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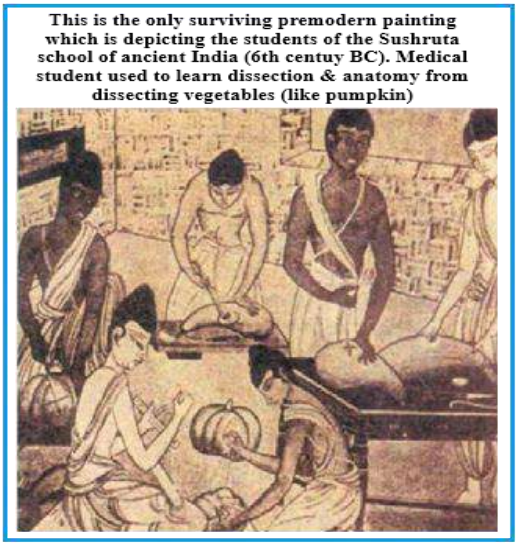

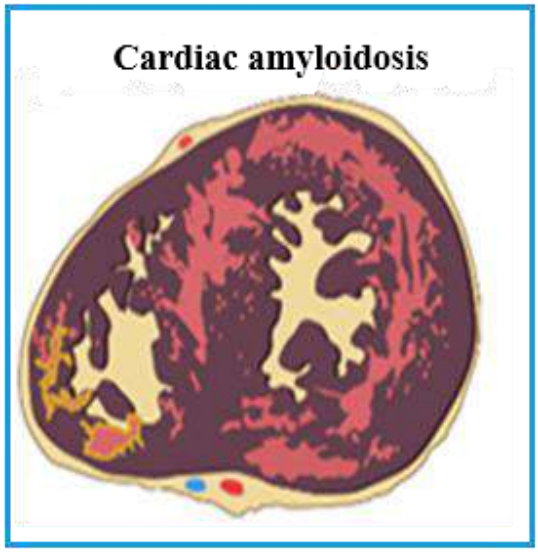

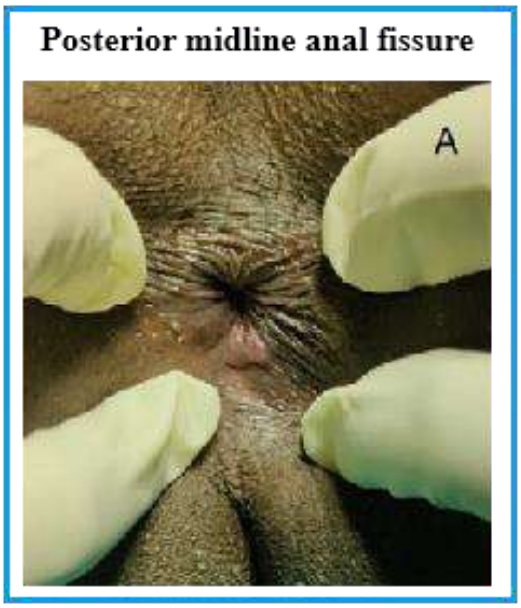

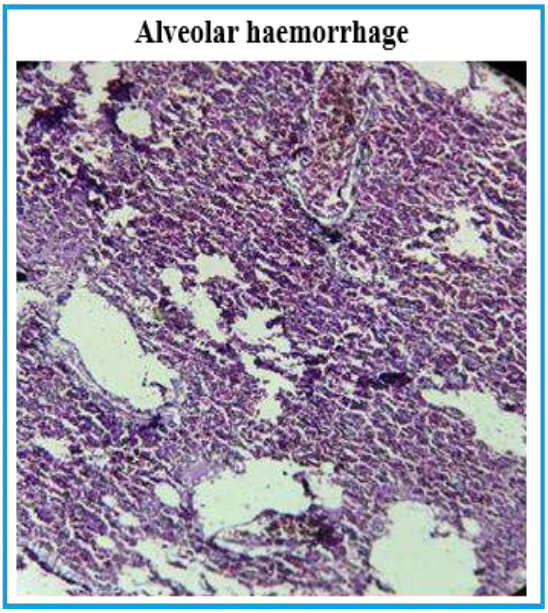

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EDITORIAL

The Doctrine & Trajectories in Medical Education: Role, Mutual Responsibilities & Accountability of Consultants and Trainees

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Medical Education as a Shared Journey. It has long been shaped by a culture of discipline, responsibility, and the willingness to sacrifice personal comfort in the service of learning and patient care. But training is not a one-directional hierarchy. It is a shared professional journey in which consultants and trainees are equal stakeholders with complementary responsibilities.

Academic departments flourish when both parties understand that:

- Consultants are custodians of knowledge, safety, and standards.
- Trainees are learners with responsibilities, rights, and accountability.

Together, they form a learning ecosystem that must be safe, ethical, and professionally enriching.

Medical training is a shared professional endeavour in which consultants and trainees are joint stakeholders with distinct yet complementary responsibilities.

Residents learn best through processes of analysis and synthesis—first asking “What is happening?” and “Why?” and then integrating clinical information, diagnostics and judgment to form a coherent diagnosis. This learning naturally occurs in an environment of complexity and uncertainty, where there is rarely a single correct answer. Training, thus, requires tracking observable achievements, creating flexible and relevant curricula, and strengthening faculty capacity through structured supervisor development programmes.

While medical education has traditionally been grounded in discipline, accountability, and a readiness to sacrifice personal comfort for learning and patient care, training itself is not a one-way hierarchical process.

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Figure 1. This is the only surviving premodern painting which is depicting the students of the Sushruta school of ancient India (6th centuy BC). Medical student used to learn dissection & anatomy from dissecting vegetables (like pumpkin). Photo from Odisha Museum.

Mutual Responsibilities: Shared Obligations for Consultants and Trainees

Respect as the Foundation: Both must uphold dignity, listen actively, and avoid personal attacks or power misuse.

Communication: Clear, timely communication prevents conflict, ensures safety, and builds trust.

Shared Ownership of the Learning Climate: Both groups influence departmental culture; both must actively contribute to a humane, academic atmosphere.

Commitment to Patient-Centred Care: The patient is always at the centre. All learning must occur within ethical boundaries of patient safety and respect.

Continuous Feedback Loop: Consultants must provide fair, constructive feedback. Trainees must receive it with openness and implement improvements.

Adherence to Institutional Policies: Compliance with duty hours, documentation norms, ethical guidelines, and academic requirements is a shared responsibility.

Zero Tolerance for Unprofessional Behaviour: Harassment, discrimination, neglect of duty, or reckless behaviour is unacceptable from either side.

Accountability Mechanisms:

1. Consultant Accountability
    - Consultants are accountable for:
    - Ensuring safe, supervised training

- Meeting curriculum and competency requirements
- Fair evaluation and reliable mentorship
- Maintaining professional behaviour
- Providing a safe work environment

2. Trainee Accountability
    - Trainees are accountable for:
    - Quality of care delivered
    - Adherence to supervision levels
    - Honest documentation
    - Professional behaviour
    - Meeting academic and clinical requirements

3. Institutional Accountability
    - Institutions must ensure:
    - Clear policies for duty hours and supervision
    - Channels for grievance redressal
    - Protection against harassment or abuse
    - Well-defined assessment and competency norms
    - Regular audits of training quality

Medical education has long been shaped by a culture of discipline, responsibility, and the willingness to sacrifice personal comfort in the service of learning and patient care.

The consultant-resident relationship is a sacred academic and clinical contract. In modern PG education, sacrifice must be meaningful and ethical—a shared investment in skill and character, not a cost of systemic neglect.

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LETTER TO THE EDITOR

Strengthening Faculty Development: A Call for an Online, Assessment-Driven Reform of NMC's Basic Course in Medical Education

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To,

Editors-in-Chief:
Dr. Minu Bajpai and Dr. Abhijat Sheth

The National Medical Commission (NMC) has made commendable progress in recent years by conducting the Basic Course in Medical Education (BCME) through live teaching delivered by nodal centre faculty within institutions. Earlier, participation in these on-site workshops was inconsistent. However, since attendance became mandatory for career progression and promotion, overall compliance has improved considerably.

In addition, NMC's introduction of the Biomedical Research Course as an online, assessment-integrated module for all postgraduate students and faculty has proven highly effective. This shift to a structured digital format has resulted in greater participation, improved monitoring of learner engagement, and enhanced uniformity in research training across diverse institutions. The success of this model offers valuable insights into how large-scale faculty development initiatives can be implemented efficiently and equitably.

