characteristics of the index case substantially influence transmission. Exposure to sputum smear-positive patients, bilateral pulmonary disease, and extensive radiological involvement has been associated with increased LTBI risk, reflecting the role of bacillary burden and disease severity in household transmission[9]. Delayed diagnosis and prolonged symptomatic periods further increase transmission opportunities. Velen *et al*[7] demonstrated that a longer duration of cough in the index case independently increased the risk of TB among household contacts.

Exposure to multiple infectious individuals may further amplify transmission. Acuña-Villaorduña *et al*[9] reported significantly higher LTBI prevalence among contacts exposed to more than one index case, while Laghari *et al*[19] identified prolonged daily exposure (>18 hours/day) and the presence of another TB case within the household as important predictors of secondary TB.

Overall, duration and proximity of exposure, infectiousness of the index case, treatment delay, and exposure to multiple tuberculosis patients are major determinants of transmission within households. These findings support prioritisation of close and highly exposed contacts for active case finding, LTBI screening, and preventive interventions.

(C) Environmental and Household Determinants

Environmental and household conditions play a critical role in TB transmission by influencing the concentration and circulation of infectious aerosols within shared living spaces. Household contacts residing in overcrowded, poorly ventilated, and socio-economically disadvantaged environments are at increased risk of both LTBI and active TB.

Household crowding is among the strongest environmental determinants of transmission. Karbito *et al*[18] demonstrated that contacts living in overcrowded bedrooms had more than fivefold higher odds of LTBI, while Laghari *et al*[19] identified overcrowding as a significant predictor of secondary tuberculosis. Limited living space increases close contact with infectious individuals and reduces opportunities for adequate air exchange.

Ventilation is another key determinant. Poorly ventilated households facilitate accumulation of airborne bacilli, increasing the likelihood of transmission. Singh *et al*[20] reported inadequate ventilation in more than half of TB-affected households, highlighting the persistence of unfavorable indoor environmental conditions in high-burden settings. Similarly, inadequate sunlight exposure, often a marker of poor housing quality, has been associated with increased TB vulnerability[20].

Indoor air pollution and household smoking exposure further contribute to risk. Biomass fuel combustion, tobacco smoke, and other indoor pollutants impair respiratory defenses and may facilitate both infection and disease progression. Laghari *et al*[19] identified household smoking exposure as an independent predictor of secondary TB among contacts.

Household size and the presence of multiple TB cases within the same residence also influence transmission dynamics. Larger households increase the number of susceptible individuals exposed to infectious patients, while multiple TB cases within a household may reflect intense transmission networks. Laghari *et al*[19] reported that the presence of another TB case within the household was among the strongest predictors of secondary disease.

Overall, crowding index, poor ventilation, inadequate housing conditions, limited sunlight exposure, indoor

air pollution, and larger household size significantly contribute to TB transmission among household contacts. Addressing these environmental factors alongside biomedical interventions may substantially reduce household transmission and strengthen TB control efforts.

(D) Socio-economic Determinants

TB is closely linked to poverty and social deprivation, with socio-economic conditions influencing exposure risk, nutritional status, healthcare access, and disease outcomes. Among household contacts, socio-economic disadvantage not only increases the likelihood of infection but also contributes to progression from latent infection to active disease.

Poverty remains one of the most consistently reported determinants of TB. Individuals from low-income households often experience overcrowding, poor ventilation, undernutrition, and limited access to healthcare services. Singh *et al*[20] reported that most tuberculosis-affected individuals belonged to economically disadvantaged households characterised by poor living conditions, low educational attainment, and inadequate access to essential services. Similarly, Laghari *et al*[19] identified low family income as a significant predictor of secondary TB among household contacts.

Educational status also influences TB risk by affecting awareness of symptoms, transmission, preventive measures, and healthcare-seeking behaviour. Lower educational attainment may delay diagnosis, reduce treatment adherence, and limit participation in contact investigation programmes. In addition, restricted access to healthcare services due to cost, distance, and limited availability of diagnostic facilities can further delay case detection and treatment initiation. Singh *et al*[20] identified these barriers as common obstacles to timely TB care.

The economic consequences of TB often perpetuate a cycle of poverty and disease. Wingfield *et al*[21] demonstrated that TB-related costs frequently reached catastrophic levels for affected households and were associated with poorer treatment outcomes. Importantly, socio-economic support interventions improved treatment success and uptake of preventive therapy among household contacts.

Beyond material deprivation, stigma and social exclusion may discourage individuals from seeking care or participating in contact screening, thereby contributing to delayed diagnosis and continued transmission. Overall, poverty, low income, limited education, poor healthcare access, economic hardship, and stigma are important determinants of TB among household contacts and should be addressed alongside biomedical interventions to achieve effective disease control.

(E) Nutritional Determinants

Nutrition is one of the most important and potentially modifiable determinants of TB susceptibility and disease progression. The relationship between TB and undernutrition is bidirectional: undernutrition increases vulnerability to TB through impaired immune function, while active disease further worsens nutritional status through increased metabolic demands and reduced dietary intake.

Adequate nutritional status is essential for effective immune responses against *Mycobacterium tuberculosis*. Undernutrition impairs macrophage function, T-cell responses, and granuloma formation, thereby increasing the risk of progression from latent infection to active disease. Evidence suggests that nutritional status influences disease progression more strongly than the initial acquisition of infection. The TB LION study[22] further demonstrated that undernutrition adversely affects both innate and adaptive immune responses involved in controlling *M. tuberculosis*.

Strong evidence supporting nutrition as a determinant of TB among household contacts comes from the landmark RATIONS trial. Bhargava *et al*[23] evaluated nutritional supplementation among more than 10,000 household contacts in India and reported a 39% reduction in overall TB incidence and a 48% reduction in microbiologically confirmed pulmonary TB among supplemented contacts. These findings provide compelling evidence that improving nutritional status can reduce progression from infection to active disease.

Additional support comes from the TB LENS study[24], which reported improvements in weight gain, physical functioning, well-being, and household food security following nutritional supplementation among household contacts. Observational studies have similarly demonstrated higher rates of active TB among undernourished contacts, suggesting that nutrition acts both as an independent risk factor and as a mediator of broader socio-economic influences on TB outcomes[33,34].

Overall, current evidence identifies nutrition as a critical determinant of tuberculosis among household contacts. Unlike many other risk factors, nutritional status is modifiable, and emerging evidence indicates that nutritional interventions can substantially reduce TB

incidence. Incorporating nutritional assessment and support into household contact investigation programmes may therefore represent an important strategy for TB prevention and control.

Table III: Key studies evaluating determinants of active tuberculosis and latent tuberculosis infection among household contacts.

Study	Country	Study Design	Sample Size	Outcome Assessed	Significant Determinants Identified
Acuña-Villaorduña *et al*[9]	USA and Canada	Prospective	3040 contacts multicentric cohort	LTBI	Age >5 years, male sex, foreign birth, smear-positive index case, bilateral disease, shared bedroom, exposure to multiple index cases, longer exposure duration
Velen *et al*[7]	Vietnam	Nested case-control	1254 contacts	Active TB	Male sex, urban residence, previous TB, diabetes mellitus, smoking, prolonged cough duration in index case
Karbito *et al*[18]	Indonesia	Cross-sectional	138 contacts	LTBI	Overcrowded bedrooms, prolonged exposure (>5 hours/day), occupation
Laghari *et al*[19]	Pakistan	Cross-sectional analytical	2397 contacts	Secondary TB	Overcrowding, household smoking, prolonged exposure (>18 hours/day), low income, presence of another TB case in household
Praveen *et al*[16]	India	Cross-sectional	220 contacts	LTBI	Female sex, diabetes mellitus, exposure to retreatment (Category II) index cases
Sangma *et al*[15]	India	Cross-sectional	330 contacts	LTBI	Female gender of index case associated with higher LTBI prevalence
Singh *et al*[20]	India	Cross-sectional	100 TB patients	TB Risk Context	Poor ventilation, inadequate sunlight exposure, indoor smoke, low income, poor education, limited healthcare access
Wingfield *et al*[21]	Peru	Prospective cohort and household-randomised intervention	876 patients; 282 households	TB outcomes and prevention	Poverty, catastrophic costs, socio-economic deprivation; socio-economic support improved preventive therapy uptake and treatment success
Bhargava *et al* (RATIONS Trial)[23]	India	Cluster-randomised controlled trial	10,345 contacts	Incident TB	Nutritional supplementation reduced tuberculosis incidence by 39%
Cintron *et al* (TB LION)[24]	India	Prospective interventional study	760 contacts	TB progression risk	Undernutrition, impaired immune responses, low BMI
Carwile *et al* (TB LENS)[22]	India	Qualitative study	Household contacts	Nutritional determinants	Nutritional supplementation improved weight, wellbeing, and perceived disease resilience

Diagnosis of Active and Latent Tuberculosis Among Household Contacts

Early identification of active TB and LTBI among household contacts is a cornerstone of TB control strategies. Because household contacts are at substantially increased risk of both infection and disease, systematic screening enables timely diagnosis, initiation of treatment, implementation of preventive therapy, and interruption of transmission.

(A) Diagnosis of Active Tuberculosis

The diagnosis of active TB among household contacts follows a structured approach combining clinical, radiological, and microbiological evaluation. Current recommendations from the World Health Organisation (WHO) and India's National Tuberculosis Elimination Programme (NTEP) emphasize systematic contact investigation, beginning with symptom screening and chest radiography. Common symptoms suggestive of active tuberculosis include persistent cough, fever, weight loss, night sweats, and fatigue. However, symptom screening alone has limited sensitivity, particularly among household contacts who may have early or subclinical disease. Consequently, chest radiography is increasingly recommended as a complementary screening tool, including for asymptomatic contacts whenever feasible[25,26].

Individuals with suggestive symptoms and/or abnormal chest radiographic findings undergo microbiological evaluation. Nucleic acid amplification tests (NAATs), including Cartridge-Based Nucleic Acid Amplification Test (CBNAAT/Xpert MTB-RIF) and Truenat, are currently recommended as frontline diagnostic tools because they provide rapid detection of *Mycobacterium tuberculosis* and information regarding rifampicin resistance[25]. Sputum smear microscopy and mycobacterial culture continue to

serve as important adjunctive investigations, particularly in resource-constrained settings or for drug-susceptibility testing. The integration of clinical assessment, chest radiography, and microbiological confirmation improves case detection and ensures exclusion of active disease before preventive interventions are considered[26].

(B) Diagnosis of Latent Tuberculosis Infection

Unlike active TB, LTBI is characterised by immunological sensitisation to *Mycobacterium tuberculosis* in the absence of clinical, radiological, or microbiological evidence of disease. Therefore, LTBI cannot be diagnosed through direct detection of bacilli and instead relies on immunological testing following exclusion of active TB[25].

The Tuberculin Skin Test (TST/Mantoux test) remains the most widely used tool for LTBI detection worldwide and continues to be the principal test employed under routine programmatic conditions in many high-burden countries. The test measures delayed hypersensitivity to purified protein derivative (PPD) and is inexpensive, simple, and field-friendly[27]. However, its specificity is reduced in Bacillus Calmette-Guérin (BCG)-vaccinated populations and may be affected by exposure to non-tuberculous mycobacteria. Additionally, false-negative results may occur in immunocompromised or malnourished individuals[28].

Interferon-gamma release assays (IGRAs) offer greater specificity by utilizing *M. tuberculosis*-specific antigens such as ESAT-6 and CFP-10, which are absent from BCG strains. These tests are less affected by prior BCG vaccination and generally demonstrate higher specificity than the Mantoux test, although their widespread use may be limited by cost and laboratory requirements. Recent evidence suggests that newer assays such as QuantiFERON-TB Gold Plus and T-SPOT.TB provide improved diagnostic performance in selected populations[29].

In recent years, antigen-specific skin tests such as Cy-TB have emerged as promising alternatives that combine the operational simplicity of skin testing with the specificity of IGRA technology. Cy-TB utilizes recombinant ESAT-6 and CFP-10 antigens and has demonstrated high specificity with diagnostic performance comparable to laboratory-based IGRAs. Because it can be administered and interpreted similarly to the Mantoux test while avoiding many of its specificity limitations, Cy-TB has generated considerable interest for large-scale screening of household contacts in high-burden settings[30].

Despite advances in diagnostic technologies, no currently available test can reliably distinguish LTBI from incipient or active TB. Consequently, all LTBI testing must be interpreted in conjunction with clinical assessment and exclusion of active disease. Effective diagnosis among household contacts therefore requires an integrated approach combining symptom screening, radiological evaluation, microbiological testing, and appropriate immunological assessment according to individual risk profiles and available resources.

Future directions, knowledge gaps and challenges

Despite substantial advances in TB control, important gaps remain in the understanding and management of active TB and LTBI among household contacts. Existing evidence consistently demonstrates a high burden of both infection and disease in this population; however, significant heterogeneity in study design, diagnostic approaches, follow-up duration, and epidemiological settings limits direct comparison of findings and reduces the generalizability of available data.

One of the most important knowledge gaps relates to the prediction of disease progression. Current diagnostic tools can identify LTBI but cannot reliably distinguish individuals who will remain asymptomatic from those who will subsequently develop active disease. The development of predictive biomarkers, host immune signatures, and risk-stratification models capable of identifying contacts at highest risk of progression remains a major research priority.

Diagnostic limitations also continue to pose challenges. While newer tests such as interferon-gamma release assays and antigen-specific skin tests including Cy-TB have demonstrated improved specificity compared with the traditional Mantoux test, evidence regarding their long-term predictive value, operational feasibility, and cost-effectiveness in large-scale household contact screening programmes remains limited. Further multicentric studies are required to evaluate their performance across diverse populations and epidemiological settings.

Although several determinants of tuberculosis among household contacts have been identified, the relative contribution and interaction of host-related, environmental, and exposure-related factors are not yet fully understood. Future studies should focus on developing comprehensive risk prediction models incorporating demographic, clinical, socio-economic, nutritional, and exposure-related variables to facilitate targeted screening and preventive interventions.

Nutrition represents another important area requiring further investigation. Recent interventional studies have demonstrated that nutritional supplementation can

significantly reduce TB incidence among household contacts; however, the optimal composition, duration, delivery mechanisms, and cost-effectiveness of nutritional interventions remain uncertain. Additional research is needed to better define the immunological pathways through which nutritional status influences susceptibility to infection and disease progression.

Implementation challenges also warrant further attention. Despite strong recommendations for contact investigation and tuberculosis preventive therapy, uptake and completion rates remain suboptimal in many high-burden settings. Operational research focusing on barriers to screening, treatment adherence, stigma reduction, healthcare accessibility, and community engagement is essential to improve programme effectiveness.

Future TB control strategies should move toward a more integrated and person-centred approach. Combining active case finding, LTBI screening, preventive therapy, nutritional support, socioeconomic interventions, and digital health technologies may substantially improve outcomes among household contacts. The integration of artificial intelligence-assisted radiography, molecular diagnostics, electronic contact tracing systems, and individualised risk assessment tools offers promising opportunities to enhance the efficiency and effectiveness of household contact investigation programmes.

Addressing these knowledge gaps through well-designed multicentric studies, longitudinal cohorts, implementation research, and interventional trials will be critical for refining tuberculosis prevention strategies and accelerating progress toward national and global TB elimination goals.

Conclusion

Household contacts of pulmonary TB patients represent one of the most vulnerable populations in the TB epidemic, bearing a substantially higher burden of both active TB and LTBI than the general population. Evidence from diverse geographical settings consistently demonstrates that a significant proportion of household contacts either harbor latent infection or develop active disease, highlighting their central role in ongoing transmission dynamics.

The occurrence of TB among household contacts is influenced by a complex interplay of host-related, exposure-related, environmental, socio-economic, and nutritional determinants. While factors such as prolonged exposure, household crowding, poor ventilation, poverty, and limited healthcare access increase the likelihood of infection, host characteristics including age, comorbidities, smoking, and particularly undernutrition play a critical role in determining progression from latent infection to active disease. Emerging evidence from nutritional intervention studies further suggests that improving nutritional status can significantly reduce TB incidence among exposed individuals.

Early identification of active TB through systematic contact investigation, combined with accurate detection of latent infection using Mantoux testing, interferon-gamma release assays, and newer antigen-specific tests such as Cy-TB, provides an important opportunity for timely intervention. Integration of effective diagnostic strategies with tuberculosis preventive therapy has the potential to substantially reduce future disease burden and interrupt transmission within households.

Achieving TB elimination goals will require strengthening household contact investigation programmes, expanding access to preventive therapy, addressing underlying social and nutritional determinants, and adopting innovative diagnostic and risk-stratification approaches. A comprehensive, person-centered strategy targeting household contacts is therefore essential for reducing tuberculosis transmission and accelerating progress toward national and global TB elimination targets.

References

1. World Health Organisation. Global tuberculosis report 2025. Geneva: World Health Organisation; 2025. Available from: https://www.who.int/teams/global-programme-on-tuberculosis-and-lung-health/tb-reports/global-tuberculosis-report-2025.
2. Government of India. India TB Report 2024. New Delhi: Central TB Division, Ministry of Health and Family Welfare, Government of India; 2024. Available from: https://tbcindia.mohfw.gov.in/wp-content/uploads/2024/10/TB-Report_for-Web_08_10-2024-1.pdf
3. Fox GJ, Barry SE, Britton WJ. Contact investigation for tuberculosis: a systematic review and meta-analysis. *Eur Respir J* 2013; 41 (1): 140-56.
4. Morrison J, Pai M, Hopewell PC. Tuberculosis and latent tuberculosis infection in close contacts of people with pulmonary tuberculosis in low-income and middle-income countries: a systematic review and meta-analysis. *Lancet Infect Dis* 2008; 8 (6): 359-68.
5. Moosazadeh M, Khanjani N, Parsaee M. The prevalence of latent tuberculosis infection and smear positive pulmonary tuberculosis in people with household close contact with tuberculosis in north of Iran. *Iran J Med Sci* 2015; 40 (2): 161-5.
6. Getahun H, Matteelli A, Abubakar I *et al*. Management of latent Mycobacterium tuberculosis infection: WHO guidelines for low tuberculosis burden countries. *Eur Respir J* 2015; 46 (6): 1563-76.
7. Velen K, Nhung NV, Anh NT. Risk factors for tuberculosis among household contacts of patients with smear-positive tuberculosis in 8 provinces of Vietnam: a nested case-control study. *Clin Infect Dis* 2021; 73 (9): e3358-e3364.
8. Lönnroth K, Jaramillo E, Williams BG. Drivers of tuberculosis epidemics: the role of risk factors and social determinants. *Soc Sci Med* 2009; 68 (12): 2240-6.

