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Journal, Indian Academy of Clinical Medicine • Vol. 27, Number 2, April-June, 2026

Contains 80 pages from 81 to 160 (inclusive of all advertisements)

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Corrigendum

The Article – ***Cardiac Sarcoidosis: A Clinical Review JIACM 2026; 27 (1): 52-64****. The editors wish to draw attention to an error in the published version of the above article. The name of one of the authors was incorrectly published as:* ***Surinder Birringt****, The correct author name is:* ***Surinder Birring.*** *This correction pertains solely to the spelling of the author's name. The scientific content, data, interpretations, and conclusions of the article remain unchanged. The editors regret this error and apologise for any inconvenience caused.*

Journal, Indian Academy of Clinical Medicine

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)."

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.

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ORIGINAL ARTICLE

JIACM 2026; 27 (2): 86-93

C-Reactive Protein and it's Correlation with Renal Parameters among Patients of Chronic Kidney Disease, not on Dialysis

Ashwini Kumar Aiyangar, Aftab Ahmed**, Jaisri Sathi***, Sreecharan Elamandala****, VVS Kameswara Rao*****, Srinivasan Krishnan*******

Abstract

***Background:** Chronic kidney disease (CKD) is commonly studied through renal, haematological and metabolic complications, but it also represents a chronic systemic inflammatory state. This analysis evaluated whether advancing non-dialysis CKD is accompanied by a measurable inflammatory gradient and whether C-reactive protein (CRP) correlates with renal dysfunction, anaemia, iron dysregulation and mineral metabolism.*

***Methods:** This cross-sectional analysis included 160 adults with non-dialysis CKD stages G3a to G5. CRP was the primary inflammatory marker. Stage-wise differences were tested using the Kruskal-Wallis test. High CRP was defined as >5 mg/L. Correlations between CRP and clinical-biochemical parameters were assessed using Spearman correlation with false-discovery-rate correction; Pearson's correlation was used as sensitivity analysis.*

***Results:** Mean CRP increased from 3.98 ± 2.24 mg/L in stage G3a to 11.00 ± 3.64 mg/L in stage G5 ($p < 0.001$). CRP >5 mg/L rose from 33.3% in stage G3a to 98.2% in stage G5 (chi-square = 51.82, $p < 0.001$). CRP correlated strongly with creatinine (rho = 0.651), urea (rho = 0.635), GFR (rho = -0.633) and TSAT (rho = -0.651), and significantly with haemoglobin, PCV, calcium, ferritin, TIBC and phosphorus. In the high-CRP group, GFR, haemoglobin, TSAT and calcium were lower, while creatinine and urea were higher. The high ferritin-low TSAT-high CRP phenotype was concentrated in advanced CKD, affecting 21.7% of stage G4 and 87.5% of stage G5 patients.*

***Conclusion:** Advancing CKD was associated with a clear systemic inflammatory signature. CRP rose with worsening CKD stage and tracked renal dysfunction, iron restriction, anemia and mineral-metabolic disturbance. These findings support CKD as an inflammatory systemic disorder, with iron-restricted erythropoiesis representing one downstream consequence rather than the sole manifestation.*

***Key words:** chronic kidney disease; inflammation; C-reactive protein; ferritin; transferrin saturation; anaemia; mineral bone disorder; non-dialysis CKD.*

Introduction

Chronic kidney disease (CKD) is a multisystem disorder traditionally defined by persistent reduction in kidney function or evidence of kidney damage. Beyond progressive nephron loss, CKD is increasingly recognised as a chronic inflammatory condition in which uraemic toxin accumulation, oxidative stress, endothelial dysfunction, altered gut-derived metabolites, comorbid diabetes and hypertension, volume overload and mineral-metabolic dysregulation contribute to persistent immune activation. This inflammatory state has clinical relevance because it links renal dysfunction to anaemia, vascular injury, cardiovascular risk, protein-energy wasting and progression of disease[1-4].

CRP is a pragmatic clinical marker of systemic inflammation. Although it does not define the complete inflammatory network of CKD, it is widely available, inexpensive and interpretable in routine practice. Ferritin, Transferrin Saturation (TSAT), haemoglobin, calcium, phosphorus and PTH may also reflect downstream consequences of inflammation and CKD metabolic disturbance. Ferritin is both an iron-storage marker and an acute-phase reactant; therefore, high ferritin with low TSAT in a high-CRP patient may indicate inflammatory iron sequestration rather than adequate bioavailable iron[5-8].

The present original analysis reframes the parent CKD anaemia dataset around the broader question of whether CKD behaves as a systemic inflammatory state. The primary objective was to evaluate stage-wise CRP behaviour across CKD stages G3a to G5. Secondary objectives were to test correlations of CRP with renal function, anaemia, iron indices and mineral metabolism parameters, and to interpret iron-

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restricted erythropoiesis as one downstream manifestation of CKD-associated inflammation.

Abbreviations

Table A: Abbreviations

Abbreviation	Full form
ACD	Anaemia of chronic disease
CKD	Chronic kidney disease
CRP	C-reactive protein
eGFR	Estimated glomerular filtration rate
FDR	False discovery rate
GFR	Glomerular filtration rate
Hb	Haemoglobin
IDA	Iron deficiency anaemia
MBD	Mineral bone disorder
PCV	Packed cell volume
PTH	Parathyroid hormone
SD	Standard deviation
TIBC	Total iron-binding capacity
TSAT	Transferrin saturation

Material and Methods

Study design and population

This was a prospective cross-sectional analysis of 160 adult non-dialysis CKD patients evaluated between April and September 2024 at Apollo Hospitals, Secunderabad. Patients had GFR <60 mL/min/1.73 m^2 for more than 3 months and were classified into CKD stages G3a, G3b, G4 and G5. Patients on dialysis, post-transplant patients, those with recent transfusion, recent parenteral iron, overt bleeding, malignancy, chronic infections, malabsorption, steroid therapy, haemoglobinopathies or erythropoietin therapy were excluded in the parent study.

Variables and definitions

The analysis included age, sex, hypertension, diabetes, urea, creatinine, GFR, haemoglobin, RBC count, PCV, red cell indices, WBC count, platelet count, serum iron, ferritin, TIBC, TSAT, CRP, PTH, calcium, phosphorus and anaemia type. CRP was analysed as the principal marker of systemic inflammation. High CRP was defined as CRP >5 mg/L. An inflammatory iron-restriction phenotype was defined as ferritin ≥100 ng/mL, TSAT <20% and CRP >5 mg/L.

Statistical analysis

Continuous variables are presented as mean ± SD. Categorical variables are presented as number and percentage. Stage-wise comparisons were performed using Kruskal-Wallis testing. Associations between CKD stage and categorical inflammatory phenotypes were tested using the chi-square test. Low-CRP and high-CRP groups were compared using the Mann-Whitney test. Spearman's rank correlation was used as the primary correlation test for CRP versus other continuous variables; Pearson's correlation was performed as sensitivity analysis. Multiple comparisons were controlled using Benjamini-Hochberg false discovery rate correction.

Results

Cohort profile

Table I: Cohort characteristics.

Variable	n or mean ± SD	%
Total sample	160	100.0
Age, years	53.21 ± 10.76	-
Male sex	92	57.5
Female sex	68	42.5
Hypertension	150	93.8
Diabetes mellitus	102	63.7
CKD G3a	9	5.6
CKD G3b	35	21.9
CKD G4	60	37.5
CKD G5	56	35.0

The cohort contained 160 non-dialysis CKD patients. Advanced CKD predominated, with 37.5% in stage G4 and 35.0% in stage G5. Hypertension and diabetes were common comorbidities, present in 93.8% and 63.7% respectively.

CRP gradient across CKD stages

Table II: Stage-wise inflammatory burden by CRP

CKD stage	n	CRP, mean ± SD	CRP >5 mg/L	% CRP >5 mg/L
G3a	9	3.98 ± 2.24	3/9	33.3%
G3b	35	5.48 ± 1.86	21/35	60.0%
G4	60	8.87 ± 2.83	58/60	96.7%
G5	56	11.00 ± 3.64	55/56	98.2%
Overall/statistical test	160	Kruskal-Wallis **p = <0.001**	$\chi^2 = 51.82$	**p = <0.001**

CRP increased stepwise across CKD stages, indicating an inflammatory gradient accompanying progressive renal

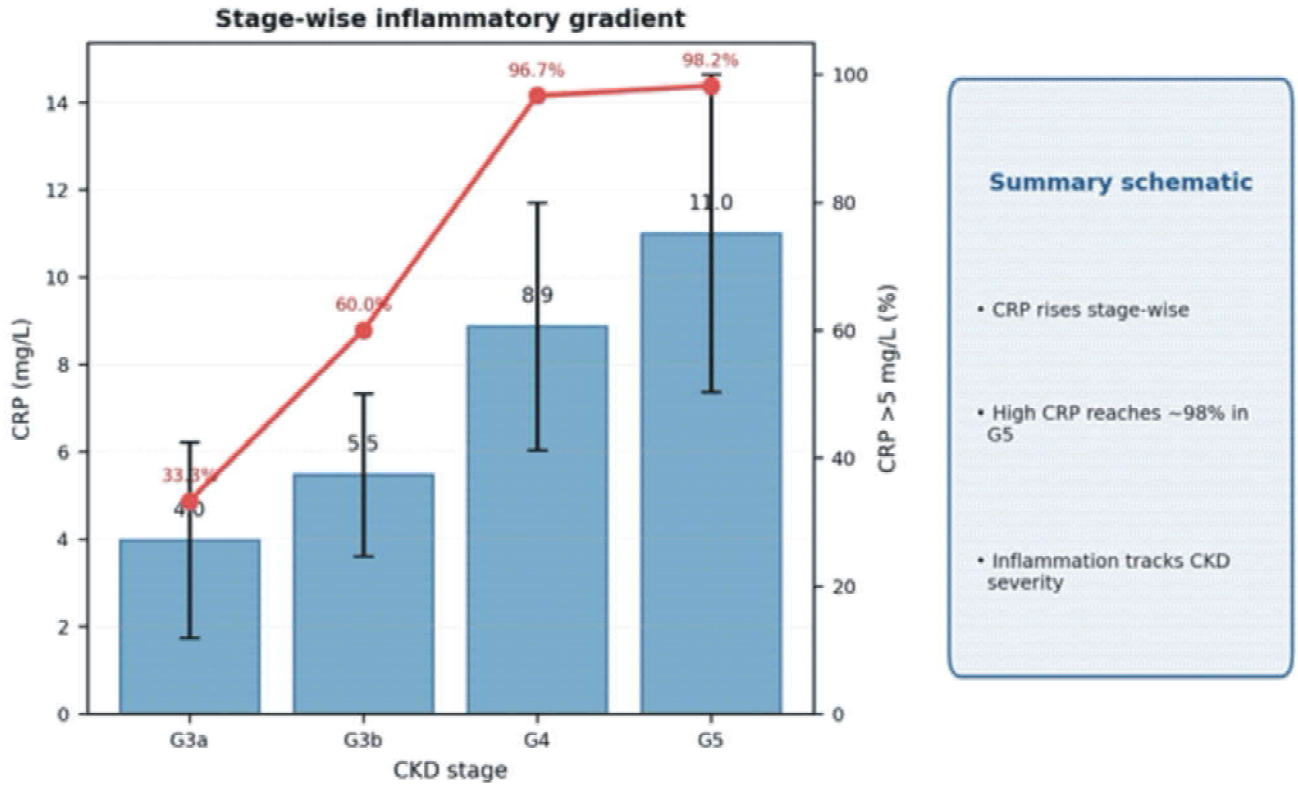

Fig. 1: *Stage-wise CRP gradient and prevalence of high CRP across CKD stages. Bars show mean CRP with SD; the line shows the percentage of patients with CRP >5 mg/L. Take-home: CRP rises progressively with CKD stage, supporting CKD as a systemic inflammatory state.*

dysfunction. The proportion of patients with CRP >5 mg/L increased from 33.3% in stage G3a to 98.2% in stage G5.

Multisystem biochemical pattern accompanying inflammation

Table III: Renal, haematological, iron and mineral parameters across CKD stages.

Parameter	G3a	G3b	G4	G5	p value
GFR	49.33 ± 3.61	36.51 ± 4.18	20.50 ± 4.05	11.14 ± 2.04	**<0.001**
Creatinine	1.69 ± 0.10	2.05 ± 0.29	3.19 ± 0.64	5.00 ± 0.61	**<0.001**
Urea	23.89 ± 4.14	29.34 ± 7.67	46.80 ± 15.05	69.27 ± 16.53	**<0.001**
Haemoglobin	11.67 ± 1.10	10.89 ± 0.99	10.21 ± 1.29	9.79 ± 1.48	**<0.001**
Ferritin	154.11 ± 79.02	177.77 ± 77.45	175.23 ± 84.70	310.61 ± 146.00	**<0.001**
TSAT	28.93 ± 0.93	26.08 ± 2.13	21.37 ± 1.85	15.91 ± 2.61	**<0.001**
Calcium	9.27 ± 0.34	8.91 ± 0.47	8.70 ± 0.40	8.17 ± 0.58	**<0.001**
Phosphorus	4.18 ± 0.65	4.74 ± 0.64	4.73 ± 0.67	5.05 ± 0.70	**0.003**
PTH	47.68 ± 7.62	66.10 ± 30.45	62.70 ± 27.23	74.18 ± 33.02	**0.036**

The CRP gradient was accompanied by worsening renal parameters, lower haemoglobin, increasing ferritin, lower TSAT, lower calcium, higher phosphorus and higher PTH. This pattern supports CKD-associated inflammation as a multisystem phenotype rather than a single haematological mechanism.

High-CRP phenotype versus low-CRP phenotype

Table IV: Biological profile of low-CRP versus high-CRP patients.

Parameter	CRP ≤5 mg/L	CRP >5 mg/L	Mann-Whitney p
GFR	38.83 ± 10.53	19.58 ± 9.77	**<0.001**
Creatinine	2.00 ± 0.67	3.74 ± 1.25	**<0.001**
Urea	26.74 ± 8.53	53.39 ± 20.54	**<0.001**
Haemoglobin	11.23 ± 0.97	10.14 ± 1.39	**<0.001**
Ferritin	178.13 ± 93.85	229.34 ± 129.62	0.141
TSAT	27.03 ± 3.10	19.89 ± 4.24	**<0.001**

Calcium	9.00 ± 0.54	8.52 ± 0.57	**0.002**
Phosphorus	4.59 ± 0.65	4.85 ± 0.70	0.083
PTH	56.02 ± 23.40	68.40 ± 30.68	0.061

Patients with high CRP had significantly lower GFR, higher creatinine and urea, lower haemoglobin, lower TSAT and lower calcium than those with CRP ≤5 mg/L. Ferritin, phosphorus and PTH were numerically higher in the high-CRP group, but the between-group differences were weaker than the renal and TSAT relationships.

CRP correlation analysis

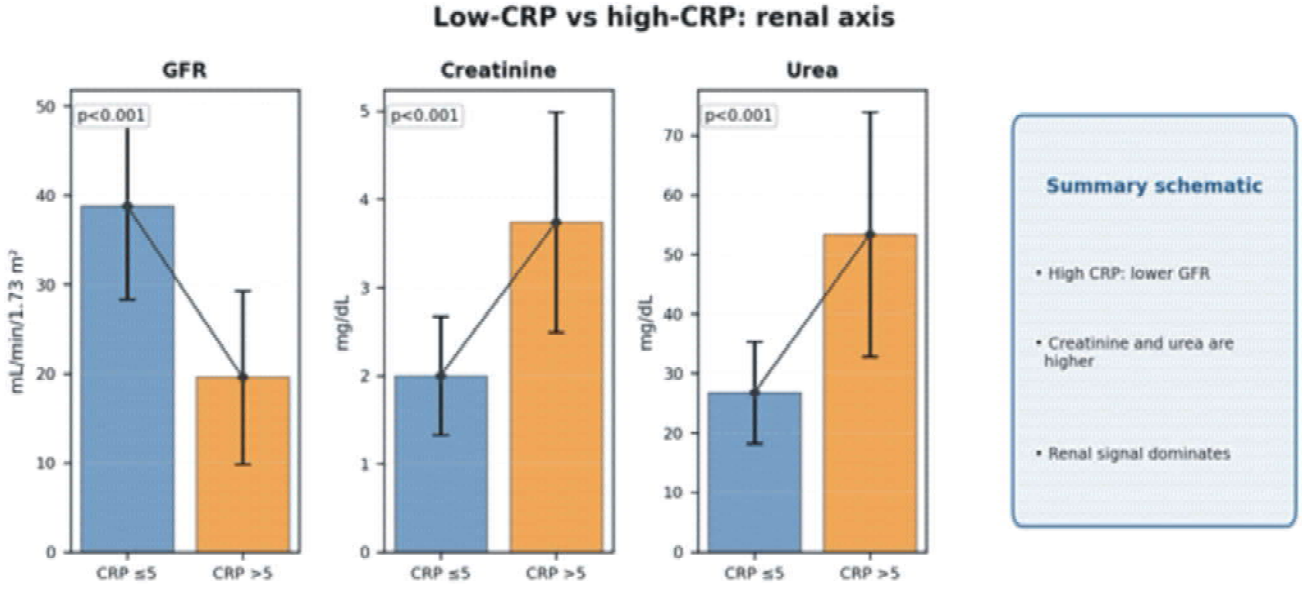

Fig. 2: *Low-CRP versus high-CRP renal phenotype. Mean ± SD plots compare GFR, creatinine and urea. Take-home: high CRP identifies worse renal dysfunction.*

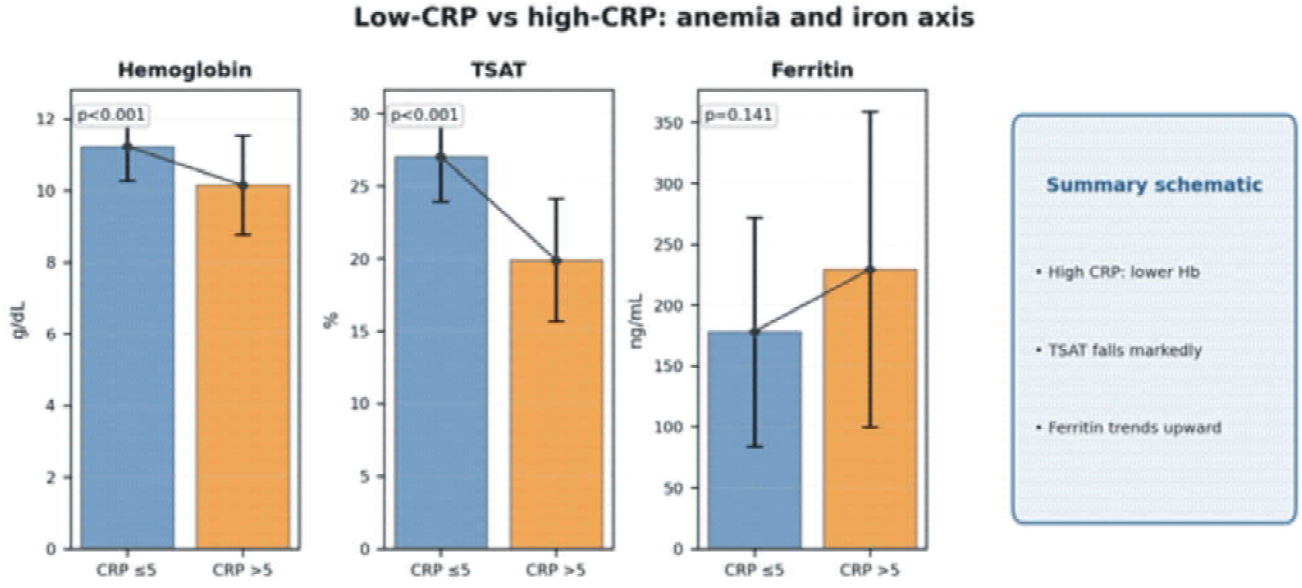

Fig. 3: *Low-CRP versus high-CRP anaemia/iron phenotype. Mean ± SD plots compare haemoglobin, TSAT and ferritin. Take-home: high CRP is accompanied by lower haemoglobin and lower TSAT.*

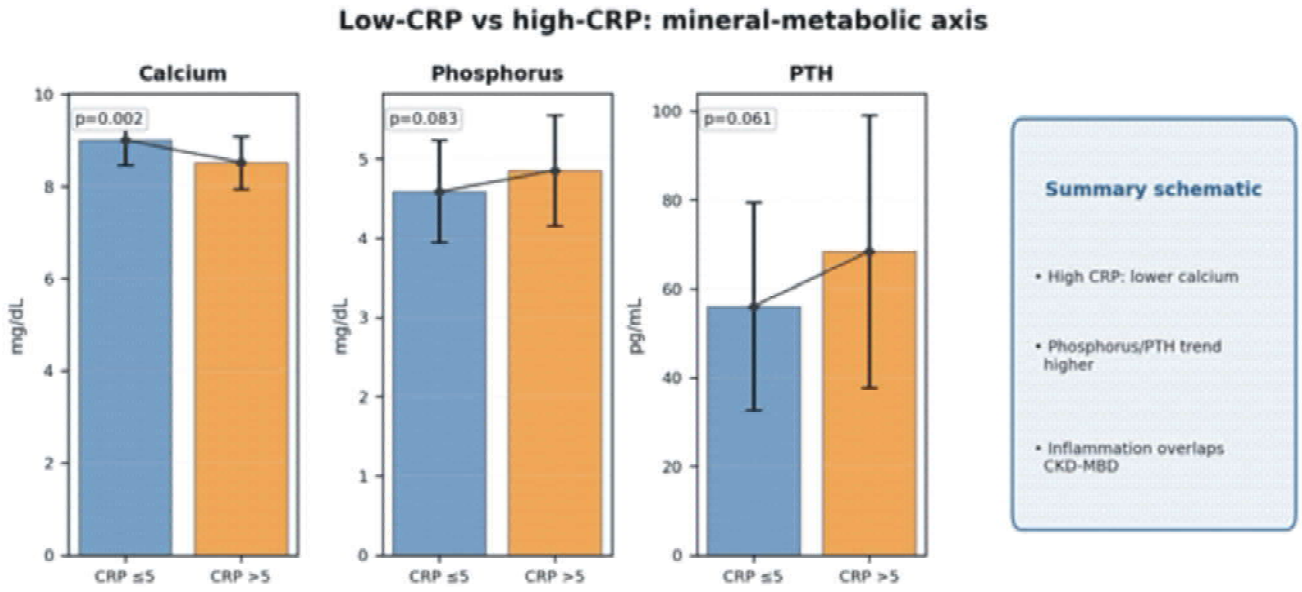

Fig. 4: *Low-CRP versus high-CRP mineral-metabolic phenotype. Mean ± SD plots show calcium, phosphorus and PTH by CRP category. Take-home: high CRP is associated with lower calcium and a trend toward greater CKD-MBD burden.*

Table V: Correlation of CRP with all continuous parameters.

Parameter	Domain	Spearman ρ	p	FDR q	Pearson r	Strength	FDR sig.
Creatinine	Renal	0.651	**<0.001**	**<0.001**	**0.623**	**Strong**	Yes
Urea	Renal	0.635	**<0.001**	**<0.001**	**0.571**	**Strong**	Yes
Ferritin	Iron profile	0.215	**0.006**	**0.012**	0.283	Weak	Yes
TIBC	Iron profile	0.202	**0.011**	**0.018**	0.178	Weak	Yes
Phosphorus	Mineral metabolism	0.180	**0.023**	**0.034**	0.207	Very weak	Yes
PTH	Mineral metabolism	0.058	0.465	0.551	0.069	Very weak	No
Platelet count	Haematological	0.055	0.493	0.551	0.010	Very weak	No
Age	Demographic	0.020	0.801	0.832	0.066	Very weak	No
MCH	Haematological	0.017	0.832	0.832	0.021	Very weak	No
Serum iron	Iron profile	-0.080	0.316	0.401	-0.093	Very weak	No
WBC count	Haematological	-0.099	0.214	0.291	-0.116	Very weak	No
MCHC	Haematological	-0.188	**0.017**	**0.027**	-0.201	Very weak	Yes
MCV	Haematological	-0.214	**0.007**	**0.012**	-0.262	Weak	Yes
RBC count	Haematological	-0.236	**0.003**	**0.006**	-0.263	Weak	Yes
Calcium	Mineral metabolism	-0.301	**<0.001**	**<0.001**	-0.307	Weak	Yes
PCV	Haematological	-0.323	**<0.001**	**<0.001**	-0.382	Weak	Yes
Haemoglobin	Haematological	-0.327	**<0.001**	**<0.001**	-0.390	Weak	Yes
GFR	Renal	-0.633	**<0.001**	**<0.001**	**-0.646**	**Strong**	Yes
TSAT	Iron profile	-0.651	**<0.001**	**<0.001**	**-0.624**	**Strong**	Yes

CRP correlated most strongly with TSAT, creatinine, urea and GFR. Significant correlations after FDR correction were also observed with haemoglobin, PCV, calcium, ferritin, TIBC, phosphorus, RBC count, MCV and MCHC. These results show that CRP tracked multiple biological domains of CKD severity.

Inflammatory iron restriction as a downstream manifestation

Table VI: Downstream inflammatory iron-restriction phenotype by CKD stage (ferritin ≥100 ng/mL, TSAT <20%, CRP >5 mg/L).

CKD stage	n	Phenotype present (n)	%
G3a	9	0	0.0%
G3b	35	0	0.0%
G4	60	13	21.7%
G5	56	49	87.5%
Statistical test	160	$\chi^2 = 91.29$	**p = <0.001**

The high ferritin-low TSAT-high CRP phenotype was absent in stage G3a and G3b and became common in advanced CKD, particularly stage G5. This supports iron-restricted erythropoiesis as one consequence of systemic inflammation in CKD, but the broader CRP correlation pattern demonstrates that inflammation extends beyond anaemia.

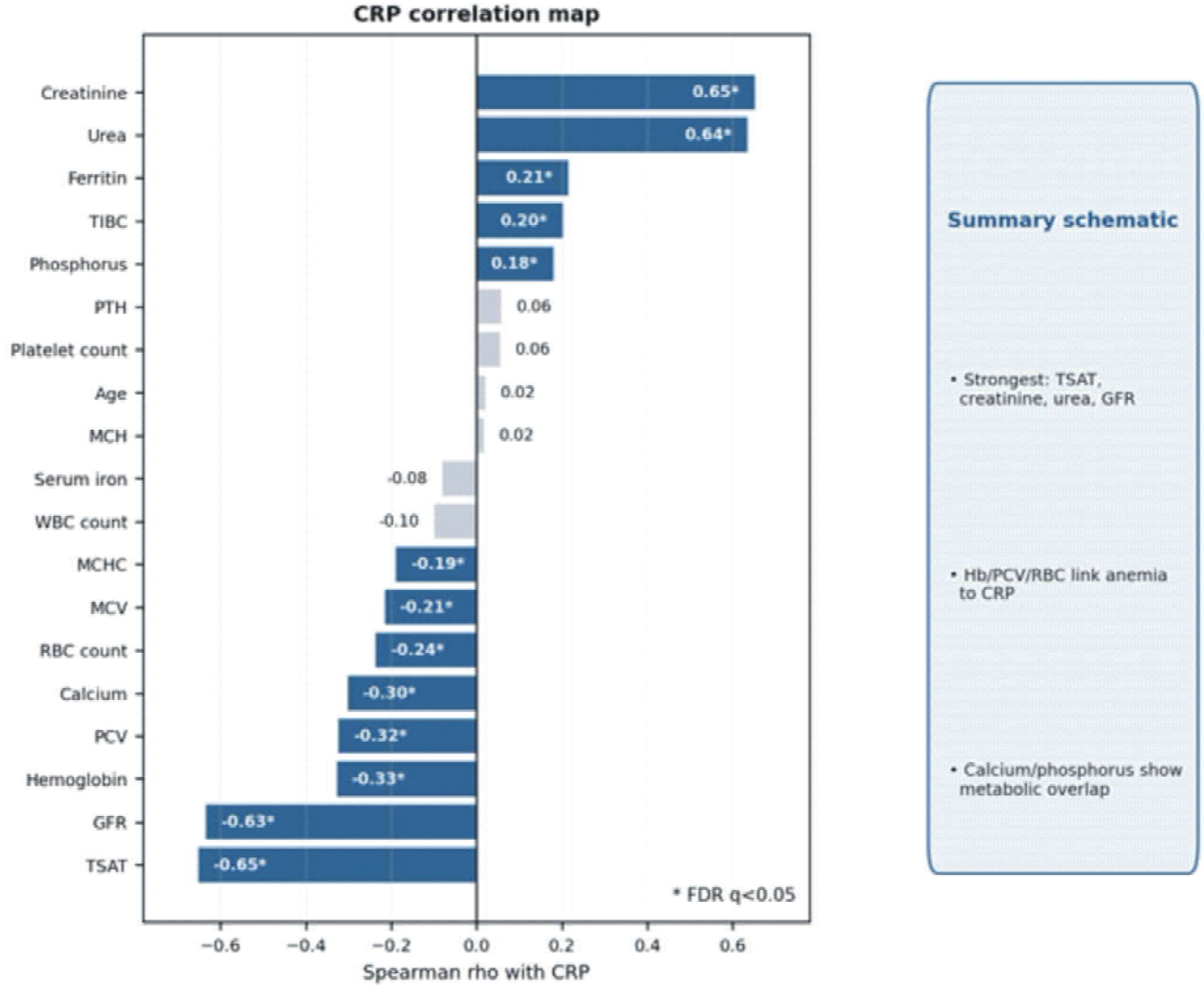

Fig. 5: *CRP correlation map. Bars represent Spearman rho; asterisks indicate FDR q <0.05. Take-home: the strongest links are renal dysfunction and iron restriction.*

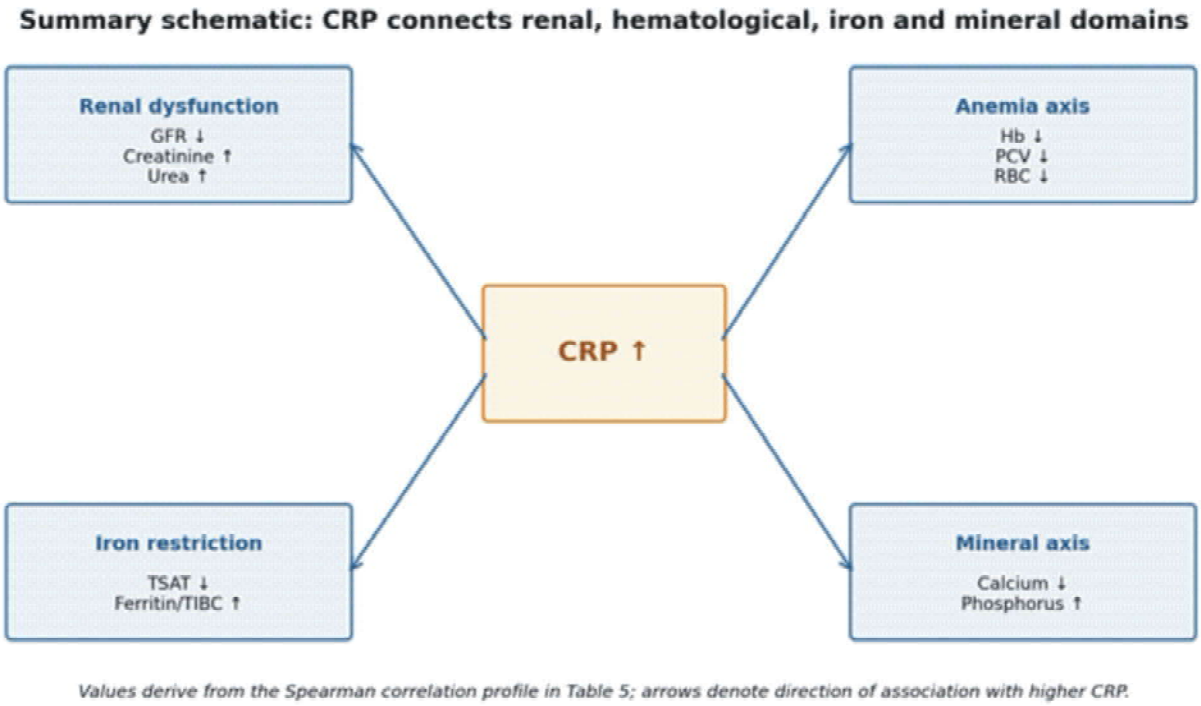

Fig. 6: *Multidomain summary schematic of CRP correlations. The schematic summarizes the main statistically supported directions of association from Table V. Take-home: CRP connects renal dysfunction, iron restriction, anaemia and mineral-metabolic change.*

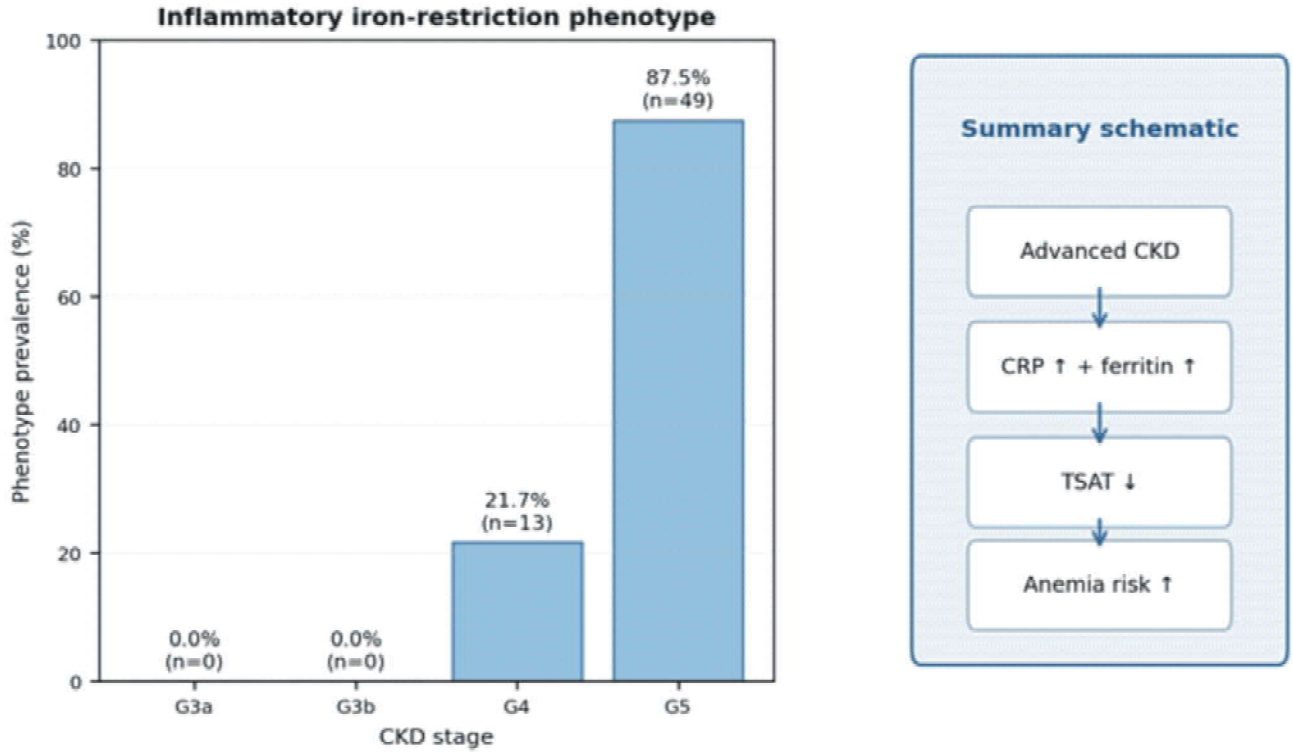

Fig. 7: *Stage-wise prevalence of the inflammatory iron-restriction phenotype. Bars show the percentage of patients meeting ferritin ≥100 ng/mL, TSAT <20% and CRP >5 mg/L. Take-home: this downstream phenotype emerges predominantly in advanced CKD.*

Discussion

This original analysis reframes a non-dialysis CKD anaemia dataset through the broader lens of systemic inflammation. The main finding is that CRP rose in a graded manner across CKD stages, from G3a to G5, and high CRP became nearly universal in advanced disease. This stage-wise inflammatory gradient was accompanied by worsening renal function, anemia, iron dysregulation and mineral-metabolic disturbance.