Considering these encouraging outcomes, we would like to propose that NMC consider transitioning the Basic Course in Medical Education to a similar online, assessment-driven format for both faculty members and postgraduate trainees. Converting BCME into a structured, self-paced digital module would make learning more accessible and learner-centred, while ensuring standardization of content, continuous knowledge updating, and measurable competency acquisition. Such a model would also benefit faculty who face time, travel, or institutional constraints, thereby promoting a more inclusive and scalable approach to faculty development. We believe that this transition would further strengthen academic governance, enhance teaching quality, and contribute meaningfully to the ongoing advancement of medical education in India.

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REVIEW ARTICLE

Unmasking Cardiac Amyloidosis: From Pathophysiology to Emerging Therapies

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Abstract

The spectrum of disease which is characterized by misfolded proteins that get deposited in extracellular tissues, (as an aggregate of fibrils called Amyloid fibrils) is called as Amyloidosis. Cardiac Amyloidosis, an aggregate of fibrils called Amyloid fibrils which gets deposited in heart consequently resulting into Cardiomyopathy which is “Infiltrative” Type and which is progressive in course, resulting, into wide spectrum of cardiovascular manifestations that range from Heart Failure, Arrhythmias, Ventricular arrhythmias to coronary vascular involvement. This Review Article analyzes and summarizes advancements in the field of pathology, physiology, genetics, Diagnostic modalities, Management strategies, and Novel Therapeutics. The increasing trend in diagnosis of transthyretin amyloidosis (ATTR) is due to improved diagnostic imaging and heightened clinical awareness. Development of noninvasive diagnostic tools, is playing a major role in identifying the cases in early course of disease. Endomyocardial biopsy, an invasive diagnostic approach in diagnosing the cases is a “A GOLDSTANDARD TEST”, however non-invasive tests often obviate the need for biopsy. Emerging Novel therapeutic agents like tafamidis, patisiran, vultisiran, and many more are transforming management and improving outcomes (both morbidity and mortality-related outcomes).

Keywords: Cardiac Amyloidosis, Pathophysiology, Cardiovascular manifestations, Early diagnosis, Emerging therapies, Disease-modifying Treatment, Genetic testing

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Introduction

Amyloidosis is a part of under-recognized and often underdiagnosed diseases, leading to a delay in diagnosis and management. Amyloidosis is the spectrum of clinical conditions with different etiologies, which share a characteristic microscopic appearance. The development of Amyloidosis is due "to amyloid fibrils buildup" extracellularly, which are "collections of unfathomable/insoluble, low-molecular-weight protein subunits", at specific sites based on etiology [1,3].

Cardiac Amyloidosis

Amyloidosis involving the heart, is a severely progressive ailment, due to accumulation of fibrils extracellularly. This condition is characterized by distinctive pathological findings of "*green birefringence, which is visible when examined after staining with Congo red dye examined by cross-polarized light, microscopic technique*". Amyloid fibrils, when they get deposited in the myocardial interstitium, results in increasing thickness of Ventricular wall, which leads to both systolic and diastolic Heart failure, which has a progressive clinical course and outcome [2,3].

Figure 1. Differentiating- Normal Heart and Heart with deposition of Amyloid fibrils

Cardiac Amyloidosis-Overview

- There are over 30 Amyloidogenic proteins capable of forming amyloid fibrils. Out of these "THIRTY", only NINE has been identified, which involves Heart, by accumulating in the myocardium, resulting in a wide spectrum of cardiac manifestations. Secondary cardiac amyloidosis, which is less frequent, is a consequence of chronic infections and inflammations (AA). Monoclonal Ig light chains (AL) or transthyretin (ATTR) are the leading varient of Amyloidosis involving Heart. Variants of ATTR are "ATTRv (hereditary) and ATTRwt (acquired)" [3,4].
- Deposition of monoclonal light chains, primarily affecting individuals over 50 years and involving multi-organ systems, is a characteristic finding of AL (light chain) amyloidosis. (Only 10 to 15 percent of AL is associated with Multiple Myeloma)
- Deposition of transthyretin, with forms being hereditary (ATTRv) due to mutations, as well as acquired (ATTRwt) with age, is a characteristic finding of ATTR amyloidosis. [21]
- Chronic conditions that less commonly affect the heart are linked to AA amyloidosis. [5]

Epidemiology

- AL amyloidosis predominantly affects individuals older than 40 years and is *rare* in non-white populations and those younger than 40. (Median age of diagnosis is 63years of age) [7,8]
    - Demographically men and women population is same in term of "Prevalence"
- Prevalence of Wild-type transthyretin amyloidosis (senile type) is more in elderly population.76 years is the "Median diagnostic Age" (black men are three time more susceptible than white men). This form involves the accumulation of structurally normal transthyretin (wt-TTR) leading to cardiac dysfunction. [22]
- Hereditary cardiac amyloidosis due to transthyretin gene mutation is observed more often among black individuals compared to white individuals. [23]

2.3. Pathogenesis

Protein misfolding can result from genetic mutations or aging, causing *susceptible proteins to aggregate as non-branching, cross-beta-sheet fibrils that stain with Congo red dye.*

Table 1(a). Types of Amyloid protein affecting the heart

Amyloidosis Type	***Involved Proteins***	***Inheriting Trend***	***Heart Involvement (In percentage)***
Light Chain (AL)	*Ig light chain*	*Nil*	*Around 70%*
ATTRwt	*Transthyretin*	*No*	*100%*
ATTRv	*Transthyretin*	*Yes*	*Involvement of heart varies, which depend upon type and extent of mutation. It can range from 30 to 70 percent*
amyloid A (AA)	*amyloid A*	*No*	*5%*
AFib	*Fibrinogen alpha*	*present*	*Rarely affect Heart*
AApoAI	*Apolipoprotein A-I*	*Yes*	*Rarely affect Heart (mutation dependent)*
AApoAII	*Apolipoprotein A-II*	*Yes*	*Rarely affects heart however affection of Heart depends on mutation type. Kidneys are commonly involved. [63]*
Aβ2M	*β2-microglobin*	*No*	*80%*
AGel	*Gelsolin*	*Yes*	*Percentage affection of heart(mainly conduction pathway) around 5 percent*

Table 1(b). Summarizing-Amyloid types, with Extra Cardiac manifestation, with expected Survival Duration (in untreated cases) in months

Amyloidosis Type	***Survival Duration, in Untreated Cases (expressed in months)***	***Extra cardiac manifestations***
Light Chain (AL)	*24* *(Survival duration is of 6 months only, if Patient presents in heart failure (untreated cases))*	***Renal**-Nephropathy, proteinuria (proteins in urine). [48]* ***CNS**-Autonomic dysfunction, polyneuropathy.* ***Tongue-** Macroglossia (Abnormally enlarged Tongue that protrude past the teeth) [47]*
Transthyretin (Varient-ATTRwt)	*57*	***Musculoskeletal**-Ruptured of Biceps tendon, Carpal tunnel syndrome.[46]*
Transthyretin (Varient-ATTRv)	*31 " (Val142Ile)"* *69 "(non-Val42Ile)"*	***CNS*** *"Polyneuropathy"* ***CVS**-orthostatic hypotension,[13] **Eye**-vitreous opacities.[49]*
Serum amyloid A(AA)	*133*	***Renal** -Kidney impairment (95%), proteinuria (proteins in urine) [50]* ***Hepatomegaly and other gastrointestinal** symptoms and signs*
Fibrinogen alpha (AFib)	*180*	***Renal**- Kidney impairment, proteinuria(proteins in urine)*
Apo lipoprotein A-I (AApoAI)	*No definite data*	*Primarily **involves kidneys, Liver and Spleen, adrenal glands insufficiency, laryngeal involvement** (may cause dysphonia)*
Apo lipoprotein A-II (AApoAII)	*No definite data*	***Involves Kidneys**-Causes Proteinuria (proteins in urine)*
β2-microglobin (Aβ2M)	*No definite data*	***Severe involvement of Kidneys which may require Long-term dialysis**,*

		Musculoskeletal involvement- *"Carpal Tunnel Syndrome, joint problems". [46]*
"Gelsolin" (A Gel) "Meretoja's syndrome"	*Normal life expectation*	*"Cutis laxa, Corneal lattice dystrophy, sagging/drooping eyelids, paresthesia, proteinuria (rare)".*[51]

Pathogenesis of ATTR

In ATTR, transthyretin, is produced in the Liver, and their physiological role is to act as a transporter protein for thyroxin and retinol. But when they misfolds into insoluble sheets (Beta Pleated), they get deposited as amyloid fibrils into myocardium (extracellular spaces). This center stage process of misfolding, aggregation and deposition of TTR is *due to "single point mutation" (Hereditary ATTR or hATTR).*The difference between hATTR and Wild Type variant (wtATTR) is the former variant is heritable while the later one is sporadic.[22]

Genetic mutation of gene encoding for transthyretin, results into a rare "Autosomal Dominant" inheritance, resulting into ***hATTR,*** which increases the predisposition of TTR, "monomers to misfold" and get deposited as 'collection or aggregates' of amyloid fibrils. Incomplete penetrance in respect to Genetic mutation, phenotypically manifests as Cardiomyopathy and/or polyneuropathy. [9]