9. Acuña-Villaorduña C, Jones-López EC, Fregona G *et al*. Intensity of exposure to pulmonary tuberculosis determines risk of tuberculosis infection and disease. *Eur Respir J* 2018; 51 (1): 1701578.
10. Cegielski JP, McMurray DN. The relationship between malnutrition and tuberculosis: evidence from studies in humans and experimental animals. *Int J Tuberc Lung Dis* 2004; 8 (3): 286-98.
11. Seid G, Alemu A, Dagne B. Tuberculosis in household contacts of tuberculosis patients in sub-Saharan African countries: a systematic review and meta-analysis. *J Clin Tuberc Other Mycobact Dis* 2022; 29: 100337.
12. Daniel W, Tadesse S, Tamirat T. Epidemiology of active tuberculosis among adult household contacts of patients with smear-positive pulmonary tuberculosis in Kembata-Tembaro zone, southern Ethiopia: a cross-sectional study. *BMJ Public Health* 2025; 3: e001531.
13. Singh J, Sankar MM, Kumar S *et al*. Incidence and prevalence of tuberculosis among household contacts of pulmonary tuberculosis patients in a peri-urban population of South Delhi, India. *PLoS One* 2013; 8 (7): e69730.
14. Chawla S, Gupta V, Gour N *et al*. Active case finding of tuberculosis among household contacts of newly diagnosed tuberculosis patients: a community-based study from southern Haryana. *J Family Med Prim Care* 2020; 9 (7): 3701-6.
15. Sangma VSC, Jaggi S, Saini V. Prevalence of latent tuberculosis infection in household contacts of pulmonary tuberculosis, time to treat. *Monaldi Arch Chest Dis* 2023; 94: 2563.
16. Praveen V. Prevalence of latent tuberculosis infection among household contacts of sputum positive TB patients receiving DOTS chemotherapy. *Indian J Tuberc* 2020; 67 (4): 459-65.
17. Barik BS, Kar CD, Das S *et al*. Latent tuberculosis infection among household contacts of tuberculosis patients, healthcare workers, and tuberculosis patients using QuantiFERON-tuberculosis Gold Plus and tuberculin skin test in a tertiary care hospital setting Bhubaneswar, Odisha - a cross-sectional study. *J Glob Infect Dis* 2025; 17 (1): 52-9.
18. Karbito K, Susanto H, Adi MS. Latent tuberculosis infection in family members in household contact with active tuberculosis patients in Semarang City, Central Java, Indonesia. *J Public Health Afr* 2022; 13 (2): 2157.
19. Laghari M, Sulaiman SAS, Khan AH. Contact screening and risk factors for TB among the household contact of children with active TB: a way to find source case and new TB cases. *BMC Public Health* 2019; 19 (1): 1274.
20. Singh R, Singh P, Srivastava K. Environmental and socio-economic factors affecting tuberculosis. *IP Indian J Immunol Respir Med* 2025; 10 (4): 253-60.
21. Wingfield T, Tovar MA, Huff D *et al*. Beyond pills and tests: addressing the social determinants of tuberculosis. *Clin Med (Lond)* 2016; 16 (6 Suppl): s79-s91.
22. Cintron C, Narasimhan PB, Locks L *et al*. Tuberculosis – Learning the Impact of Nutrition (TB LION): protocol for an interventional study to decrease TB risk in household contacts. *BMC Infect Dis* 2021; 21: 1058.
23. Bhargava A, Bhargava M, Meher A *et al*. Nutritional supplementation to prevent tuberculosis incidence in household contacts of patients with pulmonary tuberculosis in India (RATIONS): a field-based, open-label, cluster-randomised, controlled trial. *Lancet* 2023; 402 (10402): 627-40.
24. Carwile M, Jain K, Dauphinais M *et al*. TB-learning about experience with nutritional supplementation (TB LENS): perspectives on a nutritional supplementation for persons with TB and their household contacts. *Glob Public Health* 2025; 20 (1): 1-14.
25. Central TB Division. Guidelines for programmatic management of tuberculosis preventive treatment in India. New Delhi: Ministry of Health and Family Welfare, Government of India; 2023. Available from: https://tbcindia.mohfw.gov.in/wp-content/uploads/2023/05/Guidelines-for-Programmatic-Management-of-Tuberculosis-Preventive-Treatment-in-India.pdf
26. Central TB Division. Guidance document on TB Mukt Bharat Abhiyaan. New Delhi: Ministry of Health and Family Welfare, Government of India; 2025. Available from: https://tbcindia.mohfw.gov.in/wp-content/uploads/2025/09/Guidance-Document-on-TB-Mukt-Bharat-Abhiyan_0.pdf
27. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. Geneva: World Health Organisation; 2018. Licence: CC BY-NC-SA 3.0 IGO. Available from https://www.who.int/publications/i/item/9789241550239.
28. Sheikh NT, Akhtar S, Tabassum S. Role of tuberculin skin test (Mantoux test) as an aid in the diagnosis of tuberculosis disease and to identify persons with latent tuberculosis in highly endemic hilly region of Jammu and Kashmir. *East J Med Sci* 2021; 6 (1): 31-5.
29. Aishwarya R, Maheshwary D, Leela KV. Performance of current diagnostic tools in detecting latent tuberculosis among healthcare workers: a systematic review. *Cureus* 2024; 16 (10): e70621.
30. Choudhary S, Saurabh S, Gupta MK. Latent tuberculosis infection diagnostics: comparative performance of TST, IGRAs, and Cy-Tb. *JEFI* 2026; 3 (2 Suppl).
31. Pinto P, Teixeira C, Ichihara M *et al*. Incidence and risk factors of tuberculosis among 420854 household contacts of patients with tuberculosis in the 100 Million Brazilian Cohort (2004-18): a cohort study. *Lancet Infect Dis* 2024; 24: 46-56.
32. Odera S, Mureithi M, Aballa A. Latent tuberculosis among household contacts of pulmonary tuberculosis cases in Nairobi, Kenya. *Pan Afr Med J* 2020; 37: 87.
33. Mathew JL, Indumathi CK, Mohan P. Nutritional supplementation to prevent infection in household contacts of tuberculosis patients. *Indian Pediatr* 2023; 60: 941-6.
34. Larsson L, Calderwood CJ, Marambire ET *et al*. Body mass index trajectories and association with tuberculosis risk in a cohort of household contacts in Southern Africa. *Clin Infect Dis* 2025; 81 (6): e600-e611.

CASE REPORT

JIACM 2026; 27 (3): 211-14

Autoimmune Polyglandular Syndrome Type II Presenting as Seronegative Autoimmune Addison's Disease with Mixed Connective Tissue Disease

Amit Sharma, Deepak Jain**, Divyajyoti Das*, Manjri Garg***, Shatakshi*****

Abstract

***Background:** Autoimmune Polyglandular Syndrome Type II (APS II) is defined by autoimmune primary adrenal insufficiency with autoimmune thyroid disease and/or type 1 diabetes. Mixed Connective Tissue Disease (MCTD) is characterised by anti-U1-snRNP antibodies. In MCTD, interstitial lung disease (ILD) typically presents as nonspecific interstitial pneumonia (NSIP), whereas usual interstitial pneumonia (UIP) is less common. The coexistence of APS II, seronegative autoimmune adrenalitis, MCTD, and UIP-pattern ILD is exceptionally rare, particularly in tuberculosis-endemic regions, where adrenal calcification is often presumed to be tubercular.*

***Case Presentation:** A 45-year-old woman with autoimmune hypothyroidism presented with weakness, hyperpigmentation, weight loss, and basal crackles. Morning cortisol was 3.75 µg/dL with ACTH >1250 pg/mL, confirming primary adrenal insufficiency. Anti-TPO >1300 IU/mL, ANA 1:1000, high anti-U1-snRNP, and anti-Sm positivity met Alarcón-Segovia criteria for MCTD. HRCT showed basal honeycombing and traction bronchiectasis consistent with UIP. CT abdomen revealed unilateral adrenal calcification; a CyTb induration of 2 mm indicated a negative test. Interferon-Gamma Release Assay (IGRA) was negative as well. She was treated with hydrocortisone, fludrocortisone, levothyroxine, and cyclophosphamide.*

***Conclusion:** This case represents an extraordinarily rare overlap of APS II, seronegative autoimmune Addison's disease, MCTD, and UIP-pattern ILD. This rare combination underscores the importance of distinguishing autoimmune adrenalitis from tuberculosis and demonstrates that unilateral adrenal calcification is not pathognomonic for TB.*

Introduction

Primary adrenal insufficiency is a life-threatening endocrine disorder and often presents with hyperpigmentation of the skin and mucosa, chronic fatigue, hypotension, hypoglycaemia, hyponatraemia and hyperkalaemia. A high degree of clinical suspicion is required for rapid diagnosis as delayed diagnosis may lead to adrenal crisis. Autoimmune adrenalitis is now the predominant cause of primary adrenal insufficiency, although tuberculosis still remains an important cause in endemic regions[1,2]. Autoimmune adrenalitis characteristically progresses with lymphocytic infiltration and cortical destruction of the adrenal glands. Anti-21-hydroxylase antibodies are highly specific but may be absent in up to 20% of advanced cases[2,3]. Autoimmune Polyglandular Syndrome (APS) type II reflects a genetically determined clustering of autoimmune adrenal, thyroid, and other endocrine disorders[4].

Mixed Connective Tissue Disease (MCTD) is defined by high-titre anti-U1-snRNP antibodies and overlapping features of Systemic Lupus Erythematosus (SLE), systemic sclerosis, and polymyositis[5]. ILD occurs in up to 75% of MCTD patients, but UIP is significantly less common[6].

Here we present an extraordinary overlap of APS II, seronegative autoimmune adrenalitis, MCTD, and UIP ILD with unilateral adrenal calcification.

Case Report

A 45-year-old woman with a 10-year history of autoimmune hypothyroidism on levothyroxine presented with progressive generalised weakness for 15 months, diffuse hyperpigmentation for 6 months, and unintentional weight loss of approximately 5 kg. She did not have a history of fever, cough, haemoptysis, night sweats, tuberculosis, diabetes, or prior glucocorticoid use. She had longstanding secondary amenorrhoea for nearly a decade and had never conceived. She also reported episodic cold-induced discolouration of the fingers suggestive of Raynaud phenomenon. On examination, she was thin with a body mass index of 16 kg/m^2; blood pressure was 90/60 mmHg without postural drop, pulse was 84/min, respiratory rate was 20/min, and oxygen saturation was 95% on room air. There was no pallor, icterus, cyanosis, clubbing, lymphadenopathy or pedal oedema. There was marked diffuse hyperpigmentation involving

**Resident, **Senior Professor, ****Assistant Professor, Department of Medicine, ***Professor, Department of Pathology, Pandit BD Sharma University of Health Sciences, PGIMS Rohtak - 124 001, Haryana.*
Corresponding Author: Dr Deepak Jain, Senior Professor, Department of Medicine, Pandit BD Sharma University of Health Sciences, PGIMS Rohtak - 124 001, Haryana. Tel: 9416147887, E-mail: jaindeepakdr@gmail.com

the face, neck, knuckles, elbows, palmar creases, tongue, and buccal mucosa (Fig. 1). Fine end-inspiratory "Velcro-like" crackles were audible over both lung bases, while cardiovascular, abdominal, and neurologic examination was unremarkable. Laboratory evaluation showed haemoglobin 10.3 g/dL, total leukocyte counts 6,300/mm^3, platelet counts 2.2 lakh per mm^3, MCV 91.1 fL, MCH 27.3 pg, MCHC 32.1 g/dL, fasting glucose 72 mg/dL, sodium 131 mmol/dL, potassium 4.9 mmol/L, and elevated ESR of 79 mm/hr. HbA1c was 5.6 %, corrected calcium 9.7 mg/dL, and phosphate 3.3 mg/dL. Liver and renal functions were normal. Endocrine evaluation revealed a markedly low morning serum cortisol concentration of 3.75 µg/dL (reference 5.27 - 22.40 µg/dL) with profoundly elevated ACTH levels >1250 pg/mL (reference 0 - 46 µg/mL), confirming primary adrenal insufficiency[1]. Thyroid profile showed elevated TSH of 22.56 µIU/mL with anti-thyroid peroxidase antibody titres >1300 IU/mL. Evaluation for infectious aetiologies revealed a negative interferon-gamma release assay (IGRA) and a CyTb skin test induration of 2 mm, interpreted as negative[7]. ECG showed, sinus rhythm. Chest X-ray showed mild bilateral basal reticular opacities with reduced lung volumes, without focal consolidation or pleural effusion. Pulmonary function testing showed a restrictive ventilatory defect with reduced diffusing capacity for carbon monoxide, consistent with interstitial lung disease. An echocardiography revealed preserved left ventricular systolic function without pulmonary hypertension. High-resolution CT scan of the chest demonstrated basal and subpleural honeycombing, traction bronchiectasis, and a straight-edge sign consistent with a usual interstitial pneumonia pattern[8] (Fig. 2). Contrast- enhanced CT scan of the abdomen revealed a bulky right adrenal gland with coarse calcification and a normal left adrenal gland, with no lymphadenopathy or features of active granulomatous disease. Extractable nuclear antigen analysis demonstrated a high-titre antinuclear antibody with a speckled pattern (1:1000; reference <1:80). Anti-U1-snRNP antibody levels were markedly elevated (>200 U/mL; reference <20 U/mL), with concomitant positivity of anti-RNP (>180 U/mL; reference <20 U/mL) and anti-Sm antibodies (65 U/mL; reference <20 U/mL). Antibodies to double-stranded DNA (anti-dsDNA 8 IU/mL; reference <30 IU/mL), SSA/Ro and SSB/La (both <10 U/mL; reference <20 U/mL), Scl-70 (<5 U/mL; reference <20 U/mL), Jo-1 (<5 U/mL; reference <20 U/mL), rheumatoid factor (6 IU/mL; reference <14 IU/mL), and anti-cyclic citrullinated peptide antibodies (4 U/mL; reference <20 U/mL) were negative. This ENA profile was strongly supportive of mixed connective tissue disease. As the patient had ILD and features of autoimmune serology, based on high-titre anti-U1-snRNP positivity along with Raynaud phenomenon, hand oedema, and synovitis, the patient fulfilled Alarcón-Segovia criteria for mixed connective tissue disease[9]. She was diagnosed with autoimmune polyglandular syndrome type II with seronegative autoimmune Addison's disease and UIP-pattern interstitial lung disease and was initiated on hydrocortisone, fludrocortisone, and levothyroxine after steroid replacement. Patient was started on IV Cyclophosphamide 600mg/m^2 every 4 weeks for interstitial lung disease[10]. She is on regular follow-up currently, and has improved significantly.



Fig. 1: *Progressive hyperpigmentation of face, neck and dorsum of hands.*

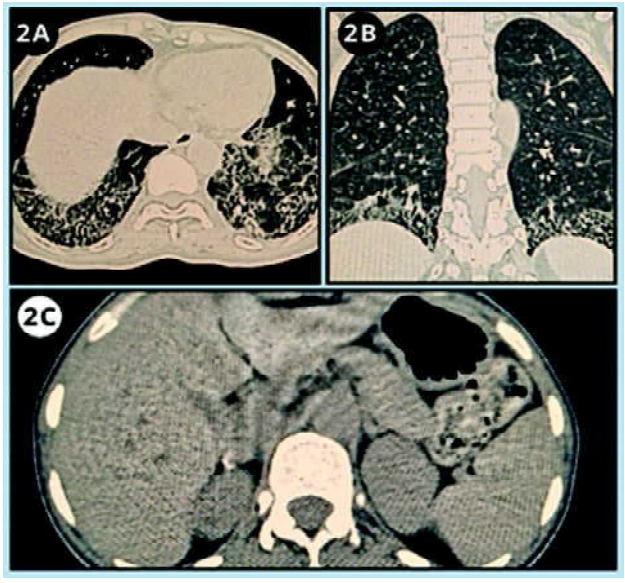


Fig. 2: *High-resolution computed tomography of Chest and contrast enhanced computed tomography of Abdomen.*

Discussion

This case represents an exceptionally rare and diagnostically challenging coexistence of autoimmune polyglandular syndrome type II, seronegative autoimmune adrenalitis, mixed connective tissue disease, and usual interstitial pneumonia-pattern interstitial lung disease. Primary adrenal insufficiency was unequivocally established by the biochemical profile of markedly low cortisol with disproportionately elevated ACTH, and the coexistence of autoimmune thyroiditis strongly supported the diagnosis of APS II[1,4]. Although anti-21-hydroxylase antibodies are highly specific markers of autoimmune adrenalitis, up to 10 - 20% of patients may be seronegative, particularly in advanced disease when extensive cortical destruction leads to antigen depletion, making seronegativity a recognised and clinically important phenomenon[2,3]. In tuberculosis-endemic regions, adrenal calcification often leads to diagnostic anchoring toward tuberculous adrenalitis; however, classical tuberculous involvement typically produces bilateral adrenal enlargement followed by coarse bilateral calcification, whereas unilateral adrenal calcification, as observed in this patient, is atypical and broadens the differential diagnosis to include autoimmune adrenalitis, prior haemorrhage, vascular insult, or idiopathic calcification[11,12]. The absence of constitutional symptoms, lack of pulmonary or nodal tuberculosis, a negative interferon-gamma release assay, and a negative CyTb skin test (2 mm) significantly reduced the likelihood of both active and latent tuberculosis, favouring an autoimmune aetiology[7]. Hence , unilateral adrenal calcification should be interpreted in the overall clinical context rather than being considered diagnostic of tuberculous adrenalitis[11]. Mixed connective tissue disease was confirmed using Alarcón-Segovia criteria[9], and although interstitial lung disease is common in MCTD, the predominant pattern is nonspecific interstitial pneumonia; usual interstitial pneumonia occurs in a minority of cases and is associated with a more fibrotic phenotype, poorer response to corticosteroids, and worse long-term prognosis[6,13].

The high-resolution CT findings of basal honeycombing, traction bronchiectasis, and a straight-edge sign in this patient were characteristic of a UIP pattern, necessitating immunosuppressive therapy with cyclophosphamide, extrapolated from evidence in other connective tissue disease-associated fibrotic interstitial lung diseases[8,10,14]. Epidemiologically, autoimmune polyglandular syndrome type II (~14-20 per million), mixed connective tissue disease (~1-4 per 100,000), seronegative autoimmune adrenalitis (~10-20% of autoimmune Addison's disease), and UIP-pattern interstitial lung disease in MCTD (~8-20%) are individually uncommon[3,4,15]. Their coexistence therefore represents an exceptionally rare convergence of low-prevalence disease entities, even after accounting for autoimmune clustering. Autoimmune adrenalitis is initiated by loss of immune tolerance, leading to autoreactive T-cell infiltration and antibody-mediated targeting of steroidogenic enzymes, most notably 21-hydroxylase, resulting in progressive destruction of the adrenal cortex[2]. Over time, chronic inflammation culminates in cortical atrophy, fibrous replacement, and in some cases dystrophic calcification; advanced disease stages may lack detectable circulating autoantibodies due to near-complete loss of antigenic tissue, accounting for seronegative presentations[2,3]. Autoimmune polyglandular syndrome type II arises from shared immunogenetic susceptibility, particularly HLA-linked defects in central and peripheral immune tolerance, enabling simultaneous or sequential autoimmune involvement of multiple endocrine organs[4]. Mixed connective tissue disease is driven by anti-U1-snRNP-mediated immune activation, with downstream interferon signalling, endothelial dysfunction, and fibroblast activation contributing to systemic manifestations[13]. In the lung, repeated immune-mediated alveolar epithelial injury with aberrant repair mechanisms leads to interstitial fibrosis, manifesting most commonly as nonspecific interstitial pneumonia; however, in a subset of patients, dysregulated wound healing and fibroblast proliferation result in the usual interstitial pneumonia pattern, characterised by fibroblastic foci, architectural distortion, honeycombing, and irreversible fibrosis, which confers a more aggressive disease course and poorer prognosis[8,13]. To our knowledge, the coexistence of APS II with seronegative autoimmune Addison's disease, MCTD, UIP-pattern ILD, and unilateral adrenal calcification has rarely, if ever, been reported in the published literature, highlighting the diagnostic complexity of autoimmune endocrine–rheumatological overlap syndromes[4,15].

Key Learning Points

1. Unilateral adrenal calcification is not pathognomonic of tuberculosis; evaluate for autoimmune, vascular, or other causes.
2. Seronegative autoimmune adrenalitis occurs in up to 20% and must be considered despite negative 21-OH antibodies.
3. CyTb induration of 2 mm should be interpreted as negative and reduces the likelihood of TB in the appropriate clinical context.
4. UIP-pattern ILD in MCTD is uncommon but signals a fibrotic phenotype with worse prognosis.
5. Cyclophosphamide is an evidence-based induction therapy for severe fibrotic CTD-ILD.