The strength of the CRP correlations is important. CRP showed strong positive correlations with creatinine and urea and a strong inverse correlation with GFR, indicating that inflammation closely tracked renal dysfunction. These findings are consistent with the concept that progressive CKD promotes inflammation through uraemic toxin accumulation, oxidative stress, endothelial injury, gut dysbiosis and comorbidity-driven immune activation[1-4].

The iron and anaemia findings should therefore be interpreted as part of a wider inflammatory phenotype. CRP correlated strongly and inversely with TSAT, weakly but significantly with ferritin and TIBC, and significantly with haemoglobin and PCV. This supports a model in which inflammation contributes to iron-restricted erythropoiesis through impaired iron mobilisation, while ferritin may partially behave as an acute-phase marker rather than a pure reflection of available iron stores[5-8].

The relationship between CRP and mineral metabolism adds a further systemic dimension. CRP correlated negatively with calcium and positively with phosphorus, while PTH showed only a weak non-significant relationship. This suggests that the inflammatory signature of CKD may coexist with CKD-mineral bone disorder, although the present dataset cannot prove causality. The combination of inflammation, mineral dysregulation, anaemia and iron restriction may help explain the high cardiovascular and metabolic burden of advanced CKD[3,4,9].

The clinical implication is that inflammation should be considered an integral part of CKD assessment rather than an incidental laboratory finding. In advanced CKD, elevated CRP may identify patients with a broader inflammatory-metabolic phenotype, including low TSAT, high ferritin, anemia, lower calcium and higher phosphorus. Such patients may require more careful interpretation of iron markers, evaluation for occult inflammatory triggers, optimisation of CKD-MBD care and individualised anaemia management.

Strengths and limitations

The strengths of this study include a well-defined non-dialysis CKD cohort, availability of CRP across CKD stages, simultaneous assessment of renal, haematological, iron and mineral variables, and use of FDR correction for multiple correlation testing. The main limitations are the cross-sectional design, lack of hepcidin, interleukin-6, albumin, oxidative stress markers, albuminuria and longitudinal outcomes. CRP was measured once, and subclinical infection or comorbidity-related inflammation cannot be completely excluded despite parent-study exclusions. The cohort was hospital-based and enriched for advanced CKD, which may limit generalizability.

Conclusion

CKD in this non-dialysis cohort showed a clear systemic inflammatory signature. CRP increased progressively with CKD stage and correlated with renal dysfunction, iron restriction, anaemia and mineral-metabolic disturbance. These findings support CKD as a systemic inflammatory state, with inflammation-associated iron-restricted erythropoiesis representing one downstream manifestation rather than the sole explanation. Routine interpretation of CRP alongside GFR, ferritin, TSAT, haemoglobin, calcium, phosphorus and PTH may better characterize the inflammatory phenotype of advanced CKD.

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ORIGINAL ARTICLE

JIACM 2026; 27 (2): 94-99

Proton Pump Inhibitors and Gastrointestinal Bleeding in Patients Taking Oral Dual Antiplatelet Therapy

Desai Jay, Subhendu Mohanty**, Deepak Sharma***, Abhishek Deepak**, Pokala Sai Badrinath*, Sanket Pale**

Abstract

Background: Dual antiplatelet therapy (DAPT) increases the risk of gastrointestinal (GI) bleeding. Proton pump inhibitors (PPIs) are commonly prescribed for gastroprotection, but real-world prescribing practices and their impact on bleeding outcomes in Indian settings remain unclear.

Objectives: To evaluate PPI prescribing patterns in adults receiving DAPT and to determine the association between PPI use and GI bleeding.

Material and Methods: This cross-sectional observational study was conducted at a tertiary care centre in North India. A total of 150 adults on DAPT for ≥6 months were enrolled. Data on demographics, clinical profile, DAPT duration, and PPI use (type and duration) were collected. GI bleeding was assessed using clinical history, faecal occult blood test (FOBT), and endoscopy where indicated. Statistical analysis included chi-squared test, Fisher's exact test, and Welch's t-test, with $p < 0.05$ considered significant.

Results: The mean age was 59.50 ± 9.74 years, and 56% were males. GI bleeding was observed in 10.7% of patients. PPIs were prescribed in 51.3% of patients, with Pantoprazole being the most common agent. No significant association was found between PPI use and overall GI bleeding ($p = 0.600$). However, PPI use was significantly associated with a lower incidence of clinically significant haemoglobin drop (>3 g/dL) (2.6% versus 11%; $p = 0.016$). Shorter PPI duration was associated with greater haemoglobin decline ($p < 0.001$). Increasing age was a significant risk factor for GI bleeding ($p = 0.027$), while other baseline variables were not significantly associated.

Conclusion: PPI co-prescription in patients on DAPT was associated with reduced clinically significant haemoglobin decline, suggesting a protective effect against meaningful bleeding. Although no association was observed with test-defined GI bleeding, haemoglobin-based outcomes provided additional clinical insight. Targeted and sustained PPI use in high-risk patients, particularly older individuals, appears justified. Further prospective studies are needed to confirm these findings.

Key words: Dual antiplatelet therapy; proton pump inhibitors; gastrointestinal bleeding; haemoglobin decline; pantoprazole; risk factors.

Introduction

Gastrointestinal (GI) Bleeding is a serious medical event with direct clinical and public health consequences. It is a leading cause of hospital admissions and can result in prolonged stays, transfusions and increased mortality. In patients receiving Dual Antiplatelet Therapy (DAPT), the risk of GI Bleeding rises further. DAPT is essential in managing Cardiovascular Disease, yet it carries well-known risks to Gastrointestinal safety[1-3].

DAPT involves the combination of Aspirin and a P2Y12 receptor antagonist such as Clopidogrel, Prasugrel, or Ticagrelor. This combination reduces Platelet Aggregation and prevents thrombotic events in patients with Acute Coronary Syndromes or those who undergo Percutaneous Coronary Intervention. It is a widely accepted therapy based on strong clinical evidence. Despite proven benefits - DAPT increases the risk of Upper Gastrointestinal mucosal injury, Ulcer formation and Bleeding[3-5].

Proton Pump Inhibitors (PPIs) are the most commonly used agents to reduce gastric acid secretion. By increasing gastric pH, they help preserve mucosal integrity and reduce the risk of acid-related injury. Clinical trials have shown that PPIs can significantly lower the risk of Upper GI Bleeding in patients on Antiplatelet therapy. Based on the existing evidence major cardiology and gastroenterology guidelines recommend co-prescribing PPIs for high-risk patients receiving DAPT[6].

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Real world practice often does not align with guideline-based care. Some patients are prescribed PPIs without a clear indication. Others do not receive any gastroprotective therapy even with obvious risk factors. This inconsistency can lead to both over-treatment and under-treatment. The overuse of PPIs also comes with consequences. Long term PPI therapy has been linked to increased risk of *Clostridium difficile* infections, bone fractures, magnesium deficiency and potential interactions with Clopidogrel due to shared metabolic pathways[8]. This creates a dilemma for physicians. The decision to prescribe a PPI along with DAPT must balance protection from GI Bleeding with the potential harms of chronic acid suppression. The challenge lies in identifying which patients truly benefit from PPI use and ensuring they receive appropriate care[7,8].

In India, cardiovascular disease is the leading cause of death and disability. The use of DAPT is widespread in tertiary care centres and in smaller hospitals. Limited research exists on how PPIs are used in patients receiving DAPT in the Indian setting. Most studies are from Western countries with different prescribing patterns, healthcare access and patient risk profiles. Applying these findings to India without local data may result in poor decisions being made[9,10].

Data on the prevalence of GI Bleeding in Indian patients receiving DAPT are also scarce. Most evidence is limited to small hospital-based studies or retrospective chart reviews. These often lack detailed risk assessment or standardised reporting. As a result - there is not a clear understanding of how often GI Bleeding occurs in this population or whether it could be prevented with more appropriate use of PPIs. Hence, this study was planned to address these knowledge gaps. The objectives of the study were as follows:-

- To determine the association between concomitant PPI prescription and the occurrence of GI Bleeding in patients on DAPT.
- To describe PPI prescribing patterns in DAPT patients (agent, dose, frequency, timing relative to DAPT initiation, and duration).
- To estimate the occurrence of GI bleeding (overall and classified as upper vs. lower GI where ascertainable) among patients on DAPT.

Material and Methods

This cross-sectional observational study was conducted in the Department of General Medicine, School of Medical Sciences and Research, Sharda Hospital, Greater Noida, Uttar Pradesh during April 2024 – November 2025. The study commenced after Institutional Ethics Committee approval. Participants were recruited from the Cardiology OPD, Gastroenterology OPD, and Medicine OPD. Adults (≥18 years), either sex, on Dual Antiplatelet Therapy (DAPT) and willing to participate after informed consent. This includes patients on DAPT with CAD and intervention.

Inclusion Criteria

- Patients on DAPT for at least 6 months with CAD and intervention
- Patients with stroke on DAPT
- Age >18 years
- Both sexes
- Willing to participate (informed consent).

Exclusion Criteria

- Concomitant NSAIDs or corticosteroids
- Patients on newer oral anticoagulants
- Known bleeding disorders
- Severe liver disease
- Severe kidney disease.

Sample Size

The sample size is estimated for a single-proportion (prevalence) objective using:-

$$\frac{Z^2 P(1-P)}{d^2}$$

Where (Z) is the standard normal deviate (1.96 for 95% CI), (P) is the expected prevalence, and (d) is the absolute precision.

The protocol assumed P = 56% (Jinadu *et al*[11]) for Co-prescription of DAPT with PPI and d = 8%. Substituting values:-

$$n = \frac{1.96 \times 0.56 \times (1 - 0.56)}{0.08^2} \sim 147.9 \Rightarrow 148$$

Final sample size (rounded): 150.

Variables and Operational Definitions

1. Exposure: PPI Co-prescription among patients receiving DAPT (agent, dose, timing *versus* DAPT start, and duration) was captured via history and drug chart/ records in the case record form (CRF).
2. Outcomes: Gastrointestinal (GI) bleeding was ascertained clinically and by investigations as available:

history of melena/hematemesis, new anaemia on CBC, FOBT, and Upper GI endoscopy where indicated. When feasible, classify as upper *versus* lower GI bleeding.

Variables and Parameters: Demographics (age, sex, address, education), lifestyle (smoking/alcohol), clinical profile, vitals, general/systemic examination, and relevant investigations (CBC with haemoglobin/PCV/platelets, lipid profile, RBS, ECG, 2D echo).

Data Collection Procedures: After institutional ethics committee approval and written informed consent, eligible patients were enrolled consecutively. A structured case-record form was used to capture demographics, clinical examination, DAPT duration, PPI intake, and GI-bleeding assessments (melena, hematemesis, anaemia); FOBT and endoscopy were performed where indicated.

Statistical Analysis: Continuous variables were summarised as mean ± SD with minima and maxima, and categorical variables as counts and percentages. Age was banded into four groups and GI-bleeding proportions across bands were compared using the chi-squared test. Binary associations in 2 × 2 Tables (e.g., PPI use *versus* significant haemoglobin fall >3 g/dL; bleeding-consistent endoscopy by PPI use) were evaluated with Fisher's exact test. Group differences for continuous exposures (e.g., PPI duration among users by bleeding status; DAPT duration by haemoglobin-drop status) were assessed using Welch's t-tests to accommodate unequal variances. GI-bleeding period prevalence was calculated from the FOBT/endoscopy-based definition, and two-sided p-values were reported with a significance threshold of <0.05.

Results

The mean age of the study population was 59.50 ± 9.74 years, with majority of patients belonging to the 50 - 59 years age group (35.3%), followed by 60 - 69 years (32.7%). Males constituted 56% of the study population. A history of smoking and alcohol use was present in 25.3% and 17.3% of patients, respectively. The mean body mass index (BMI) was 25.81 ± 5.23 kg/m^2, and the mean blood pressure was 132.55 ± 15.27/82.91 ± 9.76 mmHg. Gastrointestinal (GI) bleeding was observed in 16 patients, yielding a prevalence of 10.7%, while 89.3% of patients did not experience any bleeding episode (Table I).

The mean duration of DAPT was 8.37 ± 3.63 months. Proton pump inhibitors (PPIs) were prescribed in 51.3% of patients. Among these, pantoprazole was the most commonly used PPI (27.3%), followed by rabeprazole (18.7%) and esomeprazole (5.3%). The mean duration of PPI therapy was 7.44 ± 2.30 months (Table II).

Table I: Baseline demographic, clinical characteristics and prevalence of gastrointestinal bleeding (n = 150).

Variable	Value
Age (years), mean ± SD	59.50 ± 9.74
Age group, n (%)	<50: 25 (16.7)
	50 - 59: 53 (35.3)
	60 - 69: 49 (32.7)
	≥70: 23 (15.3)
Gender, n (%)	Male: 84 (56.0)
	Female: 66 (44.0)
Smoking, n (%)	Yes: 38 (25.3)
	No: 112 (74.7)
Alcohol use, n (%)	Yes: 26 (17.3)
	No: 124 (82.7)
Past illness, n (%)	Present: 115 (76.7)
Family history, n (%)	Present: 45 (30.0)
BMI (kg/m^2), mean ± SD	25.81 ± 5.23
SBP/DBP (mmHg), mean ± SD	132.55 ± 15.27/82.91 ± 9.76
Prevalence of gastrointestinal bleeding, n (%)	16 (10.7)

Table II: DAPT characteristics and PPI prescribing pattern.

Variable	Value
DAPT duration (months), mean ± SD	8.37 ± 3.63
PPI use, n (%)	Yes: 77 (51.3)
	No: 73 (48.7)
PPI type, n (%)	Pantoprazole: 41 (27.3)
	Rabeprazole: 28 (18.7)
	Esomeprazole: 8 (5.3)
	None: 73 (48.7)
PPI duration (months), mean ± SD	8.81 ± 2.54

A statistically significant association was observed between PPI use and reduction in significant haemoglobin (Hb) drop (>3 g/dL). Patients receiving PPI had a lower incidence of Hb drop (2.6%) compared to those not receiving PPI (11%), and this difference was statistically significant (p = 0.016). However, when different types of PPIs were compared, no statistically significant association was found with the occurrence of GI bleeding (p = 0.600) (Table III).

Table III: Association between PPI use and bleeding outcomes.

PPI use	Hb drop n (%)	No drop n (%)	p-value
Yes (n = 77)	2 (2.6)	75 (97.4)	**0.016**
No (n = 73)	8 (11.0)	65 (89.0)	
PPI type	GI bleed n (%)	No bleed n (%)	
Esomeprazole (n = 8)	0 (0)	8 (100)	0.600
Pantoprazole (n = 41)	3 (7.3)	38 (92.7)	
Rabeprazole (n = 28)	3 (10.7)	25 (89.3)	

No significant association was observed between duration of PPI therapy and occurrence of GI bleeding (p = 0.532). However, shorter duration of PPI therapy was significantly associated with greater risk of significant Hb drop (p <0.001). Additionally, DAPT duration showed a borderline association with Hb drop (p = 0.05) as shown in Table IV.

Table IV: Effect of therapy duration on bleeding outcomes.

PPI use	Hb drop n (%)	No drop n (%)	p-value
PPI duration (months)	8.33 ± 1.75	8.85 ± 2.61	0.532
PPI duration vs Hb drop	6.11 ± 0.33	7.52 ± 2.34	**<0.001**
DAPT duration (months)	12.89 ± 1.96	14.47 ± 3.69	0.05

We compared select baseline characteristics between those with and without GI Bleeding using Welch's t-tests for continuous variables and Fisher's exact tests for binary variables. Those with GI Bleeding were older on average (64.75 ± 9.25 *versus* 58.87 ± 9.64 years; p = 0.027). Differences in BMI, DAPT duration, baseline haemoglobin and platelets were not statistically significant (all p ≥0.20). Categorical comparisons for gender, smoking, alcohol and past illness (present/absent) showed no significant differences (all p ≥0.30) as shown in Table V.

Table V: Potential risk indicators.

Variable	Group	N	Min	Mean ± SD	Max	p value
Age (years)	GI bleed = Yes	16	47	64.75 ± 9.25	83	
	GI bleed = No	134	37	58.87 ± 9.64	82	**0.027**
BMI (Kg/m^2)	GI bleed = Yes	16	18.6	27.80 ± 6.47	41.7	
	GI bleed = No	134	13.9	25.57 ± 5.04	43.9	0.201
DAPT Duration (months)	GI bleed = Yes	16	10	14.31 ± 3.74	21	
	GI bleed = No	134	9	14.38 ± 3.62	27	0.892
Haemoglobin (g/dL)	GI bleed = Yes	16	10.8	12.97 ± 1.41	15.5	
	GI bleed = No	134	9	12.60 ± 1.42	16.3	0.341
Platelet Count (x10^9/L)	GI bleed = Yes	16	146	231.13 ± 66.14	351	
	GI bleed = No	134	116	251.94 ± 56.48	389	0.243
Gender	GI bleed = Yes (M)	11				
	GI bleed = Yes (F)	5				0.303
Smoking Y/N	GI bleed = Yes (Y)	2				
	GI bleed = No (N)	2				0.76
Alcohol Y/N	GI bleed = Yes (Y)	10				
	GI bleed = No (N)	6				0.48
Past Illness	GI bleed = Yes (Present)	12				
	GI bleed = No(Absent)	4				1

Discussion

We set out to evaluate prescribing patterns of proton pump inhibitors among adults receiving Dual Antiplatelet Therapy; we aimed to determine whether PPI prescription correlated with gastrointestinal bleeding in this population. The primary objective focused on any correlation between PPI use and GI bleeding while on DAPT; secondary objectives addressed how PPIs were being prescribed in routine practice and the incidence of GI bleeding among patients on DAPT at our centre.

In this study, the prevalence of GI bleeding among patients on DAPT was 10.7%, which is higher than the incidence reported in several international studies (1 - 2.5%) but comparable to observations in real-world and high-risk populations[3,12]. This variation may be attributed to differences in patient demographics, comorbidity burden, and variability in adherence to risk stratification protocols, particularly in the Indian healthcare setting[9,10].

Age was found to be a significant predictor of GI bleeding, with affected patients being older than those without bleeding (64.75 ± 9.25 *versus* 58.87 ± 9.64 years; p = 0.027). This finding is consistent with previous studies demonstrating that advanced age is an independent risk factor due to impaired mucosal defence, polypharmacy, and increased comorbidities[13,14]. Elderly patients on prolonged antiplatelet therapy are particularly vulnerable and require careful monitoring and preventive strategies.

PPI co-prescription was observed in 51.3% of patients, indicating moderate adherence to gastroprotective strategies. This is lower than rates reported in Western populations (60 - 80%) but comparable to data from other Asian and Indian studies, where prescribing patterns remain inconsistent[15-18]. Pantoprazole was the most commonly prescribed PPI, followed by rabeprazole and esomeprazole. This preference aligns with pharmacological evidence suggesting lower CYP2C19 inhibition and reduced interaction with clopidogrel[19-21].

A statistically significant association was observed between PPI use and reduction in clinically significant haemoglobin

drop (>3 g/dL), with lower incidence in PPI users (2.6% *versus* 11%; p = 0.016). This supports the protective role of PPIs in reducing the severity of bleeding events. Similar findings have been reported in multiple meta-analyses, where PPI co-therapy significantly reduced upper GI bleeding risk in patients receiving antiplatelet therapy[22,23]. However, no statistically significant association was found between PPI use and overall GI bleeding incidence (p = 0.600). This finding is consistent with studies suggesting that while PPIs reduce the severity and complications of bleeding, they may not completely prevent bleeding events, particularly in patients with multiple risk factors[13,22]. This highlights the multifactorial nature of GI bleeding in patients on DAPT.

The duration of PPI therapy showed important clinical relevance. Although no direct association was observed between PPI duration and GI bleeding, shorter duration of therapy was significantly associated with higher haemoglobin drop (p <0.001). This finding suggests that continuous and adequate duration of gastroprotection is essential, especially in patients receiving prolonged DAPT. Similar observations have been reported in studies emphasising sustained acid suppression to prevent mucosal injury[24,25].

The mean duration of DAPT in this study was 8.37 ± 3.63 months, and a borderline association was observed between longer DAPT duration and haemoglobin drop (p = 0.05). This aligns with previous evidence demonstrating that prolonged antiplatelet therapy increases bleeding risk, necessitating individualised duration based on risk-benefit assessment[4,26].

Interestingly, traditional risk factors such as smoking, alcohol use, BMI, and baseline laboratory parameters did not show statistically significant association with GI bleeding in this study. This may reflect the cumulative and multifactorial nature of bleeding risk, where individual factors alone may not be predictive without comprehensive risk assessment tools[27,28].

The study also highlights a significant gap between guideline recommendations and clinical practice. While international guidelines recommend PPI co-prescription in high-risk patients on DAPT, real-world adherence remains inconsistent, with both underuse in high-risk patients and overuse in low-risk individuals[15,16]. Similar discrepancies have been reported globally and are often attributed to lack of awareness, absence of standardised protocols, and variability in physician practice patterns[15,29].

The potential interaction between PPIs and clopidogrel remains a topic of debate. Although pharmacokinetic studies suggest reduced activation of clopidogrel due to CYP2C19 inhibition, clinical evidence has not consistently demonstrated adverse cardiovascular outcomes[30,31]. Current evidence supports the use of PPIs, particularly pantoprazole and rabeprazole, in patients at high risk of GI bleeding, as the benefits outweigh theoretical risks[32].

Overall, the findings of this study are consistent with existing literature in demonstrating that PPIs play a significant role in reducing the severity of bleeding in patients on DAPT. However, variability in prescribing patterns underscores the need for improved implementation of guideline-directed therapy.

Strengths and Limitations: This study provides valuable real-world data from an Indian tertiary care setting, addressing a gap in regional literature. However, the cross-sectional design limits causal inference. The relatively small sample size and lack of universal endoscopic confirmation may affect the generalisability and accuracy of bleeding classification.

Conclusion

PPI co-prescription in patients receiving DAPT was associated with a reduction in clinically significant haemoglobin decline, indicating a protective effect against meaningful bleeding events. Although no clear association was observed with FOBT or endoscopy-defined bleeding, haemoglobin-based outcomes provided important complementary insight into clinically relevant harm. Increasing age emerged as a key risk factor for GI bleeding, underscoring the importance of risk stratification in guiding gastroprotective therapy. Overall, sustained and selective PPI use in higher-risk patients appears justified in routine practice; however, further large-scale prospective and randomised studies are needed to better define optimal prescribing strategies and confirm these associations.

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ORIGINAL ARTICLE

JIACM 2026; 27 (2): 100-105

Prognostic Importance of Serum Potassium in Acute Myocardial Infarction: A Prospective Study

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Abstract

Background: Worldwide, acute myocardial infarction (AMI) is associated with high morbidity and mortality in hospitalised patients. The study was aimed to generate evidence regarding prognostic value of serum potassium among newly diagnosed AMI patients in a tertiary care center.

Material and Methods: It was a facility-based, observational study with a prospective design. 120 patients of acute myocardial infarction, during the 18 months period of data collection, were included in study population. Routine blood tests and echocardiography was done for each study subject. Patients were followed up till end of therapy in the study facility and then repeat follow-up was done at 1-month and 3-months of therapy.

Results: Around 50% study subjects had normal serum potassium level, 36.7% study subjects had hypokalaemia and remaining had hyperkalaemia. At 1-month follow-up, minimum serum potassium level was 2.8 mEq/L, maximum serum potassium level was 4.4 mEq/L and mean serum potassium was 3.517 mEq/L. At 3-months follow-up, minimum serum potassium level was 3.0 mEq/L, maximum serum potassium level was 4.4 mEq/L and mean serum potassium was 3.762 mEq/L. Nearly 33.3% study subjects developed post-AMI arrhythmia; among them 55% died in the study facility. Post-AMI arrhythmia was found to be statistically significantly associated with in-hospital treatment outcome (p - value 0.000). Serum potassium status at baseline was found to be statistically significantly associated with in-hospital mortality and ventricular arrhythmia.

Conclusion: Baseline serum potassium level was found to have prognostic significance in early prediction of favourable outcome. Early detection and correction of any serum potassium imbalance could effectively reduce mortality burden of AMI.

Key words: Myocardial infarction, hypokalaemia, follow-up, serum potassium level.

Introduction

Worldwide acute myocardial infarction (AMI) is associated with high morbidity and mortality in hospitalised patients[1]. Serum sodium, potassium and calcium are major electrolytes involved with electrophysiological properties of myocardial membrane. The sarcolemma is impermeable to Na^+ in the resting state. It has Na^+-K^+ ATPase pump that plays an important role in establishing the resting potential. This pump exports Na^+ from the cell out and imports K^+ inside the cell against their concentration gradient. Thus, when intracellular K^+ is relatively high, then Na^+ is low, and when extracellular Na^+ is high, then K^+ is low. There are 4 phases of action potential dependent on sodium, potassium and calcium. Serum electrolyte imbalances after an episode of acute myocardial infarction are common[3]. But clinical importance of these imbalances in both STEMI and NSTEMI has not been fully understood. These electrolytes play an important role in altering the prognosis of myocardial infarction patients[4]. Hypokalaemia is defined as serum potassium levels <3.5 mEq/L[5]. The prevalence and role of hypokalaemia in myocardial infarction has been under investigation for a long time. Hypokalaemia in patients with AMI is thought to predict increased in-hospital morbidity, particularly arrhythmias and mortality[6]. Several studies have shown an association between hypokalaemia and an increased occurrence of cardiac arrhythmias in AMI patients[7]. Recent guidelines suggest that K^+ levels should be monitored and routinely replaced in patient with heart failure and MI, even if on admission K^+ appears normal[8]. Hyperkalaemia is also associated with increased mortality and should be avoided[9]. The total body potassium levels in the body are 3500 mmoL, out of which 98 % is intracellular. Its main regulation is by the renal excretion and shift between the intracellular and extracellular compartments. The sodium-potassium ATPase pump is mainly responsible for preserving intracellular potassium. Aldosterone and vasopressin stimulate potassium secretion by up-regulating the luminal Na^+-K^+ ATPase pump and opening the luminal Na^+ and K^+ channels[10]. Sudden cardiac death after MI (death within 1 hour) is mainly due to alteration in environment at the level of myocytes and Purkinje fibers that are regulated by electrolyte imbalances and autonomic nervous system activity[11]. Hypokalaemia is associated with a

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wide variety of arrhythmias in AMI such as ventricular tachycardia and ventricular fibrillations[19]. Sudden cardiac deaths after MI are mainly due to alteration of environment at the level of myocyte and Purkinje fibers that are mainly caused by electrolyte imbalances. A leading hypothesis for the mechanism of generation of arrythmias in the setting of acute coronary syndromes is alteration of electrophysiological properties of the ischaemic myocardium. There are few studies regarding prognostic value of serum potassium in AMI patients. By assessing the prognostic significance of serum potassium among AMI patients in a prospective manner, this study has provided necessary inputs for ensuring provision of care of AMI patients.

Material and Methods

This observational study was done among newly diagnosed patients of acute myocardial infarction, admitted in IPD of General Medicine, North Bengal Medical College and Hospital, Darjeeling district, West Bengal from April 2024 to October 2025.

Inclusion criteria

1. Newly diagnosed patients of acute myocardial infarction, admitted during the period of data collection.

Exclusion criteria

1. Those who did not give informed consent.
2. Renal insufficiency.
3. Those who were on diuretics.

Sample size

For estimating the incidence rate of adverse outcome of AMI among study participants, considering the relative precision (ε) of 20% and 95% confidence interval (CI), the sample size was calculated by using the following formula[63]:

$N = (Z_{1-\alpha/2} \div \varepsilon)^2$
Thus, the calculated minimum sample size was –
$N = (1.96 \div 0.2)^2$
~96.

Considering anticipated non-response rate 25%,
The final sample size was fixed at:
96 + (96 × 25%)
~120.

Sampling technique:

Consecutive sampling was applied. Each patient after initial interview and data collection was followed up at 1-month and 3-months of therapy.

Study tools and techniques:

Tools

- A semi-structured, pre-designed, pre-tested schedule to collect background information.
- Serum potassium, urea, creatinine, random blood sugar, CPK-MB, Trop-T
- ECG
- 2D-Doppler echocardiography

Techniques

- Patient-interviews (PI) for background information.
- Relevant record reviews for clinical information.

Data Collection: Data was collected after ethical clearance and approval of the synopsis by the Institutional Ethics Committee of North Bengal Medical College and Hospital, Darjeeling, West Bengal. During the data collection period, 2 - 3 patients were interviewed per day, twice per week.

Data management and analysis: The principles of descriptive statistics were applied to organise and present the data in tables and diagrams. Qualitative data was expressed in proportion. Data analysis was done by using Statistical Package for Social Sciences (SPSS) version 23. Association between serum potassium level and incidence of ventricular arrhythmia was checked by Chi-square test. Association between serum potassium level and in-hospital mortality was checked by unpaired-t test. Correlation between serum potassium and LVEF and LVEDD was checked by using Pearson's correlation co-efficient at 1-month and 3-months of therapy. p-value ≤0.05 was considered statistically significant.

Observation and Results

Table I: Distribution of study participants as per their age (n=120).

Age (in years)	Frequency (%)
<50	16 (13.3)
50-60	60 (50)
>60	44 (36.7)
Total	120
Mean age	59.07 years
Standard Deviation (SD)	7.958

Table I shows that out of 120 study subjects, 16 (13.3%) were within <50 years age group. Another 60 (50%) study subjects were within 50 - 60 years age group. Another 44/120 (36.7%) study subjects were within >60 years age group. Mean age was 59.07 years (SD ± 7.958).

Table II: Bivariate analysis between background characteristics of study participants and in-hospital treatment outcome (n = 120).

Background characteristics	Total study subjects (N=120)	Frequency of study subjects based on in-hospital treatment outcome		Chi-Squared test (χ^2)		
		Discharge (n = 96)	Death (n = 24)	(χ^2) value	Degree of freedom (df)	p-value
Age (in years)						
<50	16	16	0	28.485	2	**0.000**
50 - 60	60	56	4			
>60	44	24	20			
Gender						
Male	72	56	16	0.556	1	0.456
Female	48	40	8			
Educational status						
Primary	24	12	12	38.137	3	**0.000**
Mid-school	68	64	4			
Secondary	24	20	4			
Higher-second	4	0	4			
Socio-economic status						
Upper-middle	44	8	36	0.162	2	0.922
Middle	56	12	44			
Lower-middle	20	4	16			
BMI						
Normal	20	16	4	2.778	2	0.249
Overweight	64	48	16			
Obese	36	32	4			
Substance use						
No	40	28	12	11.250	3	**0.010**
Smoking	48	44	4			
Alcohol	8	8	0			
Both	24	16	8			

**Socio-economic status as per modified BG Prasad scale [October 2023; CPI (IW): 138.4]. In table-II statistical association was analysed by using Chi-squared test between in-hospital treatment outcome of study subjects with various background characteristics. In-hospital treatment outcome was found to be statistically significantly associated with age (p-value 0.000), education (p-value 0.000) and substance abuse (p-value 0.010) of study subjects.*

Fig. 2 show that 40/120 (33.3%) study subjects developed post-AMI arrhythmia; among them 22/40 study subjects (55%) died in the study facility. 80/120 study subjects (66.7%) did not have post-AMI arrhythmia; among them 2/80 study subjects (2.5%) died in study facility. Post-AMI arrhythmia was found to be statistically significantly associated with in-hospital treatment outcome (p-value 0.000).

Fig. 2 show that out of 60 study participants with normal serum potassium at baseline, 59/60 (98.3%) were discharged and in-hospital mortality rate was 1/60 (1.7%); but among 44 study subjects with hypokalaemia at baseline, 20/44 (45.5%) was the in-hospital mortality rate; among 16 study participants with hyperkalaemia at baseline, 13/16 (81.2%) were discharged and in-hospital mortality rate was 3/16 (18.7%). Serum potassium status at baseline was found to be statistically significantly associated with in-hospital mortality. Out of 60 study participants with normal serum potassium at baseline, 2/60 (3.3%) study subjects developed ventricular arrhythmia; but among 44 study subjects with hypokalaemia at baseline, 36/44 (81.8%) developed ventricular arrhythmia; among 16 study participants with hyperkalaemia at baseline, 2/16 (12.5%) developed ventricular arrhythmia.

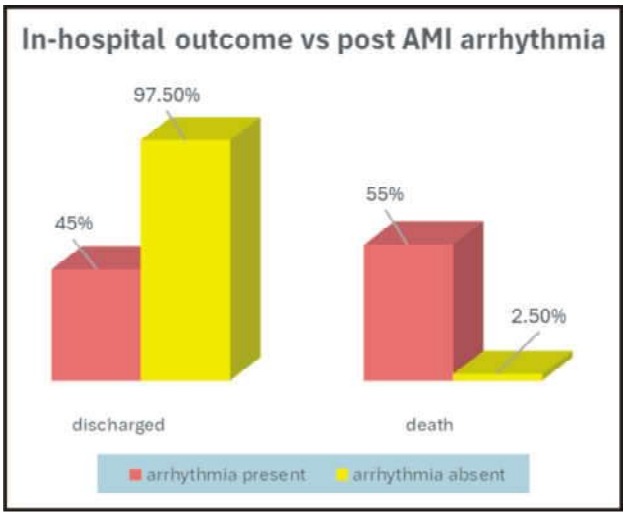

Fig. 1: *Distribution of study subjects as per in-hospital treatment outcome (n = 120).*

ROC curve shows that serum potassium level at baseline has significant discriminative power (AUC >0.5 and p-value 0.000) in early prediction of favorable outcome of AMI.

Discussion

In our study nearly (50%) study subjects were within 50 - 60 years age group with mean age was 59.07 years (SD ± 7.958). Nearly 60% study subjects were male and remaining female. Another 26% were from urban area and remaining rural. Around 50% study subjects had normal serum potassium level, 36.7% study subjects had hypokalaemia and remaining had hyperkalaemia. Minimum serum potassium level was 2.1 mEq/L, maximum serum potassium level was 6.1 mEq/L and mean potassium level was 3.780 mEq/L (SD ± 1.108). Regarding LVEF at baseline, minimum observed value was 30%, maximum value was 54% and mean value was 46.233 (SD ± 6.062). Regarding LVEDD, minimum observed value was 38 mm, maximum value was 62 mm, and mean value was 48.667 (SD ± 6.617).