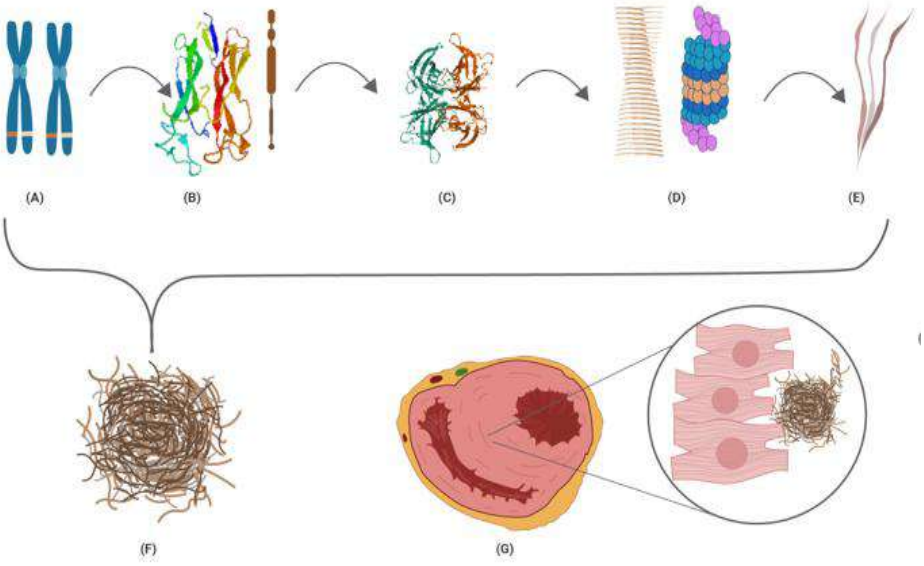

Figure 2. Amyloid formation

Description of Figure 2

(A) Genetic encoding for (TTR) proteins.
(B) Production of TTR monomer.
(C) TTR tetramer materialization.
(D) Severance of TTR tetramer as well as monomer "leads to the formation of amyloid fibril".
(E) Formation of "amyloid beta fibrils".

(F) Fibrils aggregates to form amyloids.
(G) These Fibrils aggregates gets deposition in extracellular spaces of Heart muscles (Leading to cardiomegaly)

Pathogenesis of AL

Primary AL amyloidosis occurs in those over 40 and is not sex-specific. It arises from plasma cell dyscrasia or may coexist with other plasma cell disorders.

Abnormal lambda or kappa light chains from monoclonal plasma cells misfold, become insoluble, and deposits in tissues. Lambda light chains are more common in primary AL, while kappa chains predominate in multiple myeloma.

Amyloid infiltration damages cardiac tissue through two mechanisms:

1. Direct deposition, which causes cardiomyocyte necrosis and subsequent fibrosis.
2. Circulating light chain toxicity, leading to oxidative stress damage.

A unique manifestation of AL (light chain) is, it causes oxidative stress leading to direct myotoxicity and necrosis which may lead to fibrosis of cadiomyocytes. [9]

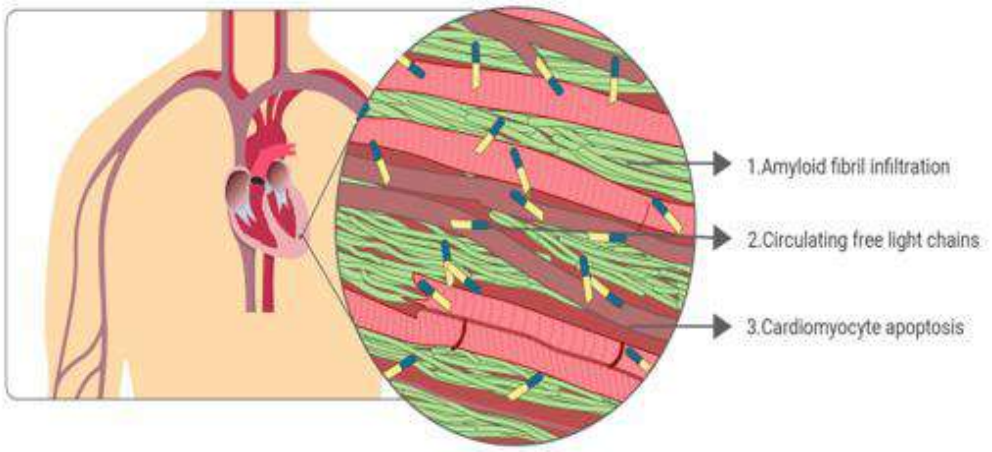

Figure 3. Pathophysiology of AL amyloidosis

1. *Amyloid fibril infiltration* leading to "Diastolic dysfunction"; 2. *Circulatory light chains* leads to dysfunction of myocardium; 3. *Cardiomyocytes apoptosis*, results from local effects of fibril infiltration.

Pathogenesis of AA amyloidosis (Causing secondary Amyloidosis)

Serum amyloid A, which is leads to inflammation and causes secondary amyloidosis, which commonly occurs due to chronic inflammatory conditions like Autoimmune diseases and infections which are chronic in nature and their sequels. *Kidneys are the primary pathological target of Secondary Amyloidosis, with rare involvement of the myocardium.*

Cardiovascular manifestations

- Clinically, it presents as heart failure with preserved ejection fraction (HFpEF). Impaired diastolic function and reduced left ventricular end-diastolic volume resulting into decreased stroke volume and persevered Ejection Fraction, which in turn leads to reduced cardiac output and clinically manifests as "*fatigue and generalized weakness"*. [64] The resulting congestion associated with heart failure leads to respiratory symptoms such as *Breathlessness on*

exertion and in later course of disease progression orthopnea. Venous congestion manifests *as increased JVP, Abdominal distention due to fluid accumulation, and congestive Liver enlargement.* [10,11]

In An Advanced Course of Disease Cardio Vascular System Examination will reveal clinically:

- The Cardiac apex is typically not displaced and is difficult to palpate.
- "The Third heart sound (S3) is appreciated by auscultation".
- "A fourth heart sound (S4) is rarely appreciated on auscultation, even in presence of restrictive cardiomyopathy". [12,16]
- *Atrial dilatation* develops because of "raised left ventricular filling pressures, due to the development of restrictive cardiomyopathy". [12,16]
- Arrhythmias associated with cardiac amyloidosis include atrial fibrillation and ventricular arrhythmias. (Commonly Arrhythmias). [65]
- Predominant signs of right heart failure include-
  - Swelling in both lower limbs (pitting in nature)
  - Increased jugular venous pressure (JVP)
  - Liver enlargement
  - Ascites.
- Acute Coronary Syndrome may be clinically presented due to "amyloid deposition in the coronary arteries" in Cardiac Amyloidosis. [24]

AL and its Cardiovascular manifestations (90%)

- AL most commonly involves cardiovascular system due to infiltration of any cardiac structure with amyloid.
- Vascular involvement leads to heart failure.
- In Diastolic dysfunction due to involvement of conducting pathways, it can manifest as a rhythm disturbance. Commonly, sinoatrial fibrosis or atrioventricular fibrosis occurs, leading to conduction defect, which can manifest clinically as various types of arrhythmias and Heart Blocks, [15,25]

ATTR and its Cardiovascular manifestation:

- ATTR and AL both clinically manifests chiefly as "Right heart failure "and "Heart Failure with Preserved Ejection Fraction" (HFpEF).
- Mutations in Val30Met transthyretin present clinically as serious involvement of conduction pathways, warranting pacemaker implantation.
- Other variants, like" Val122Ile and Thr60Ala (T60A)", affect the mechanical function of the heart but spares, conducting pathways. [49]
- Mutations in wtATTR involves mostly conducting system, leading to arrhythmia. Atrial fibrillation is the commonest arrhythmias [7,8,26].
- Wild-type ATTR is paradoxically associated with Aortic Stenosis (AS) with low flow and low gradient [27]

Extra cardiac manifestations (Table 1b)

Secondary amyloidosis

Secondary amyloidosis rarely occurs due to "chronic inflammatory conditions" (Autoimmune diseases like

'Rheumatoid Arthritis' and Chronic infections like 'Tuberculosis' and there sequels) Cardiovascular manifestations of secondary amyloidosis include progressive ventricular wall thickening which results in "Supply Demand" mismatch (Coronary artery supply mismatch with the myocardial oxygen demand, which over the period of time, if left untreated may result into " Acute coronary syndrome" which may present into "Regional Wall Motion Abnormalities". [6,8]

Diagnosis [5,7,9]

The diagnosis of cardiac amyloidosis involves a structured, stepwise approach to ensure comprehensive assessment and accurate identification of the disease markers. The following steps outline a typical diagnostic pathway:

Suspicion Phase

In the initial suspicion phase, clinicians should be vigilant for red flags [15] of cardiac amyloidosis. These include unexplained "*heart failure with preserved ejection fraction*" (HFpEF). Biochemical markers includs *elevated NT-proBNP levels*, *signs and symptoms of right heart failure*., and the presence of extracardiac symptoms such as proteinuria (due to Nephrotic Syndrome), macroglossia, skin bruises, Carpal Tunnel syndrome. Clinicians should use these clues, along with cardiac imaging findings [23], to suspect cardiac amyloidosis (Table 2).