Conclusion

This patient's combination of APS II, seronegative autoimmune Addison's disease, MCTD, and UIP-ILD is exceptionally rare. Unilateral adrenal calcification, negative CyTb testing, and strong autoimmune serology guided correct diagnosis and avoided inappropriate anti-tubercular therapy. Early identification and appropriate immunosuppression were essential to address the progressive fibrotic lung disease and life-threatening adrenal insufficiency.

References

1. Bornstein SR, Allolio B, Arlt W *et al*. Diagnosis and treatment of primary adrenal insufficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2016; 101 (2): 364-89.
2. Husebye ES, Pearce SH, Krone NP. Adrenal insufficiency. *Lancet* 2021; 397 (10274): 613-29.
3. Betterle C, Morlin L. Autoimmune Addison disease. *Endocr Dev* 2011; 20: 161-72.
4. Kahaly GJ, Frommer L, Schuppan D. Polyglandular autoimmune syndromes. *J Endocrinol Invest* 2018; 41 (1): 91-8.
5. Sharp GC, Irvin WS, Tan EM. Mixed connective tissue disease – an apparently distinct rheumatic disease syndrome associated with a specific antibody to an extractable nuclear antigen. *Am J Med* 1972; 52 (2): 148-59.
6. Gunnarsson R, El-Hage F, Aaløkken TM *et al*. Associations between interstitial lung disease and autoantibodies in mixed connective tissue disease. *Rheumatology (Oxford)* 2016; 55 (1): 103-08.
7. Lewinsohn DM, Leonard MK, LoBue PA *et al*. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention clinical practice guidelines: diagnosis of tuberculosis in adults and children. *Clin Infect Dis* 2017; 64 (2): e1-e33.
8. Raghu G, Remy-Jardin M, Myers JL *et al*. Diagnosis of idiopathic pulmonary fibrosis: an official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2018; 198 (5): e44-e68.
9. Alarcón-Segovia D, Villarreal M. Classification and diagnostic criteria for mixed connective tissue disease. In: Kasukawa R, Sharp GC, editors. *Mixed Connective Tissue Disease and Antinuclear Antibodies*. Amsterdam: Elsevier; 1987; p. 33-40.
10. Johnson SR, Bernstein EJ, Bolster MB *et al*. 2023 American College of Rheumatology (ACR)/American College of Chest Physicians (CHEST) guideline for the treatment of interstitial lung disease in people with systemic autoimmune rheumatic diseases. *Arthritis Care Res (Hoboken)* 2024; 76 (8): 1051-69.
11. Lam KY, Lo CY. A critical examination of adrenal tuberculosis and a 28-year autopsy experience of active tuberculosis. *Clin Endocrinol (Oxf)* 2001; 54 (5): 633-9.
12. Rao RH. Bilateral massive adrenal enlargement due to tuberculosis: diagnostic features and clinical significance. *Am J Med* 1989; 86 (1): 29-34.
13. Antoniou KM, Distler O, Gheorghiu AM *et al*. ERS/EULAR clinical practice guidelines for connective tissue disease associated interstitial lung disease developed by the task force for connective tissue disease associated interstitial lung disease of the European Respiratory Society (ERS) and the European Alliance of Associations for Rheumatology (EULAR) endorsed by the European Reference Network on rare respiratory diseases (ERN LUNG). *Ann Rheum Dis* 2026; 85 (1): 22-60.
14. Joy GM, Arbiv OA, Wong CK *et al*. Prevalence, imaging patterns and risk factors of interstitial lung disease in connective tissue disease: a systematic review and meta-analysis. *Eur Respir Rev* 2023; 32 (167): 220210.

CASE REPORT

JIACM 2026; 27 (3): 215-19

Idiopathic Multicentric Castleman Disease Presenting as TAFRO Syndrome

Rajnish Singh, Shreyasee Patra**, Brijesh Sharma***, Madhubala Negi***, Archana Mohan****, Tanvi Suri****, Shivanshu Gangwar******

Abstract

Idiopathic multicentric Castleman disease (iMCD), particularly the TAFRO variant, is a rare and potentially life-threatening lymphoproliferative disorder that often presents a profound diagnostic dilemma due to its nonspecific systemic manifestations. We report a 42-year-old previously healthy woman who presented with prolonged high-grade fever followed by progressive anasarca with ascites, pleural effusion, lymphadenopathy and hepatosplenomegaly. The constellation of symptoms of fever, polyserositis, organomegaly and laboratory results showing bicytopenia, renal dysfunction, hypoalbuminaemia, elevated inflammatory markers, and marked hyperferritinaemia raised suspicion for autoimmune diseases, chronic infections such as tuberculosis, haematologic malignancy, and other lymphoproliferative disorders which were ruled out after extensive work-up. PET-CT demonstrated generalised FDG-avid lymphadenopathy. Excisional lymph node biopsy showed plasma cell–type Castleman disease; HHV-8 was negative and POEMS criteria were not met. Elevated interleukin-6 levels, together with thrombocytopenia, anasarca, renal dysfunction, and organomegaly, supported a diagnosis of idiopathic multicentric Castleman disease, TAFRO variant. Treatment with high-dose corticosteroids followed by tocilizumab led to rapid clinical and laboratory improvement. This case underscores the importance of maintaining a high index of suspicion for idiopathic-MCD in patients with unexplained systemic inflammation and multiorgan involvement, and highlights the central role of histopathology in resolving a complex diagnostic challenge.

Introduction

Castleman's disease (CD), first described in 1954 by Dr Benjamin Castleman[1], is a rare, nonclonal lymphoproliferative disorder characterised by lymph node enlargement often mimicking malignant and benign conditions. Although exact mechanism is unclear, CD is believed to arise from immune dysregulation leading to proliferation of B lymphocytes and plasma cells[2]. Clinically, it is classified into unicentric (UCD), involving a single nodal region, and multicentric (MCD), which features multiple lymph node regions. UCD typically presents as localised, asymptomatic lymphadenopathy, whereas MCD manifests with systemic involvement such as constitutional symptoms, organomegaly, anaemia, and elevated inflammatory markers[3]. Idiopathic MCD (iMCD) is particularly rare (incidence approximately 5 per million patient-years)[4] and poses significant diagnostic and therapeutic challenges due to its heterogenicity.

We report an unusual case of a 42-year-old woman presenting with fever and anasarca, subsequently diagnosed with MCD.

Case Presentation

A 42-year-old previously healthy woman presented with a 6-week history of daily high-grade fever with chills (up to 102° F), followed two weeks later by progressive generalised oedema beginning in the lower limbs, advancing to facial puffiness and abdominal distension. She also reported dry cough with pleuritic chest pain.

There was no history of weight loss, night sweats, loss of appetite, jaundice, any rash, joint pains, oral ulcers, excessive hair fall, frothy urine, burning micturition, loose stools, palpitation or dizziness. She was initially admitted in a different hospital where she had received antibiotics for presumed sepsis but without any improvement.

On physical examination she had pallor, bilateral pitting pedal oedema, axillary and inguinal lymphadenopathy, hepatosplenomegaly with moderate ascites and bilateral pleural effusion.

Baseline laboratory investigations showed bicytopenia (Hb-6.5 g/dL, Platelet count - 35,000/mL). Renal function was deranged; urea - 115 mg/dL and serum creatinine - 3.4 mg/dL. Serum total protein was 5.17 gm/dL with a serum albumin of 2.10 gm/dL; rest LFTs were within normal limits. Chest X-ray showed bilateral pleural effusion. Inflammatory markers ESR and q-CRP were high, serum ferritin levels were above 2000 ng/mL, iron studies suggested anaemia of chronic disease.

**Professor and Head, **Senior Resident, ***Professor, ****Resident, Department of General Medicine, *****Senior Resident, Department of Pathology, ABVIMS and Dr Ram Manohar Lohia Hospital, Baba Kharak Singh Marg, New Delhi - 110 001.*
Corresponding Author: Dr Shreyasee Patra, Senior Resident, Department of General Medicine, ABVIMS and Dr Ram Manohar Lohia Hospital, Baba Kharak Singh Marg, New Delhi - 110 001. Tel: 8130367556, E-mail: shreyaseep@gmail.com

Ascitic fluid examination was suggestive of low SAAG high protein ascites with predominantly lymphocytic cells. Pleural fluid studies also showed exudative pattern. ADA was within normal limits in both fluid studies. Mantoux test was negative. 24 hr urinary protein came out to be 1714 mg/day. Serological tests for hepatitis B, hepatitis C and HIV were non-reactive. Urine and blood cultures were sterile.

Direct Coombs test was positive, with mildly elevated serum LDH. ANA (by IFA), ANCAs and ENA were negative. SPEP showed polyclonal gammopathy suggestive of chronic inflammation; no M spike was seen.

USG whole abdomen and pelvis showed hepatosplenomegaly with moderate ascites and a suspicious right ovarian lesion (ORADS 3-4). Tumour markers and ascitic fluid were negative for malignancy. Ovarian carcinoma was ruled out after imaging by CECT (Chest and abdomen) and MRI-Pelvis. Bone marrow aspiration and biopsy showed reactive cellular marrow with trilineage hematopoiesis, no blasts or plasma light chain restriction were seen.

A PET-CT was done which showed generalised lymphadenopathy on both sides of diaphragm (bilateral axillary, cervical, mediastinal, abdominal and inguinal) with avid uptake. Right inguinal excision biopsy was sent. IgG4 was increased but ratio of IGg4/IgG was normal. Lymph node biopsy report showed sheets of small mature plasma cells in interfollicular area and in medulla with few hyperplastic follicles, occasional mantle zone thickening with "onion skin" appearance suggestive of Castleman's disease-plasma cell type. IHC for CD 20 was positive. To find out etiological association, IHC for HHV8 was done which came out to be negative. IL-6 levels were found to be high = 30.87 pg/mL (normal <5.9 pg/mL).

Based on the presence of fever, thrombocytopenia, polyserositis, proteinuria and hepatosplenomegaly along with lymph node biopsy findings and in absence of any evidence of lymphoproliferative disorders or autoimmune conditions like Sjogren's disease, diagnosis of iMCD – TAFRO variant was made.

Management

The ECOG performance status of our patient being 2 - 3, she was initiated on in intravenous methyl prednisolone 500 mg/day for 3 days followed by in intravenous Tocilizumab (8 mg/kg) infusion. She improved clinically and laboratory parameters also showed improvement (Table I). She was discharged on oral prednisolone with advice to come for further dose of Tocilizumab biweekly.

Table I: Laboratory investigations during hospital stay.

Parameters	At Admission	3rd week of hospital stay	Before discharge
Hb (g/dL)	6.4	5.8	9.2
PLT (/cmm)	35,000	50,000	60,000
ESR (mm/hr)	85	20	5
qCRP (mg/dL)	109	25.4	18
Serum Albumin (g/dL)	2.10	2.06	4.2
Ferritin (ng/mL)	>2,000		1,000
LDH (U/L)	283	319	187
ALP U/L	167	200	156
Urea (mg/dL)	115	122	20
Creatinine (mg/dL)	3.4	1.4	0.6
Proteinuria (mg/24 hrs)	1,748	1,194	1,420

Discussion

Castleman's Disease is an exceedingly rare lymphoproliferative disorder that closely mimics more common autoimmune diseases, chronic infections, chronic lymphoproliferative disorders and malignancies.

The Castleman Disease Collaborative Network (CDCN) classifies multicentric Castleman disease (MCD) into three aetiologic subtypes: HHV-8-associated MCD, POEMS-associated MCD, and idiopathic multicentric Castleman disease (iMCD)[5]. HHV-8-associated MCD, driven by viral infection, occurs predominantly in immunocompromised individuals, most commonly with HIV co-infection while POEMS-associated MCD is distinctively linked to plasma cell dyscrasia.

The CDCN emphasizes on a diagnosis of exclusion for idiopathic multicentric Castleman disease (iMCD) which is further subdivided into iMCD not otherwise specified (iMCD-NOS) and the more aggressive iMCD with TAFRO – thrombocytopenia, anasarca, myelofibrosis, renal dysfunction and organomegaly. These criteria require the absence of HHV-8 infection and POEMS syndrome and a careful evaluation to rule-out alternative conditions that can produce Castleman-like histopathology, including autoimmune diseases, infections, haematological disorders, and inflammatory conditions such as IgG4-related disease (IgG4-RD).

Fig. 4 below describes the key steps in the diagnosis and classification of Castleman disease (CD) as proposed by the CDCN[5].

Establishing the aetiology and clinical variant holds

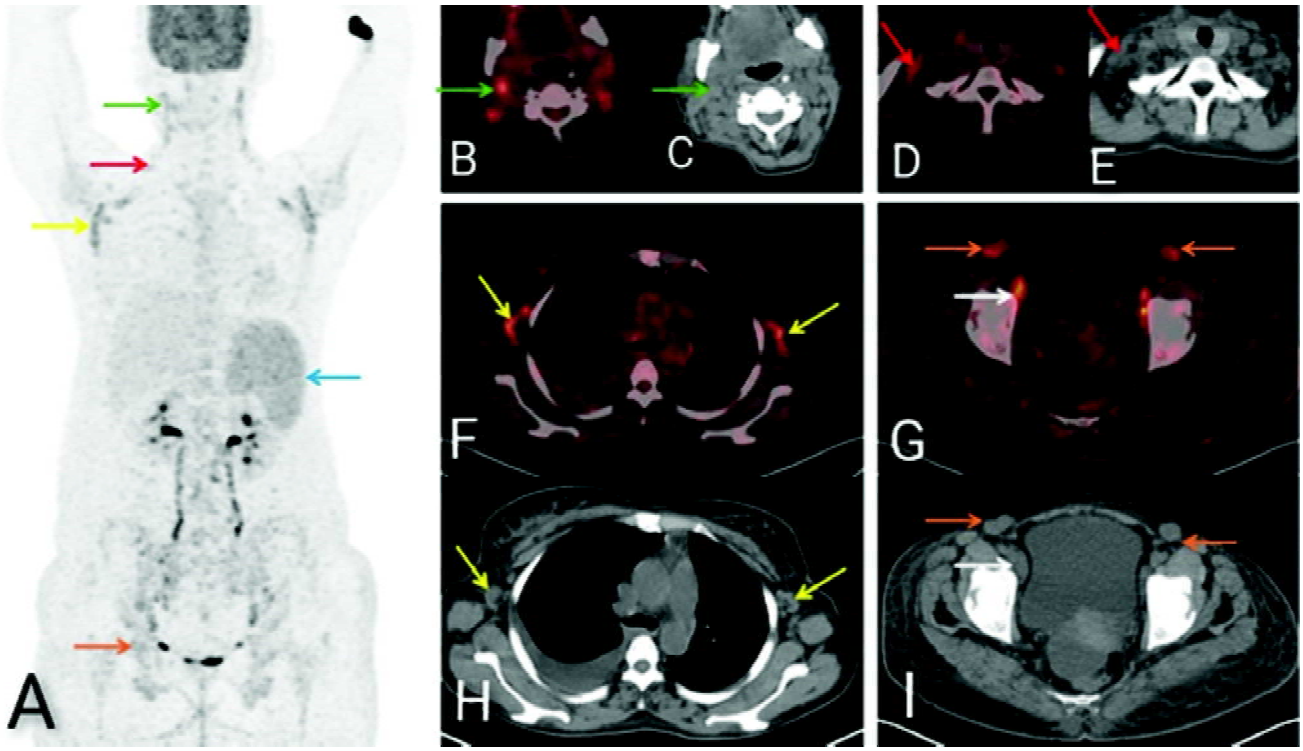


Fig. 1: *18 FDG PET/CT images (maximum intensity projection image – A); fused axial cuts showing diffusely increased FDG uptake in the spleen (blue arrow; A) and multiple FDG avid bilateral cervical (green arrow; B and C), supraclavicular (red arrow; D and E), axillary (yellow arrow; F and H), abdominal, external iliac (white arrow; G) and inguinal (orange arrow; G and I) lymph nodes; mild pleural effusion and ascites also seen.*

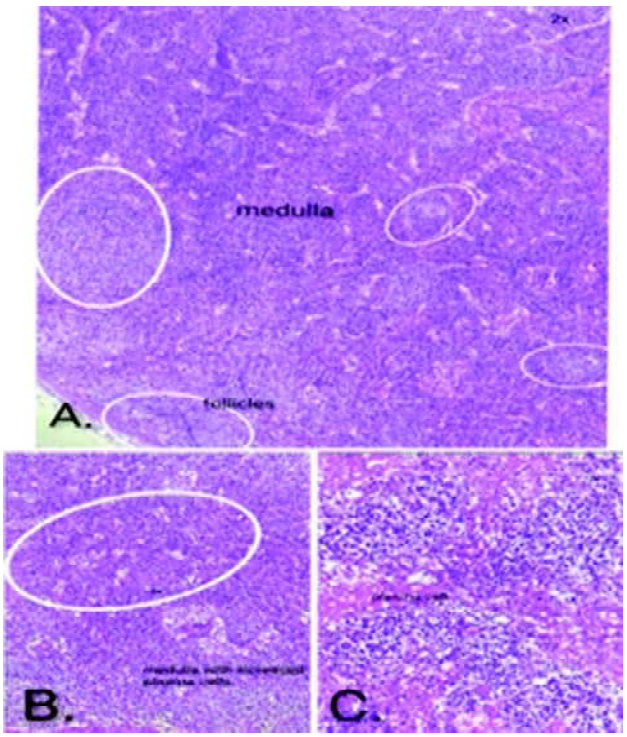


Fig. 2: *HPE of lymph node*
A – Medulla with atrophic germinal follicles; B – Medulla with increased plasma cells (x 400 H and E); C – Plasma cell (x 1000 H and E)

paramount significance as it influences the treatment modalities and prognosis. While UCD typically responds well to surgical excision with near-normal life expectancy, MCD carries a less favourable course. Before anti-IL-6 era, 5-year survival in HIV-negative MCD was approximately 65% as reported in a 2012 case series[6]. The TAFRO variant may progress rapidly with life-threatening organ dysfunction and severe clinical course[7].

Multicentric Castleman disease (MCD) requires systemic therapy guided by aetiology and the symptom severity as described in Fig. 5 below. HHV-8-associated multicentric Castleman disease is treated with rituximab alone in mildly symptomatic patients, while rituximab plus etoposide is used for severe disease or organ dysfunction; anthracycline-based chemotherapy may be considered when Kaposi sarcoma co-exists[5]. Other treatment modalities include antiviral therapy comprising of ganciclovir, foscarnet, and cidofovir effective against HHV-8 replication pathways. POEMS-associated disease requires therapy targeting plasma cell dyscrasia.

In idiopathic MCD, asymptomatic patients may be observed. Severely symptomatic or critically ill patients, including suspected TAFRO syndrome, should receive corticosteroids with anti–IL-6 therapy for rapid inflammatory control. Rituximab-based chemotherapy (e.g., R-CHOP/CVP) is

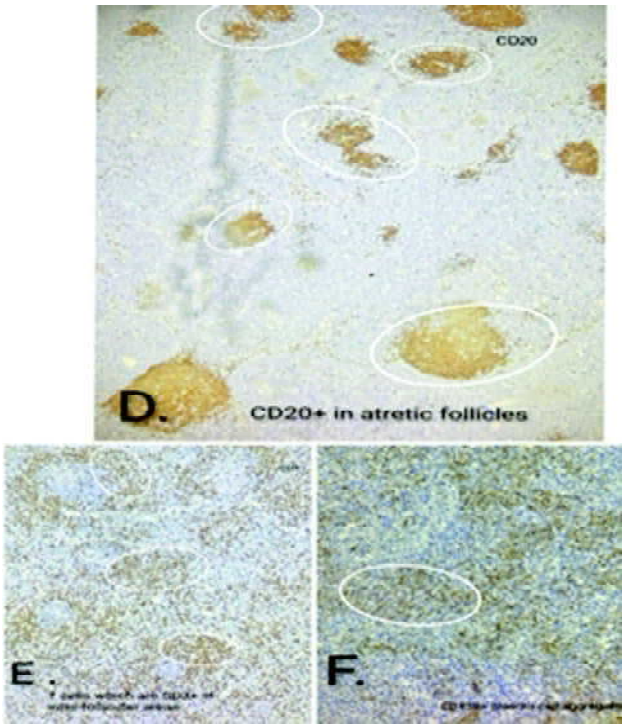


Fig. 3: *Immunohistochemistry of lymph node*
D – Showing CD 20 positivity within atretic germinal follicles; E – T-cells CD3+ in the interfollicular areas showing mantle zone thickening (onion-skin appearance), F – Sheets of plasma cell aggregates (CD 138+) in the interfollicular area; indicating plasma cell variant of Castleman's Disease.

reserved for cases refractory to or lacking access to anti-IL-6 therapy, with possible siltuximab maintenance after remission. Non-severe cases may be managed with siltuximab ± short-course steroids or rituximab with thalidomide, especially in immune cytopenias[5].