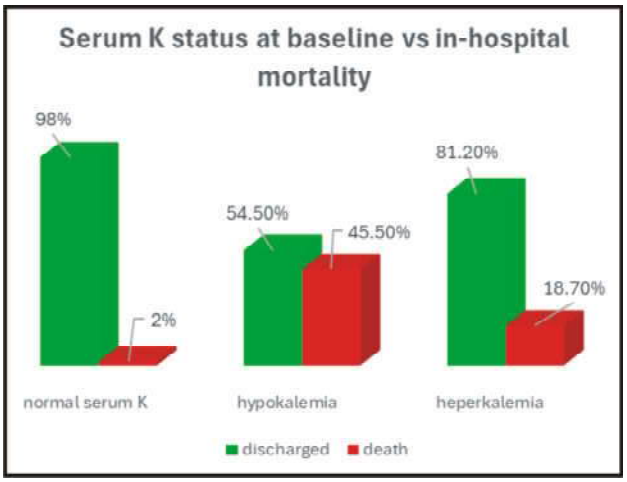

Fig. 2: *Distribution of study subjects as per in-hospital treatment outcome (n = 120).*

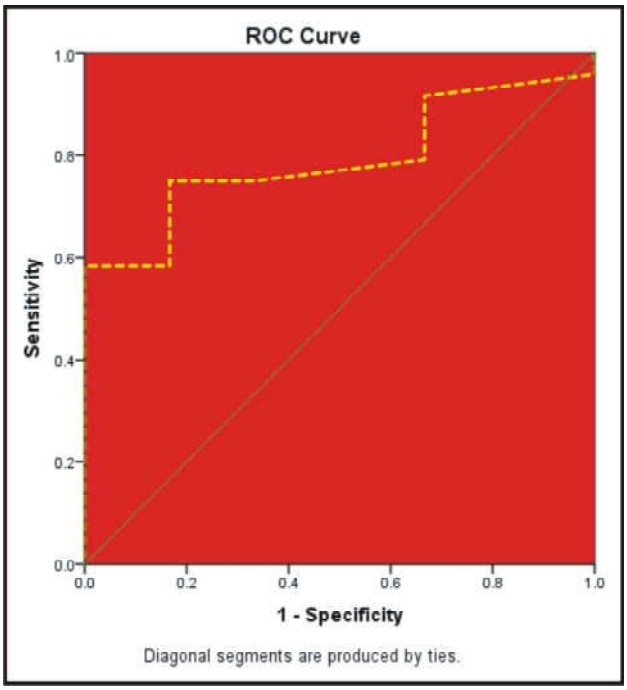

Fig. 3: *ROC curve analysis to assess predictive value of baseline serum potassium level regarding in-hospital mortality (n=120).*

At 1-month follow-up, minimum serum potassium level was 2.8 mEq/L, maximum serum potassium level was 4.4 mEq/L and mean serum potassium was 3.517 mEq/L (SD ± 0.391). At 1-month follow-up, minimum LVEF value was 22%, maximum value 56% and mean LVEF value was 42.708 (SD ± 8.932). Regarding LVEDD at 1-month follow-up, minimum value was 42 mm, and maximum value was 62 mm, and mean value was 51.00 (SD ± 5.954).

At 3-months follow-up, minimum serum potassium level was 3.0 mEq/L, maximum serum potassium level was 4.4 mEq/L and mean serum potassium was 3.762 mEq/L (SD ± 0.351). At 3-months follow-up, minimum LVEF value was 30%, maximum value 58% and mean LVEF value was 50.042 (SD ± 6.961). Regarding LVEDD at 3-months follow-up, minimum value was 44 mm, and maximum value was 57 mm, and mean value was 50.167 (SD±3.620).

96/120 (80%) study subjects were discharged from the study facility and remaining 26/120 (20%) died. Nearly 40/120 (33.3%) study subjects developed post-AMI arrhythmia; among them 22/40 study subjects (55%) died in the study facility. 80/120 study subjects (66.7%) did not have post-

AMI arrhythmia; among them 2/80 study subjects (2.5%) died in study facility. Post-AMI arrhythmia was found to be statistically significantly associated with in-hospital treatment outcome (p-value 0.000).

Out of 60 study participants with normal serum potassium at baseline, most were discharged but among 44 study subjects with hypokalaemia at baseline, 45.5% was the in-hospital mortality among 16 study participants with hyperkalaemia at baseline, mortality rate was 18.7%. So serum potassium status at baseline was found to be statistically significantly associated with in-hospital mortality. Out of 60 study participants with normal serum potassium at baseline, 3.3% study subjects developed ventricular arrhythmia; but in those with hypokalaemia at baseline, 81.8% and 12% in hyperkalemia developed ventricular arrhythmia. Baseline serum potassium level at or above 3.450 mEq/L can predict favorable in-hospital treatment outcome with sensitivity of 75% and specificity of 83.3%. Serum potassium level at baseline has significant discriminative power (AUC >0.5 and p-value 0.000) in early prediction of favourable outcome of AMI.

Serum potassium and LVEF at 1-month follow-up was positively correlated; strength of correlation was high (Pearson correlation coefficient 0.792, p-value 0.000), linear and positive in nature. Serum potassium and LVEDD at 1-month follow-up was negatively correlated; strength of correlation was high (Pearson correlation coefficient 0.794, p-value 0.000), linear and negative in nature. Serum potassium and LVEF at 3-month follow-up was positively correlated; strength of correlation was moderate (Pearson correlation coefficient 0.642, p-value 0.000), linear and positive in nature. Serum potassium and LVEDD at 3-month follow-up was negatively correlated; strength of correlation was mild (Pearson correlation coefficient 0.322, p-value 0.001), linear and negative in nature.

A study done by Kiranmani *et al*[24] showed that there was significant decrease in serum magnesium and serum potassium levels in hypertensives and diabetics on 1st day of AMI when compared to controls ($p < 0.01$) with no significant change in serum Ca^{2+} and serum Na^{+} levels ($p > 0.05$). There was significant decrease in serum magnesium levels in cases with diabetes ($p < 0.05$) when compared to cases without diabetes. There was insignificant lowering of serum magnesium levels in cases with hypertension when compared to cases without hypertension. Another study by Mudaraddi *et al*[25] showed that there were statistically significant decreased levels of serum sodium ($p < 0.001$), potassium ($p < 0.001$) and elevated levels of urea ($p < 0.001$) observed in AMI. But the levels of serum chloride did not show any significant correlation between case and control groups.

The current study was one of those rare studies in West Bengal which assessed the prognostic value of serum potassium among newly diagnosed AMI patients and analyzed association between serum potassium with cardiac function during follow-up at 1-month and 3-month. Future multicentric longitudinal studies should be done for further validation.

Conclusion

Commonest type of serum potassium imbalance was hypokalaemia which was mostly due to the catecholamine response in such patients. Serum potassium imbalance was associated with cardiac arrhythmias and increased in-hospital mortality in post-AMI patients. Close monitoring of serum potassium level and prompt correction of it was necessary to improve AMI treatment outcome and prognosis.

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ORIGINAL ARTICLE

JIACM 2026; 27 (2): 106-110

Outcomes of Patients on Antiviral Therapy for Chronic Hepatitis B in North Bengal

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Abstract

***Background and objectives:** There is limited evidence regarding rate and extent of regression of liver fibrosis following antiviral therapy in patients with Chronic Hepatitis B (CHB). Here we want to establish the reversibility of clinical and laboratory outcomes including HBV DNA levels and FibroScan parameters within an established time frame.*

***Methods:** 150 patients with serologically proven CHB infection on uninterrupted antiviral therapy for at least 24 months, attending Hepatitis Clinic of North Bengal Medical College and Hospital, excluding patients with any evidence of cirrhosis (clinical or radiological), concomitant Hepatitis C and HIV infection, and chronic alcoholics, during a 6 months period were enrolled in an institution based, observational, ambispective study. Post-treatment outcomes with antiviral therapy were measured in terms of fibrosis markers (APRI, FIB-4 and Median stiffness by FibroScan), HBV DNA levels, HBeAg seroconversion and laboratory parameters.*

***Results:** Significant improvement was noted in terms of biochemical, serological and radiological parameters. HBV DNA was reduced from baseline mean of 343,52,823 to 938 (SD 2051) which corroborated with the regression of liver fibrosis by reduction of non-invasive parameters like APRI and FIB-4 from baseline mean of 1.06 to 0.32 and 1.74 to 0.91, respectively. Median stiffness in FibroScan was reduced from baseline mean of 6.22 kPa to 4.87 kPa. Also, all the 8 participants who were seropositive for HBeAg at baseline, had achieved seroconversion.*

***Conclusion:** Treatment with antivirals led to significant decreased risk of decompensation and cirrhosis which was corroborated with regression of liver fibrosis, achievement of viral DNA suppression and virological seroconversion.*

***Key words:** Chronic Hepatitis B, Antivirals, FibroScan, HBV DNA quantitative assay.*

Introduction

Hepatitis B virus (HBV) is a leading cause of liver-related morbidity and mortality worldwide. An estimated 254 million people are affected globally by chronic hepatitis B infection[1]. HBV accounts for roughly 1.1 million deaths per year across the globe[2]. The estimated seroprevalence of HBV infection is as high as 0.95% in India with highest prevalence among the tribal population[3]. The incidence of chronic hepatitis B (CHB) infection is 1.46% in India, with an estimated 17 million chronic carriers[4]. It accounts for 40% of Hepatocellular Carcinoma (HCC) and 20 - 30% cases of cirrhosis in India[5]. Hepatitis B infection acquired in adulthood leads to chronic hepatitis in <5% cases, whereas infection in infancy and early childhood leads to chronic hepatitis in 95% cases[6]. The algorithm-based treatment with antiviral agents has been the most significant scientific development for treatment of HBV infection. The purpose of our study was to investigate post-treatment outcomes with anti-virals in chronic hepatitis B patients in this part of the country with respect to liver enzyme normalisation, viral DNA suppression, virological seroconversion and reversibility of liver fibrosis.

Aims

1. To study effectiveness of anti-viral therapy to prevent cirrhosis and decompensation by comparing baseline clinico-laboratory parameters with those after 24 months.
2. To study suppression of HBV DNA levels and seroconversion of HBeAg in CHB-infected patients on anti-viral therapy after 24 months.
3. To study any reversal of Liver Fibrosis after 24 months.

Material and Methods

This study enrolled chronic HBV patients attending Hepatitis Clinic of North Bengal Medical College and Hospital, Darjeeling between 1st February 2022 and 30th January 2024. It was an institution based, observational, ambispective study, which enrolled 150 patients of chronic hepatitis B infection on uninterrupted antiviral therapy for

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at least 24 months, excluding patients with any evidence of cirrhosis (clinical or radiological), concomitant Hepatitis C and HIV infection, and alcoholic liver disease (patients with liver disease having history of significant amount of alcohol intake, i.e., more than 2 drinks per day for women and more than 3 drinks per day for men for 10 years or more (1 drink equals ~14 g of ethanol, which is 1 beer, 4 oz of wine, or 1oz of 80% spirits) and other causes (e.g., Wilson's disease, Autoimmune hepatitis etc.). Baseline data on study parameters was collected during enrolment of patients for initiation of treatment. Data after 24 months of treatment was collected during follow-up at Hepatitis clinic. HBV infection was confirmed by HBV DNA quantification assay in all patients. Cirrhosis was diagnosed by experienced radiologists in the Radiology Department, based on the results of imaging modalities such as ultrasonography (USG) and FibroScan (LOGIQ P9 GE MAKE shear wave transient elastography). Decompensation of cirrhosis was assessed using clinical parameters (CTP score) and imaging such as USG. Clinical outcomes and other laboratory parameters (i.e., complete blood count, liver function tests, INR etc.) were evaluated in all patients. AST to platelet ratio index (APRI) score and FIB-4 index, two useful non-invasive methods of assessing liver fibrosis, were also evaluated.

Table I: Liver FibroScan.

Liver Fibrosis staging	METAVIR score	Median stiffness (kPa)
Normal-Mild	F1	6.48 - 6.60
Mild-Moderate	F2	6.60 - 8.07
Moderate-Severe	F3	8.07 - 9.31
Cirrhosis	F4	>9.31

Table I shows optimal LOGIQ S8 shear wave elastography cut-off values in terms of shear wave speed (m/s) and Young's Modulus (kPa) for classifying fibrosis stage in the patient population under evaluation. Data was acquired using R3.1.9 equivalent software and the C1-6-D probe.

APRI score calculation

APRI score = {(AST level/AST ULN) x 100}/platelet count (10^9/L)

For APRI, ULN signifies the upper limit of normal for AST which was taken as 40U/L in our study. APRI score greater than 1.5 and greater than 2.0 was used for predicting significant hepatic fibrosis and cirrhosis respectively[7].

FIB-4 index calculation

FIB-4 index = {Age (yr) x AST (IU/L)}/{platelet count (10^9/L) x √ALT (IU/L)}

FIB-4 index greater than 1.45 and greater than 3.25 was used for predicting significant hepatic fibrosis and cirrhosis respectively[8].

Table II: Child-Turcotte-Pugh (CTP) Score:

Points	1	2	3
Encephalopathy	None	Minimal (grade 1 or 2)	Advanced (grade 3 or 4)
Ascites	Absent	Controlled	Refractory
Total bilirubin (mg/dL)	<2	2 - 3	>3
Albumin (g/dL)	>3.5	2.8 - 3.5	<2.8
INR	<1.7	1.7 - 2.3	>2.3

Table II shows severity of cirrhosis in terms of CTP Score.

CTP Class A: 5 - 6 points (Compensated cirrhosis)

CTP Class B: 7 - 9 points (Significantly compromised liver function)

CTP Class C: 10 - 15 points (Decompensated cirrhosis)

Treatment with antivirals

Standard treatment protocol was followed as per the NVHCP guidelines[9]:

- Non-cirrhotic: Tenofovir disoproxil fumarate (TDF) 300 mg once daily.
- Cirrhosis without decompensation: Entecavir (ETV) 0.5 mg once daily.
- Cirrhosis with decompensation: Entecavir (ETV) 1 mg once daily.
- eGFR <60mL/min/1.73 m^2, on haemodialysis: Entecavir (ETV) 0.5 mg once daily.

Statistical analyses

Variables were reported as mean ± SD. Categorical variables were compared by Chi-squared test. Continuous variables were compared by Student's t-test. Statistical analyses were performed using Jamovi 2.6.21 software, with p-value <0.05 considered statistically significant.

Results

Characteristics of patients at baseline

A total of 150 patients, ranging from 15 to 75 years of age, 77 (51.3%) patients were in the age bracket of 25 to 44 years and the mean age at diagnosis was found to be 38 (± 13.59) years. Majority of the infected people were male (72.7%) *versus* female (27.3%). 15% of patients had a definite history of IV drug abuse. 64 participants (42 male and 22 female) had identified risk factors of acquiring Hepatitis B infection at baseline. Among those, high-risk sexual behaviour was the leading risk factor among male

participants (21.4%). Presence of tattoos was the second most common risk factor in both male (19.0%) and female (18.2%) participants.

Baseline biochemical parameters were recorded as mean ALT 86.3 (± 67.5) IU/L, mean AST 71.2 (± 49.6) IU/L. Pre-treatment mean platelet count was 1,81,820 (± 75,000)/mm^3. Baseline CTP Score was 5.74 (± 1.08) with 76.7% participants in class A and 23.3% in class B. Among 150 participants, 8 were found to be seropositive for HBeAg.

Characteristics of patients after 24 months of treatment (Figs. 1, 2, 3, and 4)

Mean ALT and AST reduced to 27.99 (± 12.58) IU/L and 28.35 (± 13.46 IU/L), respectively. Mean platelet count increased to 2,23,990 (± 62,880)/mm^3. CTP score improved to 5.00 (±0.14) with all participants belonging to class A. All 8 seropositive participants had achieved virological seroconversion. Mean APRI reduced from 1.06 (± 0.59) at baseline to 0.32 (± 0.13) after 24 months of treatment. Mean FIB-4 decreased from1.74 (± 0.82) at baseline to 0.91 (± 0.32) after 24 months of treatment. Mean Median Stiffness also improved from 6.22 (± 1.08) kPa at baseline to 4.87 (± 0.76) kPa after 24 months of treatment. Mean HBV DNA level had reduced from a baseline mean of 343,52,823 ± (1.02E + 8) IU/mL to 938 (± 2051) IU/mL after 24 months of treatment.

Discussion

Van Ameijden *et al* reported that the HBV prevalence in Amsterdam, Netherlands, was 68% for IDUs (Injection drug users)[10]. Quite interestingly, only 12.5% of patients (6 male and 2 female) had a definite history of IV drug abuse in our study. Whereas in South Asian (including India) context, Puri has attributed the lower prevalence of CHB to the predominant horizontal transmission in early childhood, in contrast to vertical transmission seen in South-East Asia[11]. This points to the fact that other modes of transmission in adults like unsafe injection practices, occupational exposure, repeated use of same razor for multiple people

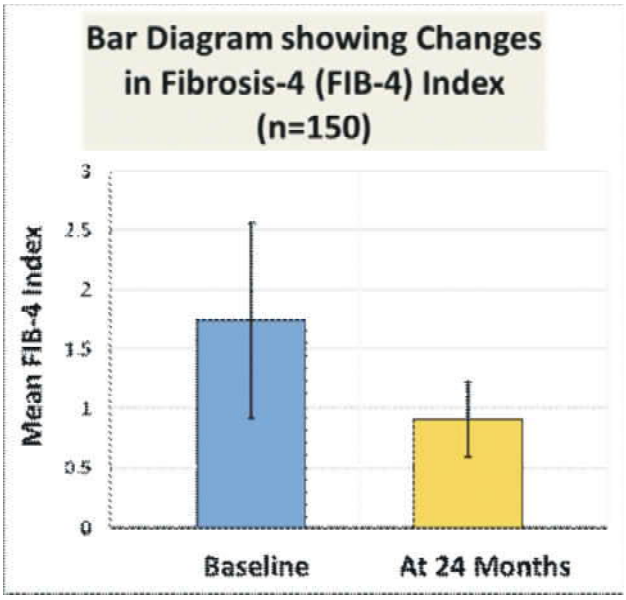

Fig. 2: *Comparison of FIB-4 index at baseline and after 24 months of treatment.*

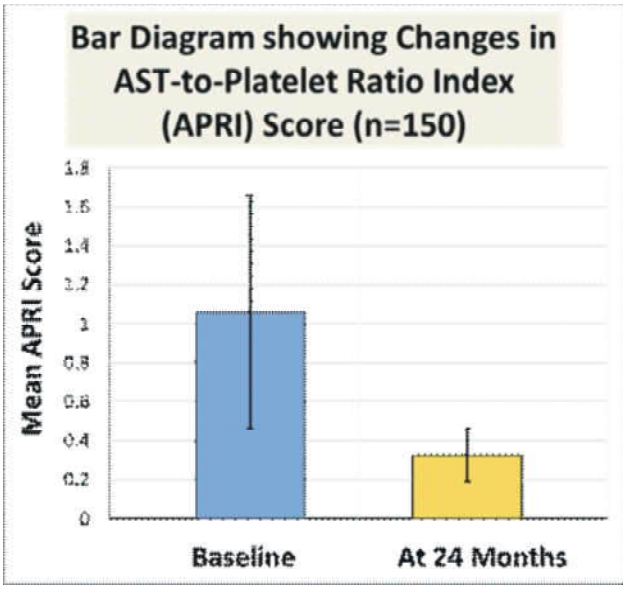

Fig.1: *Comparison of APRI score at baseline and after 24 months of treatment.*

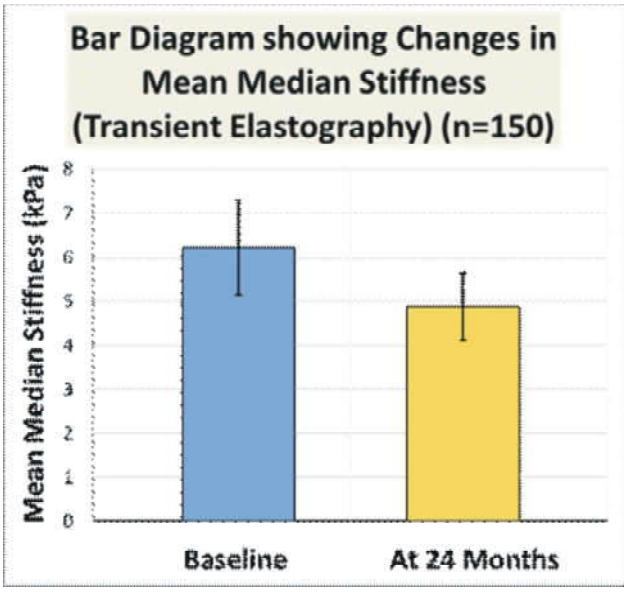

Fig. 3: *Comparison of Median Stiffness at baseline and after 24 months of treatment.*

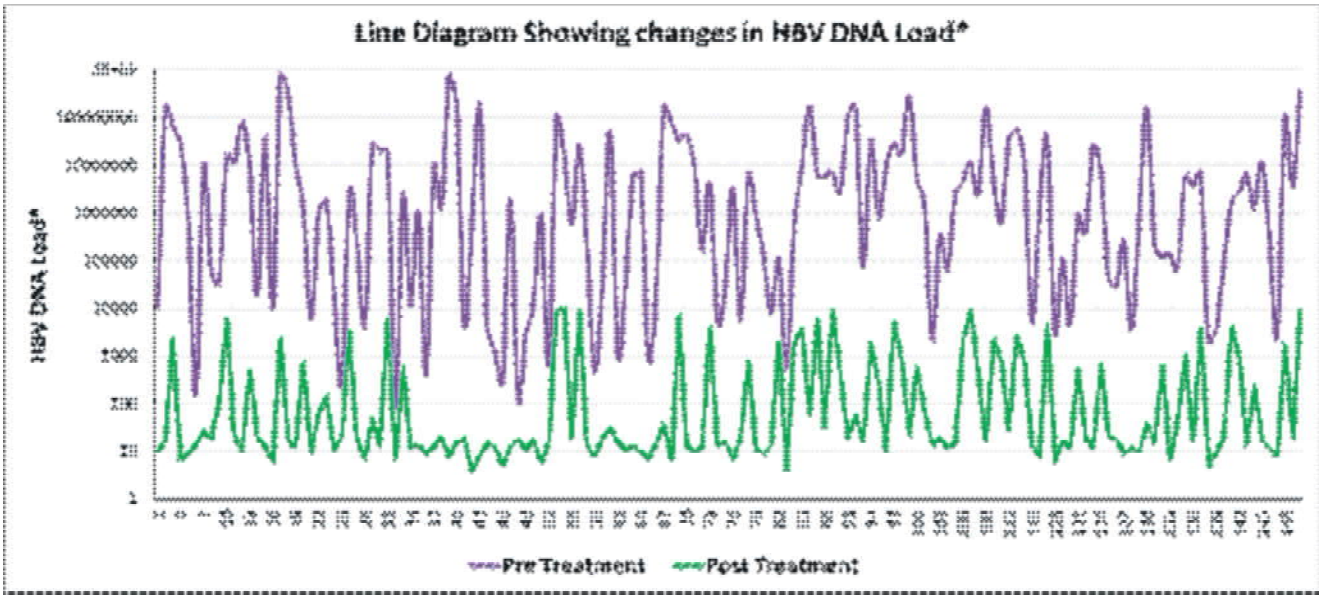

Fig. 4: *Comparison of HBV DNA Load at baseline and after 24 months of treatment.*

in saloons, sharing personal items in joint families, organ transplantation, etc., are yet to be thoroughly explored at the community level.

In our study, the most dramatic change was noticed in HBV DNA level where a baseline mean of 343,52,823 (SD 1.02E+ 8) was reduced to a mean of 938 (SD 2051) with a t-value of 4.123 and a p-value of <0.001 after 24 weeks of treatment. This data re-affirms the excellent viral DNA suppression after initiating antivirals for treating HBV infection.

APRI score was improved in a statistically significant manner after 24 weeks of treatment, from a baseline mean of 1.06 (SD 0.59) to mean of 0.32 (SD 0.13), t-value 18.285, p-value <0.001. Similarly, FIB-4 index was improved from a baseline mean of 1.74 (SD 0.82) to 0.91 (SD 0.32), t-value 16.755, p-value <0.001 after 24 months.

FibroScan data showed that the mean baseline Median stiffness improved from 6.22 (SD 1.08) to mean of 4.87 (SD 0.76) with a p-value of <0.001. In astudy by Rong-Nan Chien *et al*, it was found that 85% patients had regression in fibrosis stage after successful treatment[12]. Our study corroborated the finding, with fibrosis regression been observed in 93% and no deterioration in the rest.

Genotyping and mutation studies were not done in this study as pan-genotypic regimen was used for treatment. Scant global data shows variability in the effect of standard of care treatment upon different genotypes.

Despite limitations, the data in this study further establishes the effect of antiviral agents in CHB infection while preventing hepatic decompensation, cirrhosis and HCC, fibrosis regression and viral seroconversion which lead to improvement in hepatic outcomes and overall prognosis.

Conclusion

We conclude that those who were infected with CHB mostly presented in 2nd to 4th decade and were diagnosed either incidentally or after a complication, mainly in the form of signs and symptoms suggesting portal hypertension. So, it is mandatory to perform HBsAg along with HBV DNA quantitative assay in all such patients. Patients who had achieved viral DNA load suppression, displayed a substantial FibroScan value decline, which correlated with the improvement in the non-invasive tests for fibrosis assessment like APRI and FIB-4. Whether the improvement of these non-invasive parameters in the form of APRI and FIB-4, alongside Median stiffness represent a real fibrosis regression or merely a resolution of chronic liver inflammation with subsequent improvements in FibroScan value and laboratory parameters have to be investigated by liver biopsy for better correlation between non-invasive and invasive methods. Again, the participants need to be followed-up for a longer duration to monitor long-term effects of antivirals while treating a CHB infection and its chronic complications. Moreover, the present study was a single centre study and the sample size was small to generalise the conclusions to the entire population.

Ethics statement and Consent

All procedures performed on participants were in accordance

with the ethical standards of the institutional and/or national research committee. Informed consent was obtained from the patients regarding the use of their clinical data. All the patient specific data was kept in strict confidence.

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ORIGINAL ARTICLE

JIACM 2026; 27 (2): 111-115

Metabolic Profile in ART-Naïve HIV Patients After Initiation of Antiretroviral Therapy: A Prospective Study

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Abstract

***Background:** As people with HIV have an increased survival rate, the focus has moved to metabolic changes in the long-term as a result of antiretroviral therapy. Over time, these changes are becoming important in terms of morbidity. The assessment of early metabolic changes after therapy initiation is thus necessary to optimise long-term care of patients.*

***Methods:** This prospective cohort study involved 57 persons who had a recent HIV diagnosis, who had never been treated, and were referred to a tertiary care centre. Everyone was started with a typical first-line treatment including tenofovir, lamivudine, and dolutegravir. Laboratory tests and physical measurements, such as lipid parameters, hepatic indicators, renal indices, and glycated haemoglobin were measured during initial evaluation, six months, and twelve months.*

***Results:** Average body weight, body mass index, and waist circumference had significant increases over a period of twelve months ($p < 0.0001$). Follow-up also revealed a significant increase in the circulating triglyceride concentrations ($p < 0.0001$). Conversely, other biochemical measures, such as high-density lipoprotein, low-density lipoprotein, total cholesterol, hepatic, renal, and glycated haemoglobin, did not show significant difference.*

***Conclusion:** The introduction of antiretroviral therapy in ART-naive patients with HIV was linked to substantial improvements in anthropometric parameters and triglycerides over a period of one year of treatment. The rest of the biochemical parameters were stable, which suggests good short-time metabolic tolerance. It is advisable to monitor body composition and lipid parameters on a regular basis to determine early metabolic alterations and minimise long-term cardiometabolic risk.*

***Key words:** HIV; antiretroviral therapy; metabolic profile; triglycerides; body mass index.*

Introduction

Human immunodeficiency virus (HIV) infection is a significant global health concern despite the development of diagnostics and treatment, and has resulted in high morbidity and mortality rates, especially in low- and middle-income nations. Combination antiretroviral therapy (ART) has turned HIV into a chronic and controllable disease by suppressing viral replication, enhancing the immune system, and decreasing opportunistic infections, thus greatly increasing survival and quality-of-life[1]. As people with HIV have longer lifespans, new co-morbidities including metabolic abnormalities such as weight gain, dyslipidaemia, disturbed glucose metabolism, insulin resistance, and abnormal fat distribution have become increasingly important causes of morbidity[2]. Despite the fact that modern ART regimens, especially the ones with integrase strand transfer inhibitors (tenofovir, lamivudine, and dolutegravir) are more tolerable than former therapies, they also can affect metabolic pathways and lead to alterations in body weight, composition, and lipid profile[3]. These metabolic changes are multifactorial and include chronic immune stimulation, chronic inflammation, immune reconstitution during ART initiation (so-called return to health phenomenon), direct drug action on adipocyte and insulin signaling pathways and host factors such as age, sex, nutritional status, lifestyle, and genetic predisposition[4,5]. Assessment of metabolic parameters in ART-naïve HIV patients is necessary to differentiate disease-related alterations and therapy-induced effects and allow early detection of patients with risk of developing long-term cardiometabolic complications. Especially in resource-limited countries such as India where late presentations and increasing cardiovascular risk factors co-exist. Anthropometric data like body weight, body mass index, waist circumference, and biochemical parameters like lipid profile, liver and renal functions test, and glycated haemoglobin among others are useful indicators of metabolic status, with dyslipidaemia, in particular, hypertriglyceridaemia being one of the most frequently reported abnormalities with long-term implications[6]. Nonetheless, there are few studies on early metabolic alterations with the initiation of ART in ART-naïve patients in tertiary care units because most studies

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concentrate on long-term therapy. Thus, the current study was carried out to prospectively assess the anthropometric and metabolic variables after antiretroviral therapy in ART-naïve HIV patients to define the initial metabolic changes.

Aim and Objectives

The aim of this study was to examine alterations in physical measurements and metabolic indicators following initiation of antiretroviral therapy in previously untreated individuals with HIV infection. The study focused on tracking variations in body weight, body mass index, and waist circumference at baseline, six months, and twelve months after the start of treatment.

Additionally, the study evaluated changes in lipid-related parameters and assessed variations in hepatic markers, renal indicators, and glycated haemoglobin over a one-year observation period to better understand the metabolic effects associated with antiretroviral therapy.

Material and Methods

A prospective cohort study was conducted in the Antiretroviral Therapy unit over twelve months (May 2022 to April 2023), in a teaching institution after obtaining clearance of the Institutional Ethics Committee. Written consent was taken from all participants before enrolment. A total of 57 people who were recently confirmed to have HIV infection, previously untreated with antiretroviral medication, were recruited.

People who had co-morbidities that are known to affect metabolic outcomes, such as diabetes mellitus, tuberculosis, malignancy, nephrotic syndrome, chronic hepatic disease, thyroid abnormalities or anemia were excluded. All participants were initiated on routine first-line therapeutic plan of tenofovir, lamivudine, and dolutegravir as per NACO guidelines, and were followed up over a one year period with evaluation at baseline, 6 months, and 12 months.

Physical measurements were done, such as weight of the body, body mass index, and waist circumference documented at every visit by standardised recordings. Lab-assessment incorporated lipid-related measures (total cholesterol, triglycerides, HDL, LDL and VLDL), hepatic indicators, renal indicators, and glycated haemoglobin.

The main endpoints were variation in physical and biochemical indicators with time. All data were digitized and analysed with statistical software. Numerical data were calculated based on measures of central tendency and dispersion and categorical variables were presented in number and percentage. The evaluation of temporal changes was performed with the help of relevant comparative methods, such as variance-based methods. A pre-set limit was used on determine statistical relevance.

Results

A total of 57 ART-naïve HIV-positive patients were enrolled and followed for twelve months after initiation of antiretroviral therapy. Among them, 36 (63.16%) were male and 21 (36.84%) were female. The majority of patients belonged to the 21 - 30 years age group, followed by 31 - 40 years, indicating a higher prevalence among young adults.

Changes in Anthropometric Parameters

A progressive increase in body weight, body mass index (BMI), and waist circumference was observed over the 12-month follow-up period. These changes were statistically significant overall ($p < 0.0001$). Post-hoc analysis showed that the significant differences were primarily observed between baseline and twelve months, while changes between intermediate time points were not statistically significant.

The increase in waist circumference indicates a rise in central adiposity over time. Detailed values and statistical comparisons are presented in Table I and illustrated in Figs. 1 - 3.

Table I: Change in mean anthropometric parameters from baseline to 12 months after ART initiation.

Parameter	0 Months (Mean ± SD)	6 Months (Mean ± SD)	12 Months (Mean ± SD)	F-Ratio	p-value
Weight (kg)	52.8 ± 10.4	57.1 ± 11.2	61.3 ± 11.0	1024.8	**<0.0001**
BMI (kg/m^2)	22.1 ± 3.4	24.0 ± 3.5	25.7 ± 3.4	824.3	**<0.0001**
SGOT (U/L)	40.9 ± 20.4	45.6 ± 24.4	41.1 ± 19.0	1.16084	0.316962
SGPT (U/L)	42.2 ± 24.6	41.4 ± 25.1	36.3 ± 17.1	1.5332	0.220339
Urea (mg/dL)	27.3 ± 12.8	26.0 ± 8.5	26.5 ± 6.9	0.30786	0.735641
Creatinine (mg/dL)	0.9 ± 0.2	1.0 ± 0.29	1.6 ± 0.4	1.11767	0.330662

HDL (mg/dL)	53.4 ± 10.9	53.1 ± 10.2	50.2 ± 9.4	38.9	**<0.0001**
Triglycerides (mg/dL)	112.8 ± 34.2	113.4 ± 33.0	129.7 ± 35.0	51.71911	**<0.0001**
VLDL (mg/dL)	25.6 ± 8.2	25.3 ± 8.4	25.3 ± 8.9	3.09364	0.049232
LDL (mg/dL)	103.3 ± 39.0	102.8 ± 38.7	108.9 ± 37.8	43.4314	**<0.0001**
Total Cholesterol (mg/dL)	154.2 ± 56.8	152.2 ± 56.4	151.3 ± 57.6	2.36939	0.098211
HbA1c (%)	5.4 ± 0.2	5.5 ± 0.2	5.5 ± 0.2	1.06064	0.349685
Waist Circumference (cm)	81.2 ± 10.64	85.1 ± 10.80	91.4 ± 11.1	3318.721	**<0.0001**

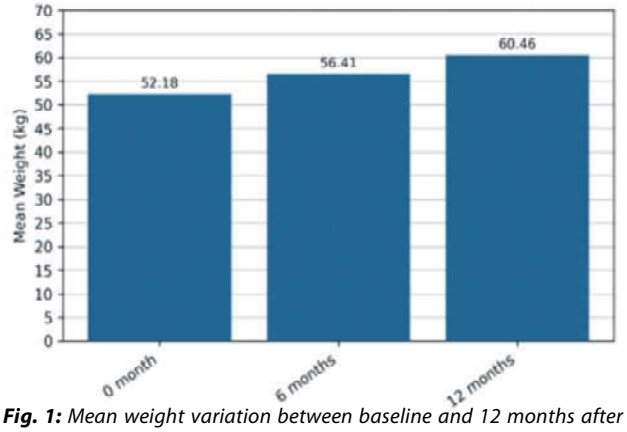

Fig. 1: *Mean weight variation between baseline and 12 months after ART initiation.*

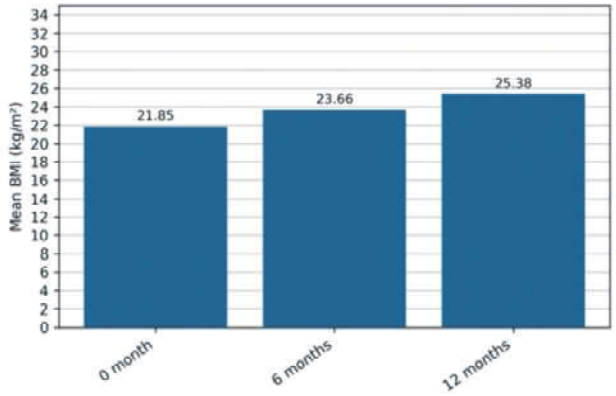

Fig. 2: *Mean BMI variation between baseline and 12 months after ART initiation.*

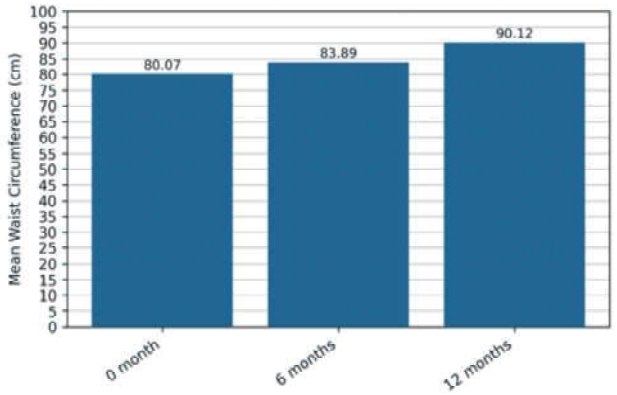

Fig. 3: *Mean waist circumference variation between baseline and 12 months after ART initiation.*

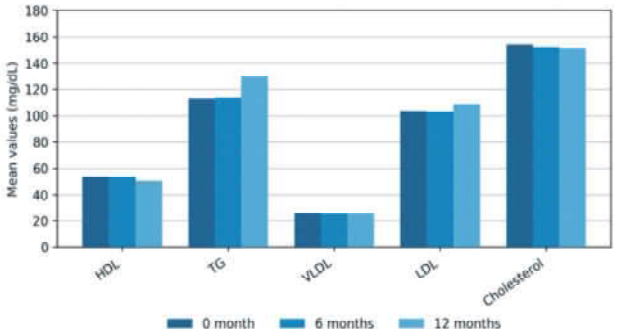

Fig. 4: *Variation in mean lipid profile parameters between baseline and 12 months after ART initiation.*

Changes in Biochemical Parameters

Triglyceride levels showed a progressive and statistically significant increase over the follow-up period ($p < 0.0001$), with significant differences observed between baseline and twelve months, as well as between six and twelve months. In contrast, other lipid parameters, including HDL, LDL, VLDL, and total cholesterol, showed minimal changes over time and did not demonstrate consistent clinically significant variation.