Table: 2 Summarizing Types (Clinical or investigation hints), Red Flag, Amyloidosis Where It is Most Frequently Found (Both Cardiac and Extracardiac)

Type	**Red Flag** [15]	**Amyloidosis Where It is Most Frequently Found**
Extracardiac		
Clinical [27]	Polyneuropathy Dysautonomia Skin bruising Skin discoloration Cutis laxa Macroglossia Deafness Bilateral Carpal tunnel syndrome Ruptured biceps tendon Lumbar spinal stenosis Vitreous deposits Corneal lattice dystrophy Family history	ATTRv, AL, AA, AGel ATTR, AL AL AApoAI AGel AL ATTRwt ATTRv, ATTRwt ATTRwt ATTRwt ATTRv AGel ATTRv, AApoAI, AApoAI
Laboratory [48,50,51]	Renal insufficiency Proteinuria	ALL, AA, AApoAI, AApoAII, AApoAIV, Aβ2M, AFib, AL, AA, AApoAI, AApoAII, AFib

Type	**Red Flag** [15]	**Amyloidosis Where It is Most Frequently Found**
	Cardiac	
Clinical/ ECG [24]	Hypotension or normotensive if previous hypertensive Pseudo infarct pattern Low and decreased QRS voltage, AV conduction disease	ATTR, AL All All
Laboratory [29,31,32]	Disproportionately elevated NT-proBNP to degree of HF Persisting elevated troponin levels	All ATTR, AL
Echocardiogram [26,42]	Granular sparkling of myocardium Increased right ventricular wall thickness Increased valve thickness Pericardial effusion Reduced longitudinal strain with apical sparing pattern	All All All All All
CMR [41]	Subendocardial late gadolinium enhancement Elevated native T1 values Increased extracellular volume Abnormal gadolinium kinetics	All All All All
AA, serum amyloid A amyloidosis; AApoAI, apolipoprotein AI amyloidosis; AApoII, apolipoprotein AII amyloidosis; AApoAIV, apolipoprotein A-IV amyloidosis; AB2M, β2-microglobulin amyloidosis; AFib, fibrinogen amyloidosis; AGel, gelsolin amyloidosis; AL, light-chain amyloidosis; ATTRv, hereditary transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; CTS, carpal tunnel syndrome; HF, heart failure; LSS, lumbar spinal stenosis; AV, atrio-ventricular; CMR, cardiac magnetic resonance; ECG, electrocardiogram; HF, heart failure; LV, left ventricular; NT-proBNP, N-terminal pro-B-type natriuretic peptide.		

Initial Diagnostic Tests

Once cardiac amyloidosis is suspected, a series of non-invasive tests should be conducted to strengthen the suspicion. These include routine serum and urine tests to identify monoclonal light chains using the serum-free light chain assay, urine protein electrophoresis with immunofixation, and serum protein immunofixation. ECG may show “low-

voltage QRS complexes in the limb leads" and Echocardiography [42] may show increased "left ventricular wall thickness", hinting towards infiltration with amyloid fibrils. [19,23]

Confirmatory Phase

The confirmatory phase focuses on the definitive diagnosis and classification of the amyloid. Invasive diagnostic criteria are employed when non-invasive methods are inconclusive. "***Endomyocardial biopsy remains the gold standard for detection"***, [18] showing "apple-green birefringence under polarized light when stained with Congo red dye". Other techniques, like mass spectrometry along with immunohistochemistry, can be used to characterize the type of amyloid. In ATTR, non-invasive cardiac scintigraphy techniques, such as 99mTc-PYP, DPD, or HMDP scintigraphy, are valuable in detecting myocardial uptake and ruling out other potential causes of cardiac involvement [17,18,25].

Genetic Testing [20, 40]

Genotyping is crucial for distinguishing between wild-type and hereditary forms of ATTR amyloidosis, once ATTR is confirmed by scintigraphy or biopsy, using the step-wise diagnostic algorithm provided by the ***European Society of Cardiology*** (Figure 4).

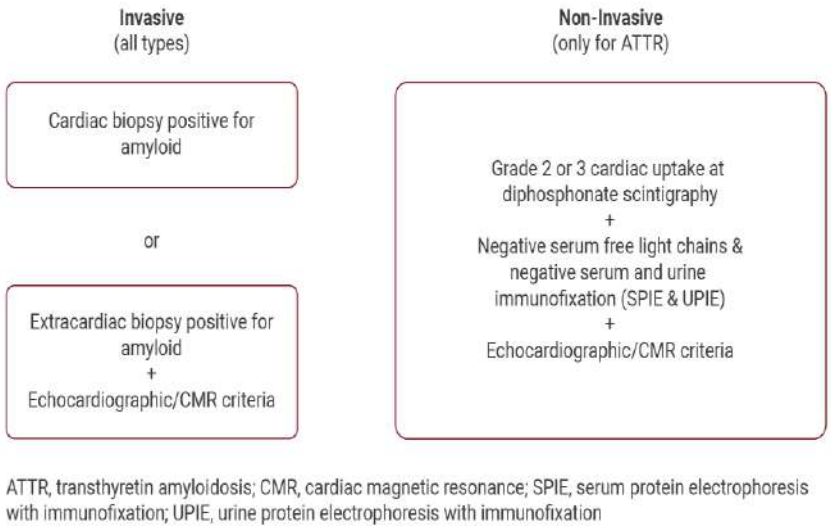

Figure 4. Algorithm showing" Approach to diagnosis of cardiac amyloidosis"

Invasive diagnostic criteria

An endomyocardial biopsy confirms amyloid deposits after Congo red staining, irrespective of the degree of left ventricular (LV) wall thickness. The classification of amyloid fibril proteins is performed after identifying amyloid using "mass spectrometry, immunohistochemistry, or immunoelectron microscopy". [17]

Diagnosis is also confirmed with amyloid deposits in an extra cardiac biopsy accompanied by characteristic features of cardiac amyloidosis, in the absence of an alternative cause for increased *LV wall*

thickness, or by characteristic features on CMR.

Proposed echocardiographic score to facilitate echocardiographic diagnosis of AL or ATTR amyloidosis in the presence of increased LV wall thickness.

- Scores>=8 points if of LV wall thickness is present
- Scores >=12 points if amyloid deposits are found in extra cardiac Biopsy.

Non-invasive diagnostic criteria

Cardiac ATTR amyloidosis is diagnosed in the absence of typical echocardiographic or CMR histological findings when 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD), 99mTc-pyrophosphate (PYP), or 99mTc-hydroxymethylene diphosphonate (HMDP) scintigraphy shows Grade 2 or 3 myocardial uptake of the radiotracer (Image 1) and clonal dyscrasia is excluded by all the following tests:

- Serum-free light chain (FLC) assay
- Urine (UPIE) protein electrophoresis and Serum (SPIE) with immunofixation [19,24] (Figure 5).