Tocilizumab, a monoclonal antibody that antagonises the IL-6 receptor (IL-6R) has been reported to exhibit significant reductions in lymphadenopathy and resolution of constitutional symptoms and signs in patients of i-MCD TAFRO[8].

Fig. 5 below describes the therapeutic algorithm for idiopathic multicentric Castleman as suggested by the CDCN.

Given the patient's prolonged fever, hepatosplenomegaly, anasarca, polyserositis, bicytopenia, and renal dysfunction, differentials included autoimmune disorders (SLE, sarcoidosis), chronic lymphoproliferative diseases, infections (tuberculosis, brucellosis), and malignancy. Extensive workup excluded these causes. PET-CT revealed generalised lymphadenopathy not detected on initial CT. Although IgG4-related disease was suspected, the IgG4/IgG ratio was normal. Excisional lymph node biopsy showed plasma cell variant Castleman disease with CD20 positivity. Histology, elevated IL-6, HHV-8 negativity, and absence of POEMS features confirmed iMCD-TAFRO.

Early initiation of corticosteroids and tocilizumab resulted in marked improvement , clinical and in laboratory parameters(Table I). Our patient was discharged on oral steroids with planned biweekly tocilizumab maintenance.

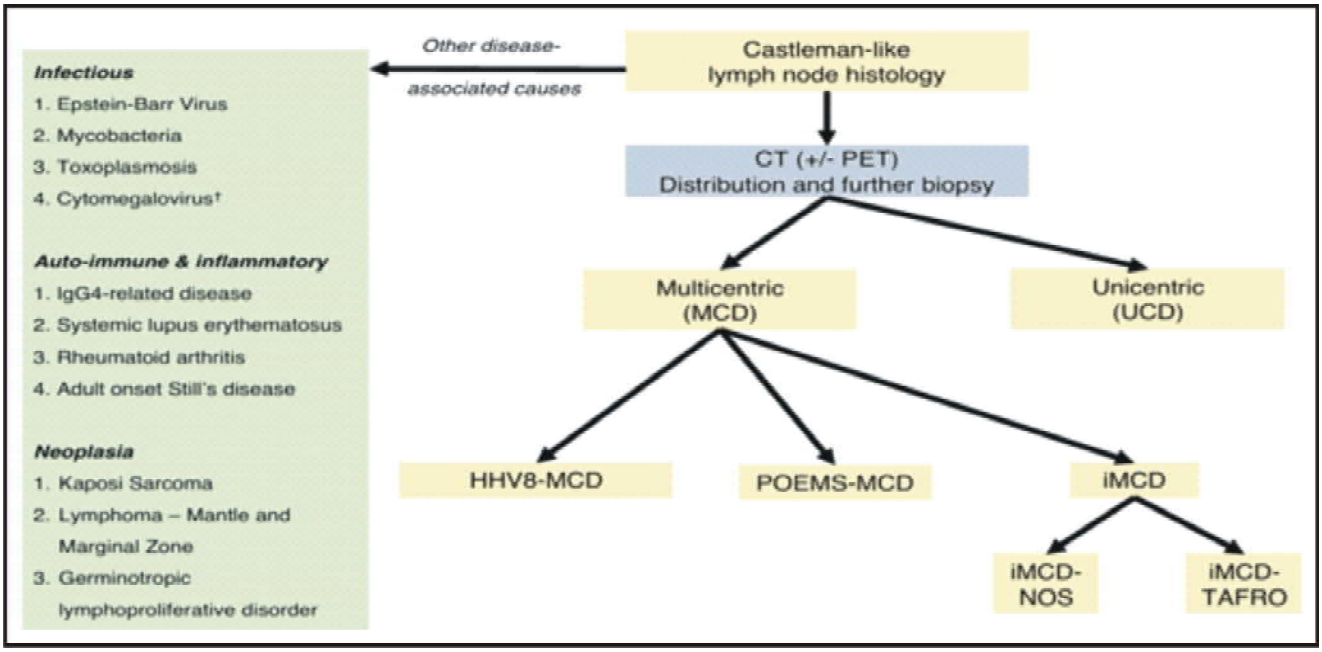


Fig. 4: *Approach to the diagnosis and classification of CD as proposed by the CDCN[5].*

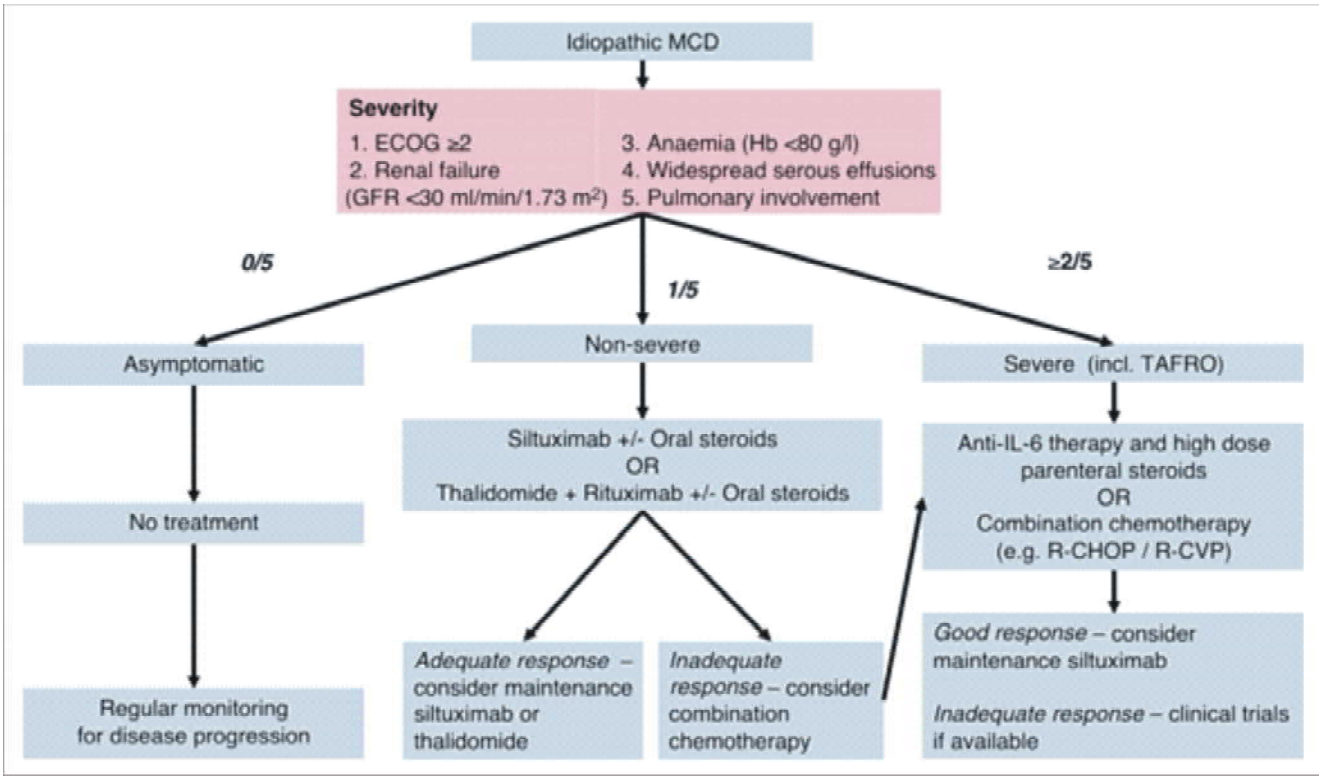


Fig. 5: *Suggested therapeutic algorithm in idiopathic multicentric Castleman disease based on severity scoring from the Castleman Disease Clinical Network. Anti-IL-6 therapy, anti-interleukin-6 therapy; ECOG, Eastern Cooperative Oncology Group Perfor mance Status score; GFR, glomerular filtration rate; Hb, Haemoglobin; MCD, multicentric Castleman disease; R-CHOP, rituximab-cyclophos phamide, doxorubicin, vincristine (Oncovin) and prednisone; R-CVP, rituximab, cyclophosphamide, vincristine, and prednisone; TAFRO, Thrombocytopenia, Anasarca, myelofibrosis, Renal dysfunction and Organomegaly*[5].

Conclusion

Castleman's disease presents a significant diagnostic challenges due to its nonspecific clinical, laboratory, and radiological findings and requires a multidisciplinary coordination amongst clinician, pathologist and radiologist as seen in this case. A high index of suspicion, careful exclusion of mimickers, and confirmatory histopathology are critical for diagnosis. Early recognition and targeted therapy, particularly anti-IL-6 agents in iMCD, can significantly improve patient-related outcomes and prevent complications.

Acknowledgement

The authors sincerely acknowledge the Department of Pathology, Dr. Ram Manohar Lohia Hospital, and the Department of Radiology, AIIMS, New Delhi, for their valuable assistance in establishing the diagnosis.

References

1. Castleman B, Towne VW. Case records of the Massachusetts General Hospital; weekly clinicopathological exercises; founded by Richard C. Cabot. *N Engl J Med* 1954; 251: 396-400.
2. Han X, Zhou DB. Advances in aetiology and management of Castleman's disease. Zhongguo Yi Xue Ke Xue Yuan Xue Bao. 2009; 31 (5): 639-43.
3. Dispenzieri A, Gertz MA. Treatment of Castleman's disease. *Curr Treat Options Oncol* 2005; 6 (3): 255-66.
4. Simpson D. Epidemiology of Castleman disease. *Haematol Oncol Clin North Am* 2018; 32 (1): 1-10.
5. Lomas OC, Streetly M, Pratt G *et al*. The management of Castleman disease. *Br J Haematol* 2021; 195 (3): 328-37.
6. Dispenzieri A, Armitage JO, Loe MJ *et al*. The clinical spectrum of Castleman's disease. *Am J Haematol* 2012; 87 (11): 997-1002.
7. Masaki Y, Arita K, Sakai T. Castleman disease and TAFRO syndrome. *Ann Haematol* 2022; 101 (3): 485-90.
8. Kapriniotis K, Lampridis S, Mitsos S, Panagiotopoulos N. Biologic agents in the treatment of multicentric Castleman disease. *Turk Thorac J* 2018; 19 (4): 220-5.

CASE REPORT

JIACM 2026; 27 (3): 220-22

Severe Haemotoxic Viper Envenomation with Recurrent VICC, Transient Myocardial Injury, Dynamic Conduction Abnormalities, and Kounis Syndrome following Antivenom Therapy

Himanth Erappra, SK Singh**, Varghese Koshy****

Abstract

Viper envenomation is predominantly associated with venom-induced consumption coagulopathy (VICC), local tissue injury, and acute kidney injury, while cardiovascular complications are uncommon but potentially life-threatening. We report a 33-year-old previously healthy male who developed severe haemotoxic envenomation following a viperid snakebite, with rapidly progressive local swelling and VICC. Following administration of polyvalent anti-snake venom (ASV), he developed severe anaphylaxis requiring intramuscular adrenaline. Subsequently, he developed acute chest pain with transient ST-segment elevation in leads II, III and aVF and positive cardiac troponin, with spontaneous resolution of the ischaemic changes, raising the possibility of Kounis syndrome. Serial electrocardiograms demonstrated dynamic conduction abnormalities progressing from 2:1 atrioventricular block to complete heart block and broad-complex bradyarrhythmia, followed by adenosine-responsive supraventricular tachycardia. His course was further complicated by hypotension, hyperkalaemia, oliguria, and acute kidney injury. Recurrent VICC necessitated repeated ASV administration, with a cumulative dose of 46 vials. With supportive and multidisciplinary management, coagulation abnormalities, renal dysfunction, local swelling, and cardiac rhythm disturbances progressively resolved, although residual left anterior fascicular block persisted at discharge. This case highlights the rare coexistence of recurrent VICC, transient myocardial injury, dynamic conduction abnormalities, supraventricular tachycardia, acute kidney injury, and probable Kounis syndrome following ASV-induced anaphylaxis. Severe viper envenomation warrants continuous cardiac monitoring with serial electrocardiography and cardiac biomarker assessment, particularly when chest pain or arrhythmias develop during antivenom therapy.

Key words: Viper bite, venom-induced consumption coagulopathy, Kounis syndrome, complete heart block, myocardial injury, snake envenomation.

Introduction

Snakebite envenomation remains a major public health problem in tropical countries, particularly India, where viperid snakes contribute substantially to morbidity and mortality. Haemotoxic envenomation commonly results in venom-induced consumption coagulopathy (VICC), bleeding manifestations, acute kidney injury, and local tissue injury[1]. Cardiac involvement is increasingly recognised but remains poorly characterised. Reported cardiovascular complications include myocardial infarction, coronary vasospasm, myocarditis, conduction abnormalities, arrhythmias, and cardiogenic shock[2]. These manifestations may result from direct venom cardiotoxicity, endothelial injury, hypercoagulability, coronary thrombosis, or allergic reactions associated with antivenom therapy[3]. Kounis syndrome, defined as acute coronary syndrome precipitated by allergic or hypersensitivity reactions, is a particularly rare but important differential diagnosis[4].

We describe a case of severe viperine envenomation complicated by recurrent VICC, transient myocardial ischaemia, dynamic conduction abnormalities, and probable Kounis syndrome.

Case Presentation

A 33-year-old serving soldier with no known comorbidities presented to a military hospital in Nagaland following a snakebite sustained over the dorsum of the right index finger at approximately 0530 hours on 03 June 2026 while working within unit premises. The offending snake was killed and photographed shortly after the incident and was morphologically consistent with a viperid species. Soon after the bite, he developed rapidly progressive painful swelling involving the right index finger extending to the wrist. On admission, fang marks were visible approximately 2 cm below the nail bed. Examination revealed diffuse swelling, erythema, and local warmth involving the affected digit without evidence of neurotoxic manifestations such as ptosis, dysarthria, dysphonia, or respiratory compromise.

Initial laboratory investigations demonstrated evidence of haemotoxic

Senior Resident, **Professor and Unit Head, ***Professor, Department of Internal Medicine and Rheumatology, Armed Forces Medical College, Pune - 411 040, Maharashtra.

Corresponding Author: Dr SK Singh, Senior Resident, Professor and Unit Head, Department of Internal Medicine, Armed Forces Medical College, Pune - 411 040, Maharashtra. Tel: 8092665282, E-mail: santoshsingh4006@gmail.com

envenomation with abnormal clotting parameters suggestive of VICC. Baseline haemoglobin was 14.4 g/dL, platelet count was preserved, and serum creatinine was 1.0 mg/dL. D-dimer levels were markedly elevated at 5,139 ng/mL and subsequently increased to >10,000 ng/mL. Given severe haemotoxic envenomation and a positive 20-minute whole blood clotting test (20WBCT), treatment was initiated with a loading dose of 10 vials of polyvalent anti-snake venom (ASV) within 06 hrs of snakebite. Shortly after receiving approximately 10 mL of reconstituted ASV, the patient developed severe anaphylaxis characterised by acute bronchospasm. He was successfully managed with intramuscular adrenaline and supportive care. After stabilisation, ASV infusion was cautiously resumed at a slower rate under close monitoring.

During ASV administration, the patient developed acute central chest pain. Simultaneous ECG demonstrated ST-segment elevation in leads II, III, and aVF with reciprocal ST-segment depression in lead V1. Cardiac troponin was positive. Differential diagnoses considered included acute coronary syndrome, coronary vasospasm, venom-induced myocardial injury, and Kounis syndrome secondary to antivenom-induced anaphylaxis. The ischaemic ECG changes subsequently resolved. Despite resolution of chest pain and ST-segment abnormalities, serial ECGs revealed progressive conduction disturbances. The patient developed 2:1 atrioventricular block which progressed to complete heart block and symptomatic broad-complex bradyarrhythmia. Intravenous atropine was administered according to Advanced Cardiac Life Support protocols. Following atropine administration, he developed supraventricular tachycardia with rapid ventricular response that successfully reverted following administration of 6 mg intravenous adenosine. The clinical course was further complicated by hypotension (lowest recorded blood pressure 88/46 mmHg), worsening local envenomation extending to the elbow, hyperkalaemia, oliguria, and AKI with serum creatinine rising from 1.0 mg/dL to 1.3 mg/dL. The patient required inotropic support, anti-hyperkalaemic therapy, broad-spectrum antibiotics, repeated ASV administration, and intensive monitoring. Temporary pacing was considered but deferred because rhythm abnormalities improved with medical management. At approximately 12 hours after the bite (Day 0), the patient was clinically stabilised following supportive management.

Persistent and recurrent VICC necessitated repeated ASV dosing. The patient ultimately received a cumulative dose of approximately 46 vials of polyvalent ASV. Serum fibrinogen reached 189 mg/dL and prothrombin time remained mildly prolonged. Despite severe coagulation abnormalities, no clinically significant spontaneous bleeding occurred and platelet counts remained preserved throughout hospitalisation. Over subsequent days, renal function normalised, coagulopathy resolved, local swelling improved, and cardiac rhythm disturbances subsided. Follow-up ECG demonstrated residual left anterior fascicular block (LAFB). The patient was discharged in a haemodynamically stable condition by 06 June 26 and referred to a tertiary cardiac center for coronary angiography and further evaluation of myocardial injury.

Discussion

Viper envenomation is characterised by complex haematological and vascular effects mediated by procoagulant toxins, metalloproteinases, phospholipases, and endothelial toxins[5]. VICC remains the hallmark of severe haemotoxic envenomation and may recur despite initial correction owing to ongoing venom redistribution. The present case is unique for the coexistence of several uncommon cardiovascular complications:-

i. Transient Myocardial Injury: The patient developed acute chest pain, positive cardiac biomarkers, and transient inferior ST-segment elevation. potential mechanisms include:-
   a. Direct venom cardiotoxicity
   b. Coronary vasospasm
   c. Microvascular thrombosis

Table I: Serial haematological, biochemical, coagulation, and electrocardiographic findings following viper envenomation.