Liver function parameters (SGOT and SGPT) and renal function parameters (urea and creatinine) remained stable throughout the study period, with no statistically significant changes observed. Glycated haemoglobin (HbA1c) showed a slight increase; however, this change was not statistically significant.

The overall variation in lipid profile parameters over the follow-up period is depicted in Fig. 4.

Discussion

The current study assessed the metabolic profile of ART naïve HIV patients who visit an ART tertiary care hospital and measured the anthropometric and biochemical changes.

Increased body weight may reflect a combination of the "return-to-health" phenomenon following viral suppression, improved appetite, and reduced catabolic effects of chronic HIV infection. Comparable findings have been reported in previous studies, where weight gain after initiation of ART was attributed to immune restoration and improved nutritional status[5].

The considerable increase in BMI after 12 months also indicates the existence of ART-related alterations in overall body mass. Even though the initial gains in BMI can be helpful in malnourished patients, higher and persistent gains can expose patients to overweight and obesity. This is of clinical importance, because high BMI is known to be one of the risks of cardiovascular disease and metabolic syndrome. Past research has revealed inconsistent impacts of ART on BMI that point to the impact of the population, baseline nutrition and course of treatment[6].

A statistically significant increase in waist circumference was found at follow-up exhibiting a rise in central adiposity. Of specific interest is the central fat accumulation, which is highly linked to insulin resistance and cardiovascular risk. Various studies have reported ART-related changes in fat distribution, central obesity, that have been attributed to the intricate interplay between antiretroviral drugs, adipocyte functions, and inflammatory processes[7]. The outcome is an apparent rise in waist circumference of this group, which highlights the importance of regular surveillance of central obesity in ART-using HIV patients.

Of all biochemical parameters, the levels of triglyceride showed a statistically significant rise throughout the 12-month follow-up time. Among the most common metabolic abnormalities in HIV patients taking ART, dyslipidaemia, especially hypertriglyceridaemia, is one of them. This increase in triglyceride levels was reported by Daniyam and Iroezindu and Yinzhong *et al*, who also reported an increase in triglyceride levels in HIV-infected people after they started taking ARTs[8,9]. High triglycerides are a risk factor in cardiovascular difease and should be monitored and treated early.

Other lipid parameters such as HDL, LDL, VLDL, and total cholesterol, did not exhibit statistically significant alterations throughout the study period. There are previous studies which have reported similar mixed outcomes with some showing LDL and total cholesterol increase and others showing slight or no change[10,11]. The relatively steady lipid profile excluding triglycerides in the current study could be an indication of the relatively good metabolic tolerance of the TLD-based regimen.

Liver parameters such as SGOT and SGPT were consistent during the study and no considerable highs were recorded. This indicates that ART regimen was tolerated well in terms of hepatic functioning in the initial year of therapy. The results seem to be consistent with other researchers who found very low clinically-significant hepatotoxicity with current ART regimens[12]. On the same note, parameters of renal function, such as serum urea and creatinine did not experience significant changes in the course of the follow-up, and therefore renal function was preserved throughout the study.

HbA1c as a measure of glycaemic status demonstrated a marginal increase over time, but this was not significant. This implies that exposure to ART over short-term did not have a significant effect on glucose metabolism in this group. Little changes in HbA1c levels among HIV patients on ART have also been reported in the previous literature, and the glucose dysregulation might appear in the long-term or with other risk factors[12-14].

On the whole, the results of this research point out that, although the introduction of ART among ART-naïve HIV-positive patients results in considerable changes in anthropometric parameters and triglycerides, the majority of other biochemical parameters do not change significantly in the initial year of treatment. The findings underscore the need to monitor early metabolism, especially weight, waist circumference and triglyceride levels to detect patients who are prone to long-term cardiometabolic complications. The research has some limitations such as a rather small sample size and the period of follow-up. More multicentric studies with longer follow-up should be conducted to have a better understanding of the long-term metabolic impact of ART and clinical implications. However, the current study contributes to understanding the early metabolic alterations upon the ART initiation in a tertiary care environment and supports the necessity of the metabolic monitoring as an inseparable part of the HIV treatment.

Conclusion

This paper proves that the implementation of antiretroviral treatment in ART-naïve HIV patients who receive medical care at a tertiary care ART center is linked to the presence of meaningful alterations in the chosen metabolic parameters within a 12-month follow-up. Significant changes of body weight, body mass index, waist circumference, and serum triglyceride were recorded, which showed a change in body composition and lipid metabolism after the initiation of ART. These results indicate the predisposition to central adiposity and dyslipidaemia, which can predispose the individuals with HIV to cardiovascular disease in the long run. Conversely, other biochemical parameters, such as liver function tests, renal function tests, HbA1c, and the majority of the lipid profile, did not change much within the study period. It indicates that the ART regime implemented was generally well-tolerated in the short-term with regards to hepatic, renal,

and glycaemic outcomes. The results underline the importance of periodic monitoring of anthropometric variables and lipid profiles, especially triglyceride levels, in HIV patients starting ART to allow early lifestyle modifications and prevention programs to reduce possible cardiometabolic dangers in the future. The metabolic long-term consequences of ART and how to make a comprehensive care plan on individuals with HIV are issues that should be studied thoroughly in bigger samples and longer follow-up.

Limitations

There are some limitations in this research that one ought to bear in mind when explaining the results. One, the sample size was small and it was chosen at a single tertiary care ART center, which can limit the generalisation of results to other settings or populations. Second, they were limited to 12 months of follow-up which is not sufficient to identify the long-term metabolic effects of antiretroviral therapy, especially in terms of cardiovascular and diabetic outcomes. Third, the authors did not have a control group of HIV-negative persons or patients who were not on ART, which limits the possibility to differentiate between the changes that could be explained only by ART and the ones that could be explained by HIV infection or immune reconstitution. Fourth, lifestyle habits like diet, physical activities, smoking, and alcohol intake were not measured in a quantitative manner and these might have contributed to the metabolic outcomes. Also, the factors of insulin resistance and biomarkers of inflammation were not measured, which could have given more understanding of the mechanisms of observed metabolic shifts. Imaging techniques were also not carried out to analyze body composition, which restricts accurate determination of fat redistribution. Nevertheless, the study yields useful prospective information on initial metabolic alterations of ART initiation in ART-naïve HIV patients despite the aforementioned limitations.

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ORIGINAL ARTICLE

JIACM 2026; 27 (2): 116-123

Blood and Sputum Cytology in Patients of Bronchial Asthma and their Correlation with Fractional Exhaled Nitric Oxide

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Abstract

Introduction: Asthma is a heterogeneous chronic airway disease characterised by variable respiratory symptoms and airflow limitation. Recent evidence suggests that asthma consists of distinct inflammatory phenotypes identified through sputum cytology and supported by biomarkers such as peripheral blood eosinophils and Fractional Exhaled Nitric Oxide (FeNO).

Aim: To evaluate the correlation between blood and sputum differential leukocyte counts and FeNO levels in patients with bronchial asthma.

Material and Methods: This analytical cross-sectional study included previously or newly diagnosed asthma patients aged 18 - 60 years attending the Department of Respiratory Medicine from April 2024 to November 2025. A total of 152 participants were enrolled using systematic sampling (K = 3). All subjects underwent clinical assessment, spirometry, blood differential leukocyte count, induced sputum cytology, chest radiography, and FeNO measurement. Data were analyzed using SPSS version 22. Correlations were assessed using Karl Pearson's co-efficient, and associations were tested with Chi-square or Fisher's exact test.

Results: Most participants were aged 30 - 44 years, with eosinophilic asthma being the most common phenotype. Blood eosinophilia (p = 0.001), absolute eosinophil count (p = 0.000), and sputum eosinophils (p = 0.000) showed significant associations with FeNO levels. A weak positive correlation was observed between blood and sputum eosinophils (r = 0.256, p = 0.001), while FeNO showed a moderate positive correlation with blood eosinophils (r = 0.406, p = 0.000). Higher FeNO values were observed in eosinophilic asthma phenotypes.

Conclusion: Blood and sputum eosinophil counts correlate with FeNO levels and may serve as reliable non-invasive markers of eosinophilic airway inflammation, supporting phenotype-based asthma assessment for personalised management.

Key words: Asthma, FeNO, blood eosinophils, sputum cytology, airway inflammation, biomarkers.

Introduction

Asthma is a heterogeneous disease usually characterised by chronic airway inflammation that affects approxmately 358.2 million people worldwide[1]. It is defined by a history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity together with variable expiratory airflow limitation. Thus, causing a substantial public health problem[2]. In India, it affects approximately 30 million people (0.96 - 11.03%)[3]. It has been recognised that among asthmatic patients there are clusters of demographics, clinical and/or pathophysiological characteristics, which have been called "asthma phenotypes"[4,5].

The pathogenetic pathway of asthma is the Th2 driven pathway which recruits eosinophil in the airway, but there is also a varied pathogenesis occurring in the airway of chronic persistent form of asthma inviting neutrophils and other granulocytes in the airway[6]. However, to date, no strong relationship has been found between specific pathological features and particular clinical or treatment responses[7].

When examining the airway inflammation using sputum analysis, patients with asthma can be classified into four different inflammatory phenotypes. Based on the percentage of eosinophils and neutrophils in sputum, one can define four airway inflammatory subgroups: eosinophilic asthma, neutrophilic asthma, mixed granulocytic asthma and paucigranulocytic asthma[8]. There is recent evidence from prospective clinical studies that airway infammatory phenotype can help to optimise therapy and disease outcome[9].

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Airway inflammatory phenotype can be measured through the airway noninvasively by induced sputum analysis[4,8] and fractional exhaled nitric oxide (FeNO)[10]. Both are considered direct, reliable, sensitive, simple, and repeatable methods of assessing inflammatory phenotypes, widely used in clinical practice.

To assess the phenotype, sputum cytology is a simple non-invasive test. Understanding the type of exacerbation and population of cells in sputum cytology may guide in the treatment of bronchial asthma. Increased sputum neutrophil count was found to be associated with enhanced chemotactic activity of peripheral blood neutrophils during allergen-induced late-phase airway inflammation in patients with allergic asthma.

Asthmatic patients with a higher FeNO level had a higher blood eosinophil count, and lower FEV1 values. Peripheral blood eosinophils has also been studied as another potential biomarker; it is associated with the patient's future risk for exacerbations[11,12], for developing fixed airflow limitation[13], and a diagnosis of eosinophilic asthma[14].

Limited studies have correlated blood and sputum cytology with FeNO[9]. The results of the present study will aid present to predict airway eosinophilic/neutrophilic inflammation and provide guidance for the individualised clinical treatment of patients with asthma.

We conducted a hospital based cross-sectional study and the aims of our study were (1) To estimate sputum and blood differential leucocyte count in Bronchial Asthma, (2) To estimate level of FeNO, (3) To study the relation of sputum cytology and blood cytology with FeNO.

Methods

Study Design and participants

We conducted a study on a series of 152 patients with asthma visiting our hospital between April 2024 and November 2025. Inclusion criteria were patients of age 18 - 60 years. Previously as well as newly diagnosed cases of asthma. Patient who give consent to be part of study.

Exclusion criteria were: Smokers (A patient who has smoked more than 100 cigarettes/bidi in his life) patients of chronic obstructive pulmonary disease as well as ACOS patients with active as well as healed pulmonary tuberculosis. Cases were enrolled only after ethical clearance.

All recruited patients (previously as well as newly diagnosed of asthma as per GINA guidelines 15 underwent: Detailed clinical history including past history: similar illness, previous hospital admissions, steroid use, exposure to allergens. Chest x-ray PA view was done to rule-out active pulmonary diseases. Anthropometric measurements were done. Spirometry with bronchodilator was done for every patient to confirm the diagnosis of asthma. Dyspnoea was graded as per Modified Medical Research Council (mMRC) Grading[16]. Severity of symptoms were adjusted according to: Asthma control questionnaire[17]. Blood differential leucocyte count-Neutrophils, Eosinophils, Monocytes and Lymphocytes was sent. Sputum for routine microscopy including – Neutrophils, Eosinophils, Lymphocytes and macrophages was sent. FeNO (Fractional Exhaled Nitric Oxide) measurements was done.

Patients were then divided into different groups on the basis of diferential counts of sputum and blood eosinophils. Patients with sputum eosinophils > = 2% were labelled as sputum eosinophilia group and patients with sputum eosinophils <2% were labelled as sputum non-eosinophilia group[18]. Patients with blood eosinophils >6% were labelled as blood eosinophilia group and patients with blood eosinophils < = 6% were labelled as blood non-eosinophilia group.[18]Then these four groups were compared with various clinical parameters.

Age was distributed among 3 groups : less than 30 yrs, 30 - 44 years and 45 - 60 years. BMI categorisation was done according to WHO categorisation[19]. Socio-economic status was divided according to latest Kuppuswamy socio-economic scale[20]. Dyspnoea categorisation was done according to mMRC grading[16]. Absolute eosinophils were divided into two groups <150 and >= 150[21]. Pre-FEV_1 was divided into 7 groups[17]. Severity of asthma was categorised on the basis of asthma control questionnaire[17], and FeNO was divided into two groups of <= 25 ppb and >25ppb[21].

Statistical Analysis

Statistical testing was conducted with SPSS (version 22). Continuous variables were presented as mean ± SD and median for normally distributed data. Categorical variables were expressed as frequencies and percentages. Correlation between two quantitative variables was tested by Karl Pearson's co-efficient of correlation. To test the association between 2 categorical variables we used Chi-squared test or Fisher's exact test. A p-value of less than or equal to 0.05 was considered as statistically significant.

Results

In this study, population had a mean age of 35.57 ± 12.05 years (range 18 - 60), with most participants aged 30 - 44 years (38.8%), followed by those under 30 (36.2%) and 45 - 60 years (25%), indicating bronchial asthma

predominantly affected younger and middle-aged adults. Gender distribution was nearly equal (females 50.7%, males 49.3%), minimizing sex-based confounding. Anthropometric assessment showed a mean height of 159.65 cm, weight 61.43 kg, and BMI 24.12 kg/m^2, with the majority having normal BMI (55.9%), while 30.3% were overweight, 7.9% obese, and 5.9% underweight (Table I).

Sputum Eosinophils

The correlation of sputum eosinophilia with demographic and clinical parameters indicates that younger patients tended to have higher rates of sputum eosinophilia, with 63.6% of those under 30 years showing ≥2% eosinophils, compared with 54.2% in the 30 - 44 age group and 39.5% in the 45 - 60 group, although this trend did not reach statistical significance (p = 0.071). Dyspnoea severity (mMRC) showed a tendency for higher sputum eosinophilia in patients with more severe breathlessness, particularly grade 3 (87.5%) and grade 2 (58.9%), compared with grade 1 (47.7%), though the relationship narrowly missed significance (p = 0.062). Overall, sputum eosinophilia appeared more common in younger and more symptomatic patients, but demographic factors [Gender (p = 0.616), socio-economic status (p = 0.454)] and BMI (p = 0.353) did not significantly influence airway eosinophilic inflammation. The analysis of sputum eosinophilia in relation to clinical and laboratory parameters showed a strong association with blood eosinophilia, as 74.4% of patients with blood eosinophilia also had sputum eosinophilia, compared with 45.9% among those with blood non-eosinophilia (p = 0.001). Similarly, absolute blood eosinophil count was significantly correlated, with 63.6% of individuals having blood AEC ≥150 showing sputum eosinophilia, whereas only 31.1% of those with blood AEC <150 did so (p = 0.000). Pre-FEV1 percentages did not demonstrate a statistically significant relationship (p = 0.323). Asthma control as assessed by ACQ showed no significant correlation with sputum eosinophilia (p = 0.483), with elevated eosinophils present across all levels of control. In contrast, FeNO levels were strongly associated with sputum eosinophilia; 70.8% of patients with FeNO >25 ppb exhibited sputum eosinophilia, compared with 38.8% with FeNO ≤25 ppb (p = 0.000), highlighting FeNO as a robust marker of airway eosinophilic inflammation (Tables II and III).

Peripheral Blood Eosinophils

Across the study population, blood eosinophilia (>6%) showed a significant association with age, with higher eosinophil levels observed more commonly in participants younger than 30 years (40%) compared to those aged 30 - 44 years (25.4%) and 45 - 60 years (15.8%), as indicated by a p-value of 0.032. No significant gender difference was noted, as eosinophilia was nearly identical between males (28%) and females (28.6%) with a non-significant p-value of 0.938. BMI categories also showed no meaningful association with eosinophilia (p = 0.277). Socio-economic status did not demonstrate a significant relationship with eosinophil levels (p = 0.158). Dyspnoea severity (mMRC) likewise exhibited no significant association (p = 0.099). Sputum eosinophilia ≥2% was significantly linked to higher blood eosinophil levels (39%) compared with sputum eosinophilia <2% (15.7%), with a highly significant p-value of 0.001. Absolute eosinophil count also demonstrated a marked relationship, as only 2.2% of individuals with counts <150 had blood eosinophilia, whereas 39.3% of those with counts ≥150 showed elevated blood eosinophils (p = 0.000). Pre-FEV1 values did not show statistically significant differences (p = 0.138). Asthma control showed a significant correlation, where poorly controlled asthma (ACQ >1.51) had 29.4% eosinophilia, while none of the well-controlled patients (ACQ <0.75) exhibited eosinophilia (p = 0.010). Fractional exhaled nitric oxide (FENO) was also significantly associated, with eosinophilia being more prevalent among individuals with elevated FENO >25 ppb (41.7%) compared with those having FENO ≤25 ppb (16.3%), supported by a p-value of 0.001 (Tables II and III).

Table I: Mean of various parameters

Parameter	Values
Age (Mean ± SD)	35.57 ± 12.05 yrs
Males n (%)	75 (49.3%)
Females n (%)	77 (50.7%)
Height (Cms) (Mean)	159.65
Weight (Kgs) (Mean)	61.428
BMI (kg/m^2) (Mean)	24.117
Pre-FEV_1 (%) (Mean)	57.2%
Ratio FEV_1/FVC (%) (Mean)	59.7%.

Table II: Correlation of sputum and blood eosinophils with various parameters

Parameters	Sputum Eosinophilia(>=2%)	Sputum Non-eosinophilia (<2%)	p-value	Blood Eosinophilia (>6%)	Blood Non-eosinophlia (<6%)	p- value
Age (years)						
<30	35 (63.6%)	20 (36.4%)	0.071	22(40%)	33(60%)	**0.032**
30 - 44	32 (54.2%)	27 (45.8%)		15(25.4%)	44(74.6%)	
45 - 60	15 (39.5%)	23 (60.5%)		6(15.8%)	32(84.2%)	
Gender						
Male	42 (56.0%)	33 (44.0%)	0.616	21 (28%)	54 (72%)	0.938
Female	40 (51.9%)	37 (48.1%)		22 (28.6%)	55 (71.4%)	
BMI (kg/m^2)						
<18.5	5 (55.6%)	4 (44.4%)	0.353	3 (33.3%)	6 (66.7%)	0.277
18.5 - 24.9	51 (60.0%)	34 (40.0%)		28 (32.9%)	57 (67.1%)	
25 - 29.9	21 (45.7%)	25 (54.3%)		8 (17.4%)	38 (82.6%)	
>30	5 (41.7%)	7 (58.3%)		4 (33.3%)	8 (66.7%)	
Socio-economic Status						
Lower Middle	29 (48.3%)	31 (51.7%)	0.454	22 (36.7%)	38 (63.3%)	0.158
Upper Lower	47 (58.8%)	33 (41.3%)		19 (23.8%)	61 (76.3%)	
Upper Middle	6 (50.0%)	6 (50.0%)		2 (16.7%)	10 (83.3%)	
Dyspnoea grade (as per mMRC)						
3	7 (87.5%)	1 (12.5%)	0.062	3 (37.5%)	5 (62.5%)	0.099
2	33 (58.9%)	23 (41.1%)		21 (37.5%)	35 (62.5%)	
1	42 (47.7%)	46 (52.3%)		19 (21.6%)	69 (78.4%)	

Table III: Correlation of sputum and blood eosinophils with various parameters

Parameters	Sputum Eosinophilia (>=2%)	Sputum Non-eosinophilia (<2%)	p-value	Blood Eosinophilia (>6%)	Blood Non-eosinophlia (<6%)	p- value
Sputum Eosinophilia						
<2%	-	-		11 (15.7%)	59 (84.3%)	**0.001**
>=2%	-	-		32 (39.0%)	50 (61.0%)	
Blood Eosinophilia						
<=6%	50 (45.9%)	59 (54.1%)	0.001	-	-	-
>6%	32 (74.4%)	11 (25.6%)		-	-	
Absolute Eosinophil Count in Blood						
<150	14 (31.1%)	31 (68.9%)	0.000	1 (2.2%)	44 (97.8%)	**0.000**
>=150	68 (63.6%)	39 (36.4%)		42 (39.3%)	65 (60.7%)	
Pre FEV1 %						
<50%	30 (48.4%)	32 (51.6%)	0.323	21 (33.9%)	41 (66.1%)	0.138
50% - 59%	19 (67.9%)	9 (32.1%)		5 (17.9%)	23 (82.1%)	
60% - 69%	15 (62.5%)	9 (37.5%)		10 (41.7%)	14 (58.3%)	
70% - 79%	6 (40.0%)	9 (60.0%)		3 (20%)	12 (80%)	
80% - 89%	7 (50.0%)	7 (50.0%)		1 (7.1%)	13 (92.9%)	
90% - 95%	2 (100%)	0 (00.0%)		0 (0.0%)	2 (100%)	

>95%	3 (42.9%)	4 (57.1%)		3 (42.9%)	4 (57.1%)	
Asthma Control Questionnaire						
<0.75	5 (41.7%)	7 (58.3%)	0.483	0 (00.0%)	12 (100%)	**0.010**
0.75-1.5	3 (75.0%)	1 (25.0%)		3 (75.0%)	1 (25.0%)	
>1.51	74 (54.4%)	62(45.6%)		40 (29.4%)	96 (70.6%)	
FeNO						
<=25 ppb	31 (38.8%)	49 (61.3%)	**0.000**	13(16.3%)	67 (83.8%)	**0.001**
>25 ppb	51 (70.8%)	21 (29.2%)		30 (41.7%)	42 (58.3%)	

Discussion

The present study evaluated the association between inflammatory biomarkers – blood eosinophils, sputum eosinophils, and fractional exhaled nitric oxide (FeNO) – in patients with bronchial asthma. Understanding the relationship between these biomarkers is important for identifying airway inflammation and for tailoring personalised treatment strategies. Our findings highlight the potential role of non-invasive biomarkers in guiding asthma management and predicting treatment response.

The present study, suggests that bronchial asthma predominantly affects younger and middle-aged adults in our cohort. Anthropometric assessment revealed that the majority of patients had BMI within or slightly above the normal range, which may influence asthma severity and inflammatory profiles. These demographic findings are comparable to previous studies. Ganapathy *et al* reported a mean age of 41 years, with the majority of participants in the 35 - 45 year age group, and a gender distribution of 49% males and 51% females[22]. Similarly, Lobiyal *et al* reported a mean age of 30 years among patients with bronchial asthma[23]. Compared with these studies, the mean age in our cohort was slightly lower (36 years), while the gender distribution remained nearly equal.

Baseline spirometry in our study demonstrated moderate airflow limitation, with mean pre-bronchodilator FEV_1 of 57.2% predicted and mean FEV_1/FVC ratio of 59.7% (Table I). Additionally, 89.5% of participants had poor asthma control according to Asthma Control Questionnaire (ACQ) scores. In contrast, Gao *et al* reported a mean FEV_1% predicted value of 81.77% and a mean FEV_1/FVC ratio of 68.33%, suggesting relatively milder airflow limitation in their study population[18]. Similarly, Nakwan *et al* observed a mean FEV_1% predicted value of 77.6% with an interquartile range of FEV_1/FVC ratio between 0.63 and 0.78[24]. These findings suggest that airflow limitation in our cohort was comparatively more pronounced. Furthermore, pulmonary

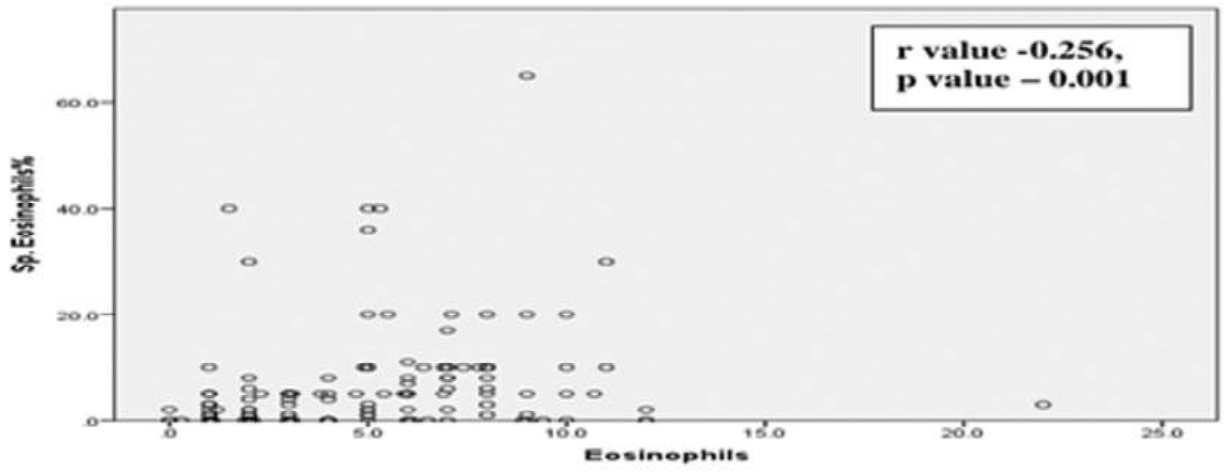

Fig. 1: *Correlation between blood eosinophils and sputum eosinophils.*

Scatter plot showing the relationship between sputum eosinophil percentage on y-axis and blood eosinophil percentage on n-axis. The r-value (0.256) indicates a weak positive correlation between blood eosinophils and sputum eosinophils. The p-value (0.001) is statistically significant. Overall, the figure demonstrates that although sputum and blood eosinophil levels are weakly correlated, the association is statistically meaningful, implying that blood eosinophil percentage may provide some – but limited – predictive information about sputum eosinophilic inflammation.

function parameters in our study did not show significant correlations with sputum or blood eosinophil levels.

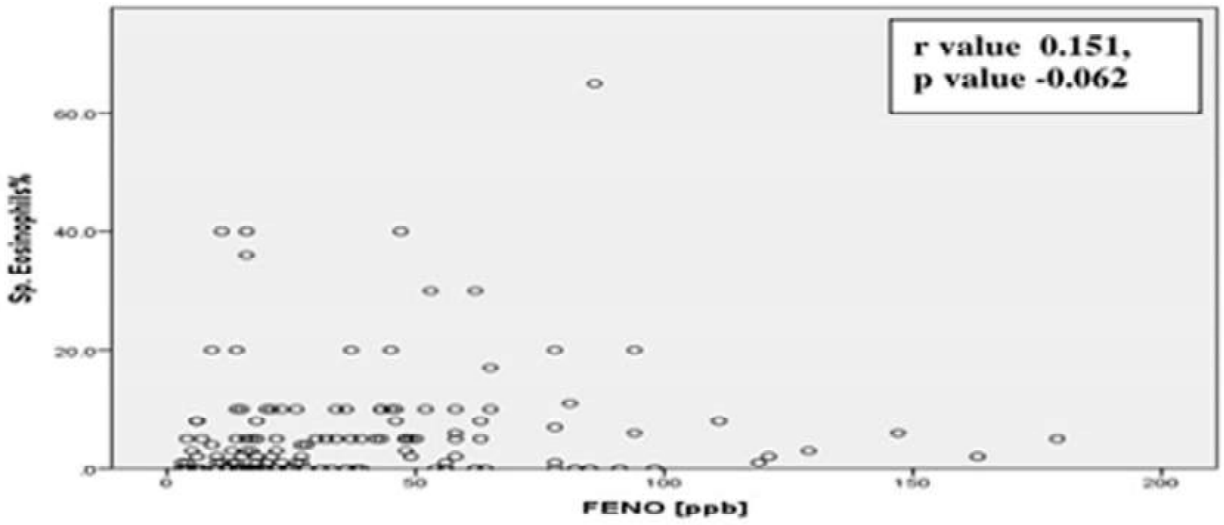

Fig. 2: *Correlation between sputum eosinophils and FeNO.*

Scatter plot showing the relationship between sputum eosinophil percentage on y-axis and fractional exhaled nitric oxide (FeNO) levels on x-axis. The r-value (0.151) indicates a very weak positive correlation between FeNO and sputum eosinophils. The p-value (0.062) is not statistically significant. Overall, the figure demonstrates that although there is a small positive trend, FeNO does not significantly correlate with sputum eosinophilic inflammation in this sample.

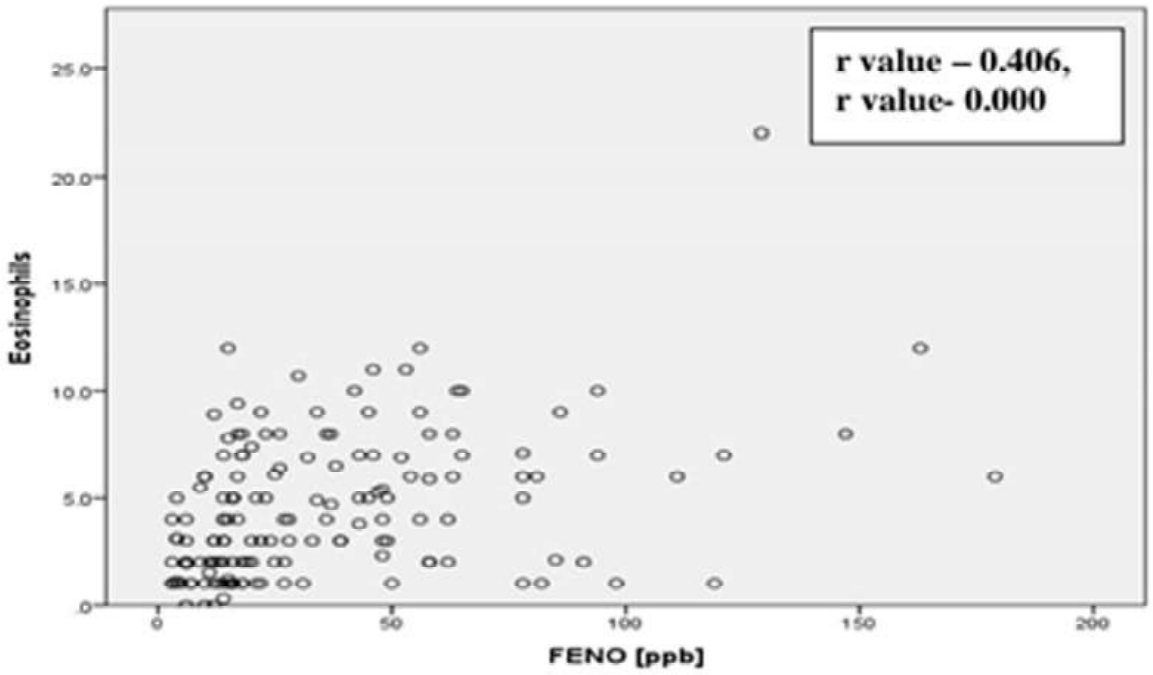

Fig. 3: *Correlation between blood eosinophils and FeNO.*

Scatter plot showing the relationship between blood eosinophil percentage on y-axis and FeNO (fractional exhaled nitric oxide) levels on x-axis. The r-value (0.406) indicates a moderate positive correlation between blood eosinophils and FeNO. The p-value (0.000) is highly statistically significant (p <0.001). Overall, the figure demonstrates a statistically significant and moderately strong relationship between systemic eosinophilia and exhaled nitric oxide, supporting FeNO as an important non-invasive marker of eosinophilic inflammation.

With respect to inflammatory biomarkers, blood eosinophilia (>6%) was observed in 28.3% of participants, while 70.4% had absolute eosinophil counts ≥150 cells/μL. Sputum analysis demonstrated a median neutrophil proportion of 57.5% and sputum eosinophils of 2%. Elevated FeNO levels (>25 ppb) were detected in 47.4% of patients. Importantly, FeNO levels showed a significant positive correlation with blood eosinophilia (r = 0.406, p <0.001) (Fig. 3), whereas the correlation with sputum eosinophils was weak and not statistically significant (r = 0.151, p = 0.062) (Fig. 2). These findings suggest that blood eosinophil counts may serve as a more reliable indicator of eosinophilic airway inflammation in this cohort.

Correlation analysis demonstrated moderate positive associations between sputum eosinophils and both blood eosinophil counts (r = 0.346, p <0.001) (Fig. 4) and eosinophil percentages (r = 0.256, p = 0.001) (Fig. 1). Additionally, blood eosinophil counts were strongly correlated with FeNO levels (r = 0.406, p <0.001) (Fig. 3). Conversely, sputum neutrophils exhibited weak negative correlations with blood eosinophil percentages and absolute eosinophil counts. These observations indicate the coexistence of different inflammatory phenotypes in asthma, including eosinophilic and neutrophilic patterns.