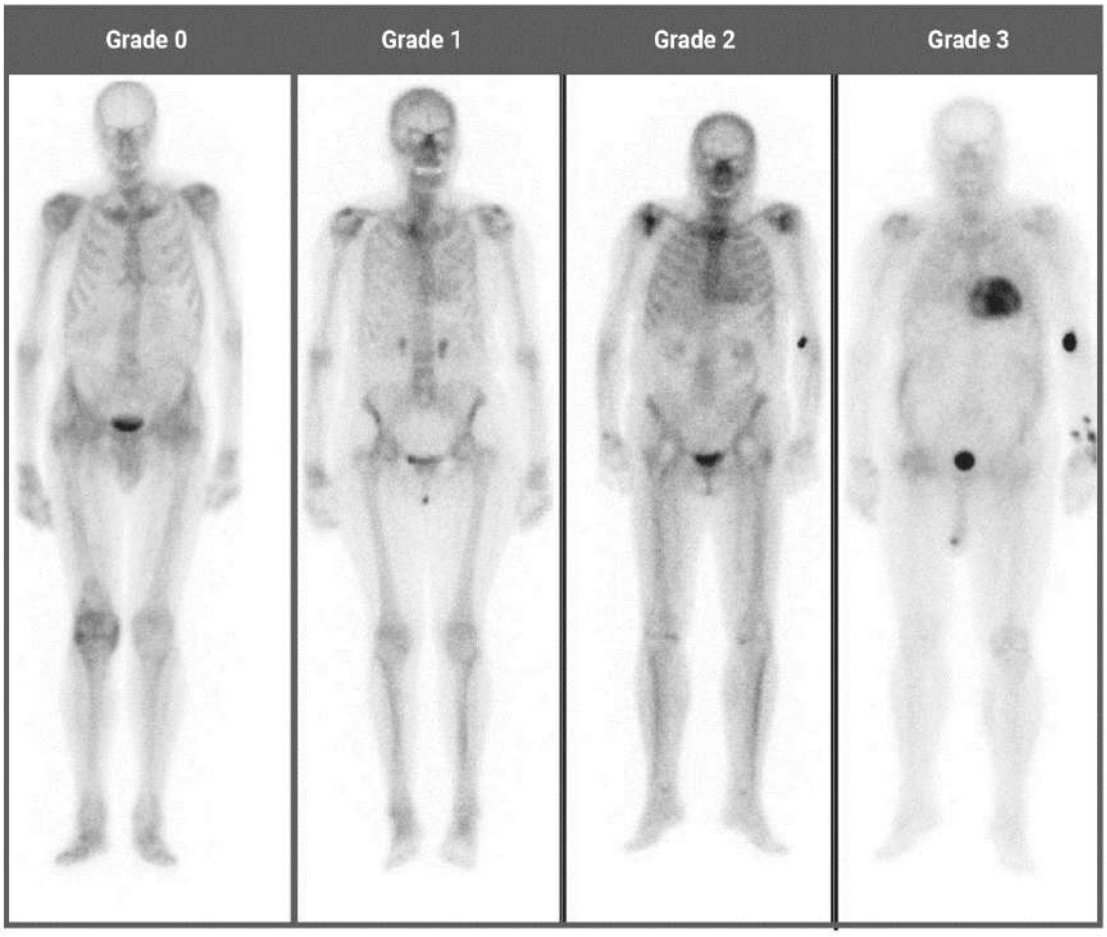

Figure 5. Showing cardiac uptake grading by bisphosphonate scintigraphy.

The combination of SPIE and UPIE quantification, *performed with immunofixation*, is used *to increase the sensitivity of the assays for detecting monoclonal proteins* (Figure 5). It is done

using cardiac uptake grading by bisphosphonate scintigraphy.

Bisphosphonate scintigraphy - cardiac uptake grading *[25]*
Grade 0: "*Normal* bone uptake"
Grade 1: "Myocardial uptake is *lower* than bone uptake"
Grade 2: "Myocardial and bone uptake are *equal*"
Grade 3: "Myocardial uptake is *more* than bone (with reduced/absent bone uptake)

Table 5. Tests to rule out light-chain amyloidosis [19]

Tests	**What Does It Detect?**	**Most Sensitive Test For:**	**Normal Range**
SPIE	Clonal immunoglobulin and/or clonal light chain	Confirming clonal immunoglobulin production	No monoclonal protein is present
UPIE	Clonal immunoglobulin and/or clonal light chain	Confirming clonal light chain production	No monoclonal protein is Present
Serum-free light-chain assay	Ratio of serum kappa: lambda light chains	Detecting low-level clonal light chain production; clonality assumed if ratio is far from 1:1	Free lite: 0.26–1.65[b] N Latex: 0.53–1.51

eGFR, estimated glomerular filtration rate; SPIE, serum protein electrophoresis with immunofixation; UPIE, urine
protein
electrophoresis with immunofixation.
[a]If any of these tests are abnormal, bone scintigraphy should not be used to establish the diagnosis of transthyretin amyloidosis.
bIn patients with kidney disease, mild elevations in the kappa: lambda ratio are frequently encountered. [b]In the setting of a normal SPIE/UPIE, a kappa, lambda ratio up to 2.0 in subjects with eGFR ≤45 mL/min/1.73 m^2 (up to 3.1 if in dialysis) can typically be considered normal.

Serum biomarkers
Non-specific serum biomarkers

"B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) are raised in cardiac amyloidosis" (Due to direct compression of cardiomyocytes and stress caused by raised filling pressures). Serial NT-proBNP measurements and analysis are used to evaluate "post-chemotherapy prognostic outcomes". *Cardiac Troponin-T (cTnT) is a reliable predictor of cardiomyocyte death and a negative prognostic indicator in AL and ATTR cardiac amyloidosis*.

AL-specific biomarkers

"Serum and Urinary quantitative free light chain (FLC) assay" can detect monoclonal gammopathy. Another non-invasive technique that can be used is immunofixation electrophoresis (IFE). [19]

Electrocardiography (ECG) [24]

The characteristic finding of cardiac amyloidosis on the ECG is "low-voltage QRS complexes in the limb leads, accompanied by poor R-wave progression in the precordial leads". ECG signs of infarction with or without coronary obstruction result from amyloid deposition in the smaller penetrating arteries affecting the microcirculation. "Prolonged P wave voltage with morphological abnormalities" indicates inter- or intra-atrial conduction delay secondary to amyloid deposition.

Echocardiography [26, 42]

Cardiac amyloidosis causes concentric bi-ventricles (left and right ventricle)" wall thickening of more than 15 mm" (*wall thickness greater than 18 mm is more typical in ATTR than in AL*).

Cardiovascular magnetic resonance (CMR) imaging [41]

"Cardiovascular magnetic resonance imaging (CMR) in cardiac amyloidosis" [19,20] is used both as a *screening tool* and to *monitor response to treatment*. CMR findings include:

- Concentric left ventricular hypertrophy is a common form of remodeling seen in AL. [61]
- Asymmetric septal hypertrophy is seen in ATTR.
- Disproportionate biatrial enlargement with atrial septal wall thickening. [62]

As per the" European Society of Cardiology (ESC)", 2021 "echocardiographic and cardiac magnetic resonance (CMR) criteria for non-invasive and invasive diagnosis of cardiac amyloidosis" are mentioned below:

Table 5. Summarizing European Society of Cardiology (ESC)", 2021 "echocardiographic and cardiac magnetic resonance (CMR) criteria for non-invasive and invasive diagnosis of cardiac amyloidosis")

Echocardiography [42]
Unexplained LV thickness (≥12 mm) plus 1 or 2:
1. Characteristic echocardiography findings (≥2 of a, b, and c have to be present):
a. Grade 2 or worse diastolic dysfunction
b. Reduced tissue Dopplers. e and a' waves velocities (<5 cm/s)
c. Decreased global longitudinal LV strain (absolute value <-15%)
d.

2. Multipara metric echocardiographic score ≥8 points: a. Relative LV wall thickness (IVS+PWT)/LVEDD >0.6: 3 points b. Doppler Ewave/e' wave velocities >11: 1 point c. TAPSE ≤19 mm: 2 points d. LV global longitudinal strain absolute value <-13%: 1 point e. Systolic longitudinal strain apex to base ratio >2.9: 3 points
CMR [41] Characteristic CMR findings (a and b have to be present): a. Diffuse sub endocardial or transmural LGE b. Abnormal gadolinium kinetics c. ECV ≥0.40% (strongly supportive but not essential/diagnostic)

CMR, cardiac magnetic resonance; ECV, extracellular volume; IVS, interventricular septum; LGE, late gadolinium enhancement; LV,
left ventricular; LVEDD, left ventricular end-diastolic diameter; PWT, posterior wall thickness; TAPSE, tricuspid annular plane systolic excursion
Abnormal gadolinium kinetics: myocardial nulling preceding or coinciding with the blood pool

Nuclear imaging [8,23]

Technetium pyrophosphate scintigraphy (PYP scan) is a nuclear imaging study that detects cardiac transthyretin and is used to diagnose TTR amyloidosis. [19,20]

Biopsy

"Endomyocardial biopsy" [43] and" histological analysis" are the *gold standards for identifying cardiac amyloidosis.* Nevertheless, these "Biopsies" (abdominal fat pad and bone marrow) are invasive and require substantive technical expertise, posing a complication risk.

- "*Fat pad fine needle aspiration is sensitive in detecting systemic AL (84%) but low for hATTR and wtATTR*" (45% and 15%, respectively). [45]
- "*Endomyocardial biopsies sensitivity and specificity of 100*". [44]

Genetic testing [20,40]

Genotyping is recommended to differentiate between wild-type (wtATTR) and hereditary variants (hATTR) after ATTR is confirmed by positive scintigraphy or cardiac biopsy.