Investigation/ECG	03 Jun 2026 (Day 0)	04 Jun 2026 (Day 1)	05 Jun 2026 (Day 2)	08 Jun 2026 (Day 5)
Hb (g/dL)	14.4	13.3	–	14.3
TLC (/mm^3)	6,600	12,700	>16,500	9,800
Platelets (lakh/mm^3)	3.73	2.94	>3.11	3.53
Urea/Creatinine (mg/dL)	34/1.0	37/1.3	–	32/1.1
Na/K (mEq/L)	135/4.3	145/5.3	–	138/4.1
D-dimer (ng/mL)	5,139	8,864	>10,000	431
Fibrinogen (mg/dL)	–	189	–	–
INR	1.3	1.2	–	–
ECG	Baseline	ST elevation II, III, aVF – 2:1 AV block	CHB – broad-complex bradyarrhythmia – SVT	LAFB

d. Demand ischaemia

e. Kounis syndrome

The spontaneous resolution of ECG changes without reperfusion therapy favours coronary vasospasm or allergic coronary syndrome over thrombotic myocardial infarction.

ii. Kounis Syndrome: Kounis syndrome is defined as acute coronary syndrome occurring in association with mast-cell activation and allergic reactions[6]. The temporal relationship between ASV-induced anaphylaxis and subsequent ischaemic ECG changes strongly supports this possibility. To our knowledge, reports of Kounis syndrome following antivenom administration remain exceedingly rare.

iii. Conduction System abnormalities: The evolution from 2:1 AV block to complete heart block and broad-complex bradyarrhythmia is particularly unusual. Proposed mechanisms include:-

a. Direct venom-mediated myocardial toxicity

b. Ischaemia of the conduction system

c. Myocarditis-like inflammatory injury

d. Electrolyte disturbances

e. Autonomic dysfunction

The subsequent recovery without permanent pacing suggests reversible toxin-mediated injury.

iv. Supraventricular Tachycardia: Development of SVT following atropine administration may reflect heightened sympathetic activity in a myocardium already sensitised by venom-induced injury.

v. Recurrent VICC: Persistent elevation of D-dimer levels (>10,000 ng/mL) and recurrent clotting abnormalities despite initial treatment illustrate delayed or recurrent VICC, a phenomenon increasingly recognised in severe viper envenomation.

An important learning point from this case is the simultaneous occurrence of multiple reversible cardiovascular complications in the setting of severe hemotoxic envenomation. While myocardial injury, atrioventricular conduction disturbances, supraventricular tachyarrhythmias, recurrent venom-induced consumption coagulopathy (VICC), and Kounis syndrome have each been reported individually, their coexistence in a single patient is exceedingly rare. The temporal sequence of events suggests that several overlapping mechanisms – including direct venom cardiotoxicity, endothelial dysfunction, transient coronary vasospasm, systemic inflammatory response, electrolyte abnormalities, and mast cell-mediated hypersensitivity following antivenom administration – may have acted synergistically. This case also highlights the diagnostic challenge of distinguishing acute coronary thrombosis from venom-related myocardial injury or allergic coronary syndrome, as management strategies differ substantially. The complete recovery of cardiac rhythm abnormalities without permanent pacing further supports the reversible nature of toxin-mediated conduction system injury when recognized early and managed appropriately. Therefore, patients with severe haemotoxic snakebite should undergo serial electrocardiography, cardiac biomarker assessment, and continuous cardiac monitoring, particularly following antivenom administration or the development of chest pain, as prompt recognition and supportive treatment may prevent potentially fatal complications.

Conclusion

Severe viper envenomation may present with a broad spectrum of cardiovascular manifestations extending beyond coagulopathy and renal injury. This case demonstrates the rare coexistence of recurrent VICC, probable kounis syndrome, transient myocardial injury, complete heart block, broad-complex bradyarrhythmia, supraventricular tachycardia and acute kidney injury.

Clinicians should maintain a high index of suspicion for cardiac complications in severe envenomation, particularly when chest pain, ECG abnormalities, or arrhythmias develop during treatment. Early multidisciplinary management and continuous cardiac monitoring are essential for favourable outcomes.

References

1. Ojha A, Hadimani P, Anthony D *et al*. Optimizing Anti-Snake Venom Strategies for Haemotoxic Envenomation in Northern India: Clinical Outcomes and Regional Challenge. *Cureus* 17 (5): e84090.
2. A Study of Clinicobiochemical and Cardiac Profile in Snakebite at a Tertiary Care Center in Northern India [Internet]. [cited 2026 Jul 30]. Available from: https://japi.org
3. Averin AS, Utkin YN. Cardiovascular Effects of Snake Toxins: Cardiotoxicity and Cardioprotection. *Acta Naturae* 2021; 13 (3): 4.
4. Rodríguez-Ruiz C, Puig-Carrión G, Delgado-Nieves A. Kounis Syndrome: A More Commonly Encountered Cause of Acute Coronary Syndrome. *Heart Views Off J Gulf Heart Assoc* 2019; 20 (3): 122-5.
5. Khelfi A. Pathophysiological and therapeutic insights into Viperidae envenomation: Mechanisms, clinical manifestations, and advances in antivenom strategies. *Toxicol Anal Clin* 2026; 38 (2): 180-97.
6. Kounis NG. Kounis syndrome (allergic angina and allergic myocardial infarction): A natural paradigm? *Int J Cardiol* 2006; 110 (1): 7-14.

CASE REPORT

JIACM 2026; 27 (3): 223-24

Renal Transplant in a Case of EHPVO with Severe Pancytopenia

Kailash N Singh, Ankit Grover**, Neerav Goyal***, Sandeep Guleria*****

Abstract

Renal transplantation in patients with extrahepatic portal vein obstruction (EHPVO) is rare and surgically challenging due to portal hypertension, hypersplenism, and altered vascular anatomy. We report a 32-year-old male with chronic kidney disease stage V on maintenance haemodialysis, associated with EHPVO, portal cavernoma, and severe hypersplenism, who successfully underwent live donor renal transplantation along with simultaneous mesocaval and lienorenal shunt surgery. Preoperatively, the patient had severe anaemia (Hb 5.5 g/dL) and thrombocytopenia (20,000/mm^3). Intraoperative findings included extensive collateralisation and splenomegaly. The postoperative course was uneventful with immediate graft function, improvement in renal parameters (serum creatinine 0.8 mg/dL at discharge), and rising platelet counts. No rejection or infectious complications were observed. This case highlights that renal transplantation is feasible in patients with complex portal hypertensive disorders when combined with appropriate portal decompressive procedures and multidisciplinary planning.

Key words: Extrahepatic portal vein obstruction; renal transplantation; portal hypertension; hypersplenism; mesocaval shunt; Lienorenal shunt.

Introduction

Extrahepatic portal vein obstruction (EHPVO) is a major cause of non-cirrhotic portal hypertension and is commonly associated with portal cavernoma and hypersplenism[1,2]. Renal transplantation in such patients is rarely performed due to technical challenges including distorted vascular anatomy, high bleeding risk, and cytopenias[3,4]. Severe thrombocytopenia further complicates the perioperative management. Literature on simultaneous renal transplantation with portal decompressive procedures remains limited. We report a rare case highlighting the successful management with a combined surgical approach.

Case Report

A 32-year-old male with chronic kidney disease stage V on maintenance haemodialysis via right internal jugular permacath was planned for renal transplantation. The patient was evaluated and found to have severe anaemia (haemoglobin 5.5 g/dL) and marked thrombocytopenia (platelet count 20,000/cumm). His liver function tests were normal and fibroscan showed a kPA value of 5.6 indicating a normal liver elastography.

He was further evaluated and ultrasonography revealed chronic EHPVO with portal cavernoma, splenomegaly, and features of portal hypertension. Triple phase CT abdomen demonstrated features of portal hypertension with massive splenomegaly. The persistent thrombocytopenia was attributable to hypersplenism after ruling out other causes.

His immunological workup including complement-dependent cytotoxicity crossmatch, flow crossmatch, and donor-specific antibodies was negative. Due medical and surgical clearance was taken from all the departments. A multidisciplinary meeting was held and given the presence of significant portal hypertension and extensive collateralisation, a combined surgical approach was planned.

The patient received induction immunosuppression with basiliximab with initiation of low dose tacrolimus and prednisolone for immunosuppression. Injection filgrastim was given twice per week for one month prior to surgery. Adequate platelet along with packed red blood cell were also transfused prior to surgery and intraoperatively to manage pancytopenia.

Intraoperatively, extensive mesenteric and splenic collaterals, portal cavernoma, and massive splenomegaly were noted. The patient underwent exploratory laparotomy followed by mesocaval shunt and lienorenal shunt (side-to-side) creation for portal decompression. Renal transplantation was then performed with the donor kidney anastomosed to the recipient's internal iliac artery and external iliac vein. Ureteroneocystostomy was done with placement of a double-J stent.

The immediate post-operative period was marked by good

**Senior Consultant, **Consultant, Department of Nephrology and Kidney Transplant, ***Senior Consultant, Department of Liver Transplant and Hepatobiliary Surgery, ****Senior Consultant, Department of Transplant Surgery, Indraprastha Apollo Hospital, New Delhi - 110 076.*

Corresponding Author: Dr Ankit Grover, Consultant, Department of Nephrology and Kidney Transplant, Indraprastha Apollo Hospital, New Delhi - 110 076. Tel: 9971978636, E-mail: angrover@gmail.com

urine output (up to 7 litres/day) and satisfactory graft perfusion. Serum creatinine improved from 3.8 mg/dL on post-operative day 0 to 1.0 mg/dL by day 5 and 0.8 mg/dL at discharge. On post-operative day 1, four units platelets were transfused and platelet counts showed gradual improvement to 40,000/mm^3 on post-operative day 2 to 65000/mm^3 on day 9. Mycophenolate mofetil was withheld on the day of transplantation due to concerns of exacerbating cytopenias and was introduced at a low dose on post-operative day 4, once platelet and leukocyte counts demonstrated an improving trend.

There were no episodes of acute rejection or infection. Doppler ultrasonography demonstrated a well-perfused graft (resistive index 0.61) and patent mesocaval and lienorenal shunts.

He was discharged on post-operative day 9 in stable condition with normal graft function and improving haematological parameters. At 1-month post-transplant patient has a good urine output of 1.8 - 2 litres/day with a serum creatinine of 0.9 mg/dL on triple drug immunosuppression with prednisolone, tacrolimus and mycophenolate mofetil and maintains his haematological parameters as Hb 9.8 g/dL, TLC 4400/cumm and platelet count of 1,25,000/cumm.

Presently, at 3 months follow-up, patient has urine output of 1.5 - 2 litres/day with a serum creatinine of 0.8 mg/dL on triple drug immunosuppression with prednisolone, tacrolimus and mycophenolate mofetil and maintains his haematological parameters as Hb 10.1 g/dL, TLC 5,600/cumm and platelet count of 1,46,000/cumm.

Discussion

EHPVO is characterised by chronic thrombosis of the portal vein leading to cavernoma formation and portal hypertension. Hypersplenism frequently results in cytopenias, particularly thrombocytopenia, which significantly increases surgical risk[1,2]. Renal transplantation in such patients poses unique challenges.

First, vascular anatomy is often distorted due to extensive collateral formation, making surgical dissection difficult[3]. Second, severe thrombocytopenia increases the risk of intraoperative and post-operative bleeding and thirdly, portal hypertension may predispose to haemodynamic instability[4].

Simultaneous portal decompressive procedures, such as mesocaval or lienorenal shunts, can alleviate portal hypertension and improve hypersplenism[5]. In the present case, combined shunt surgery likely contributed to improved platelet counts and reduced perioperative complications.

There is limited literature describing renal transplantation in patients with EHPVO. Most reported cases emphasize staged procedures; however, simultaneous surgery, as in this case, may reduce overall morbidity by avoiding multiple interventions.

Immunosuppression management is also crucial, as these patients may have altered liver function and increased infection risk and our more prone for bleeding post-operatively. In our patient, standard triple immunosuppression was well tolerated without complications.

In the presence of pancytopenia with an increased risk of bleeding and bone marrow suppression, the choice of induction agent – rabbit anti-thymocyte globulin (rATG) versus basiliximab – requires careful consideration. While rATG provides potent anti-rejection efficacy in the immediate post-operative period, it is associated with a higher risk of cytopenias and infections. In contrast, basiliximab, though relatively less potent, offers a safer profile in patients with pre-existing pancytopenia[6]. Therefore, a balanced risk – benefit assessment is essential when selecting the induction strategy.

This case highlights the importance of a multidisciplinary approach involving hepatobiliary surgeons, renal transplant surgeons, and nephrologists to achieve optimal outcomes in complex cases of EHPVO with end-stage renal disease undergoing transplantation.

This case underscores the importance of:-

- Careful preoperative planning
- Multidisciplinary collaboration
- Expertise in complex vascular and transplant surgery

References

1. Sarin SK, Agarwal SR. Extrahepatic portal vein obstruction. *Semin Liver Dis* 2002; 22 (1): 43-58.
2. Sarin SK, Khanna R. Non-cirrhotic portal hypertension. *Clin Liver Dis* 2014; 18 (2): 451-76.
3. Arora A, Sarin SK. Multimodality imaging of primary extrahepatic portal vein obstruction (EHPVO): what every radiologist should know. *Br J Radiol* 2015; 88 (1052): 20150008.
4. Shimizu T, Yoshida H, Taniai N *et al*. Clinical features of extrahepatic portal vein obstruction: Myeloproliferative neoplasms eliminate hypersplenic haematologic changes in extrahepatic portal vein obstruction. *Intractable Rare Dis Res* 2024; 13 (1): 63-8.
5. Lal R, Behari A, Sarma MS *et al*. Portosystemic shunt surgery for extrahepatic portal venous obstruction beyond endoscopic variceal eradication: two decades of pediatric surgical experience. *J Clin Exp Hepatol* 2023; 13 (6): 997-1007.
6. Brennan DC, Daller JA, Lake KD. Thymoglobulin Induction Study Group. Rabbit antithymocyte globulin versus basiliximab in renal transplantation. *N Engl J Med* 2006; 355 (19): 1967-77.

CASE REPORT

JIACM 2026; 27 (3): 225-27

Unusual Presentation of Ovarian Serous Cystadenocarcinoma

Vinay Kumar, Rajat Jhamb**, Rutu Karia***, Nausheen Farha****, Rimple khatri*****, Shrinath Nevanath**

Abstract

Ovarian epithelial cancers usually come to attention because of abdominal bloating or distension, pelvic pain, ascites, or an adnexal mass. It is very unusual for them to present first with blood-related abnormalities. Bone marrow involvement in ovarian carcinoma is rare, but can lead to pancytopenia and a leukoerythroblastic picture on peripheral smear, which may initially make the condition look like a primary haematological disorder.

We present a case of a 28-year-old woman who presented with pancytopenia secondary to metastatic adenocarcinoma infiltrating the marrow. This case highlights a rare and unusual presentation of ovarian serous Cystadenocarcinoma, where bone marrow infiltration led to pancytopenia and further affirms the need to consider an occult solid organ carcinoma in patients presenting with Pancytopenia due to Myelophthisis.

Key words: Ovarian Serous Cystadenocarcinoma, pancytopenia, myelophthisis.

Introduction

Ovarian cystadenocarcinoma is a common, highly malignant epithelial cancer of the ovary, comprising over 60% of ovarian cancers. It presents as large, complex, frequently bilateral cysts with solid, and vascular components, often causing abdominal pain and swelling. These tumours usually spread within the peritoneal cavity by transcoelomic spread where tumour cells detach and travel through peritoneal fluid, settling on the peritoneum, omentum, and abdominal organs or can grow by direct extension into the into adjacent organs such as the fallopian tubes, uterus, bladder, and rectum, while spread through the bloodstream is rare. We present a case of a 28-year-old woman who presented with Myelophthisis secondary to metastatic adenocarcinoma infiltrating the marrow.

Case Presentation

A 28-year-old woman presented with complaints of fatigue, loss of appetite, and generalised body ache for the past three months. For the last three days, she had also been experiencing low grade fever and had noticed petechial spots over her body. There was no history of significant weight loss, bleeding from any site, jaundice, pain abdomen, abdominal fullness, bony pains or any previous blood transfusion. She did report intermittent episodes of fever over the past one year. Her past surgical history was significant for cholecystectomy. She had regular menses with normal flow around 4 - 5 days with one living child of around 3 and half year (P1L1) born by NVD.

On examination, she was found to have marked pallor. There was no lymphadenopathy or organomegaly, and the rest of the systemic examination was essentially normal. Initial investigations showed pancytopenia, with haemoglobin 7.1 g/dL, total leukocyte count 2500 cells/µL, and platelet count 5000/µL. Her liver and renal function tests, as well as serum electrolytes, were within normal limits. Because she had history of fever along with cytopenias, an extensive infectious workup was carried out including dengue NS1 antigen, malaria antigen, Widal test, scrub typhus serology, leptospira testing, and blood cultures but all of these were negative. Peripheral smear showed a leukoerythroblastic blood picture, which raised suspicion of haematological malignancy or bone marrow infiltration. Patient had severe thrombocytopenia but despite this she was not suspected to have DIC because of her non-toxic presentation, no history of haematemesis, malena, epistaxis or any other bleeding manifestation, and no history of trauma/burns, Placental abruption/RPOC/ Pre-eclampsia/HEELP or any other obstetric emergency, no sign and symptoms of ALF, and no history of major transfusion in the past.

Bone marrow aspiration and biopsy was performed and it revealed atypical epithelial cells arranged in clusters and papillary patterns, suggestive of metastatic adenocarcinoma involving the marrow (Fig. 1). Following this a comprehensive work up was performed to identify the primary origin. Contrast-enhanced CT scan of the abdomen showed a complex cystic-solid lesion in the right ovary, raising the suspicion of primary ovarian malignancy, while

**Post-Graduate Resident, **Director Professor, ***Senior Resident, ****Junior Resident, Department of Medicine, *****Senior Resident, Department of Pathology, University College of Medical Sciences and Guru Teg Bahadur Hospital, Dilshad Garden, Delhi - 110 095. Corresponding Author: Dr Vinay Kumar, Post-Graduate Resident, Department of Medicine, University College of Medical Sciences and Guru Teg Bahadur Hospital, Dilshad Garden, Delhi - 110 095. Tel: 9915391868, E-mail: vinaykumar147003@gmail.com*

the left ovary appeared bulky (~3.1*1.8 cm) with cystic changes and right ovary (~4.6*2.8) (Fig. 2). A small fibrotic subpleural lung nodule was also seen.

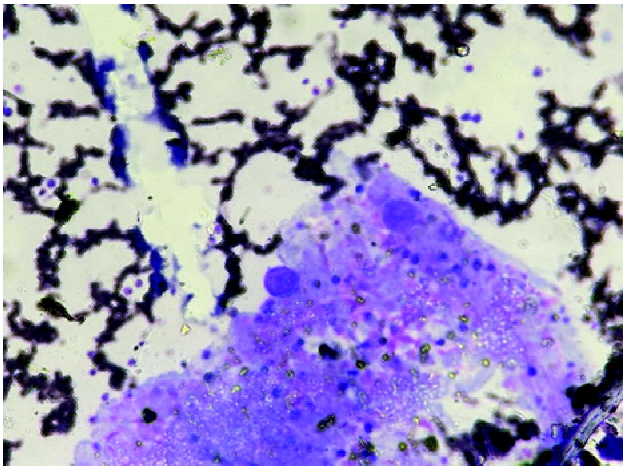


Fig. 1: *Bone marrow aspiration and biopsy revealed atypical epithelial cells arranged in clusters and papillary patterns, suggestive of metastatic adenocarcinoma involving the marrow.*

Tumour markers, including CA-125 and carcinoembryonic antigen, were within normal limits. There was no significant ascites or lymphadenopathy. Taking the marrow findings together with the imaging features, the diagnosis of ovarian serous cystadenocarcinoma with bone marrow metastasis was made. Possibility of krukenberg tumour was less likely as tumour was multiloculated with cystic solid morphology with enhancing walls/septa which shows specks of

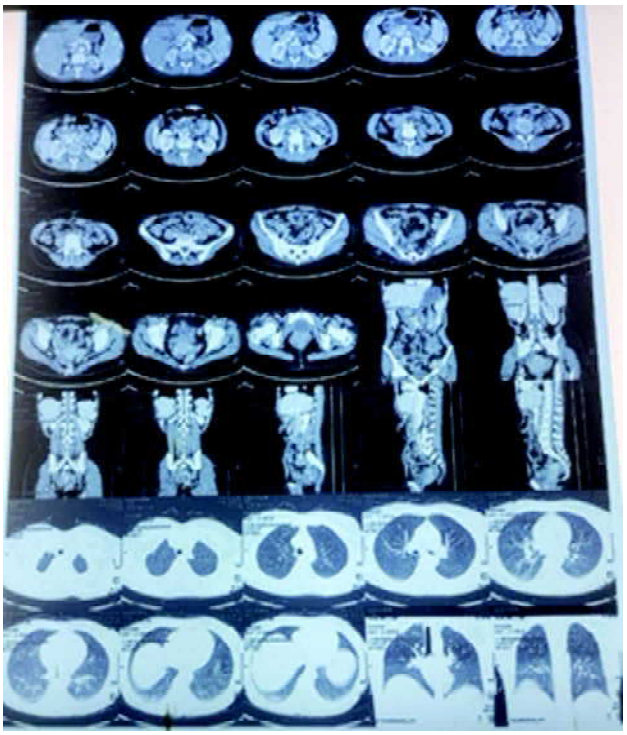




Fig. 2: *CECT scan of abdomen and chest demonstrating complex cystic-solid lesion in the right ovary and bulky left ovary with cystic changes and a small fibrotic subpleural lung nodule.*

calcification. No primary tumour was identified elsewhere with normal GI tract and no ascites on CT. Although bilateral involvement may favour krukenberg tumour, but cystic nature with calcification predominantly favours serous origin. Serous cystadenocarcinomas have peritoneal (Transcoelomic Spread) which make this case unique and interesting. During her hospital stay, she was managed supportively with packed red cell transfusions, platelet transfusions, and empirical antibiotics. She was later referred to gynaecology and oncology services for further management. Patient was planned for biopsy form tumor and PET-CT but in due course of time, patient developed LRTI (Lower Respiratory Tract Infection) leading to ARDS and patient eventually died.