Our findings are broadly consistent with previous studies. Shi *et al* reported a positive correlation between ACQ scores and sputum eosinophil counts, while ACT scores were negatively correlated with sputum eosinophilia. Furthermore, blood eosinophil counts and proportions were significantly correlated with sputum eosinophil proportions, and FeNO levels showed a positive correlation with sputum eosinophilia[25]. Similarly, Marineau *et al* observed low-to-moderate positive correlations between sputum eosinophil percentage and FeNO levels, as well as between sputum eosinophils and blood eosinophils[26]. Gao *et al* also reported significant positive correlations between FeNO levels and both sputum eosinophil percentages and blood eosinophil counts, while demonstrating a negative correlation with sputum neutrophils[18]. Nakwan *et al* reported a median FeNO level of 23 ppb and blood eosinophil count of 375 cells/mm^3, with a significant positive correlation between FeNO and blood eosinophils (r = 0.310, p = 0.004)[24]. Taken together, these findings indicate a consistent association between FeNO levels, blood eosinophils, and sputum eosinophils, reflecting the link between systemic eosinophilia and airway eosinophilic inflammation. However, the strength of these associations varies across studies, highlighting heterogeneity in asthma inflammatory phenotypes. Additionally, FeNO appears to be a poor surrogate marker for sputum neutrophilic inflammation.

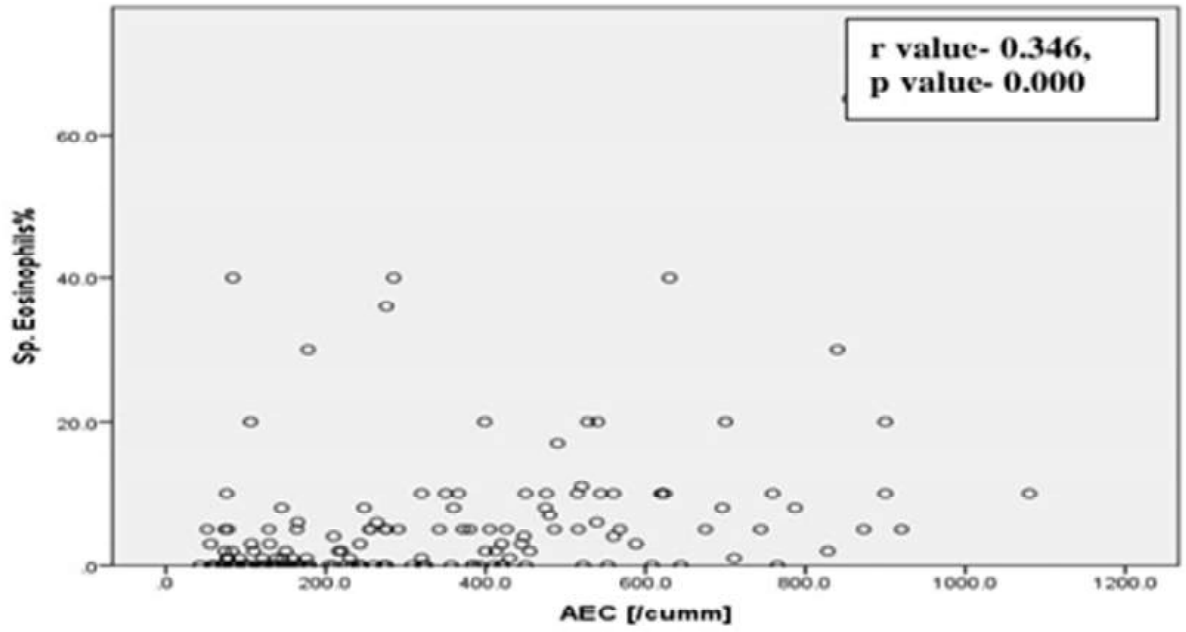

Fig. 4: *Correlation between sputum eosinophils and absolute eosinophil count.*

Scatter plot showing the relationship between sputum eosinophil percentage on y-axis and absolute eosinophil count (AEC) in peripheral blood on x-axis. The r-value (0.346) indicates a moderate positive correlation between AEC and sputum eosinophils. The p-value (0.000) is highly statistically significant (p <0.001). Overall, the figure demonstrates a significant and moderately strong relationship between peripheral blood eosinophil count and sputum eosinophilic inflammation, implying that AEC may serve as a useful indicator of airway eosinophilia.

Overall, the present study reinforces the importance of integrating biomarker assessment into routine asthma evaluation. The combined assessment of FeNO and blood eosinophil counts may provide valuable insight into airway inflammatory patterns and support personalised treatment strategies.

Conclusion

The study demonstrates a significant association between eosinophilic inflammation and FeNO levels in patients with bronchial asthma. Blood and sputum eosinophil counts reliably reflect airway eosinophilia and correlate with FeNO, supporting their role as accessible biomarkers for asthma. Therefore a holistic approach for clinical evaluation and biomarker assessment should guide personalised management rather than relying solely on patient characteristics. Future studies with larger sample sizes and longitudinal follow-up are required to validate these findings and to further elucidate the dynamic changes in asthma phenotypes over time.

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ORIGINAL ARTICLE

JIACM 2026; 27 (2): 124-128

Diagnostic Yield of Flexible Bronchoscopy in a High-Burden Setting: Clinical Performance and Projected Public Health Utility at the District Level

Manas Gujral, Desh Deepak**, Prateek Gupta****

Abstract

***Background and Objectives:** Flexible bronchoscopy provides access to microbiological and histopathological diagnosis, but its real-world performance varies by disease and sampling strategy. We evaluated diagnostic yield in routine practice and modelled the likely district-level utility of bronchoscopy services.*

***Methods:** We conducted a single-centre retrospective analysis of 801 diagnostic bronchoscopies performed at a tertiary care teaching hospital in North India. Diagnostic yield and disease-specific sensitivity were calculated. Public health utility was modelled for a prototype district population of 1,000,000 using burden-based estimates for tuberculosis, lung cancer, and sarcoidosis.*

***Results:** The overall diagnostic yield was 75.65% (606/801). Targeted tissue acquisition consistently outperformed fluid cytology and visual inspection, while multimodal sampling maximized diagnostic capture. Disease-specific sensitivity was highest for sarcoidosis, followed by tuberculosis and lung cancer. Beyond these primary targets, fluid and tissue evaluation successfully identified a substantial burden of non-tubercular bacterial infections, invasive fungal pathogens, and rare occupational lung diseases. In the epidemiological model, bronchoscopy was projected to detect a significant annual burden of core respiratory cases.*

***Interpretation and Conclusions:** Multimodal bronchoscopic sampling delivers robust diagnostic performance in high-burden settings. Decentralizing these services to district hospitals can significantly narrow case detection gaps and facilitate targeted antimicrobial therapy. However, deploying bronchoscopic equipment must be paired with parallel investments in pathology and microbiology laboratory infrastructure to achieve optimal clinical impact.*

***Key words:** Biopsy, bronchoalveolar lavage, pulmonary, sensitivity and specificity, tuberculosis.*

Introduction

The Government of India is implementing a centrally sponsored scheme to establish new medical colleges by upgrading district and referral hospitals. Although this initiative seeks to decentralise specialized healthcare services, there is limited clarity regarding which diagnostic facilities should be incorporated at district level to optimize patient care and training[1].

Respiratory diseases remain a major public health burden in India, with substantial burdens of chronic respiratory disease, tuberculosis, lung cancer, and interstitial lung diseases[2-5]. Early diagnosis is therefore critical, particularly because sputum-negative pulmonary tuberculosis often requires bronchoscopy for microbiological confirmation, suspected lung cancer needs tissue-based diagnosis, and other focal pulmonary lesions may also require invasive sampling. Flexible bronchoscopy is a key diagnostic procedure in this setting, but yield varies substantially according to disease biology, lesion accessibility, and sampling strategy[6,7].

Despite the extensive bronchoscopy literature, important gaps remain. Many studies focus on a single disease or a single sampling method within highly selected patient groups, limiting applicability to routine clinical practice. In addition, few series from India have simultaneously evaluated bronchoscopy across a broad case-mix while also estimating its likely utility for district-level service planning. Published evidence also suggests that diagnostic yield improves when tissue-based sampling is aligned with lesion accessibility and pretest probability[6,7].

To address these gaps, we performed a comprehensive clinical audit of 801 diagnostic bronchoscopies at a tertiary care centre in North India. The primary aim was to define the independent and incremental diagnostic yields of standard sampling modalities and to establish disease-specific sensitivities. In addition, we used these clinical metrics in a burden-based epidemiological model to project the public health utility of decentralizing

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bronchoscopy services to district level.

Material and Methods

Study design and setting: We retrospectively analysed data from all consecutive diagnostic flexible bronchoscopies performed at the Department of Respiratory Medicine of a tertiary care teaching hospital in North India between 2022 and 2025. The study was designed as a retrospective diagnostic audit, and no additional interventions were introduced.

Participants: Adults aged 18 years or older who underwent diagnostic bronchoscopy during the study period were included. Patients were eligible for disease-specific sensitivity analyses only if they had a confirmed final diagnosis established either through bronchoscopy or through a composite reference standard that included clinical-radiological follow-up, response to appropriate empirical therapy, surgical pathology, or microbiological confirmation. Cases requiring advanced diagnostic interventions such as endobronchial ultrasound (EBUS) or cryobiopsy were excluded so that the study reflected the utility of standard flexible bronchoscopy in secondary-care settings.

Diagnostic definitions: A modality was considered diagnostic only if it provided definitive, actionable information. Malignancy was defined as cytological or histopathological evidence of cancer; atypia alone was considered non-diagnostic. Tuberculosis was counted positive if acid-fast bacilli (AFB) smear, Mycobacterium tuberculosis culture, or GeneXpert MTB/RIF was positive. Sarcoidosis was diagnosed only when non-caseating granulomas were identified in an appropriate clinical-radiological context and alternative causes were excluded.

Bronchoscopy procedures and specimen processing: Bronchoscopies were carried out by consultants and supervised trainees using standard video bronchoscopes (BF-P150, Olympus Medical Systems; and EB-1970TK, Pentax Medical). Sedation and topical anaesthesia adhered to institutional protocols. Sampling methods included bronchial wash/BAL, brush cytology, endobronchial biopsy (EBB), transbronchial lung biopsy (TBLB), and conventional transbronchial needle aspiration (cTBNA). For cTBNA, the puncture site was determined based on pre-procedure CT evaluation to target lymph nodes or masses via the working channel. For data analysis, bronchial wash and bronchoalveolar lavage (BAL) were grouped as a single sampling modality. Samples were processed according to standardised institutional laboratory protocols. All bronchoalveolar lavage (BAL) and wash specimens underwent acid-fast bacilli (AFB) smear, Gram stain, pyogenic culture, KOH mount, fungal culture, TB-PCR and CBNAAT testing. Mycobacteria Growth Indicator Tube (MGIT) liquid culture was performed in all cases. Cytology specimens from brushing or aspiration were processed using conventional smears. All biopsy specimens were fixed in formalin and processed for histopathology, with special stains, such as periodic acid-Schiff (PAS) or Grocott's methenamine silver (GMS) applied as required to differentiate granulomatous or fungal aetiologies.

Outcome measures: The primary outcome was the per-procedure diagnostic yield of each individual sampling modality. Secondary outcomes were the diagnostic yield of multimodal sampling combinations and the disease-specific sensitivity of flexible bronchoscopy for tuberculosis, lung cancer, and sarcoidosis.

Public health utility modelling: To estimate the possible effect of decentralizing bronchoscopy services, we modelled a standard prototype district with a population of 1,000,000. Disease-burden estimates were derived from national data. For tuberculosis, we used a national annual incidence of 187 per 100,000[3], applied an estimated pulmonary fraction of 80%, and then restricted the target population to the sputum-sparse subgroup, estimated at 40% of pulmonary tuberculosis cases. For lung cancer, we used a 5-year prevalence of 8.1 per 100,000[4]. For sarcoidosis, we used a midpoint prevalence of 36 per 100,000 (range 24 - 48)[5].

Statistical analysis

This was a descriptive audit. Categorical variables are presented as counts and percentages. Diagnostic yield for each modality was calculated as the proportion of procedures in which that modality yielded a definitive diagnosis. Disease-specific sensitivity was calculated as diagnosed cases divided by total confirmed cases. Exact 95% confidence intervals were estimated using the Clopper-Pearson method. Projected expected true positives were calculated as disease burden multiplied by disease-specific sensitivity.

Ethics

The study was approved by the Institutional Ethics Committee. As this was a retrospective audit using anonymised data, the requirement for individual informed consent was waived.

Results

A total of 801 diagnostic bronchoscopies were evaluated, with an overall diagnostic yield of 75.65% (606/801). Fluid-based sampling, through bronchial wash or bronchoalveolar lavage, was the most frequently used modality. Tissue acquisition techniques, including endobronchial biopsy, transbronchial lung biopsy, and conventional transbronchial

needle aspiration, were used selectively according to clinical and radiological indications. When standalone modalities were compared, targeted tissue acquisition consistently outperformed fluid cytology and visual inspection. Transbronchial lung biopsy showed the highest individual diagnostic yield (83.33%), while standalone visual inspection had the lowest yield (7.74%) (Table I).

Table I: Diagnostic yield of individual flexible bronchoscopy sampling modalities

Procedure	Number of cases where performed	Diagnostic success (n)	Yield (%)
Flexible bronchoscopy (standalone visual inspection)	801	62	7.74
Bronchial wash/BAL	757	453	59.84
Bronchial brush cytology	180	88	48.89
Endobronchial biopsy (EBB)	179	115	64.25
Transbronchial lung biopsy (TBLB)	48	40	83.33
Conventional transbronchial needle aspiration (TBNA)	27	14	51.85

Note: BAL, bronchoalveolar lavage; EBB, endobronchial biopsy; TBLB, transbronchial lung biopsy; TBNA, transbronchial needle aspiration.

Diagnostic performance improved significantly when multiple sampling modalities were combined. The highest yields were seen when standard visual inspection was combined with both fluid-based sampling and targeted tissue acquisition, highlighting the benefit of a stepwise increase in procedural complexity (Table II).

Table II: Incremental diagnostic yield of combined bronchoscopic sampling protocols

Procedure combination	N patients	Diagnostic hits	Yield (%)
Visual inspection + BAL	757	478	63.14
Visual inspection + BAL + Brush	174	125	71.84
Visual inspection + BAL + EBB	165	143	86.67
Visual inspection + BAL + TBLB	40	35	87.50
Visual inspection + BAL + Brush + EBB	121	109	90.08
Visual inspection + BAL + EBB + TBLB	4	4	100.00
Visual inspection + BAL + TBNA	25	14	56.00
Visual inspection + TBNA + EBB	6	6	100.00
Visual inspection + BAL + TBNA + EBB	5	5	100.00
Visual inspection + BAL + Brush + EBB + TBLB	2	2	100.00

Note: BAL, bronchoalveolar lavage; EBB, endobronchial biopsy; TBLB, transbronchial lung biopsy; TBNA, transbronchial needle aspiration.

Within this high-burden cohort, disease-specific sensitivity followed a consistent pattern for the primary conditions of interest. Diagnostic capture was highest for sarcoidosis at 97.50%, followed by pulmonary tuberculosis at 89.47% and lung malignancy at 84.91% (Table III).

Table III: Disease-specific diagnostic sensitivity of flexible bronchoscopy.

Disease entity	Total confirmed cases	Diagnosed by bronchoscopy	Sensitivity (%)
Sarcoidosis	40	39	97.50
Tuberculosis (TB)	133	119	89.47
Lung cancer	106	90	84.91

Beyond these core conditions, bronchoscopy successfully identified or definitively ruled out pathology in 358 additional cases. Normal endobronchial anatomy effectively excluded airway disease in 61 patients. Fluid-based evaluation frequently identified opportunistic and Gram-positive bacterial infections, including invasive fungal pathogens such as Aspergillus and Mucor. Biopsy modalities provided important histopathological confirmation for atypical and occupational lung diseases, such as hypersensitivity pneumonitis and silicosis. Standalone visual inspection also established definitive diagnoses in structural airway emergencies such as foreign body aspiration and fistulas. In contrast, standard evaluation did not yield a specific diagnosis in 164 cases that showed only non-specific inflammation, defining the point at which advanced diagnostic interventions become necessary (Table IV).

Table IV: Additional diagnostic outcomes and residual undiagnosed cases following bronchoscopy.

Finding	Number of Cases (n)
1. Bronchoalveolar lavage	268
Aspergillus infection	41
Gram positive infection	119
Acinetobacter	12
Klebsiella	20
Pseudomonas	7
Escherichia coli	5
Mucor	12
Nocardia	4
Pseudosporium	1
Burkholderia cepacia	1
Mycobacterium abscessus	1
Hydatid disease	4
Multiple bacterial infection	13
Multiple bacterial and fungal infection	12
Stenotrophomonas maltophilia	1
Pulmonary alveolar haemorrhage (diagnosed on sequential aliquots and iron laden macrophages)	15

2.	Biopsy	18
	Candida	1
	Granulomatous disease – Eosinophilic granulomatosis with polyangiitis	1
	Granulomatous disease – Hypersensitivity pneumonitis	6
	Granulomatous disease – Granulomatosis with polyangiitis	1
	Cryptogenic organizing pneumonia (Transbronchial lung biopsy)	4
	Talcosis	1
	Silicosis	1
	Pulmonary sclerosis haemangioma	1
	Amyloidosis (Endobronchial biopsy)	1
	Xanthoma (Endobronchial biopsy)	1
3.	Visual inspection	11
	Bronchoalveolar fistula	3
	Foreign body	5
	Post-inhalational burns	3
4.	Normal and undiagnosed	225
	Normal bronchoscopy	61
	Undiagnosed (non-specific inflammation)	164
5.	Total	522

Extrapolation of these clinical metrics to a standard district prototype of one million population highlighted the public health value of decentralizing bronchoscopy services. The model projected the greatest absolute benefit for tuberculosis case detection, while also showing substantial expected true-positive rates for sarcoidosis and lung cancer (Table V).

Table V: Projected annual diagnostic utility in a prototype district (population 1,000,000)

Disease entity	Estimated annual burden	Bronchoscopy sensitivity	Expected true positives (ETP)
Tuberculosis	598 cases	89.47%	535
Lung cancer	81 cases	84.91%	69
Sarcoidosis	360 cases	97.50%	351

Discussion

In this large single-centre audit of diagnostic flexible bronchoscopy, clinical performance varied substantially according to the sampling method used. The overall diagnostic yield of 75.65% reflects the strong clinical value of the procedure in a high-burden setting, where timely diagnosis has an important impact on patient outcomes. Multimodal bronchoscopy consistently performed better than single-technique sampling, showing the advantage of combining fluid-based, cytological, and histopathological methods during routine respiratory evaluation. The stepwise improvement in diagnostic capture with combined modalities suggests that a structured sampling strategy is important for maximizing yield, especially when initial visual inspection does not provide a diagnosis. This is particularly relevant in resource-constrained settings, where each procedure should be designed to obtain the highest possible diagnostic return.

The main strength of this study is the large dataset drawn from routine clinical practice rather than a highly selected trial population, along with an epidemiological model that may be useful for health administrators. However, several limitations should be considered when interpreting the findings. As the study was retrospective and done at a referral tertiary care centre, some selection bias for more difficult cases is likely. Transbronchial lung biopsy was probably performed in patients with more favourable anatomy, which may have increased its apparent diagnostic yield. The dataset also lacked consistent radiological details, so yields could not be stratified by lesion size or by central versus peripheral location. In addition, the high diagnostic sensitivities were achieved in a high-volume tertiary centre by experienced pulmonologists and laboratory support. Operator dependence is an important factor in bronchoscopy, and yields at newly established district-level facilities may initially be lower while clinicians gain experience[7]. Finally, the projection model was based on national average prevalence estimates, which may not fully reflect local disease patterns in individual districts[3-5].

These findings are broadly consistent with earlier bronchoscopy studies showing that diagnostic yield depends strongly on sampling technique, lesion accessibility, and disease biology[6,7]. In peripheral lesions, bronchoscopy is more effective when tissue-based or guided approaches are used[7,9]. The procedure also has an established role in sputum-negative pulmonary tuberculosis, where microbiological confirmation may otherwise be delayed[8], and more complete nodal sampling improves diagnostic performance in sarcoidosis[10]. The present study supports these established observations while also showing how these diagnostic pathways work together in a single high-throughput clinical setting. The results therefore reinforce the value of a multimodal approach when bronchoscopy is performed for diagnostically challenging disease.

The generalisability of these findings has important implications for the planned decentralisation of respiratory care.[1] The strong performance of tissue acquisition indicates that district hospitals equipped with bronchoscopes will also need pathology support to process biopsy specimens effectively. Likewise, the substantial number of non-

tubercular infectious diagnoses identified through bronchoalveolar lavage highlights the need for microbiology laboratories capable of culture, smear, and fungal workup. In several cases, the identification of bacterial and invasive fungal pathogens allowed a shift from empirical to targeted therapy, which is clinically important because it can reduce unnecessary broad-spectrum antimicrobial use and help clarify prognosis earlier. At the same time, the proportion of cases remaining undiagnosed after standard bronchoscopy defines a practical threshold for escalation to advanced diagnostic procedures. This helps local centres manage straightforward cases more efficiently while referring unresolved cases for further evaluation. Overall, these findings suggest that flexible bronchoscopy can make a meaningful contribution to district-level respiratory services, provided that procedural training and laboratory infrastructure are developed alongside the equipment itself. With appropriate support, decentralised bronchoscopy could reduce diagnostic delay for tuberculosis, sarcoidosis, and lung cancer, and improve access to definitive respiratory diagnosis in high-burden settings.

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REVIEW ARTICLE

JIACM 2026; 27 (2): 129-134

The Role of Nutrition in Rheumatic Disease – A Global Perspective *As Easy As A, B, Ghee?*

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Introduction

Rheumatic diseases encompass a wide range of disorders that are characterised by inflammation and destruction of tissue, with the musculoskeletal system most frequently impacted. Several forms of categorizing rheumatic diseases exist, with one form basing rheumatic diseases on their nature – autoimmune, autoinflammatory and degenerative and metabolic disorders. The aetiopathology of rheumatic diseases are often multifactorial, with genetic, environmental, autoimmune and mechanical factors frequently involved (Calle and Gómez-Puerta, 2018).

Among environmental and lifestyle influences, diet is increasingly appreciated as being implicated in inflammatory processes in the body and therefore an important link to rheumatic diseases. With several studies demonstrating the benefit of the Mediterranean diet (MD), rich in extra virgin olive oil and vegetables, national bodies such as NICE (UK) (National Institute for Health and Care Excellence, 2018) and the French Society of Rheumatology (Daien *et al*, 2021) have recommended the MD in patients with chronic rheumatic disease, most notably in rheumatoid arthritis.

Whilst the MD has received the most attention, dietary patterns vary considerably across populations. The traditional Indian diet, largely plant based with distinctive cooking fats and spices and the rise of the Western diet globally, warrant consideration due to their potential influence on rheumatic disease.

Diet is a modifiable factor that influences the aetiopathology of various rheumatic disease. Rheumatologists and other health professionals can play a key role in encouraging patients to consider an anti-inflammatory diet to potentially lower their incidence risk and disease prognosis. However, there is currently a general lack of well-conducted clinical trials to inform relevant recommendations on more specific diet-related areas, such as the use of supplements. This review discusses the pro-inflammatory and anti-inflammatory aspects of diet globally, including the Mediterranean, Western and Indian diets and their potential impacts on rheumatic disease.

Mediterranean and Western Diet

The Mediterranean diet (MD) compared to other diets emphasizes plant-based foods such as unrefined cereals, extra virgin olive oil (EVOO) as the main fat source, a higher use of vegetables and a lower consumption of red meat and sweets (Nikiphorou and Philippou, 2023). As such, the MD is a known anti-inflammatory diet (Nikiphorou and Philippou, 2023) and in a 3-year longitudinal study, has been associated with decreased serum concentrations of pro-inflammatory cytokines implicated in rheumatic diseases, including IL-1β, IL-6 and Tumour Necrosis Factor (TNF)-α (Urpi-Sarda *et al*, 2021).

Due to the higher consumption of oily fish and EVOO in the MD, higher MD adherence is positively correlated with tissue levels of anti-inflammatory omega-3 fatty acids (FA) (Mantzioris *et al*, 2022) and negatively correlated with omega-6 FA (Monserrat-Mesquida *et al*, 2023). Omega-3 and omega-6 FA form part of the 'polyunsaturated fatty acids' (PUFA) family. FA such as alpha-linolenic (ALA, an omega-3 FA) and linoleic acid (LA, an omega-6 FA) are labelled essential as they need to be obtained from exogenous sources as the body cannot synthesize them. Whilst the long-chain FA eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can be formed via the conversion of the shorter chain omega-3s, this process in the body is inefficient and thus dietary intake of EPA and DHA is recommended, with EPA and DHA levels significantly elevated in those taking omega-3 supplementation compared to controls (Wang *et al*, 2024).

A meta-analysis involving 1464 patients - 1014 of which had rheumatoid arthritis (RA) - found PUFA supplementation led to a significant decrease in all clinical parameters studied – including Disease Activity Score (DAS)28, Health

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Assessment questionnaire and Erythrocyte Sedimentation rate – with a large effect in the Visual Analogue Scale activity (Daien *et al*, 2021). Whilst no dose-dependent effect on joint symptoms was found, a 2-gram (g) PUFA dose was suggested, in part due to a 2 g dosage used in 25 of the 31 studies. Whilst omega-3 supplementation has been associated with benefits in systemic lupus erythematosus (Duarte-García *et al*, 2020), evidence across other rheumatic (Stamp *et al*, 2022) or autoimmune diseases is inconclusive (Hong *et al*, 2024). Given the existing literature, PUFA supplementation's strongest evidence and recommendations are for its use in RA (Daien *et al*, 2021; Sigaux *et al*, 2022). Mendelian randomisation evidence, despite its limitations, provides support for the protective role of omega-3 FA in rheumatic disease, with genetically higher circulating levels of EPA associated with a reduced risk of psoriatic arthritis (Xu *et al*, 2024). Whilst no other beneficial causal effects were identified for other PUFA on gout, juvenile idiopathic arthritis, Sjögren syndrome or ankylosing spondylitis, the findings suggest the need of further clinical trials to assess omega-3 FA supplementation in rheumatic disease.

Although the MD is a known anti-inflammatory diet (Nikiphorou and Philippou, 2023), with the rise of urbanisation, nations are shifting to a more Westernised and processed diet, featuring higher salt, sugar and alcohol intake (Azzam, 2020; Baker *et al*, 2020). Alcohol consumption has complex effects on rheumatic disease, with low alcohol intake demonstrating a 17% reduction in RA risk (Jin *et al*, 2013) and a lower mean DAS28 score by 0.34 in drinkers compared to non-drinkers with RA (Turk *et al*, 2021). However, moderate alcohol intake (≥2.5 units for women, ≥3.75 units for men) may accelerate radiological progression of early-stage RA in women, whilst no significant effect was found in men (Sageloli *et al*, 2018). A genome-wide association study found no causal inverse link between alcohol and RA incidence (Bae and Lee, 2018), suggesting findings may reflect confounding rather than direct effects.

The association between alcoholism and gout is more defined, with significant dose-response relationship between alcohol consumption and risk of recurrent gout flares found (Neogi *et al*, 2014). Compared with no alcohol consumption in the preceding 24 hours, the risk of a recurrent gout flare was 1.36 for >1 - 2 drinks and 1.51 times higher for >2 - 4 alcoholic beverages.

The Indian Diet

Whilst the associations between the MD, common in Egypt, Greece and Italy (da Silva *et al*, 2009; Obeid *et al*, 2022), the WD and rheumatic disease are becoming clearer, these diets differ substantially to those traditionally consumed in other global regions. Despite this, some overarching themes across diets emerge. For example, the use of cooking oils and herbs is common across the Mediterranean, Western and Indian diets. EVOO, a staple in the MD, is high in anti-inflammatory omega-9 FA, whereas sunflower oil, frequently used in WD is high in omega-6 FA (Orsavova *et al*, 2015). Similarly, herbs such as parsley, thyme and rosemary are more common in the MD, whilst Indian diets frequently incorporate spices such as ginger and turmeric, which are increasingly known for their anti-inflammatory and anti-oxidant properties (Salis *et al*, 2021).

India, with a population of over 1.4 billion and significant regional variance in culture and geography, represents an extremely diverse dietary landscape. With prevalence rates of knee OA significantly higher in India, and SLE rates significantly lower (incidence rate of 3.2 people in India compared to 14.6 - 124 people per 1,00,000) than the worldwide average, investigation is warranted to potential dietary contributors (Misra *et al*, 2024). Whilst providing a detailed account on each diet in India is beyond the scope of this review due to the extreme diversity, there are certain themes and trends of the Indian diet which should be noted.

Traditionally, the Indian diet is plant-based, consisting of grains and pulses, such as beans and lentils. *Masalas,* a mixture of spices, is also extensively used. Other staples include pickled food, fermented food, and milk-based products such as *dahi* (curd) and *chaas* (curd-based drink) (Salis *et al*, 2021). Contributing to a higher saturated fats (SFA) intake in certain Indian households are coconut oil and ghee, with 91% and 60% SFA contents respectively (Salis *et al*, 2021). Although a genetic predisposition to higher SFA levels has been linked to having higher risk of developing RA, most studies only show a positive association rather than a causal relationship between SFA and rheumatic disease (Yao *et al*, 2024). A WHO meta-analysis of 880,835 participants showed that higher tissue concentrations of SFA is associated with an increased risk of type 2 diabetes, however whether SFA intake directly influences the development of rheumatic disease remains inconclusive (Christ *et al*, 2019; Reynolds *et al*, 2022).

However, seemingly more important than the absolute percentage of SFA is the source (Hewlings, 2020). The SFA in coconut oil is predominantly medium-chain, whilst ghee and many processed foods are higher in long-chain SFA, which may be metabolised differently and hence have different effects on the pathways implicated in rheumatic disease (Hewlings, 2020).

Featured in the modern WD and in traditional Indian cuisine are trans fatty acids (TFA) - unsaturated fatty acids

which contain at least one double bond in the *trans* configuration (Dhaka *et al*, 2011). Due to this, TFA are metabolised differently and have demonstrated different effects than their *cis* counterpart, such as increased activation of extracellular ATP-induced apoptosis (Hirata *et al*, 2017). Found naturally in small quantities in animal products, TFA are found in higher doses in industrially produced vegetable oils that have been partially hydrogenated (Dhaka *et al*, 2011). These industrially produced TFAs can be found in some margarines, Vanasphati ghee, fried foods, and commercially baked goods such as biscuits and pies (World Health Organisation, 2024). Despite the World Health Organisation (2024) recommendations of TFA not exceeding 1% of total energy intake and the Food Safety and Standards Authority of India (2020) stating TFA should not exceed 2% in foods, regulation in some nations remains difficult. For example, the TFA elaidic acid was found to range from 1.04% to 12.09% of the FA content amongst forty-five vanaspati brands found in India (Dorni *et al*, 2018).

Observational data from Nurses' Health Studies found concentrations of TNF Receptors, involved in pro-inflammatory responses, in the highest quintile of TFA consumption to be 10% higher compared to the lowest quintile of TFA consumption (Mozaffarian *et al*, 2004). Similarly, the National Health and Nutrition Examination Survey (1999 - 2010) involving 5,446 participants found that higher circulating TFA levels were associated with increased markers of inflammation, including C-reactive protein (CRP) and fibrinogen (Mazidi *et al*, 2017). Whilst causality cannot be established, even after adjusting for other potentially inflammatory impacting factors such as age, smoking and BMI (Mozaffarian *et al*, 2004), these findings demonstrate the potential role of TFA in modulating systemic inflammation.

A potential key contributor to the inflammatory processes in the everyday Indian diet is white rice, which has a high glycaemic index (GI) of approximately 70 and is also usually consumed in large portions, thus increasing the overall dietary glycaemic load (GI multiplied with the carbohydrate content) (Salis *et al*, 2021). Higher white rice consumption is associated with higher fasting blood glucose levels and as such can promote the formation of AGEs within joint tissues (Zuñiga *et al*, 2014). Increased AGEs accelerate cartilage degradation and increase the formation of reactive oxygen species, exacerbating the inflammatory pathways found in OA and RA (Wei *et al*, 2023). For individuals aiming to avoid pro-inflammatory foods, brown, long-grain rice is a good alternative to the short-grain, polished white rice. Featuring a lower GI of approximately 50, containing more nutrients such as magnesium (Salis *et al*, 2021), brown rice can help with inflammation and BMI - a study conducted in overweight and obese women found that the group consuming 150 g of brown rice every day for 6 weeks had lower CRP levels and more weight loss compared to the group consuming 150 g white rice daily (Kazemzadeh *et al*, 2014).

On the other hand, beans and pulses – such as kidney beans, red gram, and black gram – which are frequently used in traditional Indian cuisine (Salis *et al*, 2021), have a low GI. In many rheumatic diseases, the gut microbiome – the microorganisms lining the gut – is less diverse, a feature associated with systemic inflammation and altered immune tolerance (Semerano *et al*, 2017). However, beans and pulses feature high amounts of polyphenols and fermentable fibre, making them potent prebiotics (Salis *et al*, 2021), with diets rich in beans and pulses having shown to increase the gut microbiome diversity, increase the species linked to anti-inflammatory effects and increase the production of small chain FA such as butyrate (Fernando *et al*, 2010; Kadyan *et al*, 2022). Several studies have shown how increased butyrate concentrations leads to the inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells pathway, leading to decreased levels of pro-inflammatory cytokines, such as TNF-alpha (Ali *et al*, 2022). Whilst research assessing the direct impact of beans and pulses in rheumatic disease is limited, their impact on the gut-immune axis and systemic inflammation suggests a potential beneficial role that warrants further investigation.

Salt, Sugar and Spices

Salt, sugar, and spices also feature in significant amounts in the Indian diet. Starting with salt, the estimated mean daily intake in India is 8.0 g (8.9 g/day for men and 7.1 g/day for women) (Mathur *et al*, 2023), much higher than the World Health Organisation recommendation of 5 g/day for adults (World Health Organisation, 2025). Moreover, the perception of the harmful effects of high salt intake and practices to limit salt intake was low in the study population. Excessive salt intake has been shown to promote pro-inflammatory pathways, notably the increased differentiation of Th17 cells, with a linear association between salt concentration and Th17 expression found in in-vitro studies (Balan *et al*, 2020; Sharif *et al*, 2018). Th17 cells, a type of pro-inflammatory T-Helper cell which secretes cytokine IL-17, implicated in cartilage and bone degradation as well as joint destruction (Miossec, 2021), have been demonstrated to be deposited in the tissues of a range of rheumatic disease, such as the skin of psoriasis patients and in multiple joints of RA patients (Balan *et al*, 2020). Epidemiological studies support this mechanism, with a Spanish study of 18,555 individuals finding that people in the highest quartile of salt intake (>4.55 g) showed a significant association with RA, with the

association between salt intake and RA also dose-dependent across salt intakes (Salgado *et al*, 2015).