The Diagnostic approach (Flowchart) outlines the step-wise diagnostic algorithm for cardiac amyloidosis, as provided by the European Society of Cardiology (2021)

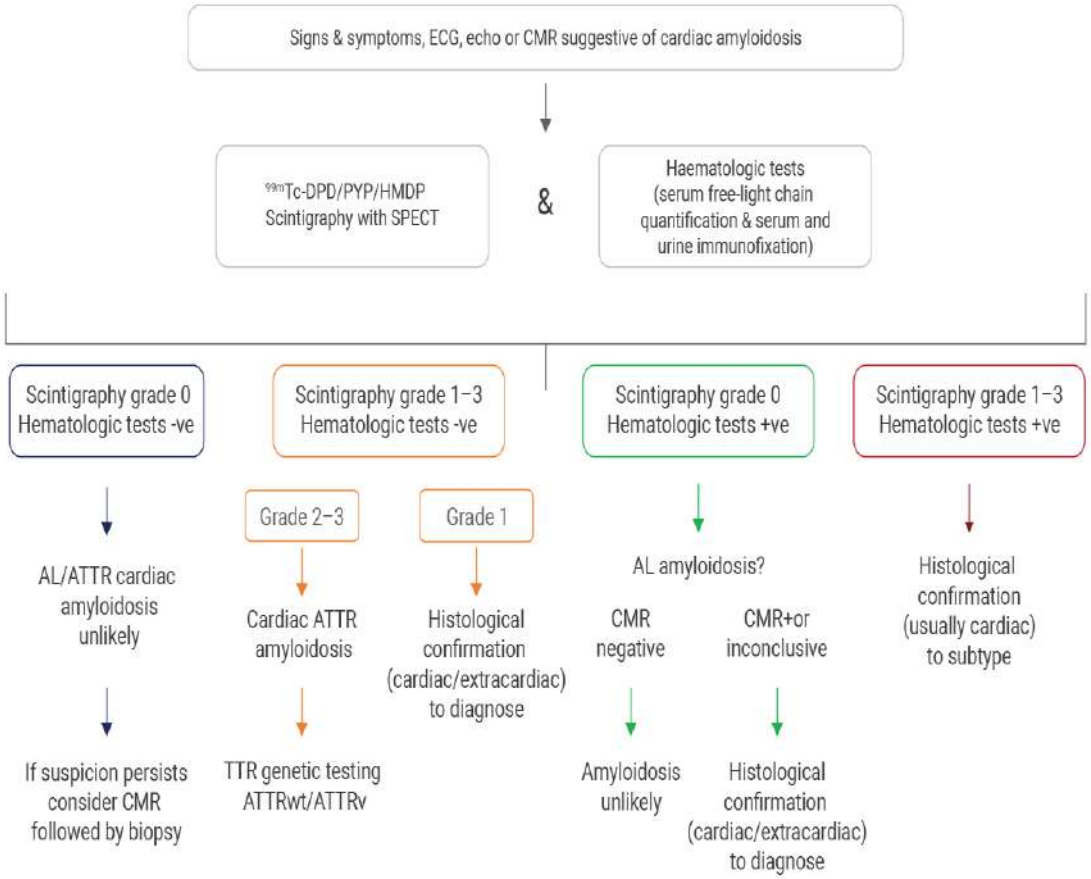

Figure 6. Diagnostic Approach

In summary, a methodical approach that combines clinical suspicion, initial screening tests, confirmatory procedures, and genetic assessment facilitates a comprehensive evaluation for effective" management of cardiac amyloidosis". [26]

Treatment

Treatment of cardiac amyloidosis and its complications focus on three areas:

- Heart failure
- Management of arrhythmias
- Initiation of disease-modifying agents.

For instance, in a patient experiencing heart failure characterized by fluid retention and generalized swelling (Anasarca), loop diuretics might be utilized to alleviate these symptoms by promoting fluid excretion. When dealing with arrhythmias, a patient presenting with atrial fibrillation would benefit from anticoagulants like warfarin to reduce the risk of stroke, other Thromboembolic Complication. Additionally, for a patient diagnosed with hereditary transthyretin amyloidosis, TTR stabilizers like diflunisal can be prescribed to slow amyloid progression and mitigate neurological deterioration. [5,9,29]

Management of heart failure [39]

- **Bioavailable loop diuretics**: Used for decongestion.
- **Aldosterone antagonists:** Used alone or in conjunction with loop diuretics in conditions with adequate blood pressure and renal function.
- **Standard guideline-directed medical therapy**: It includes angiotensin-

converting enzyme inhibitors, angiotensin receptor antagonists, angiotensin receptor blockers, and neprilysin inhibitors.

Management of arrhythmias [37]

- **Warfarin and direct oral anticoagulants**: These prevent thromboembolism and are indicated for atrial fibrillation or flutter.
- **Left atrial appendage closure devices**: Considered in patients with prohibitive bleeding risk.
- **Digoxin**: Used to control heart rate.
- **Amiodarone** is the agent of choice for both rhythm and rate control in patients where Beta-Blockade is not tolerated. Cardioversion and ablation are also recommended in a few cases.
- **Implantable cardioverter defibrillators (ICDs)**: Recommended in aborted sudden cardiac death with expected survival >1 year or significant ventricular arrhythmias. ICDs prevent sudden cardiac death.

Disease-modifying therapies for ATTR-CM [16,28]

Mechanism of Action: "Amyloid fibril aggregation occurs due to the destabilization of the TTR protein into monomers or oligomers, as seen in inherited mutations in cardiac variant transthyretin amyloidosis (ATTRv) or the aging process in wild-type disease (ATTRwt)". [52] Insoluble fibrils accumulate in the myocardium, WHICH LEADS TO restrictive cardiomyopathy, diastolic dysfunction, and congestive heart failure. [53]

Therapy targets - include several approaches: ***silencers*** reduces TTR production, therefore preventing further fibril formation; ***stabilizers*** prevent the dissociation of TTR tetramers into amyloidogenic monomers; hence helps in clearing existing amyloid fibrils from tissues.

TTR production (silencers): These protein silencers target the hepatic synthesis of TTR. Patisiran is an intravenously administered siRNA that degrades TTR mRNA, while Inotersen is a subcutaneously administered single-stranded antisense oligonucleotide that binds to TTR mRNA, leading to its degradation. [54] Vutrisiran acts by using RNA interference to trigger degradation of TTR mRNA. Vutrisiran is an effective treatment for heart failure caused by transthyretin amyloidosis Cardiomyopathy (ATTR-CM). [30]

TTR dissociation ("TTR stabilizers") binds "to the TTR tetramer" and thus preventing the "misfolding and deposition of amyloid fibrils". *NSAID diflunisal* stabilizes "TTR" in patients with ATTRv and polyneuropathy. It is associated with a reduced progression of polyneuropathy. [13]

TTR clearance from tissues (*TTR disruption*) "is the targets of clearance of amyloid fibrils from tissues". *"Doxycycline plus TUDCA (tauroursodeoxycholic acid) removes amyloid deposits"*. [60]

"Advanced heart failure therapies in ATTR-CM" [28, 39]

In ATTR-CM patients with heart failure, using an LV assist device is challenging. [55]

Heart transplantation is recommended in patients with heart failure and risk for neuropathy. [55,56]

Liver transplantation alone in ATTRv offers a prohibitive risk in the

presence of severe cardiac dysfunction and preexisting cardiac dysfunction. [57]

Targeted drug therapy for transthyretin and light-chain amyloidosis: (summary)
Transthyretin amyloidosis:

(a) <u>*TRANSTRYRATIN STABILIZERS:*</u>

1. Tafamidis: Indicated for ATTR cardiomyopathy
   Routs and frequency: PO-Daily
   NOTABLE SIDE EFFECT-GI Symptoms

2. Diflunisal: Indicated for ATTR cardiomyopathy
   Routs and frequency: PO-Twice Daily(bid)
   Notable Side Effect - Renal Dysfunctions, Increased Bleeding Tendences

(b) Transthyretin synthisis inhibiror:

1. ***Patisiran***: Indicated for Hereditary ATTR with Polyneuropathy
   Routs and frequency: IV, every Three weeks
   Notable Side Effect - Vitamin A Deficiency, infusion reaction

2. ***Inotersen:*** Indicated for Hereditary ATTR with Polyneuropathy
   Routs and frequency: Sub Cutaneous (SC). Weekly
   NOTABLE SIDE EFFECT- Thrombocytopenia, Glomerulonephritis, vitamin A Deficiency

3. ***LIGHT CHAIN AMYLOIDOSIS: (AL Amyloidosis)***

1. ***Bortezomib:***
   Routs and frequency: IV, Twice Weekly for 2 weeks per 28 days' cycle
   Notable Side Effect- Peripheral Neuropathy, Diarrhoea
   Thrombocytopenia

3. ***Cyclophosphamide***:
   Routs and frequency: PO(Orally), once weekly per 28 days' cycle
   Notable Side Effect- GI Symptoms, Pancytopenia

4. ***Daratumumab: Used for newly diagnosed AL***
   Routs and frequency: IV, once weekly (then once) per 28 days' cycle
   Notable Side Effect- Respiratory Tract infections, Diarrhoea

5. ***Doxycycline:***
   Routs and frequency: PO, bid
   Notable Side Effect- GI symptoms, Photosensitive Rash

-AL- "Light Chain Amyloidosis"
-ATTR- "Transthyretin Amyloidosis"

Complications and Comorbities in Cardiac Amyloidosis [28]
(SUMMARY OF TREATMENT)

1. ***Aortic Stenosis (AS)*** [33]
-Severe AS confers worse prognosis
-Trans catheter Aortic Valve Replacement (TAVR)

2. ***Thromboembolism*** [34, 35]
-Common complication.
-Anticoagulation Therapy specifically if AF (Atrial fibrillation is present)
(Independent on CHADS-VASc score)

3. ***Conduction defect*** [36]
-If indicated permanent Pacemaker.