Discussion

Ovarian cystadenocarcinoma is a common, highly malignant epithelial cancer of the ovary, comprising over 60% of ovarian cancers. It presents as large, complex, frequently bilateral cysts with solid, vascular components, often causing abdominal pain and swelling. These tumours usually spread within the peritoneal cavity by transcoelomic spread where tumour cells detach and travel through peritoneal fluid, settling on the peritoneum, omentum, and abdominal organs or can grow by direct extension into the into adjacent organs such as the fallopian tubes, uterus, bladder, and rectum, while spread

through the bloodstream is rare.

While ovarian cancer commonly spreads within the peritoneum; bone marrow metastasis (BMM) is estimated to occur in only 0.1 - 1% of cases, often presenting with severe anaemia and other haematological abnormalities[1,2]. The typical picture is of myelophthisis or myelophthisic anaemia, a severe form of bone marrow failure that occurs when normal marrow space is replaced by abnormal tissue, such as metastatic cancer. Metastatic cells from the ovary invade the bone marrow, destroying the haematopoietic tissue responsible for producing blood cells. This destruction leads to a "leukoerythroblastic picture" in the blood due to immature myeloid cells and nucleated red blood cells being released into the bloodstream prematurely. Patients often present with severe anaemia, fatigue, weakness, and potential thrombocytopenia .Ovarian cystadenocarcinoma, when metastasize to the bone marrow, is associated with a very poor prognosis, rapid progression, and high mortality. The survival after bone metastases of primary ovarian cancer is 33%, 15%, and 8% for 1, 3, and 5 years, respectively, with a median survival of 7.5 months (range 6 - 39 months)[3]. Dauplat *et al*[4] reported that bone metastases occurred only in 1.6% from primary ovarian cancer, hence confirming that bone involvement is rare in ovarian cancer. A leukoerythroblastic blood picture is an important clue to marrow involvement and should alert clinicians to the possibility of marrow infiltration in patients presenting with otherwise unexplained cytopenias. What makes this case interesting is that the patient presented atypically without any symptom suggestive of ovarian pathology or abdominal complaints.

CA-125 is a primary tumour marker used to monitor and help diagnose ovarian cystadenocarcinoma, with high levels commonly indicating advanced cancer. Levels are generally elevated above 35u/ML in 75 - 90% of stage III/IV cases, but it is not a conclusive diagnostic tool on its own and it can also be raised by benign conditions. For this reason, normal tumour markers as were found in our case should not lead to false reassurance when radiological and pathological findings are otherwise suggestive of malignancy[5]. Tumour markers such as PAX8, WT1, CK7, p53, and ER can be particularly useful in supporting a Müllerian high-grade serous origin and in helping to exclude a metastatic gastrointestinal primary[6].

This case is clinically relevant as it shows a rare and unusual presentation of suspected Ovarian Serous Cystadenocarcinoma. Such an atypical presentation can easily resemble infectious or primary haematological disorders which may delay the diagnosis. Further normal tumor markers may further puzzle the clinician and careful correlation of haematological investigations, imaging studies, and histopathology should be done to arrive at a logical conclusion.

Conclusion

Bone marrow metastasis in ovarian cancer is very uncommon and generally indicates advanced disease. When it does occur, patients may present with myelophthisis or myelophthisic anaemia, a leukoerythroblastic blood picture, or even disseminated intravascular coagulation. Because these findings are unusual for a gynaecological malignancy, the clinician should be aware of atypical and unusual manifestations of common malignancies. Further normal tumour markers should not lead to false reassurance when radiological and pathological findings are otherwise suggestive of malignancy and careful correlation of haematological investigations, imaging studies, and histopathology should be done to arrive at a logical conclusion.

References

1. Yamada T, Nakajima J, Ooba Y. Bone marrow metastasis of ovarian cancer: A two center retrospective study and literature review. *Mol Clin Oncol* 2025; 22 (3): 27.
2. Singhal S, Sharma R; Sharma S. Ovarian cancer with osteoblastic bone metastasis – A rare case report. *J Cancer Res Therapeut* 19 (Suppl 2): S932-S934.
3. Kumar L, Bhargava VL, Rao RC. Bone metastasis in ovarian cancer. *Asia-Oceania J Obstet Gynaecol* 1992; 18: 309-13.
4. Dauplat J, Hacker NF, Nieberg RK. Distant metastases in epithelial ovarian carcinoma. *Cancer* 1987; 60: 1561-6.
5. Charkhchi P, Cybulski C, Gronwald J. CA125 and Ovarian Cancer: A Comprehensive Review. *Cancers (Basel)* 2020; 12 (12): 3730.
6. Cobb LP, Gaillard S, Wang Y. Adenocarcinoma of Mullerian origin: review of pathogenesis, molecular biology, and emerging treatment paradigms. *Gynaecol Oncol Res Pract* 2015; 2: 1.

CASE REPORT

JIACM 2026; 27 (3): 228-30

Pancreatic Tuberculosis with Reversible Exocrine Insufficiency

Vishwa Golyan, Abrar Hussain*, Prabhat Kumar**, Bhuvnesh Guglani****

Abstract

Tuberculosis (TB) continues to be a major cause of morbidity and mortality in the Indian subcontinent. However, pancreatic tuberculosis is a rare form of abdominal tuberculosis and commonly mimics pancreatic malignancy. The literature on pancreatic tuberculosis with exocrine insufficiency is extremely sparse. Herein, we report a 44-year-old male patient who presented with pain abdomen and steatorrhoea for two years and a diagnosis of pancreatic tuberculosis with exocrine insufficiency was made after imaging and histopathological confirmation. He was successfully treated with anti-tuberculous therapy with complete resolution of pancreatic lesion and exocrine insufficiency.

Key words: Abdominal tuberculosis, fecal elastase, pancreatic mass.

Introduction

Tuberculosis (TB) remains a major global health burden, with an estimated 10.6 million new cases reported worldwide annually. India continues to account for a substantial proportion of the global TB burden. Extrapulmonary tuberculosis constitutes nearly 15 - 20% of all TB cases, while abdominal tuberculosis accounts for approximately 5 - 12% of extrapulmonary disease[1]. The ileocecal region, peritoneum, and abdominal lymph nodes are the most commonly involved sites. Pancreatic tuberculosis is an exceptionally rare form of abdominal TB, even in endemic regions, accounting for less than 5% of abdominal tuberculosis cases[2].

Exocrine pancreatic insufficiency (EPI), characterised by inadequate secretion of pancreatic enzymes leading to malabsorption and steatorrhoea, is well recognised in chronic pancreatitis and pancreatic malignancy but has not been reported in pancreatic tuberculosis[3]. Faecal elastase serves as a reliable non-invasive marker of pancreatic exocrine function. We report a rare case of pancreatic tuberculosis presenting with faecal elastase-proven exocrine pancreatic insufficiency, which subsequently demonstrated clinical and biochemical reversal following anti-tubercular therapy.

Case Report

A 44-year-old male presented to our outpatient department with complaints of central epigastric pain associated with progressive weight loss, anorexia, generalised weakness, and greasy sticky floating stools for the past one year, with worsening abdominal discomfort over the preceding 7 days. On examination, the patient was thin-built with pallor and reduced muscle mass.

Laboratory investigations revealed severe microcytic anaemia with haemoglobin of 6.7 g/dL, mean corpuscular volume (MCV) - 76.2 fl. Iron profile showed serum iron of 12 µg/dL, total iron-binding capacity (TIBC) - 420 µg/dL, and serum ferritin - 72.2 ng/mL and peripheral blood smear showed microcytic hypochromic red blood cells suggesting anaemia of chronic disease. Total leukocyte count was 9,230/mm^3 with markedly elevated inflammatory markers (CRP: 107 mg/L, ESR: 28 mm/hr) and random blood glucose level was 110 mg/dL.

Viral markers including HIV, HBsAg, and anti-HCV were negative. ANA profile was negative. Serum amylase, lipase, serum ACE levels, CA 19 - 9 and serum IgG4 levels were within normal limits. Fecal elastase level was found to be markedly reduced 98 µg/g, suggesting severe exocrine pancreatic insufficiency.

Point-of-care ultrasonography performed after admission revealed a pancreatic lump with surrounding lymphadenopathy, following which contrast-enhanced computed tomography (CECT) of the abdomen was performed. CECT abdomen demonstrated a bulky heterogeneously enhancing pancreas with multiple hypodense non-enhancing areas involving the pancreatic body and peripancreatic region, associated with marked peripancreatic stranding and multiple necrotic retroperitoneal, peripancreatic and mesenteric lymph nodes with peripheral enhancement and calcification (Fig. 1).

CT-guided biopsy of retroperitoneal lymph node was subsequently performed. Histopathological examination demonstrated epithelioid granulomas with multinucleated giant cells in a reactive lymphoid background, consistent

Post-Graduate Resident, **Senior Consultant, Department of Internal Medicine, ***Senior Consultant, Department of Radiodiagnosis, Kailash Hospital and Neuro Institute, Noida - 201 309, Uttar Pradesh.

Corresponding Author: Dr Prabhat Kumar, Senior Consultant, Department of Internal Medicine, Kailash Hospital and Neuro Institute, Noida, Uttar Pradesh. Tel: 9968123167, E-mail: drkumar.prabhat@gmail.com

with granulomatous lymphadenitis. Ziehl-Neelsen staining for acid-fast bacilli was negative (Fig. 2).

Based on the clinic-radiological findings and histopathological evidence, a diagnosis of pancreatic tuberculosis with secondary exocrine pancreatic insufficiency was established. The patient was initiated on four drug anti-tubercular therapy (ATT) along with pancreatic enzyme replacement therapy.

During follow-up, the patient demonstrated marked symptomatic improvement with resolution of abdominal pain and improvement in appetite. Repeat fecal elastase after 2 months of treatment improved to 142 µg/g and normalised after six months of ATT. Serial ultrasonography over a 6-month follow-up period demonstrated complete resolution of pancreatic swelling and peripancreatic lymphadenopathy.

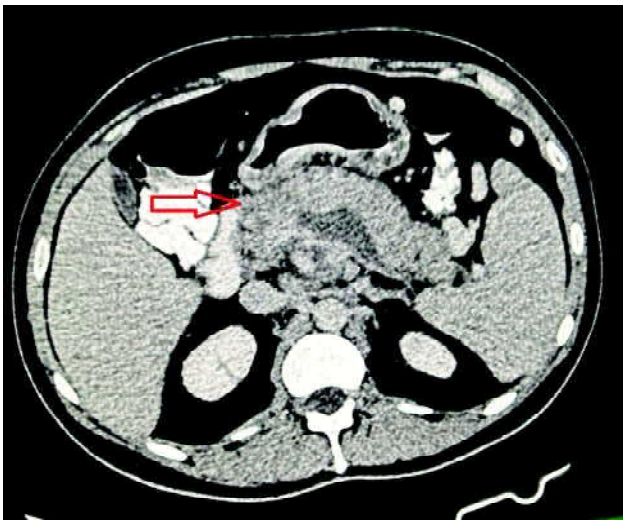


Fig. 1: *CECT abdomen showing pancreatic enlargement with necrotic peripancreatic lymphadenopathy.*

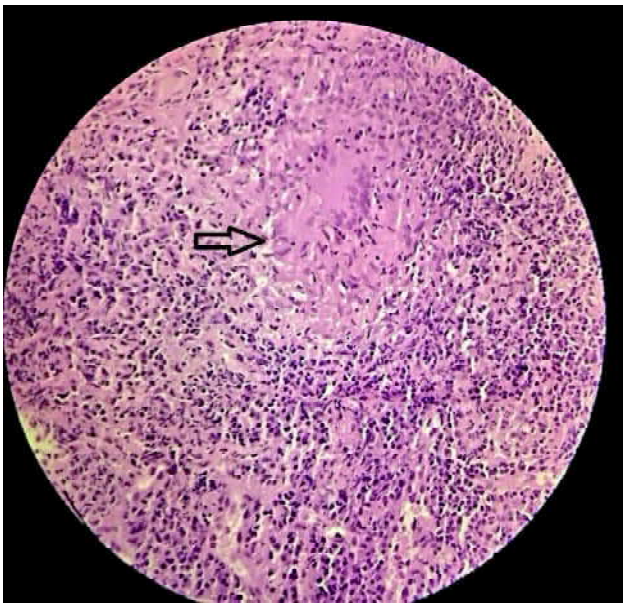


Fig. 2: *Retroperitoneal lymph node biopsy showing epithelioid granulomas and multinucleated giant cells.*

Discussion

Pancreatic tuberculosis remains an uncommon manifestation of extrapulmonary TB despite the high prevalence of tuberculosis in endemic regions. The rarity of pancreatic involvement has been attributed to the bactericidal effect of pancreatic enzymes, lipase and deoxyribonuclease, which provide relative resistance to Mycobacterium tuberculosis. Pancreatic TB may occur through haematogenous dissemination, lymphatic spread, or direct extension from adjacent lymph nodes[4].

The clinical presentation of pancreatic TB is non-specific and frequently overlaps with pancreatic malignancy. Abdominal pain, anorexia, weight loss, fever, jaundice, and pancreatic masses are commonly reported features[5]. Clinically and radiologically, pancreatic tuberculosis frequently mimics pancreatic malignancy, like in our case. Radiological modalities such as ultrasonography and contrast-enhanced computed tomography (CECT) aid in identifying pancreatic lesions; however, tissue diagnosis remains essential. Endoscopic ultrasound (EUS)-guided aspiration or image-guided biopsy demonstrating granulomatous inflammation plays a crucial role in establishing the diagnosis and preventing unnecessary surgery[6,7].

Exocrine pancreatic insufficiency secondary to pancreatic tuberculosis is exceedingly rare and poorly documented in literature. Faecal elastase is a reliable non-invasive marker of pancreatic exocrine function, with levels below 100 µg/g indicating severe insufficiency[8,9]. In the present case, reduced faecal elastase levels correlated with symptoms of steatorrhoea and malabsorption, providing objective evidence of pancreatic exocrine dysfunction.

More importantly, serial follow-up demonstrated gradual improvement and eventual normalisation of faecal elastase levels following anti-tubercular therapy, accompanied by radiological resolution of pancreatic lesion. This strongly suggests that pancreatic exocrine dysfunction in tuberculosis may be reversible with timely diagnosis and treatment.

Previous reports of pancreatic tuberculosis have primarily focused on its resemblance to malignancy and diagnostic difficulties[10]. However, to the best our knowledge this is the first case of reversible exocrine pancreatic insufficiency in pancreatic tuberculosis.

This case highlights pancreatic tuberculosis as a rare differential diagnosis of pancreatic masses and a potentially

reversible cause of secondary exocrine pancreatic insufficiency.

Conclusion

Pancreatic tuberculosis is a rare but important differential diagnosis in patients presenting with pancreatic masses and constitutional symptoms. This case highlights an unusual presentation with faecal elastase-proven exocrine pancreatic insufficiency, which demonstrated clinical, biochemical, and radiological reversal following anti-tubercular therapy. Recognition of this potentially reversible entity is crucial, particularly in endemic regions, as timely diagnosis and tissue confirmation can prevent unnecessary surgical procedures and result in excellent clinical outcomes.

References

1. World Health Organisation. Global tuberculosis report 2023. Geneva: WHO; 2023.
2. Debi U, Ravisankar V, Prasad KK. Abdominal tuberculosis of the gastrointestinal tract: revisited. *World J Gastroenterol* 2014; 20: 14831-40.
3. Panic N, Maetzel H, Bulajic M. Pancreatic tuberculosis: A systematic review of symptoms, diagnosis and treatment. *United European Gastroenterol J* 2020; 8: 396-402.
4. Sharma V, Rana SS, Kumar A. Pancreatic tuberculosis. *J Gastroenterol Hepatol* 2016; 31: 310-8.
5. Saluja SS, Ray S, Pal S *et al*. Hepatobiliary and pancreatic tuberculosis: a two decade experience. *BMC Surg* 2007; 7: 10.
6. Nagar AM, Raut AA, Morani AC. Pancreatic tuberculosis: a clinical and imaging review of 32 cases. *J Comput Assist Tomogr* 2009; 33: 136-41.
7. Song TJ, Lee SS, Park DH *et al*. Yield of EUS-guided FNA on the diagnosis of pancreatic/peripancreatic tuberculosis. *Gastrointest Endosc* 2009; 69: 484-91.
8. Capurso G, Traini M, Piciucchi M. Exocrine pancreatic insufficiency: prevalence, diagnosis, and management. *Clin Exp Gastroenterol* 2019; 12: 129-39.
9. Löser C, Möllgaard A, Fölsch UR. Faecal elastase 1: a novel, highly sensitive, and specific tubeless pancreatic function test. *Gut* 1996; 39: 580-6.
10. Nayak HK, Patra S, Rai A *et al*. Pancreatic tuberculosis. *Gastroenterol Hepatol Endosc Pract* 2023; 3: 76-81.

Regarding Updating the Address/Mobile No/Email-ID

Members are requested to send their current address, mobile number and E-mail-id to iacmnational@rediffmail.com

Dr Suresh Khushwaha
Honarary General Secretary
Mobile No: 9412253972/9068558056
E-mail: bodlahospital@yahoo.co.in

CASE REPORT

JIACM 2026; 27 (3): 231-33

Salmonella typhi Liver Abscess in an Immunocompetent Adult

Sudipta Ghosh, Gourab Bhaduri*, Manoj Jain**, Shelley Sharma Ganguly***, Sujit Chaudhuri****, Mrinmoy Pal*****, Sumeet Kumar******

Abstract

Salmonella enterica serovar typhi commonly causes enteric fever, with hepatic involvement typically manifesting as mild hepatitis. Pyogenic liver abscess due to S. typhi is rare, particularly in immunocompetent individuals. We report a 48-year-old immunocompetent man who presented with a 4-week history of right upper quadrant abdominal pain, intermittent fever, and weight loss. Laboratory investigations were largely unremarkable except for elevated C-reactive protein. Contrast-enhanced computed tomography revealed a large subcapsular hepatic abscess in segments VI–VII. The patient underwent ultrasound-guided aspiration, yielding purulent material. Blood cultures were sterile; however, culture of the aspirated pus grew Salmonella typhi. He was treated with percutaneous drainage and intravenous ceftriaxone followed by oral antibiotics, resulting in complete clinical and radiological improvement. Salmonella typhi is a rare cause of pyogenic liver abscess and may present without classical features of enteric fever or positive blood cultures. This case highlights the importance of routine microbiological evaluation of abscess fluid for accurate diagnosis and targeted therapy, even in immunocompetent patients.