Excessive sugar consumption, similarly to salt, is also associated with inflammation. Although India's average per capita sugar consumption is lower than Western countries, it is around 20 kg/year, plateauing in recent years (Ministry of Statistics and Programme Implementation, 2024). Increased consumption of sugar as well as consumption of foods with a high GI, such as the prominent consumption of large amounts of white rice in the Indian diet, can also cause systemic inflammation via multiple mechanisms. Higher GI foods lead to a steeper increase in blood glucose concentration after consumption, promoting systemic inflammation, increasing insulin resistance (Kazemzadeh *et al*, 2014), oxidative stress, and formation and accumulation of advanced glycation end products (AGEs) in joint tissues (Wei *et al*, 2023). AGEs promote cartilage degradation, formation of reactive oxygen species and synovial inflammation, all of which are linked to rheumatic disease pathology (Wei *et al*, 2023). Supporting this, a study of 9,203 Korean participants (5,275 women) aged ≥50 years found a positive association between a higher dietary GI and symptomatic knee OA in women (So *et al*, 2018). Whilst the same association was not found in men, the reasons for this remain unclear, however factors such as hormonal balance and over-reporting of energy intake by men have been hypothesized.

In contrast to the above, herbs and spices which are prominent in the traditional Indian diet for centuries have demonstrated anti-inflammatory properties, drawing attention to their uses in rheumatic disease (Daien *et al*, 2021; Mathieu *et al*, 2022; Yang *et al*, 2019), with red chili powder, turmeric powder, coriander powder and cumin seeds/powder the most commonly used (Bhathal *et al*, 2020; Siruguri and Bhat, 2015). Notably, in a meta-analysis of 539 RA individuals, curcumin supplementation (found naturally in turmeric and used to make curry) has demonstrated improvements in erythrocyte sedimentation rate, CRP, DAS28, rheumatoid factor, tender joint count, and swollen joint count (Kou *et al*, 2023). Other spices also used in the Indian diet, such as ginger, cinnamon and garlic have demonstrated clinical benefit with reductions in inflammatory markers and tender and swollen joint scores (Daien *et al*, 2021) compared to placebo. However, even with the herbs and spices that have promising clinical features, recommending their use would be preliminary due to the studies showing such results being small and limited (Amirah *et al*, 2024). Additionally, the use of such herbs and spices mixed into cuisine at standard doses is unlikely to have the same clinical benefits as the high-dose spice concentrates often used in clinical trials (Daien *et al*, 2021; Yang *et al*, 2019).

Conclusion

Although current guidelines recommend the Mediterranean diet (MD) for its anti-inflammatory benefits, further randomised controlled trials are needed to evaluate the effects of individual ingredients as well as other culturally distinct dietary patterns. In clinical practice, rheumatologists and allied health professionals should recognise the significant influence diet can have on rheumatic disease management and reflect this in patient education. Adoption of an anti-inflammatory diet should always complement pharmacological treatment rather than replace it.

Nevertheless, given the cultural and geographical differences, the direct application of the MD, as originally defined, in distant regions such as India, can be challenging. The diversity of Indian cuisine – in terms of locally available produce, cooking methods, and traditional food habits – means that the MD may not be fully replicable in its classic form. Instead, efforts in health professional and patient education could focus on the health-promoting aspects of Indian diets such as the extensive use of spices, legumes, diverse vegetables, and whole grains, many of which possess anti-inflammatory and antioxidant properties, could direct efforts in health professional and patient education. These both align with the health-promoting principles of the Mediterranean diet and complement its anti-inflammatory aspects.

In essence, while acknowledging these contextual differences, it is feasible and beneficial to incorporate healthy MD principles in the Indian culinary framework such as emphasising healthy fats (like nuts and seeds), moderate use of dairy, and minimizing processed foods and added sugars. In addition, substituting salt with spices such as turmeric, ginger, garlic, cinnamon and other spices with known anti-inflammatory effects can also be highlighted as complementary to MD principles.

In conclusion, a culturally sensitive diet should be integral to patient management using personalised, sustainable dietary strategies in combination with other lifestyle aspects that incorporate local food and other traditions and promote anti-inflammatory nutrition in patients with rheumatic disease. This management approach aligns with the recent EULAR guidelines (Nikiphorou *et al*, 2021) and allows for a more holistic care using diet and other lifestyle factors to complement pharmacological management.

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REVIEW ARTICLE

JIACM 2026; 27 (2): 135-146

Chronic Urticaria: Challenges in Diagnosis and Management

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Abstract

Urticaria encompasses a heterogeneous group of disorders characterised by transient wheals, angioedema, or both, with chronic spontaneous urticaria (CSU) posing several diagnostic and therapeutic challenges. Despite advances in understanding mast cell biology, a definitive aetiology remains elusive in most patients. Recent insights into disease endotypes, particularly autoimmune subtypes (CSU-1 and CSU-2), have reshaped management strategies. This review discusses a structured approach to diagnosis, highlights uncertainties in aetiological evaluation, and explores emerging targeted therapies, emphasizing a shift toward personalised, biomarker-driven care.

Key words: Urticaria, chronic spontaneous urticaria, mast cells, autoimmune mechanisms, endotypes, biomarkers, diagnosis, antihistamines, omalizumab, targeted therapy.

Introduction

Chronic urticaria is primarily a mast cell-driven disorder which is characterised by recurrent appearance of wheals, angioedema, or both for more than six weeks[1,2]. It is broadly divided into chronic spontaneous urticaria (CSU)and chronic inducible urticaria (CIndU). CSU, the more common subtype, occurs without any recognizable external trigger and has a complex interplay of immunological and non-immunological mechanisms. The condition markedly impairs quality-of-life and is difficult to manage due to its unpredictable course and variable therapeutic response.

Historically considered idiopathic, it is now increasingly understood as a mast cell-driven disorder with heterogeneous immunological mechanisms, including autoimmune and autoallergic pathways[3]. Recent literature emphasizes the importance of phenotypes and endotypes in guiding treatment decisions.

Aetiopathogenesis

Mast cells play a central role as the key effector cells in urticaria, showing both increased numbers in lesional skin and heightened sensitivity to activating stimuli[4]. They possess a wide array of surface receptors, enabling activation through multiple immunologic and non-immunologic pathways like IgE-dependent mechanisms through FcεRI, triggered by allergens or autoantibodies; IgE-independent pathways, particularly via MRGPRX2, responding to neuropeptides and eosinophil-derived proteins; cytokine-driven pathways (IL-33, TSLP), promoting Th2-skewed inflammation; complement activation (C5a - C5aR) and proteinase-activated receptors (PARs)[5].

Upon activation, mast cells degranulate and release preformed mediators such as histamine and tryptase, as well as newly synthesized substances (leukotrienes, prostaglandins, cytokines), producing the characteristic wheal, flare, and pruritus. Histamine plays a central role by increasing vascular permeability and stimulating sensory nerves via H1 receptors, while H4 receptor signaling sustains inflammation and promotes chemotaxis. It also contributes to coagulation activation, linking inflammation with vascular changes. In addition to histamine, mediators such as LTE4, PGD2, PAF, and multiple cytokines, (e.g., IL-33, IL-4, IL-5, IL-6, IL, TSLP) amplify inflammation (Table I)[5,6].

Mast cells participate in self-amplifying loops, where mediators like tryptase and histamine further enhance activation[4]. They also play a role in neuroimmune interactions, promoting nerve sensitisation and itch via nerve growth factor. Cross-talk with other inflammatory cells is crucial in the pathogenesis of urticaria[7]. Eosinophils interact closely with mast cells, enhancing each other's activation through direct contact and mediator release. Basophils contribute via both IgE and non-IgE pathways, including complement activation. Interactions with endothelial cells, nerves, and other immune cells sustain inflammation. Importantly, these inflammatory cells are a prominent source of cytokines besides mast cells[7].

Overall, urticaria represents a complex network of immune interactions including coagulation cascade activation, complement pathways, and neuroimmune interactions, with mast cells acting as central amplifiers of inflammation (Fig. 1).

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Table I: Key inflammatory mediators of chronic urticaria.

Category / Mediator	Source	Main Actions	Clinical Relevance
I. Preformed Mediators			
Histamine	Mast cells, basophils	Vasodilation, ↑capillary permeability, and stimulation of pruritus.	Central mediator of immediate wheal and flare reactions.
Tryptase	Mast cells	Cleaves C5 to C5a; activates PAR2 to amplify degranulation.	Marker of mast cell activation; induces non-histaminergic pruritus.
II. Lipid-Derived Mediators			
PGD2/LTE4	Mast cells, basophils	Chemotaxis of Th2 cells/eosinophils; sustains plasma extravasation.	Eicosanoids elevated in CSU and chronic inducible urticarias.
PAF	Most cells, basophils, platelets, eosinophils	Potent vasodilation and increased capillary permeability.	Linked to severe disease activity and antihistamine resistance.
III. Cytokines and Alarmins			
IL-33/TSLP/IL-25	Epithelial cells, keratinocytes	Th2 activation; sensitises mast cells to various ligands.	Key amplifiers; increased levels associated with increased disease severity and poor control.
IL-4/IL-5/IL-13	Th2 cells, mast cells	Drives IgE class switching and eosinophil recruitment/survival.	Essential for maintaining the Th2-skewed inflammatory milieu.
IV. Neuroimmune Factors			
NGF (Nerve Growth Factor)	Mast cells, eosinophils.	Promotes sensory nerve development and sensitisation; enhances itch and neurogenic flare.	Elevated in CSU; linked to stress-induced exacerbations and local mast cell accumulation.
Substance P	Sensory nerve endings	Direct mast cell activation via the MRGPRX2 receptor.	Mediates neurogenic inflammation and therapeutic refractoriness.
V. Complement Mediated Pathways			
C5a	Generated via complement activation.	Potent activator of mast cells and basophils via C5aR (CD88).	Primary mediator in Type II b autoimmune CSU; enables non-IgE degranulation.
C3a	Cleavage of C3 by tryptase or Factor Xa.	Stimulates histamine release and enhances vascular permeability.	Involved in the alternative complement pathway triggered by autoantibodies.
VI. Coagulation Factor Pathways (Cascade Activation)			
Tissue Factor (TF)	Eosinophils, monocytes, endothelial cells.	Activates the extrinsic coagulation pathway.	Expressed in lesional skin; triggers systemic thrombin and C5a generation.
Thrombin (FIIa)	Activated coagulation cascade.	Increases vascular permeability; activates PAR1 and PAR4 on mast cells.	Links systemic coagulation activation with CSU severity and mast cell "releasability".
Factor Xa/PF 1+2	Transudate plasma components.	Activates PARs and converts prothrombin to thrombin.	Elevated markers (D-dimer, PF 1+2) rise in proportion to disease activity.

Autoimmune urticaria and endotypes

Autoimmune urticaria is a form of CSU in which the disease is driven by autoantibodies that activate mast cells and basophils. Clinically, autoimmune urticaria often shows greater severity and variable response to standard therapy. The classification of autoimmune urticaria is based on molecular endotypes which forms the basis of targeted precision based management (Table II)[8]. This approach identifies CSU as a spectrum of disorders driven by different immune pathways leading to mast cell activation, rather than a single disease.

Major endotypes includes type I autoimmune urticaria, also called autoallergic endotype and type IIb autoimmune urticaria (CSU-1 and CSU-2)[9]. In the former endotype, IgE autoantibodies recognise and bind to self-antigens. These autoantigens include a wide range of endogenous proteins such as IL-24, thyroid peroxidase, thyroglobulin, and nucleic acids. These IgE autoantibodies bind to FcεRI on mast cells and basophils, leading to cross-linking and degranulation, mimicking classical allergic reactions but in the absence of external allergens.In type IIb autoimmune endotype,IgG autoantibodies (and less commonly IgM or IgA) develop against IgE or FcεRI. This binding activates mast cells directly.

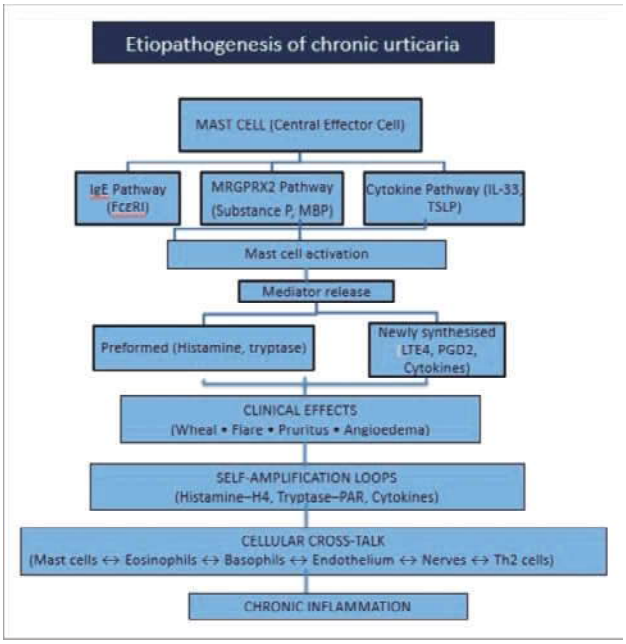

Fig. 1: *Aetiopathogenesis of chronic urticaria.*

However, not all detected autoantibodies are pathogenic, and their clinical relevance depends on functional activity. This subtype is often associated with low total IgE levels, suggesting reduced receptor occupancy facilitates autoantibody binding. However, emerging evidence suggests that chronic spontaneous urticaria endotypes are not mutually exclusive. Many patients show a mixed phenotype encompassing both type I and type IIb disease, forming a continuum rather than discrete categories. Notably, type IIb frequently coexists with type I features. Some patients may transition over time, possibly progressing from IgE-mediated to IgG-mediated disease. Additionally, some patients do not clearly fall into either subtype, indicating the presence of non-FcεRI-mediated mechanisms, further underscoring disease heterogeneity[8,9].

Various autoimmune diseases have been associated with urticaria with around one quarter to one third of patients having at least one coexisting autoimmune condition and about 30 - 40% of CSU cases mediated by autoimmune mechanisms like autoantibodies targeting IgE of FcεRI receptors. The common autoimmune diseases are thyroid disorders (Hashimoto's thyroiditis, Graves' disease), vitiligo, Type 1 diabetes mellitus, celiac disease, pernicious anaemia, Sjögren disease, SLE, inflammatory bowel disease (IBD) and Rheumatoid arthritis (RA)[2]. Thyroid autoimmunity accounts for roughly 6 - 23% of CSU patients in most series, with some studies documenting thyroid-related autoantibodies in up to about 22 - 25% of cases. Other organ specific autoimmune disorders, including pernicious anaemia, vitiligo, and haematologic autoimmune diseases, occur in about 27 - 28% of CSU cohorts, while systemic conditions such as RA, IBD, celiac disease, and psoriasis show a modestly increased risk but lower absolute prevalence, typically under 5 - 10% each in urticaria populations[10,11].

Approach to diagnosis

Urticaria is predominantly a clinical diagnosis. Since patients often do not present with active lesions during consultation, reviewing photographs or videos of previous episodes can be useful for confirming the diagnosis. The typical lesion is a transient, erythematous, or skin-colored swelling with ill-defined borders that resolves in less than 24 hours without leaving behind any pigmentation or scar (Fig. 2). Intense pruritus is the hallmark symptom and may significantly impair sleep and quality of life. Angioedema occurs in a substantial proportion of patients and involves deeper tissues, presenting as non-pitting swelling of the lips, eyelids, or extremities, often associated with pain or a burning sensation and lasting up to 72 hours. Lesions are usually migratory and can involve any part of the body, with no fixed distribution. Systemic symptoms are generally absent in uncomplicated chronic urticaria, and their presence should prompt evaluation for alternative diagnoses.

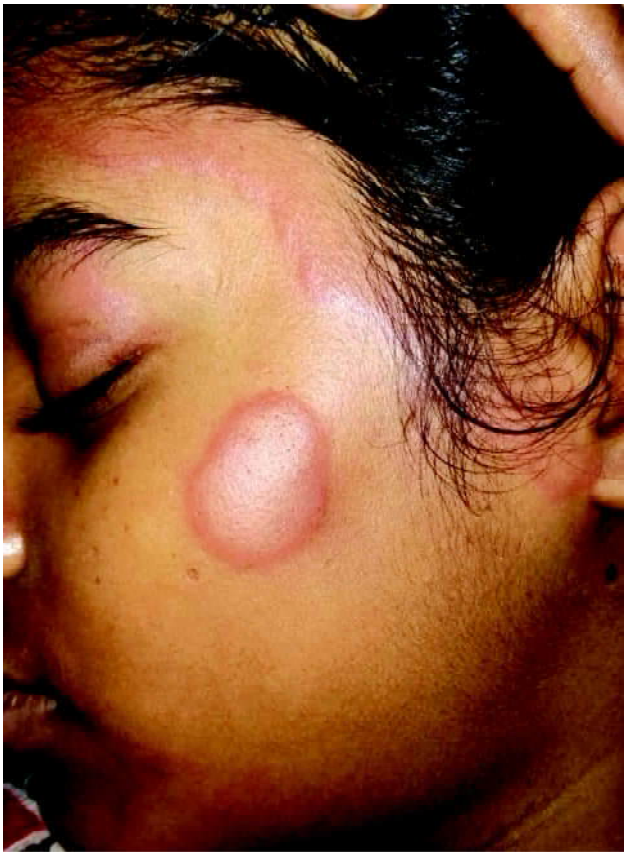

Fig. 2: *Typical wheal in a case of chronic spontaneous urticaria.*

Table II: Characteristics of various endotypes in chronic spontaneous urticaria.

Feature	Type I Autoimmune (Autoallergic) CSU	Type IIb Autoimmune CSU	Overlap / Mixed CSU	Non-autoimmune CSU
Primary mechanism	IgE autoantibodies to self-antigens	IgG (± IgA/IgM) autoantibodies	Combined IgE + IgG mechanisms	to IgE/FcαRI-independent pathways
Target	Autoallergens (e.g., IL-24, TPO)	IgE or to IgE/FcαRI receptor	Shared targets (e.g., TPO)	Unknown/diverse
Mast cell activation	IgE cross-linking	Direct receptor activation by IgG	Dual activation	Alternative pathways (e.g., MRGPRX2)
Total IgE levels	Normal to high (>43 IU/mL, usually >100 IU/mL)	Low(<43 IU/mL)	Variable	Variable
Biomarker Ratio	Low IgG anti-TPO to total IgE ratio.	High IgG anti-TPO to total IgE ratio (>2.88)	Variable	Usually absent
Haematology	Typically, normal counts	Basopenia (<0.01 × 103/μL) and Eosinopenia (<0.05 × 103/μL) are common[8].	May show basopenia/eosinopenia.	Typically, normal counts.
Autoantibodies	IgE autoantibodies	Functional IgG autoantibodies	Both present	Usually, absent
Autologous serum skin test)	May be positive/negative	Often positive	Often positive	Usually negative
Basophil tests (BAT/BHRA)	Variable	Frequently positive	Positive	Negative
Disease severity	Moderate	Often severe	More severe	Variable
Thyroid autoimmunity	May be present	Common (anti-TPO high)	Common	Variable
Treatment response	Good response to omalizumab	Poorer response to omalizumab; better to cyclosporine	Delayed/partial response	Variable
Clinical course	Relatively responsive	More refractory	Prolonged disease	Heterogeneous

Differentials of urticaria include a broad spectrum of cutaneous and systemic disorders such as urticarial vasculitis, mastocytosis,urticarial dermatitis, contact dermatitis, arthropod bite reactions, drug reactions, autoimmune bullous diseases, (e.g., bullous pemphigoid), and pregnancy-related dermatoses (PUPPP), along with rarer entities like Wells syndrome and neutrophilic eccrine hidradenitis. In addition, important systemic causes include connective tissue diseases, (e.g., SLE, Sjögren disease), other vasculitides, (e.g., polyarteritis nodosa), haematologic disorders, (e.g., Schnitzler syndrome, lymphoma, hypereosinophilic syndrome), and autoinflammatory syndromes such as cryopyrin-associated periodic syndrome[12,13].

Masquerades of urticaria should be suspected when clinical features deviate from typical transient wheals. Red flags include lesions lasting >24 - 36 hours,resolve with pigmentation or are associated with pain and burning sensation instead of pruritus, and the presence of additional lesion types (purpura, bullae, scaling). Systemic symptoms such as fever, arthralgia, malaise, or organ involvement strongly suggest alternative diagnoses. Additionally, poor response to antihistamines and abnormal laboratory findings (elevated inflammatory markers, hypocomplementaemia, eosinophilia, or monoclonal gammopathy) should prompt evaluation for underlying conditions such as urticarial vasculitis, autoimmune, autoinflammatory, or hematologic disorders (Table III).

A detailed history is essential to identify potential triggers such as recent infections,vaccinations, medications or food items (Table IV)[14,15]. In cases of chronic inducible urticaria, certain provocation tests may be help in confirmation of diagnosis[16]. These include the cold stimulation test for cold urticaria, wherein an ice cube wrapped in plastic is applied to the skin for 5 - 10 minutes and a wheal forming after rewarming confirms the diagnosis[17]. In dermographism, a blunt object is used to stroke the skin and linear wheals appearing within minutes indicate symptomatic dermographism, while in pressure urticaria a graded weight or sandbag is left on the skin for 15 - 30 minutes to elicit delayed swelling. Solar urticaria is tested by exposing small skin areas to UV or visible light, and cholinergic urticaria may be provoked by controlled exercise or passive warming to induce small, itchy wheals[16]. Assessment of disease activity and impact is done using tools like the Dermatology Life Quality Index (DLQI), Urticaria Activity Score (UAS7), Angioedema Activity Score (AAS), and Urticaria Control Test (UCT).

Table III: Differential diagnosis of chronic urticaria.

Feature	Chronic Spontaneous Urticaria	Urticarial Vasculitis	Cutaneous Mastocytosis	Autoinflammatory syndromes	Urticarial Dermatitis	Drug Eruptions	Arthropod Bite Reaction	Autoimmune Bullous Diseases
Lesion duration	<24 hours (transient wheals)	>24 - 48 hours (persistent plaques)	Persistent lesions	Variable, often prolonged	Days to weeks	Days to weeks	Days to weeks	Persistent; may precede blistering
Predominant symptoms	Intense pruritus, fleeting lesions	Burning sensation, pain >pruritus, fixed lesions	Pruritus, flushing	Fever, systemic inflammatory symptoms	Severe pruritus	Pruritus ± low-grade fever	Pruritic papules/ nodules	Pruritus, occasionally burning
Residual skin changes	Absent	Post-inflammatory hyperpigmentation, purpura	Hyperpigmented macules	Variable	May show residual pigmentation	Desquamation, transient pigmentation	Excoriations, post-inflammatory changes	Possible pigmentation or scarring
Angioedema	Frequently associated	May be present	Uncommon	May occur	Rare	Rare	Rare	Rare
Blanchability	Typically present	Often reduced/absent	Present	Variable	Variable	Present	Variable	Variable
Systemic involvement	Absent	Common (fever, arthralgia, organ involvement)	Rare (unless systemic disease)	Prominent (fever, arthritis, systemic inflammation, bone pains, etc.)	Absent	Occasionally mild systemic symptoms	Absent	Usually absent in early phase
Histopathology	Superficial dermal oedema with sparse perivascular infiltrate (mast cells, eosinophils)	Neutrophils in and around vessels, fragmentation of neutrophil nuclei forming dust, RBC extravasation, fibrinoid necrosis	Dense dermal mast cell infiltrate (CD117+)	Dense infiltrate composed of neutrophils in the superficial and mid-dermis without fragmentation of neutrophils, fibrinoid necrosis (neutrophil)	Mild epidermal spongiosis, papillary dermal oedema, superficial perivascular lymphocytic infiltrate with eosinophils	Perivascular lymphocytic infiltrate with eosinophils, epidermal involvement	Mixed inflammatory infiltrate with eosinophils	Subepidermal blister with eosinophil-rich infiltrate
Key diagnostic clues	Evanescent wheals, no sequelae	Lesions >24 h with pain and residual changes	Positive Darier sign (urticaria elicited by rubbing or stroking a skin lesion	Recurrent fever with urticarial rash	Combined urticarial and eczematous morphology	Temporal relation to drug exposure	Central punctum, exposed site predilection	Evolution to tense bullae
Response to antihistamines	Good response	Poorer response	Partial response	Poor response	Poor response	Variable	Partial response	Poor response

Investigations

Since the diagnosis is often clinical, a basic set of investigations are recommended like differential blood count, inflammatory markers (CRP, ESR), thyroid function test (± anti-TPO antibodies). Urine and stool routine microscopy to rule out parasitic infection may also be undertaken. Additional investigations are often reserved for unresponsive or refractory cases of autoimmune urticaria. Autologous serum skin test (ASST) is one such traditional test found to be useful in autoimmune urticaria. Here we detect functional autoantibodies in chronic spontaneous urticaria by an intradermal injection of a small volume (about 0.05 - 0.1 mL) of the patient's own serum into normal skin and comparing the response with a saline control. A wheal–flare reaction at the serum site ≥1.5 mm greater than the saline site within 15 - 30 minutes is considered positive, suggestingactivation of mast cells or basophils by circulating histamine releasing factors present in the serum.

Other tests that may indicate autoimmune urticaria are elevated CRP or ESR, basopenia and eosinopenia, low IgE levels, increased IgG anti-TPO antibodies, elevated IgG anti-TPO to total IgE ratio, positive basophil activation test or histamine release assay, andhigh levels of D-dimer. Various biomarkers are available for the diagnosis of autoimmune urticaria, some of which have prognostic role as well (Table V). Nevertheless, most of these investigations have not been validated and many of these are not routinely available.

Skin biopsy of a typical urticarial wheal shows a predominantly perivascular infiltrate composed of lymphocytes with scattered eosinophils in the papillary and upper dermis and mild oedema. Delayed pressure urticaria may show upper dermal predominantly perivascular inflammatory infiltrate, composed of mononuclear cells, eosinophils, neutrophils, and some lymphocytes, with variable mast cell degranulation and mild dermal oedema;

Table IV: Triggers for chronic urticaria.

Category	Specific Triggers	Mechanism	Clinical Relevance
Food and Dietary Triggers			
True Allergy (Rare)	Milk, egg, peanuts, tree nuts, fish, shellfish[24]	IgE-mediated (Type I) hypersensitivity	Extremely rare cause in CSU (<2%)[23]. More relevant in acute urticaria or cases with intermittent symptoms appearing within one hour of exposure[22].
Alpha-gal Syndrome[31]	Red meat (beef, pork), dairy products	Sensitisation to galactose-alpha-1,3-galactose via tick bites	Causes delayed reactions (3 - 6 hours post-ingestion) manifesting as urticaria or anaphylaxis (Information from outside sources; not found in provided snippets).
Pseudoallergens	Tomatoes, citrus fruits, strawberries, chocolate, spices, and aromatic compounds	Non-IgE-mediated mast cell activation; direct effect on cell releasability	May exacerbate preexisting CSU in approximately 30% of patients. Benefit may be seen with a 3 - 4-week elimination diet in selected cases.
Histamine-Rich Items	Fermented foods, aged cheese, processed meat, canned fish, alcohol	Exogenous histamine increases the total mediator load	Benefits from low-histamine diets are reported but lack proof from double-blind, placebo-controlled studies.
Food Additives[32]	Tartrazine, benzoates, sulphites, artificial colorants, and preservatives	Pseudoallergic reactions	Improvement seen in a subset of patients after 10–14 days of an additive-free diet.
Medications[23]			
NSAIDs and Aspirin	Ibuprofen, diclofenac, naproxen, high-dose aspirin	COX-1 inhibition leads to increased synthesis of pro-inflammatory cysteinyl leukotrienes	Common exacerbating factors in up to 25% of CSU patients. Paracetamol and selective COX-2 inhibitors (e.g., celecoxib) are usually safer alternatives.
ACE-Inhibitors	Lisinopril, Enalapril, and other "prils"	Non-immunologic accumulation of bradykinin	Primary cause of angioedema without wheals. Reactions can occur weeks or even years after starting the drug.
Direct Degranulators	Opioids (morphine, codeine), fluoroquinolones, neuromuscular blockers, radiocontrast media	Activation of mast cells via the MRGPRX2 receptor rather than IgE pathways	Common triggers for exacerbation; should be avoided or substituted if a temporal relationship with flares is suspected.
Infections			
Bacterial and Viral	EBV, Hepatitis (A/B/C), COVID-19, Streptococcal tonsillitis	Immune activation, induction of autoimmunity, or "priming" of mast cells	Common triggers for the initial onset of CSU or acute flares.
Helicobacter pylori	Chronic gastritis	Immune activation and induction of autoimmunity	Eradication therapy may improve CSU symptoms, but only if the underlying gastritis or inflammatory process is also healed[22].
Parasitic	*Anisakis simplex* (raw fish)[23], *Strongyloides*, *Blastocystis hominis*	Polyclonal IgE stimulation; induction of autoreactive IgE	More relevant in endemic areas; *Anisakis* is a major trigger in certain regions like the Mediterranean.
Stress and physical factors			
Psychological Stress	Emotional distress, anxiety, psychiatric comorbidities	Neuroimmune interaction; release of neuropeptides like Substance P, VIP, and NGF	Affects up to 1/3 of CSU patients. The cycle of stress, insomnia, and the itch-scratch cycle aggravates chronic inflammation.
Physical Factors	Pressure, heat, cold, friction, UV radiation	Direct mast cell degranulation or neoallergen formation in the skin	Inducible forms (CIndU) co-exist with CSU in 30 - 40% of patients and require specific provocation testing for diagnosis.
Others			
Vaccination	COVID-19 vaccines and standard immunisations[24]	Systemic immune response and release of pro-inflammatory cytokines	Reported as an occasional trigger for both acute flares and the initial onset of CSU.
Hormonal Changes	Menstruation cycle, puberty pregnancy, menopause	Multifactorial immune modulation; potential stimulation of autoimmunity	Flares are frequently linked to the menstrual cycle. During pregnancy, activity often follows a "one-third rule" (improve, worsen, or stay the same).
Metabolic Factors	Vitamin D deficiency	Reduced T-regulatory (Treg) cell function	Low Vitamin D levels are linked to higher disease activity; supplementation may serve as an adjuvant therapy.
Microbiome Dysbiosis	Gut microbiome alterations	Increased intestinal permeability ("leaky gut") and systemic inflammatory tone	Emerging evidence suggests that gut microbial alterations facilitate CSU; probiotics are being investigated as a complementary strategy.

fibrin deposits may be seen in the interstitium, but there is no vasculitis. A biopsy is often not needed and is reserved for ruling out differential diagnoses like urticarial vasculitis, mastocytosis, etc. Presence of neutrophils, RBC

extravasation, leukocytoclasia, fibrin degeneration indicates alternate diagnosis than urticaria.

Skin prick tests (SPT) can identify IgE mediated triggers in urticaria but play a limited and selective role, especially in CSU. In one Indian study of 100 urticaria patients, SPT was positive in 88%, with the most common sensitisations being house dust mites (*Dermatophagoides pteronyssinus* 30%, *D. farinae* 24%), grass (*Cynodondactylon* 24%), and peanuts (24%), suggesting SPT can cost effectively detect clinically relevant aero and food allergens when the history points to an external trigger[18]. Another hospital based study in chronic urticaria found SPT positivity in about two thirds of patients, reinforcing that SPT may help in selected populations where an underlying allergy is suspected[19]. However, guidelines note that SPT is not routinely indicated in chronic urticaria, because many positive tests are not clinically relevant: in one assessment of food allergic patients, only about 35% of those with positive SPT for food allergens developed urticaria upon exposure, so SPT findings must always be interpreted alongside the clinical history[20]. Overall, SPT is most useful in acute or inducible urticaria with a clear atopic background or suspected allergen, where it can guide avoidance and adjunctive therapy, but it has low yield in idiopathic chronic cases and should not replace standard urticaria management.

Diet elimination tests have a limited role in CSU and are offered only when there is a strong history of a food trigger, (e.g., reproducible symptoms after specific foods). A review of 1,668 CSU patients on systematic elimination diets (pseudoallergen free, low histamine, or fish avoidance) reported complete remission in about 4.9% and partial remission in 37.5%, with the best outcomes seen after at least 3 weeks on a pseudoallergen or low histamine diet, suggesting that a subset of patients are sensitive to food additives, natural pseudoallergens, or histamine rich foods[15]. Controlled low histamine trials show significant reductions in urticaria activity scores, while paediatric and oligoantigenic diet studies also report improved symptom control in some children, although the added benefit over pharmacotherapy alone is not always statistically robust[2]. Thus, such trials should be time-limited to 2 - 4 weeks and conducted with caution to avoid nutritional deficiencies[22].

Treatment

Treatment of chronic spontaneous urticaria (CSU) follows a stepwise strategy integrating general measures and targeted therapy. The immediate objective is to achieve complete symptom relief, while the long-term goals are to maintain sustained disease control, enhance quality-of-life, and prevent severe exacerbations.

General measures

Patients should be counselled to minimise identifiable triggers such as NSAIDs, stress, inducible urticaria triggers, etc. Dietary restrictions often are not advised, only indicated whenever there is a very strong clinical correlation supported by diet elimination test. In patients with angioedema, it is advised to stop use of ACE inhibitors. Infectious triggers for urticaria, ranging from viral and bacterial to parasitic and fungal agents, should be identified and ruled out as part of a comprehensive diagnostic workup. In acute urticaria, symptoms typically resolve spontaneously once the underlying infection – most commonly upper respiratory tract infections – is controlled or heals[23]. For CSU, *Helicobacter pylori* should be eliminated if detected; although meta-analyses show low overall evidence for consistent symptom improvement, studies indicate that successful eradication benefits CSU activity specifically when the associated gastritis or inflammatory process is also healed. Globally, parasitic infections show an average comorbidity of 10% with CSU, and their treatment leads to clinical improvement in approximately one-third of patients[14]. Additionally, ruling out and treating focal infections of the nasopharynx, ears, and conditions like tinea (fungal infection) or Lyme disease can significantly improve the clinical course for select individuals[2,23,24].

Based on international guidelines and recent research, identifying triggers and cofactors is a cornerstone of the diagnostic workup to better disease control and enhanced quality-of-life (Table IV).

Documentation of disease activity using validated scores like Urticaria Activity Score and Urticaria Control Test are indicated especially in refractory cases where complete symptom control may not be achieved. Stress relieving techniques like mindfulness, relaxation techniques, and psychotherapy, specifically cognitive-behavioural therapy (CBT), brief talking therapies, have been shown to improve symptoms[14,25].

Pharmacological therapy

Second-generation H1 antihistamines are the first line therapy with dose escalation up to four-fold if required[22]. Around 50 - 60% patients achieve control with antihistamines alone. Short course of oral steroids (prednisolone 0.5 mg/kg in adults, 0.5 - 1 mg/kg in children and adolescents, not exceeding 20 mg/day) up to a maximum of 2 weeks for acute flares is recommended[22]. For inadequate responders, add-on agents like omalizumab are preferred, with cyclosporine reserved for selected refractory cases. Increasingly, endotype-based and precision approaches are being explored, with newer biologics such asligelizumab, dupilumab, remibrutinib are expanding therapeutic options.

Table V: Diagnostic and prognostic role of various biomarkers in chronic urticaria[24,33].