-If high paced burden is expected consider Cardiac Resynchronization Therapy (CRT).

4. ***Atrial Fibrillation*** [37]
-Amiodarone is preferred anti arrhythmic agent.
-Digoxin should be used cautiously.
-Electrical Cardioversion has significant risk and should only be done after excluding any thrombi (Should be the last resort)

5. ***Ventricular Arrhythmias*** [38]
- "Implantable Cardioverter Defibrillator" (Only for Secondary prevention)
- "Trans venous Implantable Cardioverter Defibrillator (ICD)" is preferred over subcutaneous ICD (Implantable Cardioverter Defibrillator) [59]

6. ***Heart Failure*** [39]
-Control fluid intake
-Diuretics
-Avoid "*Beta Blockers, Angiotensin converting enzyme inhibitors/Angiotensin Receptor Blocker*s".
- "*Left Ventricular Assist Device*" nor indicated for most patients
- "*Heart Transplantation*" only for selected patients

OUTCOME/PROGNOSIS
LIGHT CHAIN AMYLOIDOSIS (AL)

- Median survival from onset of Heart Failure is around 6 months' in untreated cases. [58]
- As per the revised Mayo classification system, which utilises [29]
  - Troponin-T
  - NT-proBNP
  - Free light-chain levels (dFLC), - "differences between involved and uninvolved".
- These are utilised to classify THREE STAGES –With progressively worsening mortality.

Patient receive 1 POINT each for-
(a) "Troponin-T>= 0.025 ng/ml"
(b) "NT-proBNP>=1800 pg/ml"
(c) "dFLC>=18mg/dl"

- "After autologous stem cell transplantation (ASCT) – Median overall survival of patients with cardiac involvement is around 5 years". [30]

Transthyretin Cardiac Amyloidosis (Attr-Cm)

- In untreated cases of ATTR-CM median survival is 4.8 years. [31]
- Median survival often improves with targeted transthyretin therapy.

IF
  - "Troponin-T >= 0.05 ng/ml"
  - "NT-proBNP >= 3000 pg/ml"
  - "eGFR < 45ml/minute" (eGFR-Estimated Glomerular Filtration Rate)
  -

Above three prognostic parameters in cases of ATTR-CM, stratifies worse clinical outcomes. [31,32]

Statements and Declarations
Competing Interests

The authors have no competing interests to declare that are relevant to the content of this article

Conflict of Interest

The authors declare that they do not have conflict of interest.

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ORIGINAL ARTICLE

C.R.I.E.S Protocol for Acute Ankle Sprains: A Prospective Study

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Abstract

Ankle sprains are prevalent injuries, constituting 15%-20% of all sports-related injuries and often leading to significant loss of workdays and delayed return to athletic activities. This prospective study evaluates the efficacy of the C.R.I.E.S protocol in managing acute ankle sprains. The protocol includes clinical examination, radiographic evaluation, limited immobilization, exercises, early weight-bearing, and strength training. A total of 276 patients, aged 8 to 67 years, were assessed from May 2022 to March 2025, with a follow-up period ranging from 5 to 34 months. The study categorized injuries into three grades: Grade 1 (127 patients), Grade 2 (144 patients), and Grade 3 (5 patients). Results indicated that Grade 1 injuries had an average recovery time of 3 weeks and 5 days, Grade 2 injuries had an average recovery time of 6.2 weeks, and Grade 3 injuries were managed conservatively with a mean recovery time of 13.6 weeks. The study highlights the importance of early mobilization and muscle strengthening in the recovery process, with no recurrent sprains observed during the follow-up period. The findings suggest that the C.R.I.E.S protocol is effective in managing acute ankle sprains and facilitating a timely return to routine and sporting activities.

Keywords: Lateral ankle sprain, Functional outcome, Return to sports, C.R.I.E.S

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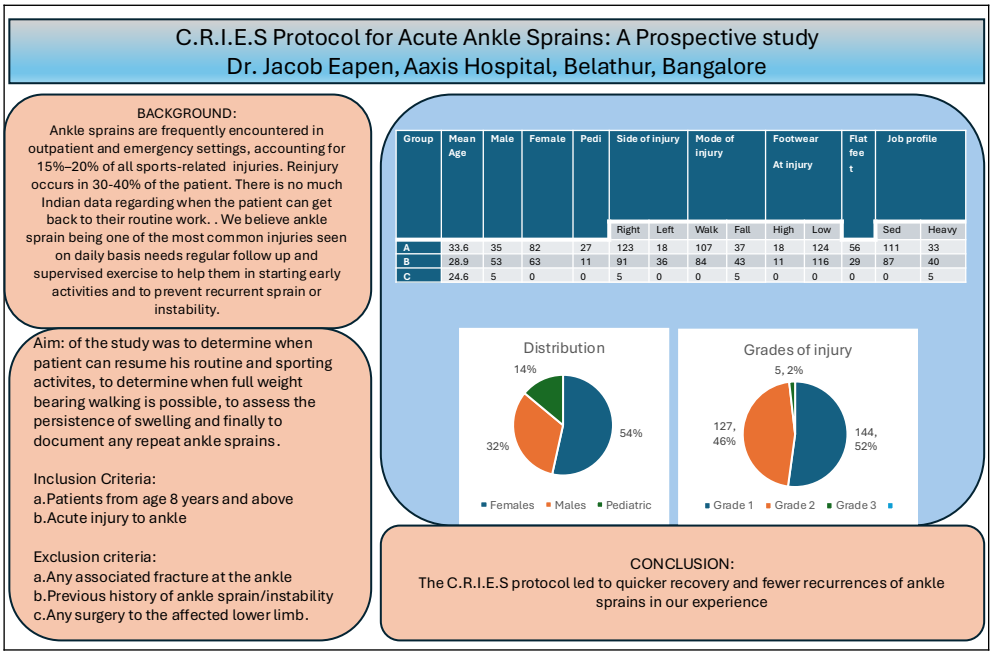
Graphical Abstract



Introduction

Ankle sprains are frequently encountered in outpatient and emergency settings, accounting for 15%–20% of all sports-related injuries [1]. They can result in considerable loss of workdays or delayed return to athletic activities. Ankle sprains are classified as mild, moderate, or severe. This grading assists in determining the appropriate management for lateral ligament injuries. Ankle injuries usually lead to persistent pain, swelling, instability and recurrence. Reinjury occurs in 30-40% of the patient.

Grade 1 injuries present with minor swelling and tenderness without functional instability. Grade 2 (moderate) injuries involve partial ligament tears, accompanied by moderate pain, swelling, some instability, and loss of function. Grade 3 denotes a complete ligament tear, significant functional impairment, and marked instability [3].

The vast majority of ankle sprains are managed conservatively, often leading to good or excellent outcomes [4]. Biological healing is typically divided into three phases: (a) inflammatory phase (up to 10 days), (b) proliferative phase (4–8 weeks), and (c) maturation phase (up to one year). Standard treatment includes immobilization, rest, bracing, bandaging, taping, non-steroidal anti-inflammatory drugs (NSAIDs), balance training, and strengthening exercises [5]. We believe ankle sprain being one of the most common injuries seen on daily basis needs regular follow up and supervised exercise to help them in starting early activities and to prevent recurrent sprain or instability.

In this study we desired on following a standard protocol for all the patients with grade 1 and 2 ankle sprain with regular follow up. All the patients were closely reviewed at each visit by the author. The clinical findings were documented, and

exercise were personally re-in forced to the patient at each visit.

Mechanism

Ankle sprains usually occur due to forefoot adduction and hindfoot inversion combined with external tibial rotation when the joint is in plantar flexion [6]. The lateral ligament complex comprises the anterior talofibular ligament (ATFL), calcaneofibular ligament (CFL), and posterior talofibular ligament. Depending on the force applied and its direction, one or more ligaments may be injured, with the ATFL being most affected due to its relative weakness [6].