Key words: Salmonella Typhi, liver abscess, hepatic abscess, typhoid fever.

Introduction

Enteric fever caused by *Salmonella enterica* serovar Typhi remains an important infectious disease in endemic regions. Hepatic involvement is frequently encountered and may manifest as hepatomegaly, mild hepatitis, or cholestatic liver dysfunction[1]. However, pyogenic liver abscess due to *Salmonella typhi* is rare and represents an unusual focal suppurative manifestation of infection[2-11].

Pyogenic liver abscesses (PLA) are typically caused by organisms such as *Klebsiella pneumoniae*, *Escherichia coli*, and Streptococcal species, while amoebic liver abscess remains an important differential diagnosis in tropical countries[12]. *Salmonella typhi* is an uncommon aetiological pathogen, and microbiologically confirmed cases from abscess aspirates are infrequently documented, particularly in immunocompetent hosts.

We report a culture-confirmed case of *Salmonella typhi* liver abscess diagnosed by aspirate culture of a solitary hepatic abscess in an immunocompetent patient, highlighting an uncommon presentation of enteric infection and the diagnostic value of microbiologic evaluation of drained abscess material.

Case Summary

A 48-year-old man, with no pre-existing comorbidity presented with a history of dull aching right upper abdominal pain for 4 weeks. He also reported intermittent fever with chills and rigors. There was a history of intermittent over-the-counter antibiotic use without symptomatic relief. His appetite had declined during this period, and he reported a weight loss of 3 kg. There was no jaundice or dark urine, no burning micturition and no cough or expectoration.

His complete blood count and liver function tests were unremarkable. However, C-reactive protein was mildly elevated, i.e., 24 mg/L. Ultrasonography (USG) of abdomen revealed an ill-defined peri-hepatic collection. Contrast enhanced computed tomography (CECT) abdomen was done for further characterisation.

CECT demonstrated a sub-capsular septated abscess involving hepatic segments VI and VII measuring 9.7cm x 7.6 cm x 3.1 cm (Fig. 1). He was started on piperacillin-tazobactam and metronidazole. Under USG guidance 50 mL of purulent material was aspirated. Culture of the aspirate using the BACTEC automated system identified *Salmonella typhi* (Fig. 2). The isolate was sensitive to most first-line antibiotics (Table I). Accordingly, antimicrobial therapy was changed to intravenous ceftriaxone.

The patient became afebrile within three days of aspiration and initiation of targeted antibiotic therapy. IV antibiotics were continued for 10 days. Repeat ultrasonography demonstrated only 30 mL of residual abscess cavity. He was discharged with advice to continue oral cefixime for four weeks.

Consultant, ****Consultant and Head, *****Resident, Department of Gastroenterology, **Consultant, Department of Radiology, ***Consultant and Head, Department of Microbiology, Manipal Broadway Hospital, Kolkata - 700 106, West Bengal. Corresponding Author: Dr Gourab Bhaduri, Consultant, Department of Gastroenterology, Manipal Broadway Hospital, Kolkata - 700 106, West Bengal. Tel: 8017926387, E-mail: gourab.bhaduri@gmail.com



Fig. 1: *CECT abdomen showing multiseptated abscess.*



Fig. 2: *Smooth grey-white translucent non-haemolytic colonies in blood agar.*

Discussion

Salmonella typhi classically presents with fever, accompanied by chills, headache, arthralgia and myalgia in the first week. Abdominal pain and transient macular erythematous rashes appear in the second week of illness. Delayed initiation of antimicrobial therapy can result in ileal perforation during the third week, complicated by secondary bacteraemia and peritonitis[1,13].

S*almonella* species can disseminate haematogenously and establish extra-intestinal foci of infection involving the hepatobiliary system, spleen, bone, meninges, urinary tract, and vascular endothelium[13]. Predisposing conditions reported in the literature include diabetes mellitus, immunosuppression, malignancy and chronic carrier states[1,7]. Nevertheless, isolated cases in immunocompetent hosts have also been reported, suggesting that clinically significant focal hepatic infection may occur even in the absence of overt immunodeficiency (Table II).

Table I: Biochemical and microbiological parameters.

Parameters	Normal range	Reports
Hb (in g/dL)	13 - 16	12.2
TLC (x10^9/L)	4 - 11	7.69
Plt (x10^3/uL)	1.5 - 4	263
CRP (in mg/L)	<5	26
Bilirubin (D) (mg/dL)	0.3 - 1.3	0.22 (0.14)
AST (IU/L)	20 - 50	13
ALT (IU/L)	20 - 50	10
ALP (IU/L)	90 - 120	320
Total Protein (g/dL)	6 - 8	7.79
Serum Albumin (g/dL)	3.5 - 5.5	4.15
Serum creatinine (mg/dL)	<1	0.72
Blood culture	–	Sterile
Pus culture from liver abscess	–	*Salmonella typhi* sensitive to Ciprofloxacin, Ceftriaxone, Cefotaxime, Azithromycin, Cotrimoxazole

Table II: Summary of few reported cases of Salmonella liver abscess.

Author	Country	Gender and age	Predisposing condition	Diagnosis
Soni *et al*[2]	South Africa	Male/47 y	None	Positive culture from abscess aspirate and widal
Ciraj *et al*[4]	India	Male/64 y	Cholelithiasis	Positive culture from abscess aspirate
Morajelo *et al*[11]	Spain	Male/84 y	None	Positive culture from abscess aspirate
Kabra *et al*[12]	India	Male/8 y	None	Positive culture from abscess aspirate and widal
Gomceli *et al*[6]	Turkey	Male/30 y	Solitary simple liver cyst	Positive culture of the abscess aspirate
Jorge *et al*[9]	Brazil	Male/24 y	Metastatic melanoma liver	Positive culture of the abscess aspirate plus positive blood culture
Gailson *et al*[13]	India	Female/5 y	None	Positive culture from abscess aspirate and widal
Rajan *et al*[14]	India	Male/60 y	Diabetes Mellitus	Positive culture from abscess aspirate
Neki *et al*[15]	India	Male/65 y	Diabetes Mellitus	Positive culture from abscess aspirate
Mnif *et al*[10]	Tunisia	Male/77 y	Cholelithiasis	Positive culture of surgical drain fluid
Present case	India	Male/48 y	None	Positve culture from abscess

Our patient, an immunocompetent man presenting with prolonged fever and right upper quadrant pain without diarrhoea, illustrates several diagnostically important aspects of this uncommon entity. First, the clinical presentation lacked classical enteric fever manifestations.

Similar atypical presentations have been observed in prior reports, where patients often presented predominantly with fever, abdominal pain, weight loss or constitutional symptoms rather than overt gastrointestinal disease. In a recent report from Tunisia, an immunocompetent elderly male with *S. typhi* liver abscess presented mainly with abdominal symptoms and constitutional features, with diagnosis established from abscess culture despite negative blood cultures[11]. Our patient mirrors this diagnostic pattern, reinforcing that typhoidal liver abscess may masquerade as conventional pyogenic abscess. Moreover, our case highlights the diagnostic value of abscess aspirate microbiology. Blood cultures in typhoid fever may become negative because of delayed presentation, low bacteraemic burden, or antecedent antibiotic exposure[1,8,13]. In the present case, blood culture was negative whereas aspirated pus yielded *Salmonella typhi*, directly establishing microbiologic causality. Similar discordance between blood and abscess cultures has been documented in published reports, emphasizing the importance of microbiological examination of drained material (Table II).

The pathogenesis of *S. typhi* liver abscess remains incompletely understood. Proposed mechanisms include haematogenous seeding during transient bacteraemia, ascending biliary infection, direct extension from adjacent hepatobiliary infection, or secondary infection of pre-existing hepatic lesions (Table II). Several published reports support the role of anatomical hepatobiliary abnormalities as predisposing substrates. Gömceli *et al* described *S. typhi* abscess developing within a pre-existing simple hepatic cyst, suggesting that abnormal hepatic architecture may facilitate localised infection[6]. Jorge *et al* reported *Salmonella typhi* liver abscess developing in association with metastatic melanoma, suggesting malignancy-related susceptibility[7]. In the recent Tunisian case report, liver abscess occurred in a patient with cholecystitis and cholelithiasis, supporting a possible biliary route of infection[11]. In contrast, our patient had no apparent immunosuppression or major hepatobiliary predisposition, underscoring that clinically significant focal hepatic infection may occasionally occur in immunocompetent hosts.

Management of *Salmonella typhi* liver abscess follows established principles for pyogenic liver abscess: source control combined with targeted antimicrobial therapy. Our patient responded well to drainage and antibiotic therapy with complete clinical resolution, further supporting the pathogenic role of *S. typhi*.

Conclusion

Salmonella typhi should be recognised as a rare but important cause of pyogenic liver abscess. This case broadens the spectrum of extra-intestinal salmonellosis by demonstrating culture-confirmed hepatic abscess formation in an immunocompetent patient presenting without classical enteric fever or positive blood cultures. Careful microbiological evaluation of aspirated abscess material remains crucial for identifying unusual pathogens and guiding targeted treatment.

References

1. Crump JA, Mintz ED. Global trends in typhoid and paratyphoid fever. *Clin Infect Dis* 2010; 50 (2): 241-6.
2. Soni PN, Hoosen AA, Pillay DG. Hepatic abscess caused by *Salmonella typhi*: a case report and review of the literature. *Dig Dis Sci* 1994; 39 (8): 1694-6.
3. Ciraj AM, Reetika D, Bhat GK. Hepatic abscess caused by *Salmonella typhi*. *J Assoc Physicians India* 2001; 49: 1021-2.
4. Moralejo ML, Montero MJ, Fuertes A. Absceso hepaiticopor *Salmonella typhi* (Liver abscess due to *Salmonella typhi*). *Enferm Infecc Microbiol Clin* 2002; 20 (1): 41.
5. Kabra S, Wadhwa V. Hepatic abscess caused by *Salmonella typhi*. *Indian Pediatr* 2006; 43 (1): 81-2.
6. Gomceli I, Gurer A, Qzdooan M. *Salmonella typhi* abscess as a late complication of simple cyst of the liver: a case report. *Turk J Gastroenterol* 2006; 17 (2): 151-2.
7. Jorge JF, Costa ABV, Rodrigues JLN *et al*. *Salmonella typhi* liver abscess overlying a metastatic melanoma. *Am J Trop Med Hyg* 2014; 90 (4): 716-8.
8. Gailson T, Pandit S. Salmonella liver abscess: an unusual complication of typhoid fever with hepatitis: a coinfection. *Inter J Contemporary Paediatr* 2019; 6 (5): 2212.
9. Rajan A, Ranganathan U, Thiyagarajan M. A rare presentation of *Salmonella Paratyphi B* associated enteric fever and liver abscess: a case report and brief review. *Indian J Case Reports* 2019; 5 (3): 205-7.
10. Neki NS, Jain A, Bajaj R. Hepatic abscess caused by Salmonella-A Case Report. *Ann Int Med Dent Res* 2016; 2 (1): 44-5.
11. Mnif K, Daoud R, Chaabouni H *et al*. *Salmonella typhi* liver abscess, an unusual complication in an immunocompetent host: case report. *PAMJ Clin Med* 2026; 20: 6.
12. Kurland JE, Brann OS. Pyogenic and amoebic liver abscesses. *Curr Gastroenterol Rep* 2004; 6 (4): 273-9.
13. Pegues DA, Miller SI. *Salmonella* species, including *Salmonella typhi*. In: Bennett JE, Dolin R, Blaser MJ, editors. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 9th ed. Philadelphia: Elsevier 2020; p. 2817-43.

CASE REPORT

JIACM 2026; 27 (3): 234-37

Hereditary Spherocytosis with Conjugated Hyperbilirubinaemia, Chronic Liver Disease and Portal Hypertension

Mukesh K Sarna, Manish Pahadia**, Animesh Gaur***, Shivam Bansal****, Akash Aggarwal****, Abheet Sonkhya****, Nikhil Mehta****, Sudha Sarna******

Abstract

Hereditary spherocytosis (HS) is the most common inherited haemolytic anaemia and is classically associated with anaemia, splenomegaly, and unconjugated hyperbilirubinaemia. Chronic liver disease and portal hypertension are rare and atypical manifestations, particularly in young adults. We report a 36-year-old male with a long-standing history of jaundice and transfusion-dependent anemia who presented with pancytopenia and massive splenomegaly. Laboratory evaluation revealed severe hyperbilirubinaemia with a striking predominance of conjugated bilirubin, despite clear biochemical evidence of ongoing haemolysis. Peripheral blood smear demonstrated spherocytes, and the diagnosis of hereditary spherocytosis was confirmed by whole-genome sequencing identifying a pathogenic red blood cell membrane protein mutation. Liver stiffness assessment showed advanced hepatic fibrosis, and upper gastrointestinal endoscopy confirmed portal hypertension. Other causes of chronic liver disease, including autoimmune, metabolic, infectious, and inherited hepatobiliary disorders, were systematically excluded. The predominant conjugated hyperbilirubinaemia was attributed to secondary hepatocellular dysfunction and intrahepatic cholestasis resulting from long-standing haemolysis and transfusion burden. The patient was managed conservatively with blood transfusions, folic acid supplementation, and non-selective beta-blockers, while splenectomy was deferred due to portal hypertension. This case highlights a rare hepatic manifestation of hereditary spherocytosis and emphasizes that predominant conjugated hyperbilirubinaemia does not exclude hemolytic anaemia, particularly in patients with long-standing disease and secondary hepatic involvement.

Introduction

Hereditary spherocytosis (HS) is the most common inherited haemolytic anaemia, resulting from structural defects in red blood cell membrane proteins, most commonly ankyrin, spectrin, band 3, and protein 4.2[1,4]. These defects lead to loss of membrane surface area, reduced erythrocyte flexibility, and the formation of spherical red blood cells that are prone to sequestration and destruction within the spleen[1]. The condition exhibits considerable genetic and phenotypic heterogeneity, with autosomal dominant, autosomal recessive, and sporadic inheritance patterns[1,3]. Clinical manifestations range from asymptomatic disease to severe, transfusion-dependent haemolytic anaemia presenting early in life[1,2].

The classical clinical triad of HS includes anaemia, jaundice, and splenomegaly, with additional complications such as reticulocytosis, pigment gallstone disease, and episodic haemolytic crises[1,5]. Hepatobiliary involvement is commonly limited to unconjugated hyperbilirubinaemia and cholelithiasis; however, the development of chronic liver disease (CLD) and portal hypertension is distinctly uncommon and sparsely reported in the literature[6]. When present, these complications may arise due to chronic haemolysis, transfusion-related iron overload, long-standing hypersplenism, and progressive hepatic vascular and parenchymal injury, posing significant diagnostic and therapeutic challenges[7,8]. Reporting such rare associations is essential to improve recognition, facilitate timely diagnosis, and guide optimal long-term management[2].

Case Presentation

A 36-year-old male presented with fever and chills for one week, abdominal pain for 15 days, productive cough for four days, and progressive dyspnoea on exertion for the past three years. He had a history of jaundice and anaemia (Table I) since fifteen years of age and had received multiple blood transfusions over the period of time, frequency being once or twice in every 4 to 5 years, with the first transfusion administered during childhood following hernioplasty. There was no history of alcohol consumption, hepatotoxic drug use, or known family history of haemolytic anaemia or liver disease.

On examination, the patient was malnourished, icteric, febrile, tachycardic, and dyspneic, with marked pallor. Abdominal examination revealed massive splenomegaly, while cardiovascular and neurological examinations were

**Professor and Unit Head, **Professor, ***Associate Professor, ****Junior Resident, Department of General Medicine, *****Professor and Head, Department of Palliative Medicine, Mahatma Gandhi Medical College and Hospital (MGUMST), Jaipur - 302 022, Rajasthan. Corresponding Author: Dr Mukesh K Sarna, Professor and Unit Head, Department of General Medicine, Mahatma Gandhi Medical College and Hospital (MGUMST), Jaipur - 302 022, Rajasthan. Tel: 9829117488, E-mail: mukeshsarna@gmail.com*

normal. Laboratory evaluation (Table II) showed severe anemia (haemoglobin 5.4 g/dL), leukopenia (total leukocyte count 3.6 × 10^3/µL), thrombocytopenia (platelet count 85,000/µL), Corrected reticulocyte count was 3.21%, Immature platelet fraction was 13% (signifies optimal bone marrow function) and severe hyperbilirubinaemia (total bilirubin 75.9 mg/dL) with a predominant conjugated fraction (direct bilirubin 66.4 mg/dL). Evidence of ongoing haemolysis was present, including markedly reduced haptoglobin levels (<10 mg/dL). Peripheral blood smear examination revealed numerous spherocytes, suggestive of hereditary spherocytosis.

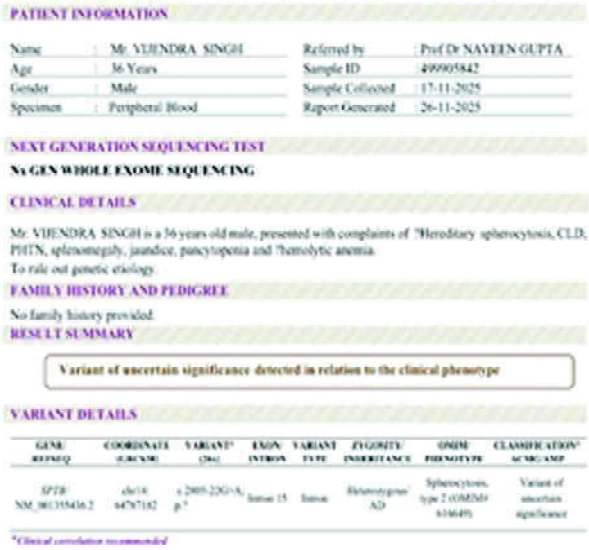
Table I: Past available medical records of the patient signifying long standing aneamia and indirect hyperbilirubinaemia.

Parameter	2013	2021	2023	2024
Pre-Transfusion Haemoglobin (g/dL)	5.0	6.7	8.5	7.6
Post-Transfusion Haemoglobin (g/dL)	6.0			
Total Bilirubin (mg/dL)	11.2	–	5.9	5.98
Direct Bilirubin (mg/dL)	4.2	–	1.0	1.59
Indirect Bilirubin (mg/dL)	7.0	–	4.9	4.39
AST (U/L)	28	–	59	21
ALT (U/L)	31	–	42	27
Total Protein (g/dL)	6.8	–	6.5	6.09
Albumin (g/dL)	4.3	–	3.4	4.17
ALP (U/L)	–	–	192	59

Table II: Investigations during the hospital stay signifying direct hypebilirubinaemia and severe anaemia.

Parameter	28/10/ 2025	31/10/ 2025	01/11/ 2025	04/11 2025
Pre-Transfusion Haemoglobin (g/dL)	9.7	9.6	5.1	8.1
Post-Transfusion Haemoglobin (g/dL)			7.4	
Total Bilirubin (mg/dL)	75.9	12.3	8.9	7.1
Direct Bilirubin (mg/dL)	66.4	8.4	6.1	4.4
Indirect Bilirubin (mg/dL)	9.5	3.9	2.8	2.7
AST (U/L)	30	20	25	36
ALT (U/L)	47	49	58	82
Total Protein (g/dL)	8.2	6.0	5.8	6.2
Albumin (g/dL)	4.4	3.4	3.2	3.6
ALP (U/L)	84	45.38	48	67

Liver stiffness assessment by transient elastography demonstrated advanced hepatic fibrosis (14.6 kPa, consistent with F3 fibrosis). Upper gastrointestinal endoscopy showed prominent gastric vein, confirming


PATIENT INFORMATION

Name	Mr. VIJENDRA SINGH	Referred by	Prof Dr NAVEEN GUPTA
Age	36 Years	Sample ID	499905842
Gender	Male	Sample Collected	17-11-2025
Specimen	Peripheral Blood	Report Generated	26-11-2025

NEXT GENERATION SEQUENCING TEST

NxGEN WHOLE EXOME SEQUENCING

CLINICAL DETAILS

Mr. VIJENDRA SINGH is a 36 years old male, presented with complaints of Hereditary spherocytosis, CLD, PHTN, splenomegaly, jaundice, pancytopenia and Hemolytic anemia.
To rule out genetic etiology.