Biomarker	Diagnostic/Endotyping Role	Disease Activity/Severity	Treatment Response Prediction	Prognostic Implications
Total IgE	High → Type I autoallergic; Low → Type IIb	Inconsistent correlation with severity	High IgE → good response to omalizumab; Low IgE → better response tocyclosporine	High IgE → higher relapse risk after omalizumab; possible persistence
IgG anti-FcεRI/anti-IgEantibodies	Marker of Type IIb autoimmune CSU	Linked with severe phenotype	Predict poor response with antihistamines and omalizumab; better response to cyclosporine	Suggest chronic, refractory disease course
IgE autoantibodies (e.g., anti-TPO, IL-24)	Support Type I autoallergic CSU	May reflect immune activation	Associated with good response to omalizumab	May indicate relapsing but treatment-responsive disease
Anti-TPO (IgG)	Indicates autoimmune association/ endotype	Linked with severe disease	May predict poor response with antihistamines. Raised IgG-anti-TPO/Total IgE ratio (>2.88) is a key predictor of omalizumab failure.	Associated with longer disease duration
Basopenia	Suggests Type IIb CSU	Correlates with higher disease activity	Predicts poor response to omalizumab	Marker of severe, persistent disease
Eosinopenia	Seen in autoimmune CSU	Associated with high disease activity	Linked to treatment resistance	Suggests unfavorable prognosis
CRP	Non-specific inflammatory marker	Correlates with disease activity	High CRP → poor antihistamine response; better cyclosporine response	Reflects high inflammatory burden
D-dimer	Reflects coagulation pathway activation	Associated with disease severity (variable evidence)	May indicate severe/refractory CSU	Potential marker of active disease
ASST (Autologous serum skin test)	Indicates autoreactivity	Often linked to more severe disease	May predict poorer response to standard therapy	Suggests autoimmune phenotype
BAT / BHRA (functional assays)	Type IIb	Associated with high disease activity	Predict refractoriness to antihistamines/ omalizumab	Strong marker of severe, persistent CSU
Basophil activation markers (CD63, CD203c)	Reflect mast cell–basophil activation	Correlate with disease activity	Potential predictors of response (emerging)	Under investigation
Complement (C4)	Not diagnostic	May correlate with severity	Unclear	Limited prognostic role. Primary role in ruling out mimics.

Table VI: Characteristics of second generation antihistamines used in CSU.

Drug	Usual Adult Dose	Common Side Effects	Renal Impairment	Hepatic Impairment	Pregnancy Category	Lactation Safety
Cetirizine	10 mg once daily (up to 20 mg in urticaria)	Mild sedation, dry mouth	Dose reduction required	Usually safe	B	Safe (minimal transfer)
Levocetirizine	5 mg once daily (up to 20 mg)	Somnolence, fatigue	Dose reduction required	Not required	B	Safe
Loratadine	10 mg once daily	Headache, dry mouth (non-sedating)	Caution in severe renal	Dose adjustment in severe hepatic disease	B	Safe
Desloratadine	5 mg once daily	Headache, fatigue	Caution	Caution	C	Probably safe
Fexofenadine	120 - 180 mg once daily	Headache, dizziness (least sedating)	Dose adjustment required	Safe	C	Safe (minimal secretion)
Bilastine	20 mg once daily	Headache, drowsiness (rare)	Not necessary	Not necessary	B	Limited data (avoid if possible)
Rupatadine	10 mg once daily	Somnolence, headache	Limited data	Avoid in hepatic impairment	C	Avoid (insufficient data)

Second-generation H1 antihistamines primarily act as inverse agonists of H1 receptors, stabilizing the inactive receptor state. Treatment is started at the usual recommended dose which may be increased four-fold if needed. Combining multiple second-generation antihistamines does not provide additional benefit. Some patients may benefit from the use of montelukast (10 mg at night, for adults). They typically begin acting within 1 - 4 hours and the effect lasts for about 24 hours (Table VI). If symptoms remain controlled for 3 - 6 months, treatment can be gradually tapered. Most second-generation H1 antihistamines demonstrate comparable efficacy in CSU, with no single agent consistently outperforming others. Evidence from comparative analyses shows only minor differences in effectiveness and tolerability. Hence, treatment choice is best individualised based on patient

response and safety profile. First-generation H1 antihistamines are generally not recommended due to adverse effects such as sedation, anticholinergic effects, and disruption of REM sleep.

H2-blockers like ranitidine can be considered an alternative add-on therapy in CSU patients who do not achieve adequate control with H1-antihistamines, and they may be particularly beneficial for patients whose urticaria is associated with dyspepsia[26,27]. Despite these potential benefits, current international guidelines do not provide a clear recommendation for or against their use owing to a lack of strong evidence of their efficacy in the majority of patients[22].

hypertension, nephrotoxicity, hypertrichosis, and gingival hyperplasia, necessitating regular blood pressure and renal function assessment. In contrast to omalizumab, patients with low IgE tend to respond better, and remission may be more sustained after discontinuation, while those with higher IgE levels may show comparatively less robust responses.

Agents such as azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil, dapsone, and hydroxychloroquine have been used in refractory CSU, mainly as steroid-sparing or add-on therapies[24]. Their evidence base is limited and heterogeneous, largely derived from small studies and observational data. Meta-analyses suggest these drugs may provide benefit in

Table VII: Characteristics of various oral immunosuppressants used in CSU.

Drug	Mechanism of Action	Dose (Typical)	Evidence/Efficacy	Adverse Effects/Limitations	Clinical Role
Azathioprine	Purine synthesis inhibitor → ↓ T- and B-cell proliferation	1 - 2 mg/kg/day	Moderate evidence from small studies; steroid-sparing effect	Myelosuppression, hepatotoxicity, infections	Alternative in refractory CSU, especially autoimmune
Methotrexate	Folate antagonist → ↓ lymphocyte proliferation	10 25 mg/week	Limited evidence; mixed results	Hepatotoxicity, marrow suppression, GI intolerance	Occasional use in resistant cases
Cyclophosphamide	Alkylating agent → profound immunosuppression	1 - 2 mg/kg/day (oral) or pulse IV	Sparse evidence; used in severe refractory disease	Haemorrhagic cystitis, infertility, malignancy risk	Rarely used due to toxicity
Mycophenolate mofetil	Inhibits inosine monophosphate dehydrogenase → ↓ lymphocytes	1 - 2 g/day	Some supportive observational data	GI upset, infections, teratogenicity	Safer alternative to other immunosuppressants
Dapsone	Anti-inflammatory; inhibits neutrophil function	50 - 150 mg/day	Beneficial in some cases, especially with neutrophilic urticaria	Hemolysis (G6PD), methemoglobinaemia	Selected phenotypes
Hydroxychloroquine	Immunomodulatory; interferes with antigen presentation	200 - 400 mg/day	Limited evidence; slow onset	Retinopathy (long-term), GI upset	Mild/moderate refractory CSU

Omalizumab, amonoclonal antibody targeting IgE, is widely used as an effective second-line treatment for chronic spontaneous urticaria refractory to antihistamines. It is given subcutaneously at 300 mg every 4 weeks (150 mg in selected cases), usually for at least 6 months, with longer use based on response. Efficacy rates of up to 90% has been seen in certain cohorts with rapid symptom control within the first 12 weeks, particularly in patients with elevated baseline IgE levels and type 1 autoimmune urticaria[28]. Interestingly, higher levels of IgE have also been linked to greater relapse rates after discontinuation of omalizumab, whereas low IgE may predict a more sustained remission. It is generally well tolerated with headache and injection site reactions described as common adverse effects, while anaphylaxis is rare.

Cyclosporine, a calcineurin inhibitor, is used as a third-line therapy in patients not adequately controlled with antihistamines and omalizumab[20]. The usual dose is 3 - 5 mg/kg/daygiven for 3 - 6 months, depending on clinical response. It is particularly effective in patients with type IIb autoimmune CSU, low baseline IgE levels, positive ASST test, but requires careful monitoring. Common adverse effects include

selected patients, particularly those with autoimmune CSU, but their overall efficacy and safety remain less predictable and adverse effects often limit long-term use (Table VII).

Biologicals and targeted therapy are now being tried in refractory CSU. Dupilumab (targeting IL-4/IL-13 signaling) has shown reductions in wheal activity and itch, although responses may be slower and somewhat variable[29]. BTK inhibitors liker remibrutinib and rilzabrutinib act by suppressing mast cell and basophil activation and have shown encouraging results[30]. Barzolvolimab (CDX-0159), anti- KIT monoclonal antibody has shown marked disease improvement in early studies. Benralizumab, through eosinophil depletion, may offer benefit in selected cases. Collectively, these therapies reflect a move toward mechanism-based, individualised treatment approaches in refractory CSU (Table VIII)[30].

Challenges in diagnosis and management

The main challenge faced by the physicians or the patient is establishing an etiological diagnosis of CSU. It is due to its varied and often unclear pathogenesis, with most cases

being autoimmune or idiopathic rather than trigger-driven. Up to 80 - 90% of patients have no identifiable external cause, and there is no single diagnostic test, so the diagnosis is mainly by exclusion. Factors such as infections, drugs, stress, and comorbid autoimmune conditions – often coexist, but their causal role is not fully established. Additionally, overlapping phenotypes (autoimmune *versus* autoallergic, inducible components) and variability in disease response to treatment further complicates interpretation[9].

and symptom control, keeping in mind that a definitive cause may not be found in most cases.

Beyond diagnosis, other challenges include variable response to standard therapies. Some patients may remain symptomatic despite high-dose antihistamines. Access, cost, and long-term safety considerations of advanced therapies such as biologics can limit their use especially in a resource-limited setup. There is uncertainty about the optimal duration of treatment, timing of step-down,

Table VIII: Biologicals and targeted therapy in CSU[34,35]

[34]Drug	Target Molecule	Mechanism of Action	Dose	Frequency	Route	Indications	Contraindications	Common Adverse Effects
Omalizumab	Free IgE	Binds circulating IgE → ↓ FcεRI expression on mast cells/basophils	150 - 300 mg	Every 4 weeks	SC	Antihistamine-refractory CSU	Hypersensitivity	Injection site reactions, headache, rare anaphylaxis
Ligelizumab (investigational)	IgE (high affinity)	Stronger IgE neutralisation vs omalizumab	72 - 240 mg	Every 4 weeks	SC	CSU (trials) Phase 3 trials failed to show superiority over omalizumab[34].	Hypersensitivity	Injection reactions, URTI, headache
Dupilumab	IL-4Rα (IL-4/IL-13 pathway)	Inhibits Type 2 inflammation signaling	600 mg loading → 300 mg	Every 2 weeks	SC	CSU refractory to antihistamines ± omalizumab; atopic overlap	Hypersensitivity	Conjunctivitis, injection reactions, eosinophilia
Remibrutinib	BTK (Bruton tyrosine kinase)	Inhibits mast cell and basophil activation (FcεRI signaling)	25 mg	Twice daily	Oral	FDA Approved as of September 2025 for antihistamine-refractory adult CSU.	Severe hepatic impairment, hypersensitivity	Headache, URTI, mild infections, petechiae
Rilzabrutinib (investigational)	BTK	Reversible BTK inhibition → ↓ mast cell activation	400 mg	Twice daily	Oral	CSU (trials)	Hypersensitivity	GI upset, diarrhoea, headache
Fenebrutinib (investigational)	BTK	Non-covalent BTK inhibition	Variable (trial-based)	–	Oral	CSU (trials)	–	Headache, infections
Barzolvolimab (CDX-0159)	KIT receptor (CD117)	Mast cell depletion via KIT inhibition	IV doses (trial-based)	Monthly	IV/SC	Refractory CSU	Pregnancy (caution), hypersensitivity	Hair depigmentation, taste changes, infusion reactions
Tezepelumab (investigational)	TSLP	Blocks upstream epithelial cytokine → ↓ Th2 cascade	210 mg	Every 4 weeks	SC	CSU with Type 2 inflammation	Hypersensitivity	Injection reactions, URTI
Secukinumab (exploratory)	IL-17A	Modulates inflammatory pathways (limited role)	300 mg	Monthly	SC	Selected refractory CSU (limited evidence)	Infection risk	URTI, candidiasis
Benralizumab (exploratory)	IL-5Rα	Eosinophil depletion	30 mg	Every 4 - 8 weeks	SC	CSU with eosinophilic phenotype. Ddiscontinued for SCU after the Phase 2b ARROYO trial failed to reach its therapeutic primary endpoint[34].	Hypersensitivity	Headache, pharyngitis

To address these challenges, physicians should focus on detailed history-taking, examination, and basic baseline investigations, rather than extensive workup. Identification of triggers should be history-driven, confirmed by short elimination trials or symptom diaries when appropriate. Emphasis should be placed on excluding differentials, identifying comorbidities, and assessing disease activity. Thus, management should prioritize pragmatic evaluation

and predicting relapse. In addition, there are no widely available biomarkers for endotype-driven therapy which hinders precision medicine approaches. Patient-related factors, including poor adherence, psychosocial stress, and impaired quality-of-life, further complicate management. Collectively, these challenges necessitate an individualised, stepwise, and patient-centered approach to care (Fig. 3).

In conclusion, CSU remains a complex condition and its exact causes are not fully understood despite advances in pathophysiological understanding. The recognition of distinct endotypes, especially autoimmune forms, has improved our understanding and helped develop more targeted interventions. However, uncertainties in diagnosis and variability in treatment response continue to pose challenges in routine practice. A structured, stepwise approach based on clinical evaluation with judicious use of investigations is essential. In the future, the use of validated

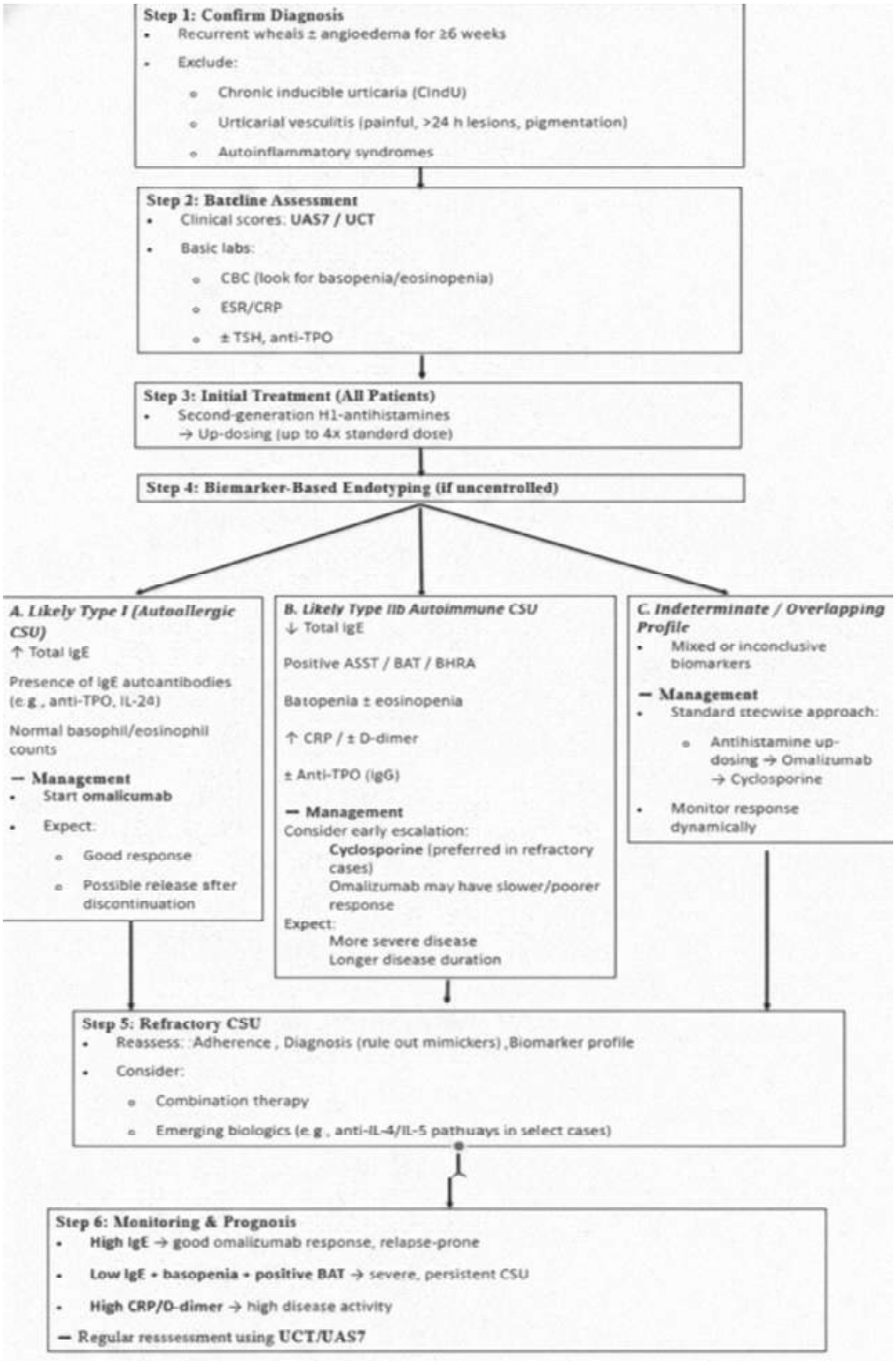

Fig. 3: *Biomarker-Guided Management Algorithm in Chronic Spontaneous Urticaria (CSU).*

biomarkers and endotype-driven strategies may help improve outcome allowing more personalised care.

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REVIEW ARTICLE

JIACM 2026; 27 (2): 147-154

GLP-1 Receptor Agonists and Respiratory Outcomes: Mechanisms, Evidence, and Clinical Implications

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Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) - including semaglutide, liraglutide, dulaglutide, and tirzepatide – were developed for type 2 diabetes and obesity, but converging evidence now shows substantial pleiotropic effects on the respiratory system that extend beyond glycaemic control and weight loss. GLP-1 receptors are highly expressed in pulmonary tissue, in cluding bronchial smooth muscle, alveolar type II cells. alveolar macrophages, pulmonary vascular endothelium, and eosinophils, providing biological rationale for direct airway and vascular activity. Receptor activation suppresses NF-κB (Nuclear factor kappa-light-chain-enhancer of activated B cells) signaling, NLRP3 (NOD-like receptor protein 3) inflammasome assembly, TGF (Transforming growth factor)-β1-driven fibrogenesis, and Th2 (T helper type 2)/ILC2 (Group 2 innate lymphoid cells)-mediated inflammation, while augmenting surfactant production and nitric oxide bioavailability through eNOS (endothelial nitric oxide synthase) pathways. A meta-analysis of 28 randomised controlled trials in 77,485 participants demonstrated a 14% reduction in overall respiratory disease risk, with subsequent analyses confirming benefit across obstructive sleep apnoea, COPD (chronic obstructive pulmonary disease), asthma, pneumonia, and pulmonary arterial hypertension. Mendelian randomisation studies provide causal genetic evidence independent of confounding by indication, and proof-of-concept trial data - including the first human hemodynamic data in pulmonary arterial hypertension - now complement a growing observational evidence base. Safety considerations relevant to pulmonologists, including aspiration risk during procedural sedation and lean mass loss in cachectic patients, warrant attention. This review synthesizes mechanistic, translational, and clinical evidence through 2026 and outlines priorities for dedicated respiratory trials.

Key words: GLP-1 receptor agonists, semaglutide, liraglutide, tirzepatide, asthma, COPD, obstructive sleep apnoea, pulmonary arterial hypertension, pulmonary fibrosis.

Introduction

Respiratory diseases are the third leading cause of death globally and among the top contributors to disability-adjusted life years worldwide[1]. COPD affects an estimated 213 to 392 million individuals globally and asthma approximately 260 million, with absolute case burdens rising despite declining age-standardised rates[2]. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) – originally developed for type 2 diabetes mellitus (T2DM), and now including semaglutide, liraglutide, dulaglutide, exenatide, and the dual GLP-1/GIP agonist tirzepatide – have demonstrated cardiovascular, renal, and metabolic benefits beyond glucose lowering, and their subsequent approval for obesity expanded their clinical reach considerably. Diabetes and obesity are common comorbidities across obstructive airway disease, present in roughly 20 - 30% of patients with COPD[3], compounding disease burden further.

These respiratory benefits were initially attributed to weight loss, but growing evidence now reveals receptor-mediated, weight-independent, anti-inflammatory and cytoprotective effects directly within the lung. An umbrella review of 123 meta-analyses covering 464 outcomes confirmed trends toward improved respiratory outcomes with GLP-1 RAs, though evidence quality is heterogeneous[4]. This review synthesizes mechanisms, disease-specific data, and research priorities.

GLP-1 Biology and Pulmonary Receptor Distribution

GLP-1 is a 30-amino acid incretin hormone secreted by intestinal L-cells that acts through the GLP-1 receptor (GLP-1R), a class B G-protein coupled receptor, to stimulate insulin secretion, suppress glucagon, and delay gastric emptying[5]. Native GLP-1 is rapidly degraded by dipeptidyl peptidase-4 (DPP-4); GLP-1 RAs are engineered analogues resistant to this degradation. GLP-1R mRNA expression in the lung ranks among the highest of all extra-pancreatic organs[6], and GLP-1 concentrations in bronchoalveolar lavage fluid substantially exceed serum levels, suggesting paracrine pulmonary

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functions[7]. GLP-1R is expressed in submucosal glands of the trachea, pulmonary artery smooth muscle, alveolar type II (ATII) cells, alveolar macrophages, and eosinophils[8,9]. Receptor activation in ATII cells stimulates surfactant protein expression and phosphatidylcholine secretion[10], while in airway smooth muscle cells, GLP-1R expression is reduced in COPD and its overexpression suppresses proliferation, migration, and pro-inflammatory cytokine release via an ABCA1-mediated pathway[11]. Eosinophils from asthmatic patients also express GLP-1R, with agonism attenuating activation markers and reducing IL-4, IL-8, and IL-13 production[8] (Fig. 1).

Mechanistical GLP-1R activation triggers cAMP/PKA signaling that suppresses NF-κB activation, reduces NLRP3 inflammasome assembly, and downregulates TGF-β1 signaling relevant to fibrosis[12]. Via ERK1/2 pathways, this reduces pro-inflammatory cytokines (TNF-α, IL-6, IL-1β, IL-17, IFN-γ) while increasing IL10; in the airway epithelium, it reduces IL-33 and TSLP, suppressing ILC2, Th2 cells, and eosinophil-derived IL-4, IL-5, and IL-13, while decreasing mucus secretion[13]. eNOS augmentation contributes to vasodilatory and anti-proliferative pulmonary vascular effects (Fig. 1). Beyond these direct actions, GLP-1 RA-induced weight loss reverses obesity-related mechanical lung compromise - diaphragmatic restriction and reduced functional residual and total lung capacity – while reducing adipose-derived pro-inflammatory mediators (leptin, IL-6, TNF-α), creating a systemic anti-inflammatory milieu that complements direct airway effects[14] (Fig. 2).

Evidence Overview: Meta-Analyses and Umbrella Reviews

A foundational meta-analysis by Yu *et al* (28 RCTs, 77,485 participants with T2DM, overweight, or obesity) found GLP-1 RA use associated with a 14% lower overall risk of respiratory disease (RR 0.86, 95% CI 0.81 - 0.93), with semaglutide, liraglutide, and dulaglutide each individually significant (RR 0.82 - 0.86), and significant reductions in pulmonary oedema and bronchitis[15]. A larger meta-analysis by See *et al* (55 RCTs, 99,870 participants through October 2024) found significant reductions in COPD (RR 0.82), sleep apnoea (RR 0.59), pulmonary oedema (RR 0.62), and pneumonia (RR 0.82) versus placebo, with greater benefit in the overweight/obese subgroup[16]. The umbrella review by Kong *et al* (123 meta-analyses, 5,617 articles) confirmed directional trends toward improved respiratory outcomes, including reduced pneumonia risk in high-cardiovascular-risk T2DM and reduced COVID-19 hospitalisation and mortality, while noting predominantly low GRADE evidence quality[4].

GLP-1 RAs and COPD

COPD is characterised by poorly reversible airway obstruction and chronic inflammation[17]; T2DM affects 15 - 30% of COPD patients, and metabolic syndrome components are

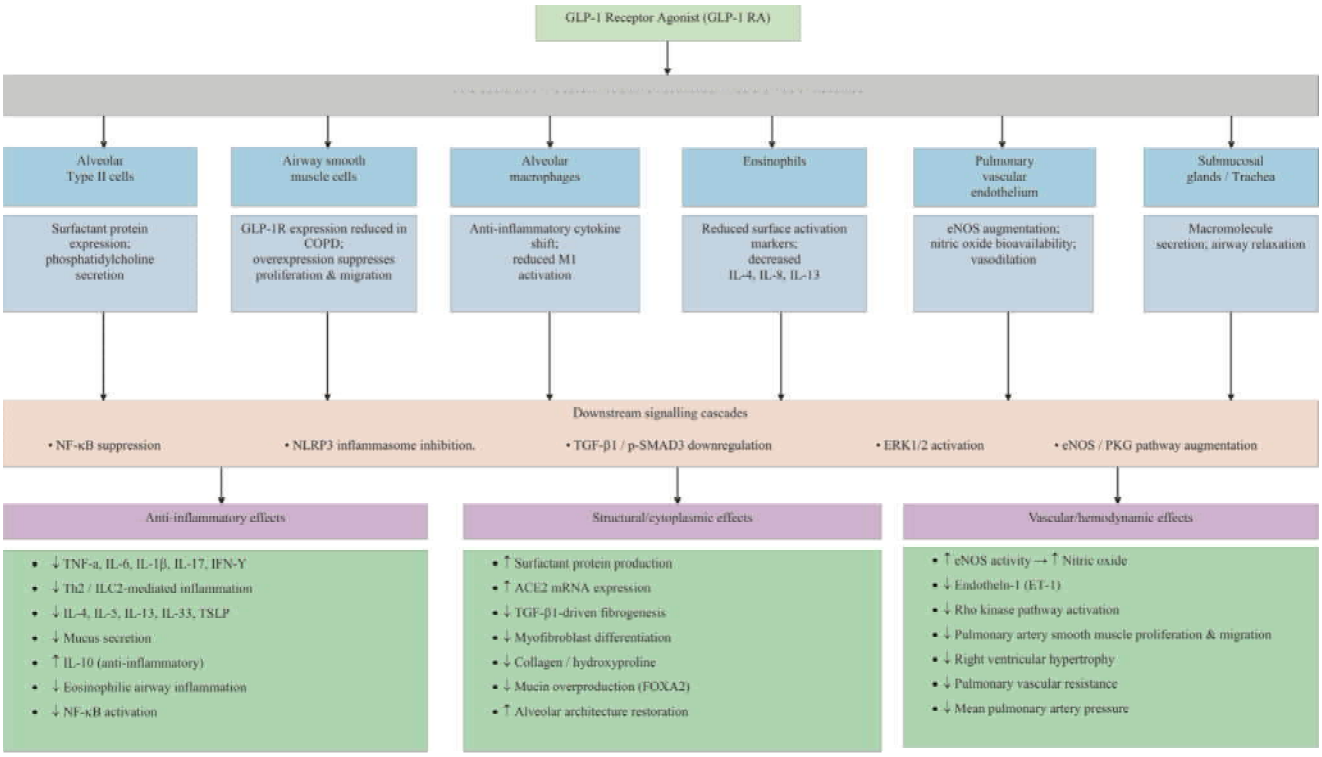

Fig. 1: *Pulmonary cell targets and downstream signalling mechanisms of GLP-1 receptor agonists.*

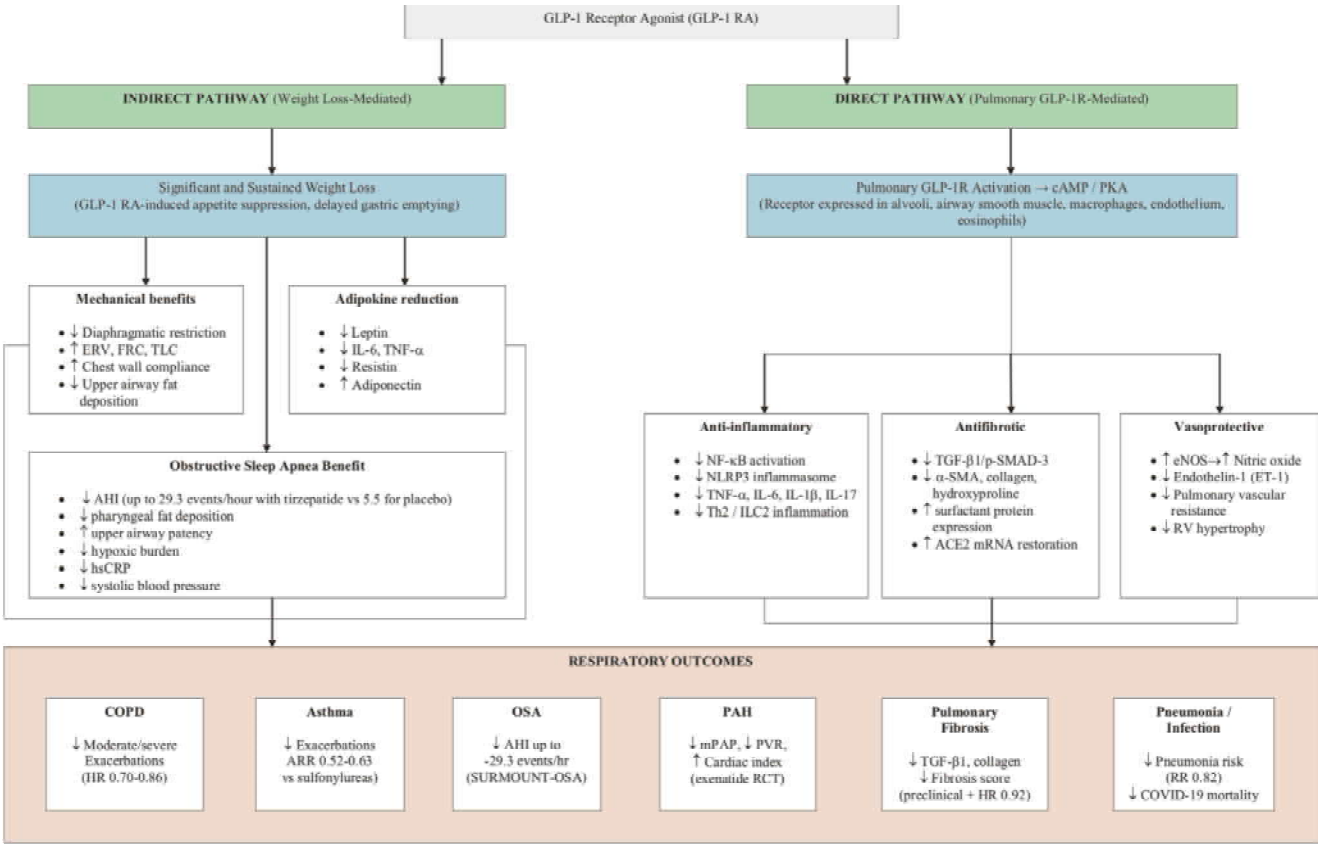

Fig. 2: *Direct and indirect pathways by which GLP-1 receptor agonists produce respiratory benefits.*

independent risk factors for small airway dysfunction, with disproportionately higher exacerbation and mortality rates in patients with both conditions[3]. Preclinically, exendin-4 reinstated FOXA2 expression and reduced mucin production and bacterial load in COPD mouse models[18], supporting a direct mucociliary mechanism of benefit.

Population-based evidence consistently links GLP-1 RA use with reduced COPD exacerbations. In the UK CPRD cohort, Pradhan *et al* reported a 30% reduction in severe exacerbations (HR 0.70, 95% CI 0.49 - 0.99) and 37% reduction in moderate exacerbations versus sulfonylureas[19]. Ray *et al*, across three US insurance databases (>32,000 matched pairs), found a 14% lower risk of moderate-to-severe exacerbations versus DPP-4 inhibitors (HR 0.86, 95% CI 0.81 - 0.91)[20]. A network meta-analysis by Pirera *et al* (nine observational studies) confirmed both GLP-1 RAs (RR 0.66) and SGLT-2 inhibitors (RR 0.64) were significantly superior to sulfonylureas for moderate-to-severe exacerbations[21], while a Mendelian randomisation study by Lai *et al* provided causal genetic evidence for lower risks of COPD (OR 0.838), early-onset COPD (OR 0.751), and asthma (OR 0.872), substantially reducing concerns about confounding by indication[22]. Proof-of-concept randomised data complement these findings: in a placebo-controlled trial of 40 patients with obesity and COPD, liraglutide significantly improved FVC, DLCO, and CAT scores over 40 weeks[23], and the LIRALUNG crossover trial similarly demonstrated improved FVC in T2DM patients[24].

GLP-1 RAs and Asthma

Obese patients with asthma represent a distinct low-Th2, neutrophilic, corticosteroid-resistant phenotype driven by adipokine dysregulation, which is directly relevant to GLP-1 RA therapy given its dual action on both adipokine and ILC2-mediated inflammatory pathways[25]. In obese asthma mouse models, GLP-1R agonism inhibits ILC2 activation and neutrophilic airway inflammation, reducing epithelial ICAM-1 and inflammatory chemokines (CCL11, CXCL1, CXCL5) and IL-33 expression[26]; tirzepatide produced greater IL-5/IL-13 reduction than semaglutide monotherapy, while semaglutide was superior for IL-33 suppression, reflecting differential receptor pharmacology[27].

Clinically, Lee *et al* (UK CPRD; self-controlled case series and cohort analyses) found GLP-1 RA add-on therapy associated with a 40% reduction in asthma exacerbations (IRR 0.60, 95% CI 0.49 - 0.73) independent of glycaemic and weight changes[28]. Wang *et al* (US MarketScan, n = 17,088) found an absolute risk reduction of 1.6% in acute

exacerbations versus sulfonylureas, rising to 2.8% in patients with frequent prior emergency visits[29], and Sheikh *et al*, in a propensity-matched analysis of 47,843 patients per group, found lower exacerbations and emergency visits at one year and significantly lower all-cause mortality at three years[30]. A Mendelian randomisation study confirmed a causal association between genetically proxied GLP-1R agonism and reduced asthma risk[22], and the ongoing GATA-3 trial at Vanderbilt University Medical Center is evaluating semaglutide in obesity-related symptomatic asthma without T2DM to disentangle weight-dependent from weight-independent effects[31].

GLP-1 RAs and Obstructive Sleep Apnoea

OSA is strongly linked to obesity-driven pharyngeal fat deposition and upper airway collapsibility, which in turn worsens metabolic dysfunction through intermittent hypoxia and systemic inflammation. GLP-1 RAs are positioned to interrupt this cycle through both weight-mediated mechanical improvement and direct pulmonary GLP-1R agonism. The landmark SURMOUNT-OSA trial evaluated tirzepatide in adults with moderate-to-severe OSA and obesity across two double-blind, placebo-controlled studies (PAP-naive and PAP-user populations), achieving AHI reductions of up to 62.8% (approximately 25 - 30 fewer events/hour), with 51.5% of PAP-naive participants meeting disease-resolution criteria and significant reductions in hsCRP, systolic blood pressure, and hypoxic burden[32]. A meta-analysis of four RCTs by Dandamudi *et al* confirmed a pooled AHI reduction of - 13.89 events/hour alongside significant weight loss and blood pressure reductions[33], consistent with earlier evidence from the SCALE Sleep Apnoea trial, in which liraglutide reduced AHI by - 12.2 events/hour versus - 6.1 with placebo in non-diabetic patients[34].

Beyond AHI improvement, Hwang *et al*, using 5-year TriNetX propensity-matched data in OSA patients with T2DM, found GLP-1 RAs reduced new-onset pulmonary hypertension (HR 0.724 versus DPP-4 inhibitors), intubation (HR 0.603), and new-onset COPD, extending benefit to prevention of downstream pulmonary complications[35].