FAMILY HISTORY AND PEDIGREE

No family history provided.

RESULT SUMMARY

Variant of uncertain significance detected in relation to the clinical phenotype

VARIANT DETAILS

GENE/ REFSEQ	COORDINATE (GRCh38)	VARIANT* (Zyg)	EXON/ INTRON	VARIANT TYPE	ZYGOSITY/ INHERITANCE	OMIM PHENOTYPE	CLASSIFICATION/ ACMG/AMP
SPTB NM_001355416.2	chr14: 64787182	c.2005-2282+3_ p.?	Intron 15	Intron	Heterozygous/ AD	Spherocytosis, type 2 (#616649)	Variant of uncertain significance

*Clinical correlation recommended

Fig. 1: *Shows variant of unknown significance in whole genome sequencing, confirming diagnosis of hereditary spherocytosis.*

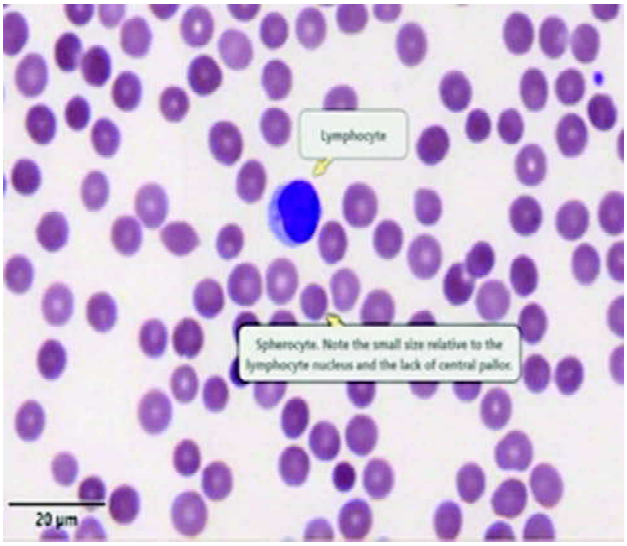


Fig. 2: *Peripheral blood smear of the patient showing characterstic spherocytes.*

portal hypertension. Whole-genome sequencing identified a pathogenic mutation that is Genetic variant of uncertain significance (VUS) involving a red blood cell membrane protein. Thus, in prescence of characterstic peripheral blood smear, and signs of haemolysis the diagnosis of hereditary spherocytosis was confirmed. Differential diagnosis, including autoimmune haemolytic anaemia (negative direct and indirect coombs test), thalassaemia (Normal Hb Electrophoresis), Wilson's disease (Serum Cerruloplasmin level - 16.2 which was normal), Hereditary hyperbilirubinaemia syndromes like Dubin Johnson, Rotor Syndrome (prescence of severe haemolysis is not seen in

these conditions) Benign Intrahepatic Cholestasis syndrome (Absence of recurrent self limiting episodes of Jaundice in the patient), and parvovirus B19 infection (no reticulocytopenia/aplastic crisis features) were systematically excluded based on clinical findings, laboratory evaluation, imaging, and genetic confirmation. Also, no familial association was found on pedigree analysis of the patient.

During hospitalisation, the patient was managed conservatively. He received 2 units packed red blood cell transfusions to correct severe anaemia and maintain haemoglobin levels above 7 g/dL. Empirical intravenous ceftriaxone was administered at a dose of 1 g twice daily for suspected infection. Oral prednisolone at a dose of 15 mg once daily was initiated during the initial diagnostic evaluation when immune-mediated haemolysis was considered and later tapered and discontinued. Supportive management included oral folic acid 5 mg once daily, multivitamin supplementation, and paracetamol 650 mg as required for fever. The patient remained haemodynamically stable throughout hospitalisation.

Following confirmation of hereditary spherocytosis, long-term folic acid supplementation was continued. In view of portal hypertension with esophageal varices, non-selective beta-blocker therapy with propranolol was initiated at a dose of 20 mg twice daily for primary prophylaxis. Splenectomy was considered but deferred due to the presence of portal hypertension and advanced hepatic fibrosis. The patient was discharged with advice for close follow-up under general medicine, haematology services. The patient has been regularly following up on outpatient basis in General Medicine OPD since last 5 months and is being adviced conservative management for CLD with Portal Hypertension and Folic acid supplementation for HS. His Condition has been stable and no blood transfusion has been required since his discharge from the hospital.

Discussion

HS is usually diagnosed in childhood; however, milder or atypical phenotypes may remain undiagnosed until adulthood, particularly in resource-limited settings[1,2]. In the present case, despite a long-standing history of jaundice and transfusion dependence since early childhood, diagnosis was delayed until adulthood, highlighting the diagnostic challenges associated with atypical presentations.

Diagnosis of HS relies on characteristic clinical features, laboratory evidence of haemolysis, and peripheral blood smear findings[2]. Specialised investigations such as eosin-5-maleimide binding assays and osmotic fragility testing may support the diagnosis[9], while genetic testing has emerged as a crucial tool in confirming the diagnosis, particularly in complex cases with overlapping haematologic and hepatic features[3,5]. In this patient, whole-genome sequencing was pivotal in establishing the diagnosis and excluding alternative aetiologies.

Haemolytic anaemias classically result in unconjugated hyperbilirubinaemia due to increased red cell breakdown[1,2]. However, this patient exhibited marked predominance of conjugated hyperbilirubinaemia, an unusual finding in isolated haemolysis. This pattern is best explained by secondary hepatocellular dysfunction and intrahepatic cholestasis resulting from long-standing haemolysis, chronic bilirubin overload, and progressive hepatic injury[11], iron overload due to repeated transfusions, congestive hepatopathy due to chronic anaemia, rarely due to coexisting inherited conjugation/excretion defects like Dubin – Johnson Syndrome and Rotor Syndrome, biliary obstruction[13]. Chronic haemolytic states have also been linked to porto-sinusoidal vascular disease and non-cirrhotic portal hypertension, which can impair bile canalicular transport and contribute to conjugated hyperbilirubinaemia[10,14]. Repeated transfusions and sustained haemolysis further promote hepatic oxidative stress, Kupffer cell activation, and progressive fibrosis, culminating in impaired excretion of conjugated bilirubin[7,12]. "In this patient, predominant conjugated hyperbilirubinaemia was most consistent with secondary hepatocellular dysfunction and intrahepatic cholestasis related to long-standing haemolysis and transfusion burden, as alternative inherited conjugation or excretory defects were excluded on genetic testing."

The coexistence of hereditary spherocytosis with chronic liver disease and portal hypertension is rare and sparsely reported[7]. What makes this case particularly unique is the presence of advanced hepatic fibrosis and clinically significant portal hypertension with esophageal varices at a young age, in the absence of other identifiable causes of chronic liver disease[10]. This expands the recognised hepatic spectrum of HS and highlights the potential for progressive liver injury in long-standing disease.

Management of HS in the presence of portal hypertension is challenging. While splenectomy remains the definitive treatment for moderate to severe HS, the presence of portal hypertension significantly increases perioperative bleeding risk[11]. Therefore, individualised management with supportive care, optimisation of liver disease, careful risk – benefit assessment, and multidisciplinary decision-making is essential in such complex clinical scenarios.

Conclusion

This case highlights a rare and clinically significant association between hereditary spherocytosis and chronic liver disease with portal hypertension. It also demonstrates

that predominant conjugated hyperbilirubinaemia may occur in long-standing haemolytic disorders due to secondary hepatocellular dysfunction and cholestasis. A high index of suspicion for inherited haemolytic anaemia should be maintained in patients presenting with chronic jaundice, splenomegaly, and unexplained liver disease. Early diagnosis, supported by genetic testing, is essential to prevent diagnostic delay and guide appropriate management, particularly regarding the timing and feasibility of splenectomy. This case highlights that predominant conjugated hyperbilirubinaemia does not exclude haemolytic anaemia and may reflect secondary hepatic involvement in long-standing disease.

References

1. Perrotta S, Gallagher PG, Mohandas N. Hereditary spherocytosis. *Lancet* 2008; 372 (9647): 1411-26.
2. Bolton-Maggs PHB, Langer JC, Iolascon A, Tittensor P. Guidelines for the diagnosis and management of hereditary spherocytosis – 2011 update. *Br J Haematol* 2012; 156 (1): 37-49.
3. Kalfa TA. Diagnosis and clinical management of red cell membrane disorders. *Haematol Am Soc Hematol Educ Program* 2021; 2021 (1): 331-40.
4. Gallagher PG. Red cell membrane disorders. *Haematol Am Soc Hematol Educ Program* 2005; 13-8.
5. Da Costa L, Galimand J, Fenneteau O. Hereditary spherocytosis, elliptocytosis, and other red cell membrane disorders. *Blood Rev* 2013; 27 (4): 167-78.
6. Yang X, Wang W, Fan W. Hereditary Spherocytosis with Liver Transplantation after Cirrhosis: A Case Report. *Front Med (Lausanne)* 2022; 9: 823724.
7. van Straaten S, Biemond BJ, Kerkhoffs JL. Iron overload in patients with rare hereditary haemolytic anaemia: Evidence-based suggestion on whom and how to screen. *Am J Haematol* 2018; 93 (11): E374-E376.
8. Pietrangelo A. Hereditary haemochromatosis – a new look at an old disease. *N Engl J Med* 2004; 350 (23): 2383-97.
9. King MJ, Behrens J, Rogers C. Rapid flow cytometric test for the diagnosis of membrane cytoskeleton-associated haemolytic anaemia. *Br J Haematol* 2000; 111 (3): 924-33.
10. De Gottardi A, Rautou PE, Schouten J. VALDIG group. Porto-sinusoidal vascular disease: proposal and description of a novel entity. *Lancet Gastroenterol Haepatol* 2019; 4 (5): 399-411.
11. Schilling RF. Risks and benefits of splenectomy versus no splenectomy for hereditary spherocytosis – a personal view. *Br J Haematol* 2009; 145 (6): 728-32.
12. Erlinger S, Arias IM, Dhumeaux D. Inherited Disorders of Bilirubin Transport and Conjugation: New Insights Into Molecular Mechanisms and Consequences. *Gastroenterol (Internet)* 2014 Jun (cited 2019); 146 (7): 1625-38.
13. Han N, Huang W, Wang J. Hereditary spherocytosis complicated by intrahepatic cholestasis: two case reports. *Ann Transl Med* 2022; 10 (22): 1255.
14. Schouten JN, Garcia-Pagan JC, Valla DC. Idiopathic noncirrhotic portal hypertension. *Haepatol* 2011; 54 (3): 1071-81.

PICTORIAL CME

JIACM 2026; 27 (3): 238-39

Poly-Hill Sign and Popeye Arm in Facioscapulohumeral Muscular Dystrophy

Devavrata Sahu, Karan Khatri**, Ketan Bhatnagar**, Jyoti Garg***, Ashish Kumar Duggal*****

A 22-year-old man presented with gradually progressive proximal weakness and thinning of all four limbs for 5 years. There was no relevant family history. Neurological examination revealed facial weakness with an inability to blow, and a characteristic facioscapulohumeral pattern of muscle involvement with prominent shoulder-girdle and upper-arm wasting. A positive Beevor sign, reflecting preferential weakness of the lower abdominal muscles, was also present.

Posterior examination with shoulder abduction and elbow flexion demonstrated prominent scapular winging and a characteristic undulating contour of the shoulder girdle – the poly-hill sign (Fig. 1A). The scapulohumeral wasting was asymmetric and more pronounced on the left. On anterior inspection, there was marked wasting of the upper-arm musculature with relative preservation of the deltoids and forearm muscles, producing the characteristic "Popeye arm" appearance (Fig. 1B). Lower-limb examination demonstrated relative preservation of the calf musculature (Fig. 1C).

The combination of facial weakness, scapular stabilizer weakness, asymmetric humeral muscle wasting with relative deltoid and forearm sparing, a positive Beevor sign, and relative preservation of the calf musculature was characteristic of facioscapulohumeral muscular dystrophy (FSHD)[1-3]. Genetic confirmation could not be performed because of financial constraints.

FSHD is characterised by a selective and often asymmetric pattern of muscle involvement, typically affecting the facial and scapular muscles followed by the humeral and abdominal musculature[1,2,3]. Preferential wasting of the biceps and triceps with relative preservation of the deltoid and forearm musculature produces the characteristic

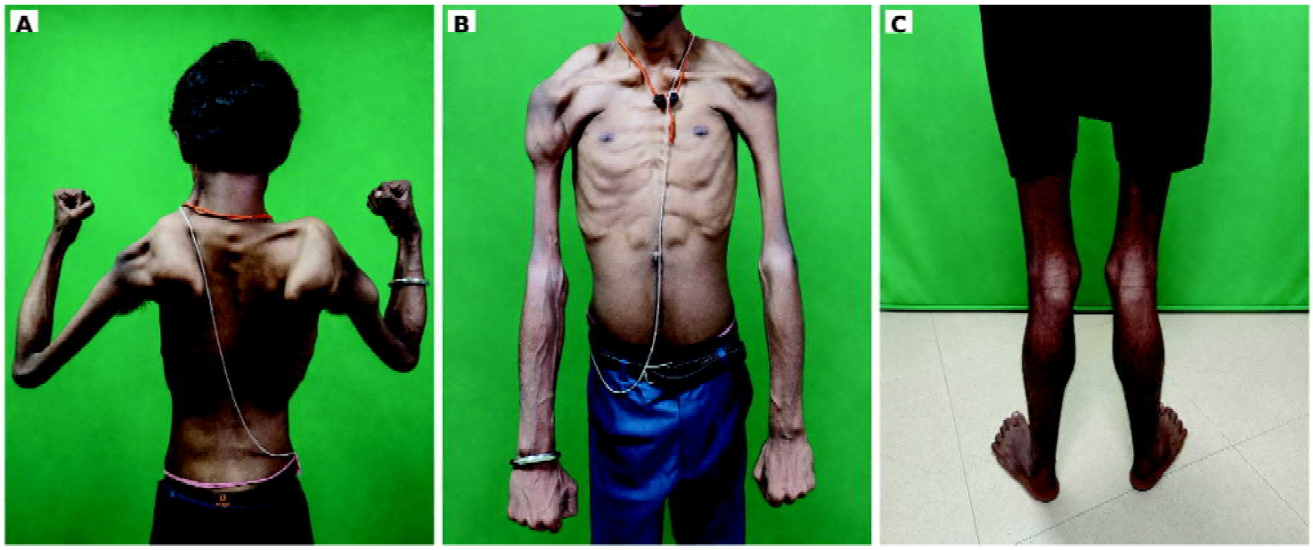


Fig. 1: *Characteristic clinical findings in facioscapulohumeral muscular dystrophy.*

A: Posterior view with shoulder abduction and elbow flexion demonstrating asymmetric scapular winging and the characteristic poly-hill sign, produced by selective scapulohumeral muscle wasting with relative preservation of portions of the deltoid. The muscle wasting is more pronounced on the left side.

B: Anterior view demonstrating asymmetric humeral muscle wasting, more marked on the left, with relative preservation of the forearm musculature, producing the characteristic "Popeye arm" appearance.

C: Posterior view of the lower limbs demonstrating relative preservation of the calf musculature.

Assistant Professor, **Senior Resident, ***Professor and Head, ****Professor, Department of Neurology, ABVIMS and Dr Ram Manohar Lohia Hospital, Baba Kharak Singh Marg, New Delhi - 110 001.

Corresponding Author: Dr Devarata Sahu, Assistant Professor, Department of Neurology, ABVIMS and Dr Ram Manohar Lohia Hospital, Baba Kharak Singh Marg, New Delhi - 110 001. Tel: 8800815928, E-mail: devsahu.90@gmail.com

Popeye arm. Differential involvement of the scapular stabilizers with relative preservation of portions of the deltoid and prominence of underlying bony landmarks produces the alternating elevations and depressions of the poly-hill sign. A positive Beevor sign, resulting from preferential lower abdominal muscle weakness, is another useful bedside clue[2,3].

Recognition of these characteristic bedside signs can provide an important diagnostic clue to FSHD, particularly where molecular testing is unavailable or inaccessible.

References

1. Tawil R, Kissel JT, Heatwole C. Evidence-based guideline summary: Evaluation, diagnosis, and management of facioscapulohumeral muscular dystrophy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the Practice Issues Review Panel of the American Association of Neuromuscular and Electrodiagnostic Medicine. *Neurology* 2015; 85 (4): 357-64.
2. Knox RN. Facioscapulohumeral muscular dystrophy. *CONTINUUM: Lifelong Learning in Neurology* 2025; 31 (5): 1329-43.
3. Mul K, Lassche S, Voermans NC. What's in a name? The clinical features of facioscapulohumeral muscular dystrophy. *Practical Neurol* 2016; 16 (3): 201-7.

Indian Association of Clinical Medicine

Headquarter : P. G. Department of Medicine, S. N. Medical College, Agra.

Membership No._____

The Honorary Secretary
Indian Association of Clinical Medicine (IACM)
Bodla Hopsital, Shahganj Bodla Road, Bodla
Agra-282010.

Date: _____

Passprt Size Photograph

We hereby propose the admission of

Name (in full) : _____
(Block Letters)
Qualification : _____
(Branch of Medicine for P. G. Degree)
University: _____
Year of obtaining First Postgraduate Qualification : _____
Address : _____

_____

Contact No: _____ E-mail : _____

As an Associate Life Member / PG Member / Life Member / Fellow of the Association

To the best of my knowledge and belief the above particulars are correct and we consider him/her a fit and proper person to be admitted as Associate Life Member / PG Member / Life Member / Fellow of the Association. A demand draft No. _____dated _____ of _____for Rs. _____ is enclosed herewith.

Signature _____ **(Proposer)**
Name _____
Fellowship/Membership No. _____

Signature _____ **(Seconder)**
Name _____
Fellowship/Membership No. _____

Subject to approval of the Governing Body, I agree to become a Associate Life Member / PG Member / Life Member / Fellow if admitted to abide by the rules & regulations of the Association.

Signature of the candidate

Note by Hony. General Secretary

- Fellowship Subscription - Rs. 9000/-.
  (Minimum 10 years standing after P.G. Qualification or 5 years after life membership)
- Life Membership Subscription - Rs. 3000/-.
  (Minimum Qualification - P.G. qualification as specified in constitution)
- Provisional Life Membership Subscription - Rs. 3000/- for postgraduate student.
  (For *P. G. student as specified in constitution))
- Associate Life Member Subscription - Rs. 3000/-.
  (Diploma or P.G. Qualification not covered as per constitution)
- Please attach attested photocopy of P.G. Degree/Diploma, *Certificate from HOD.
- Cheques shall not be accepted.

DD in favour of "Indian Association of Clinical Medicine"

Bank Details : - State Bank of India (07892)- S. N. Medical College, Agra, Uttar Pradesh
Account No. : 10039634520 **MICR** : 282002014 **IFS Code** : SBIN0007892

Correspondence Address :
DR. SURESH KUSHWAHA Honorary General Secretary, IACM
Bodla Hospital Shahganj Bodla Road, Bodla, Agra-282 010 Mob. : 94122 53972, 92670 50503