GLP-1 RAs and Pulmonary Arterial Hypertension

PAH is characterised by pulmonary vascular remodeling, endothelial dysfunction, and smooth muscle proliferation. GLP-1R is expressed on pulmonary arterial smooth muscle and endothelial cells, and its activation promotes eNOS activity and nitric oxide bioavailability while suppressing endothelin-1 and Rho kinase signaling – targeting key drivers of pulmonary vascular disease. In the monocrotaline rat model, liraglutide both prevented and reversed PAH, right ventricular hypertrophy, and vascular remodeling, and inhibited smooth muscle cell migration and proliferation[36], providing proof-of-concept preclinical mechanism.

Clinically, intravenous exenatide in 17 patients with idiopathic PAH and CTEPH undergoing right heart catheterisation was well tolerated and reduced mean pulmonary artery pressure (45 ± 15 to 40 ± 18 mmHg), improved cardiac index, and reduced pulmonary vascular resistance – the first direct human haemodynamic data confirming GLP-1 RA activity in the PAH vasculature and establishing proof-of-concept for dedicated trials[37]. Indirect evidence also supports cardiopulmonary benefit: among OSA patients with T2DM, GLP-1 RAs were associated with lower pulmonary hypertension risk than other antihyperglycaemic classes[35], and in heart failure with preserved ejection fraction – the most prevalent cause of group 2 pulmonary hypertension - semaglutide reduced cardiovascular death or worsening heart failure (HR 0.69, 95% CI 0.53 - 0.89)[38], with tirzepatide reducing the same composite by 38% in the SUMMIT trial[39].

GLP-1 RAs and Pulmonary Fibrosis

Idiopathic pulmonary fibrosis is driven by aberrant TGF-β1 signaling, NLRP3 inflammasome activation, and excessive myofibroblast differentiation, mechanisms directly targeted by GLP-1R-mediated TGF-β1-p-SMAD3 supperssion and reduced extracellular atrix deposition. In the bleomycin mouse model, liraglutide decreased collagen and hydroxyproline expression, restored ACE2 mRNA, increased surfactant protein production, and partially restored alveolar architecture at both pro-inflammatory and established-fibrosis phases[40]. A targeted pulmonary delivery system using gelation-coated chitosan microparticles significantly attenuated bleomycin-induced fibrosis with reductions in TGF-β1, p-SMAD3, and collagen, positioning inhaled GLP-1 RA delivery as a compelling translational concept[41]. Clinically, a TriNetX-based study of 158,224 matched pairs by Ho *et al* found GLP-1 RA use associated with 8% lower pulmonary fibrosis risk (HR 0.92, 95% CI 0.87 - 0.98) versus DPP-4 inhibitors[42]; while no dedicated prospective IPF trials yet exist, this observational signal in a large cohort warrants further investigation.

GLP-1 RAs and Pneumonia, Infection, and Acute Lung Injury

People with diabetes face two-to-four-fold higher infection hospitalisation risk, a vulnerability starkly evident during COVID-19. Preclinically, GLP-1 RAs demonstrate protective effects in infectious and non-infectious lung inflammation: in pneumonia-induced sepsis models, liraglutide reduced TNF-α and IL-6, promoted surfactant protein secretion, and improved survival[43]. Clinically, the See *et al* meta-analysis found an 18% lower pneumonia risk versus placebo (RR 0.82)[16], and

Song *et al*, in a network meta-analysis, found GLP-1 RAs associated with a 27% reduction in COVID-19 mortality and 16% lower severe disease risk compared with insulin, with benefit most pronounced in non-elderly patients[44] - findings corroborated by the Kong *et al* umbrella review[4]. Using DPP-4 inhibitors as comparator, Ho *et al* found a more conservative but still significant 6% lower risk of respiratory infections (HR 0.94, 95% CI 0.92 - 0.96), an estimate less susceptible to confounding by disease severity[42].

An important counterpoint nuances this picture: circulating endogenous GLP-1 rises during acute critical illness and correlates with worse outcomes. Hansell *et al*, studying 297 critically ill patients with acute respiratory failure, found higher endogenous GLP-1 levels in non-survivors and patients with ARDS, independently associated with 90-day mortality (OR 2.02, 95% CI 1.23 - 3.31)[45]. This likely reflects a physiological stress-response marker rather than a causal harmful mechanism, since pharmacological GLP-1 RA therapy acts through sustained receptor agonism distinct from the endogenous surge of critical illness – but it signals the need for caution in interpreting GLP-1 biology in acute critical illness.

GLP-1 RAs and Lung Cancer

Diabetes and prediabetes are linked to increased lung cancer risk, and GLP-1 RAs may favourably modify this association. In an analysis of over one million electronic health records spanning 15 years, Tabernacki *et al* found GLP-1 RAs carried the lowest lung cancer risk among non-insulin antidiabetic drugs compared with insulin (RR 0.49, 95% CI 0.41 - 0.59), independent of histological type, sex, race, or smoking status[46]. This estimate is notably larger than the 14% reduction observed by Ho *et al* using DPP-4 inhibitors as comparator[42] – a divergence likely explained by greater confounding by indication when insulin, typically reflecting more advanced diabetes, is used as the reference group.

Agent-specific evidence across these disease areas is summarised in Table I, and key clinical studies in Table II.

Table I: Respiratory evidence profile of individual GLP-1 receptor agonists.

Agent	Respiratory Evidence	Highest Level of Evidence	Key Effect Size(s)	Notable Respiratory Safety Signal
Semaglutide	Overall respiratory disease risk reduction; antifibrotic preclinical (targeted pulmonary delivery); HFpEF/ group 2 PH (pooled RCT analysis)	Meta-analysis of RCTs; preclinical	18% reduction in overall respiratory disease risk (RR 0.82, Yu *et al*)[15]; HFpEF: HR 0.69 (95% CI 0.53 - 0.89)[38]	FAERS signal for asthma-like events and deaths; not corroborated by cohort studies or meta-analyses[48]
Liraglutide	Broadest respiratory evidence base of any individual agent: COPD exacerbations (observational + RCT), asthma exacerbations (observational), OSA-AHI reduction (RCT), pulmonary fibrosis (preclinical), PAH (preclinical)	RCTs (SCALE Sleep Apnoea; Altintas *et al*); observational cohorts; preclinical	OSA AHI: - 12.2 events/hour vs placebo[34]; COPD severe exacerbations: HR 0.70 (0.49 - 0.99)[19]; asthma exacerbations: IRR 0.60 (0.49 0.73), add-on to metformin[28]	FAERS signal for asthma-like events; aspiration risk related to delayed gastric emptying in perioperative setting[48]
Dulaglutide	Overall respiratory disease risk reduction only	Meta-analysis of RCTs (Yu *et al*)	18% reduction in overall respiratory disease risk (RR 0.82)[15]	No specific respiratory pharmacovigilance signal identified in reviewed literature
Tirzepatide (GLP-1/GIP dual agonist)	OSA: largest AHI reduction of any agent in RCT data; obese asthma preclinical (greater IL-5/IL-13 reduction than semaglutide monotherapy); HFpEF/ group 2 PH (SUMMIT RCT)	RCTs (SURMOUNT-OSA; SUMMIT); preclinical	OSA AHI: up to - 29.3 events/hour vs - 5.5 for placebo; 51.5% PAP-naive patients met OSA resolution criteria[32]; SUMMIT: 38% relative risk reduction in cardiovascular death or worsening heart failure[39]	Fewer respiratory/asthma-like events in FAERS compared to exenatide and liraglutide; GIP receptor co-agonism may confer additional anti-inflammatory benefit
Exenatide	PAH: only agent with direct human haemodynamic data (acute IV study, N=17); COPD preclinical (FOXA2/mucin pathway)	Proof-of-concept acute haemodynamic study; preclinical; meta-analysis (non-significant for overall respiratory disease)	Acute IV in PAH/CTEPH: mPAP 45 ± 15 to 40 ± 18 mmHg; PVR 7.8 ± 8.0 to 5.9 ± 5.0 WU; cardiac index 2.1 ± 0.6 to 2.4 ± 0.9 L/min/m^2 [37]	Highest proportion of asthma-related deaths in FAERS among GLP-1 RAs[48]; higher immunogenicity attributed to lower structural homology to human GLP-1 (53%)[49]

Table II: Key clinical studies on GLP-1 receptor agonists and respiratory outcomes.

Study (Author, Year)	Design	Population	Comparator	Primary Respiratory Outcome	Key Result	Limitations
Yu *et al*, 2023[15]	Meta-analysis, 28 RCTs	T2DM/overweight/ obesity; N = 77,485	Placebo/active control	Overall respiratory disease risk	RR 0.86 (0.81 - 0.93); bronchitis pulmonary oedema RR 0.66; RR 0.86	Outcomes were adverse-event reports, not primary endpoints

See *et al*, 2025[16]	Meta-analysis, 55 RCTs	T2DM/overweight/ obesity; N = 99,870	Placebo	COPD, OSA, pulmonary oedema, pneumonia	COPD RR 0.82; OSA RR 0.59; pneumonia RR 0.82	No prespecified respiratory endpoints; safety-data derived
Kong *et al*, 2026[4]	Umbrella review, 123 meta-analyses	Multiple disease contexts (T2DM, COVID-19)	Placebo/active comparators	Respiratory outcomes across disease areas	Reduced pneumonia risk in high-CV-risk T2DM; reduced COVID-19 hospitalisation/mortality	Predominantly low GRADE evidence; methodological shortcomings in source meta-analyses
Pradhan *et al*, 2022[19]	Population-based cohort (UK CPRD); N = 56,243	COPD + T2DM	Sulfonylureas	Severe/moderate COPD exacerbations	Severe HR 0.70 (0.49 - 0.99); moderate HR 0.63 (0.43 - 0.94)	Retrospective; no spirometry; residual confounding
Ray *et al*, 2025[20]	Comparative effectiveness, 3 US databases; N >32,000 pairs	COPD + T2DM	DPP-4i, SGLT-2i	Moderate-to-severe vs COPD exacerbations	DPP-4i HR 0.86 (0.81 - 0.91); vs SGLT-2i HR 0.94	Retrospective; claims-based; median follow-up 142 days
Altintas *et al*, 2022/ Lopez-Cano *et al*, 2022 (RCTs)[23,24]	Two placebo-controlled RCTs; N = 40 and crossover design	Obesity/T2DM + COPD	Placebo	FVC, DLCO, CAT score	Liraglutide significantly improved FVC in both trials; DLCO and CAT score also improved	Small samples; short follow-up; FEV1 and 6MWD unchanged
Lee *et al*, 2025[28]	UK CPRD; SCCS and cohort analysis; n = 4,278/8,424	Asthma + T2DM	Metformin baseline	Asthma exacerbations	IRR 0.60 (0.49 - 0.73); independent of glycaemic/ weight change	Retrospective; SCCS design limits generalisability
Sheikh *et al*, 2025[30]	Propensity-matched cohort, US TriNetX; N = 47,843/group	Obese asthma ± T2DM	Non-GLP-1 RA users	Exacerbations, ED visits, mortality	1-year exacerbations 7.3% vs 8.0%; 3-year mortality 3.1% vs 4.2%	Retrospective; conference abstract; limited methodological detail
Malhotra *et al*, 2024 SURMOUNT -OSA (RCT)[32]	Two parallel double-blind RCTs (PAP-naive/PAP users)	Moderate-to-severe OSA + obesity	Placebo	AHI reduction	Up to -29.3 events/hour vs -5.5 placebo; 51.5% met resolution criteria	52-week duration; long-term durability not established
Samaranayake *et al*, 2026[37]	Prospective acute haemo-dynamic study; N = 17	Idiopathic PAH/CTEPH, right heart catheterisation	Within-patient (IV exenatide)	mPAP, cardiac index, PVR	mPAP 45 ± 15 to 40 ± 18 mmHg; PVR 7.8 ± 8.0 to 5.9 ± 5.0 WU	Small sample; acute single-dose only; no chronic outcome data
Ho *et al*, 2025[42]	Retrospective cohort, US TriNetX; N = 158,224 pairs	T2DM	DPP-4 inhibitors	Pulmonary fibrosis, lung cancer, infections	Fibrosis HR 0.92; cancer HR 0.86; infections HR 0.94	Retrospective; no spirometry
Hansell *et al*, 2025[45]	Retrospective cohort, UPMC ICUs; N = 297	Critically ill adults, acute respiratory failure	Comparison across severity subgroups	90-day mortality vs endogenous GLP-1	Higher endogenous GLP-1 linked to non-survival/ ARDS; OR 2.02 (1.23 - 3.31)	Endogenous GLP-1 measured, not pharmacological use; does not contradict therapeutic benefit
Tabernacki *et al*, 2024[46]	Nationwide retrospective cohort, >1,000,000 EHRs; 15-year follow-up	T2DM	Insulin and other antidiabetic drugs	Lung cancer risk	Lowest risk among non-insulin agents: RR 0.49 (0.41 - 0.59) vs insulin	No dosage/duration data; confounding by indication possible

Safety Considerations Relevant to Pulmonologists

Delayed gastric emptying with GLP-1 RAs increases aspiration risk (1 in 3,000 - 4,000 procedures) during bronchoscopy or other sedated airway procedures, and anesthesiology societies recommend withholding GLP-1 RAs before elective procedures[47]. FAERS analysis identified increased asthma and asthma-like event reporting with semaglutide, liraglutide, and particularly exenatide, including deaths, though such spontaneous-reporting signals carry inherent limitations (reporting bias, no denominator data) and have not been corroborated by major population-based cohort and meta-analytic studies of exacerbation endpoints[48]. The higher immunogenicity of exenatide – which shares only 53% structural homology with human GLP-1 – may partly explain this differential signal across agents[49]. Excessive lean mass loss is a recognised concern, particularly relevant in cachectic or sarcopenic COPD patients, who warrant caution and monitoring; newer combination regimens with resistance exercise preserve lean mass more effectively[50].

The Observational Evidence Gap: Caveats And Limitations

Most clinical respiratory evidence for GLP-1 RAs derives from retrospective observational studies, with confounding by indication a pervasive concern – patients prescribed GLP-1 RAs often differ systematically from comparator-agent recipients in age, disease severity, and comorbidity burden. Unmeasured confounders (smoking status, FEV1, blood

eosinophil counts) are frequently unavailable in claims-based datasets, and heterogeneous exacerbation definitions and variable follow-up introduce further uncertainty; generalizability may also be limited by the predominance of data from high-income, insured populations. Large cardiovascular outcome RCTs have generally shown neutral respiratory effects, but this more likely reflects the absence of prespecified pulmonary endpoints and limited event capture than true biological absence of effect – making the contrast with consistent observational benefit a probable methodological artifact rather than a biological paradox.

Future Directions

Dedicated RCTs powered for respiratory exacerbation endpoints are the most immediate priority. The GATA-3 trial in obesity-related asthma and a completed liraglutide COPD trial incorporating spirometry, imaging, and exercise capacity are first steps toward this goal, and tirzepatide trials in group 3 pulmonary hypertension represent a tractable next design given the high obesity prevalence in this population. Head-to-head comparisons between agents are warranted to determine whether differences in receptor affinity or pharmacokinetics translate into differential respiratory benefit, and real-world IPF registries measuring FVC decline represent a feasible, low-cost evidence source. Inhaled pulmonary delivery systems bypassing systemic exposure remain a compelling translational concept. Biomarker-driven patient selection - using fractional exhaled nitric oxide, blood eosinophil counts, and leptin-to-adiponectin ratio - will ultimately help determine which patients derive the greatest pulmonary benefit, while mechanistic substudies disentangling direct pulmonary effects from weight-loss-mediated effects remain necessary.

Conclusion

GLP-1 receptor agonists have evolved from cardiometabolic agents into a drug class with meaningful respiratory relevance. Their widespread pulmonary expression underpins direct anti-inflammatory, anti-fibrotic, and vasoprotective effects that complement the established benefits of weight reduction. Genetic, mechanistic, and clinical evidence consistently supports benefit in obstructive sleep apnoea, asthma, COPD, pulmonary arterial hypertension, and potentially pulmonary fibrosis. Dedicated randomised trials powered for respiratory endpoints are now an urgent priority. In patients with active obstructive airway disease and obesity or frequent exacerbations, current evidence supports preferring GLP-1 RAs or SGLT-2 inhibitors over sulfonylureas or DPP-4 inhibitors, while prospective data continue to mature.

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CASE REPORT

JIACM 2026; 27 (2): 155-157

Turner's Syndrome and Hashimoto's Thyroiditis: An Association between Genetics and Autoimmunity

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Abstract

Worldwide approximately 1.5 million women suffer from Turner Syndrome . X chramasome aberrations can be of different types, which comprise of the X monosomies like (45, X) and mosaicism (50 - 70%), which includes 45X/46 XX, 45 X/46 XY, 45 X/46 XX/47 XXX, 45 X/46 X, i (Xq), 45 X/46, and X del (Xp), as well as structural aberrations, such as the total or partial deletion of the short arm of an X chromosome (46, X del (Xp)), the isochromosome of the long arm of an X (46, X, i (Xq), ring chromosome (46, X, r (X), and marker chromosome (46, X + m). It has been seen that, the presence of two X chromosomes and skewed inactivation of one of them are thought to play a protective role in females, who generally mount a stronger immune response to different types of pathogens. However, the hyperresponsiveness of the immune system in females results in a predisposition towards auto-immune diseases. Autoimmune diseases are 2 - 3 times more frequent in women with Turner syndrome.

Key words: Turner syndrome, Hashimoto's Thyroiditis, X chromosomes

Introduction

Turner syndrome (TS) is a genetic disease characterised by quantitative or structural aberrations in one of two X chromosomes with frequent mosaicism. Incidence of Turner syndrome (TS) is estimated between 1 in 2000 to 1 in 2500 live female births[2,3].

There is no correlation between the onset of TS and age of the parents, environmental factors, or use of specific drugs/ toxins. Turner syndrome is observed in all races all over the world, and it is not hereditary; therefore, it can occur even in families with healthy individuals.

Women with Turner syndrome show typical phenotypic features, including short stature; a short and webbed neck; cubitus valgus; a broad chest with widely spaced nipples; and lymphoedema of the hands and feet, which is particularly common at birth. The characteristics of Turner Syndrome comprise low positional and dysplastic ears, antimongoloid slant, epicanthus, poor facial expression, low descending hairline on the neck, gothic palate, and micrognathia. The frequency of signs and symptoms varies in different patients with Turner syndrome and may depend on the type of X chromosome aberrations.

Individuals with Turner syndrome (TS) are prone to develop autoimmune disorders, particularly thyroiditis, the most frequent of which is Hashimoto's disease. Thyroid autoimmune diseases are characterised by abnormal lymphocytic activation, directed against self-antigens. The cause of autoimmune diseases in TS remains unclear, although there are several mechanisms that suggest a potential correlation between the X-isochromosome and increased prevalence of anti-thyroid peroxidase (TPO-Ab) antibodies. Other researchers, in turn, suggested that a genetic factor located on the X-gene could play a role in the development of thyroid autoimmune diseases. This claim can be confirmed by screening each TS women for thyroid diseases. Nonetheless, the risk of hypothyroidism or hyperthyroidism in Turner syndrome remains independent of the karyotype, and the treatment of thyroid abnormalities do not differ from those established for healthy populations. We present the case of young lady who was diagnosed as Turner syndrome and Hashimotos thyroiditis.

Case report

A 23-year-old lady presented with complaints of generalised weakness, constipation facial puffiness and primary amenorrhoea along with not gaining height and weight according to her age. Her mother also complained about her poor scholastic performance as compared to other children of same age.

Obstetric history: She was borne of a non-consanguineous marriage, normal vaginal delivery with normal milestones according to her age and sex up to 8 years.

On examination her height was120 cm, the weight was 28 kg, and body mass index was 19.4 kg/m^2. Her heart rate was 84 beats/minutes, blood pressure was 98/68 mm Hg.

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She had mild pallor, webbed neck, broad shield chest, cubitus valgus and her external genitalia were juvenile, with a pubertal state of A1M1P1 (Tanner staging). All other systemic examination was normal. As phenotypic examination was in favour of Turner syndrome (Fig. 1), we sent hormonal assays, chromosomal karyotyping, abdominal and pelvic ultrasound, thyroid profile, X-ray chest PA view and X-ray of forearm for confirmation of her age, ECG, echocardiography and other routine examination were done. X-ray chest showed cardiomegaly. Her bone age was 12 - 13 years, which lagged behind her chronological age.

The results of karyotyping demonstrated a gene karyotype of 46, X, psu idic (X) (q28).

Thyroid function analysis showed that the thyroid-stimulating hormone (TSH) level was >100 μIU/mL (normal range, 0.35 - 4.94 μIU/mL), free FT4 level <0.4 ng/dL (normal range 0.7 - 1.48 ng/dL), freeT3 level <1.5 pg/mL (normal range 1.58 - 4.91 pg/mL), and anti TPO 829.67 IU/mL (normal range 0 - 5.61 IU/mL).

Fig. 1: *Phenotype of Turner Syndrome.*

Other hormonal tests showed the prolactin level was 6.62 ng/mL (reference range 5.18 - 26.53 ng/mL), luteinizing hormone level was 7.7 mIU/mL, and the of follicle-stimulating hormone was 73.08 mIU/mL.

Ultrasound whole abdomen was suggestive of a hypoplastic uterus with bilateral streak and atrophic ovaries. Ultrasound of thyroid gland was suggestive of multiple small cystic nodules in bilateral lobes of with normal size. ECG was suggestive of low voltage complexes, and 2D Echo showed moderate circumferential pericardial effusion. After complete evaluation, patient was diagnosed as a case of Turner syndrome with autoimmune thyroiditis. She was given symptomatic treatment in the form of thyroxine 62.5 microgram per day, and diuretic. Patient and her mother were counselled about treatment and prognosis. She was discharged in satisfactory condition.

Discussion

Autoimmune thyroid disorders are the most common autoimmune condition seen in patients with Turner syndrome, with a prevalence significantly higher than in the general population. The absence of one X chromosome is thought to contribute to immune dysregulation, and increasing susceptibility to autoimmune diseases.

The largest number of immune-related genes is housed on the X chromosome, where genes FOXP3 and PTPN22 are presumed to contribute most commonly to the pathogenesis of Turner syndrome. Women suffering from TS present at higher-than-average risk of developing autoimmune thyroid diseases, where hypothyroidism appears most commonly, mainly in the subclinical form, occurring in about 58% of TS women. It may develop not only in adolescence and adult age, but also in childhood, and is characterised by elevated TSH levels, while maintaining normal T4 concentrations. Scientific literature also provides a case of Hashimoto's encephalopathy co-existing with Turner syndrome, which is a rare disease with an autoimmune pathogenesis. Nevertheless, up to now, the autoimmune mechanism underlying this syndrome has not been completely understood and, requires further research.

Due to a higher incidence of autoimmune diseases in patients with TS, current guidelines recommend screening for hypothyroidism at the time of diagnosis using TSH and a fT4 (free-thyroxine), which should commence in early childhood

and be subsequently performed annually. However, there are no recommendations for routine testing of thyroid antibodies.

Patients with TS suffer from an increased risk of celiac disease, vitiligo, psoriasis, type 1 diabetes, adrenocortical insufficiency, juvenile idiopathic arthritis, and inflammatory bowel disease.

Another noteworthy issue is the screening for cardiovascular abnormalities of TS itself. Both congenital heart malformation and acquired disorder such as ischaemic heart disease contributes greatly to morbidity and mortality in patients with TS. Bicuspid aortic valve is the most common congenital malformation with a prevalence of 14 - 34%. Other common phenotypic characteristics of heart include coarctation of the aorta (7 - 14%) and aortic dilation/ aneurysm (3 - 42%)[4]. These cardiovascular malformations can occur in isolation or in combination in patients with TS[13]. Hypertension occurs in 50% of patients with TS[4]. Persistent elevation of systolic blood pressure is a risk factor for aortic root dilation and the consequent aortic dissection.

Hypothyroidism in Turner syndrome can worsen growth failure, delay puberty, and affect cognitive performance. Therefore, early detection and prompt treatment is essential. Gravholt *et al* in their study demonstrated that the genes IL3RA and CSF2RA located on the X chromosome are differentially methylated in women with Turner syndrome in comparison to healthy women with a karyotype of 46, XX. Furthermore, they hypothesized that IL3RA could be associated with an increased risk of autoimmune diseases in Turner syndrome, such as thyroiditis[4].

The causes of pericardial effusion are numerous, among which hypothyroidism is an uncommon one. The prevalence of pericardial effusion is 3 - 6% in patients with mild disease and 80% in myxoedema. It is revealed during cardiovascular evaluation in most cases, but can also be the initial presentation. Increased capillary permeability and reduced lymphatic drainage result in gradual accumulation of fluid in the pericardial space, though the mechanism has not been fully elucidated[6]. The process usually takes from months to years, as the severity and chronicity of hypothyroidism varies[7]. Mortensen *et al* and Chen *et al* reported an increased frequency of AITDs with age[8,9]. In our patient also X-ray chest, ECG and echocardiography suggested pericardial effusion. Her chronological age did not correspond with her bone age which may be due to both Turner syndrome as well as thyroid disorder. Though euthyroidism is a common clinical phenotype, transition to subclinical or overt hypothyroidism can occur, emphasizing the importance of screening for thyroid diseases through the life-span[10,11]. A higher prevalence of autoimmune thyroiditis was reported in iso-chromosome Xq population[2,12]. Further studies are required to elucidate the underlying mechanism. Despite the well documented role of oestrogen in AITDs, no association between oestrogen administration and the occurrence of AIDs was revealed in TS patients.

The exact genetic and epigenetic mechanism of cardiopathies in TS remains unclear. Acquired heart abnormalities are associated with obesity, dyslipidaemia, hypertension, diabetes mellitus and low oestrogen levels. Cardiovascular diseases, both congenital and acquired ones, should be screened in patients with TS.

In conclusion, this case highlights that hypothyroidism should be screened in patients with pericardial effusion, and also emphasized the link between autoimmune thyroid diseases and Turner Syndrome.

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CASE REPORT

JIACM 2026; 27 (2): 158-160

Sequential Onset of Inflammatory Myositis Following Autoimmune Pancreatitis in IgG4-Related Disease

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Abstract

Immunoglobulin G4-related disease (IgG4-RD) is a systemic fibro-inflammatory disorder that can involve multiple organs, most commonly the pancreas, biliary tree, and salivary glands. Extra-pancreatic manifestations may precede, coexist, or follow autoimmune pancreatitis (AIP), and skeletal muscle involvement is exceedingly rare. We present the case of an 80-year-old female with bronchial asthma, who was diagnosed with type 1 AIP based on clinical, biochemical, imaging, and histopathological features. Two weeks following steroid initiation, she developed proximal muscle weakness and elevated muscle enzymes, consistent with inflammatory myositis. Notably, myositis occurred despite ongoing corticosteroid therapy. This case highlights the importance of recognizing unusual organ involvement in IgG4-RD, as it may mimic or overlap with other autoimmune conditions. To our knowledge, IgG4-related myositis as a sequential manifestation after AIP has rarely been reported in literature.

Introduction

IgG4-related disease (IgG4-RD) is a chronic, immune-mediated condition characterised by tumefactive lesions, storiform fibrosis, obliterative phlebitis, and lymphoplasmacytic infiltration rich in IgG4-positive plasma cells and mimics many inflammatory and malignant conditions[1]. First recognised in the context of autoimmune pancreatitis (AIP), it is now understood as a multisystem disorder affecting the pancreas, hepatobiliary tract, salivary glands, retroperitoneum, kidneys, lungs, and rarely, skeletal muscle[2].

Autoimmune pancreatitis is the prototypical manifestation of IgG4-RD, with diagnostic features including characteristic imaging (diffuse or focal pancreatic enlargement with ductal narrowing), elevated serum IgG4 levels, histology, and response to corticosteroids[3,4]. While extrapancreatic involvement is common, muscular manifestations are extremely rare. Only a handful of case reports have described IgG4-related myositis[5,6].

We report an unusual case of an elderly woman, with biopsy-proven AIP, who subsequently developed inflammatory myositis despite corticosteroid therapy, emphasizing the diagnostic and therapeutic challenges in managing multi-organ IgG4-RD.

Case Presentation

An 80-year-old woman, known case of bronchial asthma, presented in July 2025 with complaints of dull aching epigastric pain, radiating to the back, without any aggravating factors or relieving factors and vomiting for 3 days. She also developed progressive jaundice. There was no history of fever, hematemesis, or melena. On examination, she was icteric, with epigastric tenderness but no palpable organomegaly.

Baseline investigations revealed predominantly conjugated hyperbilirubinaemia with mild elevation of transaminases and alkaline phosphatase, along with baseline renal dysfunction. Serial trends are shown in Table I.

Fine Needle Aspiration biopsy of a pancreatic mass revealed dense lymphoplasmacytic infiltrate with storiform fibrosis and abundant IgG4-positive plasma cells, consistent with IgG4-related autoimmune pancreatitis (type 1 AIP). ERCP was performed and biliary stent was placed to relieve the cholestasis.

The pattern was consistent with predominantly conjugated hyperbilirubinaemia, mild transaminitis with ALP elevation, biochemical features of mixed hepatocellular – cholestatic injury eventually improved by day 4 after ERCP. She was started on oral corticosteroids (prednisolone 40 mg/day) and discharged home.

Second episode

Two weeks later, she re-presented with acute-onset severe myalgia, initially in proximal lower limbs, rapidly progressing to involve hip girdle, trunk, and neck flexors, causing difficulty rising from sitting, squatting, and ambulating

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without support. There was no diplopia, dysphagia, respiratory difficulty, skin rash, sensory loss, or bowel/bladder involvement. On clinical examination, she had Medical Research Council (MRC) grade 2/5 proximal muscle power with preserved distal strength and intact reflexes and sensation.

Investigations revealed marked elevation of serum creatine phosphokinase (>10,000 U/L) and leukocytosis, while repeat lever function tests showed worsening transaminases (Table II). Myositis panel was positive for Mi-2β antibody, while viral serology and thyroid profile were normal. MRI thigh was not performed due to logistic limitations. Muscle biopsy demonstrated inflammatory infiltrates without IgG4-positive plasma cells, raising the possibility of autoimmune myositis coexisting with IgG4-RD rather than direct IgG4-mediated myopathy.

Given the severity of muscle involvement and unsatisfactory steroid response, she was started on pulse intravenous methylprednisolone 1 g/day for 7 days, followed by oral prednisolone 50 mg/day and mycophenolate mofetil as a steroid-sparing agent. Over the next two weeks, pain resolved, CK levels reduced, and she regained ambulatory ability with minimal support. She remained clinically stable at follow-up, with ongoing physiotherapy and slow steroid taper.

Table I: Laboratory parameters during first episode (July 2025).

Date	Hb/TLC/Plt (×10y /L)	Na/K (mmol/L)	TB/DB (mg/dL)	SGOT/SGPT (U/L)	ALP (U/L)	TP/Alb/Glob/A:G (g/dL)	Creatinine (mg/dL)	PT INR	Comment
07/07/25	11.8 / 7780 / 3.5	138/4.0	6.19 / 4.95	128 / 96	242	8.2 / 3.1 / 5.1 / 0.6	2.3	1.5	Predominantly conjugated hyperbilirubinaemia, mixed hepatocellular – cholestatic picture, mild coagulopathy
08/07/25	11.3 / 4990 / 3.5	–	4.87 / 3.91	210 / 162	217	6.8 / 2.8 / 4 / 0.70	2.24	–	Bilirubin improving, but worsening transaminitis, possible inflammatory flare
09/07/25	11 / 11,990 / 4.79	–	4.97 / 4.04	223 / 182	237	6.6 / 3 / 3.6 / 0.83	–	–	Bilirubin plateaued, persistent hepatocellular injury, leukocytosis suggestive of secondary inflammation
11/07/25	10.4 / 8170 / 3.2	–	4.01 / 2.95	94 / 39	242	6 / 2.5 / 3.5 / 0.71	2.13	–	Improvement in bilirubin and creatinine

Table II: Laboratory parameters during second episode (July-August 2025).

Date	Hb/TLC/Plt (×10y /L)	Na/K (mmol/L)	TB/DB (mg/dL)	SGOT/SGPT (U/L)	ALP (U/L)	TP/Alb/Glob/A:G (g/dL)	Creatinine (mg/dL)	PT INR	Comment
24/07/25	11.9 / 12160 / 1.74	134/3.5	2.32 / 1.55	348 / 336	311	5.3 / 2.6 / 2.7 / 0.9	0.7	1.13	Raised transaminases and Alkaline phosphatase correlates with Inflammatory Myositis
06/08/25	12.4 / 13840 / 4.5	137/3.2	2.1 / 1.14	71 / 158	146	5.1 / 2.6 / 2.5 / 1.1	0.7	–	Investigations post pulse steroid therapy showing reduction in transaminases and alkaline phosphatase

Discussion

IgG4-related disease (IgG4-RD) is a fibroinflammatory disorder that can involve virtually any organ, with autoimmune pancreatitis (AIP) type 1 being its pancreatic manifestation. Skeletal muscle involvement, however, remains exceedingly rare, with only a handful of cases reported in the literature. In our patient, myositis developed within two weeks of an episode of IgG4-related pancreatitis, despite corticosteroid therapy, making the chronology unusual and noteworthy.

Hart *et al* (2015) reviewed the systemic spectrum of IgG4-RD and emphasized pancreaticobiliary disease, but did not identify skeletal muscle as a frequent site of involvement[3]. Similarly, the International Consensus Diagnostic Criteria (ICDC) for AIP established by Shimosegawa *et al* (2011) do not list skeletal muscle among common extrapancreatic sites[4]. Thus, our case expands the known spectrum of IgG4-RD.

Inoue *et al* (2015), in a cohort of 235 patients with IgG4-RD, found salivary glands, kidneys, lungs, and retroperitoneum to be commonly affected, but no cases of myositis were described[5]. This discrepancy underlines the rarity of skeletal muscle involvement and suggests either under-recognition or misclassification of myositis in IgG4-RD patients.

Casteleyn *et al* (2019) reported one of the few detailed descriptions of IgG4-related myositis, with biopsy-proven IgG4-positive plasma cell infiltration of skeletal muscle[6]. Unlike their case, our patient's muscle biopsy did not demonstrate IgG4-positive cells.

The possible explanation of the absence of IgG4-positive cells on biopsy in our case may be patchy disease involvement, as IgG4-related disease often shows focal lesions leading to potential sampling error; by the prior use of corticosteroids for pancreatitis, which could have suppressed IgG4-positive cell infiltration at the time of muscle biopsy; or by an immune overlap, wherein the

presence of anti-mi-2β antibody suggests that autoimmune myositis in this patient may represent a secondary autoimmune process ("second hit") triggered in the setting of IgG4-related disease rather than direct IgG4-mediated involvement.

An additional point of interest is that our patient developed myositis despite being on corticosteroids. Steroid-refractory or steroid-breakthrough manifestations in IgG4-RD are unusual but have been described. Inoue *et al* also reported that 30 - 40% of patients with IgG4-RD relapse after steroid tapering[5]. It is plausible that skeletal muscle disease may be more resistant to glucocorticoids, or that the concurrent autoimmune myositis pathway (indicated by Mi-2β positivity) required additional immunosuppression.

Finally, the age and co-morbidities of our patient (80 years and asthma) make this case distinctive, as most reported IgG4-RD series include elderly men with relatively lesser systemic involvement.

Taken together, our case illustrates the possibility of sequential organ involvement in IgG4-RD, the diagnostic challenge when biopsy is negative for IgG4-positive cells, and the potential overlap with other autoimmune myositis syndromes. It emphasizes the importance of considering IgG4-RD in atypical presentations of myositis, especially when there is a recent history of IgG4-related pancreatitis.

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