Materials and Methods

Inclusion Criteria:

a. Patients from age 8 years and above
b. Acute injury to ankle

Exclusion criteria:

a. Any associated fracture at the ankle
b. Previous history of ankle sprain/instability
c. Any surgery to the affected lower limb.

We evaluated 347 patients who came to our emergency room with history of ankle twisting injury from May 2022 to March 2025. Seventy-one patients were excluded from the study as they had associated lateral malleoli, medial malleoli or posterior malleoli fracture or a combination of these three fractures. Only 276 patients with no radiographic features of fractures were included in the study. The age of the patients ranged from 8 years to 67 years. The minimum follow up was 5 months and maximum follow up is 34 months.

All patients received the C.R.I.E.S protocol, which consists of the following components:

1. Clinical examination by a single consultant
2. Radiographic evaluation
3. Immobilization for limited period
4. Exercises and Early weight bearing
5. Strength training.

Aim of the study was to determine when patient can resume his routine and sporting activities, to determine when full weight bearing walking is possible, to assess the persistence of swelling and finally to document any repeat ankle sprains.

All patients underwent thorough clinical examination by the author which included OTTAWA ankle rules, palpation of Medial collateral ligament, Lateral collateral ligament and whole foot. Visual Analogue score, swelling, tenderness, ankle movements, anterior drawer test and talar tilt test were documented. We also documented the mode of injury whether its twisting injury while walking, sporting activities or fall from height. Age group, Sex, side of injury, footwear worn at the time of injury, presence of flat feet, preinjury activity levels, type of work. Patients underwent radiographic evaluation next. Those with even hairline fractures were excluded from the study. Based on the clinical examination the patients were assigned three groups A, B, C based on whether the ankle sprain is grade 1,2 or 3 respectively.

Demographics

In our study which included 276 patients with ankle sprain. The demographics is as shown in Table 1.

Table 1. Demographics

Group	Mean Age	Male	Female	Pedi	Side of injury		Mode of injury		Footwear At injury		Flat feet	Job profile	
					Right	Left	Walk	Fall	High	Low		Sed	Heavy
A	33.6	35	82	27	123	18	107	37	18	124	56	111	33
B	28.9	53	63	11	91	36	84	43	11	116	29	87	40
C	24.6	5	0	0	5	0	0	5	0	0	0	0	5

Results

A total of 127 patients had grade 1, 144 had grade 2, and 5 had grade 3 ankle sprains. All underwent thorough clinical exams. Grade 1 and 2 patients received anti-inflammatories, ice every eight hours, limb elevation, and used an ankle brace while walking. They were allowed full weight-bearing with limited walking for two weeks and advised to use an ankle binder for 2–4 weeks. Heat therapy was avoided. Dorsiflexion, plantar flexion, quadriceps, VMO, and calf strengthening exercises (25 reps daily for 6 weeks) began on day one as tolerated.

Five patients exhibiting probable ankle instability were immobilised with a slab for two weeks. Individuals presenting with significant swelling and instability were referred for MRI scans of the ankle to confirm injury grade. Of 18 patients who underwent MRI, five were diagnosed with a grade 3 tear of the lateral collateral ligament and a grade 2 tear of the deltoid ligament, categorising them as Group 3. Six patients had associated fractures and were consequently excluded from the study. Seven patients were assigned to Group B (Grade 2 ankle sprain).

Group A: All patients were followed up at 7 days, 4 weeks, 2 months, 6 months and one year. Patients were checked for VAS score, ankle movements, gait pattern, ankle instability. The time to resume sporting activities and work loss days were also calculated.

Of the 127 patients with grade 1 injury the average recovery time was 3wk 5 days. The mean VAS score was 4.3 on the day of presentation and 0 at the end of 2.5 weeks. All patients were fully weight bearing from day 1. Fifty-six patients complained of swelling persisting for more than 5 weeks, but they did not have restriction any activity. 61 patients were working from home as they had the option for 2.3 weeks and 39 patients continued going for work. There was no ankle instability or recurrent sprain noted in Group A patients at the end of follow up.45 patients who were regular in sports/weight training were able to resume their activities by third week. They could gradually get back to their pre-injury levels by 7^{th} week. No patient complained of altered gait at the end of 6.5 weeks.

Group B: 144 patients with grade 2 injury recovery time was 6.2 weeks. Pain free movements and ability to do weight

bear walking to do daily chores were considered as good recovery. On presentation the VAS score was 6.7, 3 at 3 weeks and mean of 1.9 at 5.6 weeks. 49 patients took work from home for 3.1 weeks, 27 patients resumed traveling to office from the first day, 48 patients took complete rest at home for 4.5 days and then resumed daily office work. The mean follow up was 11.6 months. They could resume sporting activities by 8.2 weeks. There was continued pain for 12 patients; 8 patients underwent MRI scan was taken and it showed Grade 2 LCL sprain and grade 1 MCL sprain with mild ankle synovitis. 39 patients complained of gait abnormality for up to 8.8 weeks. 23 patients admitted that exercises protocol was not followed as advised. 16 patients had gait problems despite doing exercise due to swelling. There was no restriction of activities for 90 patients by 7.2 weeks.

At the end of follow up there were 12 patients with mild gait abnormality due to calf muscle wasting. There is no incidence of recurrence of sprain.

Group C: This group had 5 patients with grade 3 ankle sprain. All patients underwent MRI scan after detecting ankle instability on clinical examination. Patients were advised for surgery for ligament reconstruction. All 5 patients were daily wage workers and not willing for surgery. They were managed conservatively in below knee cast and strict non weight bearing for 4 weeks. They were also advised on exercises for the Quadriceps, VMO and static calf muscle strengthening. At the end of 4 weeks the cast was removed and the protocol for Grade 1 and 2 injuries were followed. All patients complained of stiffness at ankle till 3 weeks. VAS score was 8.2 on arrival, 4.5 at the end of 4 weeks and 2.7 at 13.6 weeks. 4 patients complained of swelling for 6 months. 3 patients were followed up for 14 months. During this period none of them had another sprain episode (Table 2 and Figure 1).

Table 2. VAS score at the time of injury and final follow up in each group

Group	VAS (initial)	VAS (final)
A	4.3	0 (2.5wk)
B	6.7	1.9(5.6wk)
C	8.2	2.7(13.6wk)

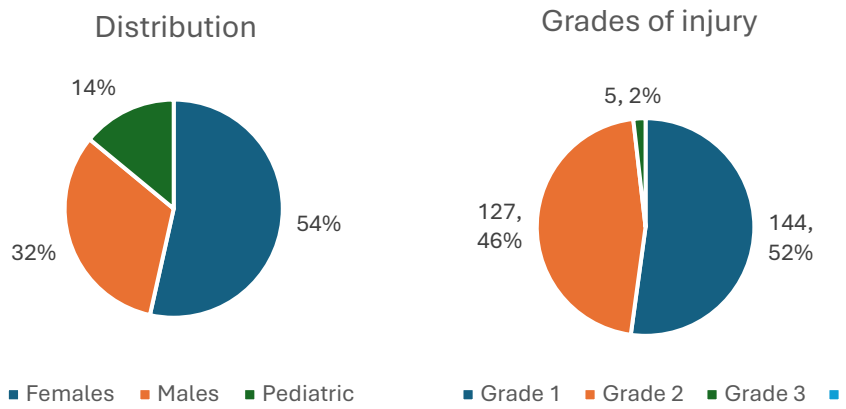


Figure 1. Gender Distribution and Number of patients in each group

Discussion

Post-ankle sprain concerns often include determining appropriate timelines for returning to work, resuming sporting activities, and understanding potential long-term consequences. This study aimed to address these questions in a hospital setting that serves patients from various socio-economic backgrounds and to assess the functional outcomes of the C.R.I.E.S protocol. Most components of this protocol aligned with existing treatment approaches, with particular emphasis on quadriceps, vastus medialis oblique (VMO), and calf muscle strengthening, as well as early mobilization. Patients were encouraged to maintain adherence through regular follow-up visits.

In this study we followed up 276 patients with a minimum follow up of 8 months. We assigned three groups based on the grades of sprain. Our objective was to develop a standard protocol in lines of conservative management which would help the patients resume their routine activities and sports at the earliest.

Studies have shown that exercise-based interventions reduce the rate of re-injury [7-11]. But no study has shown any association between reinjury and increasing the training period. In our study we noticed there was no re injury during the period of follow up except for 2 patients which was diagnosed as grade 1 sprain. Both the patients were again followed up for a year, and ankle was found to be stable. Lazarou et al. [12] reported significant reduction in pain in patients who followed exercise protocol versus patients who did not have regular follow ups. In our study Grade 1 patients reported zero visual analogue score at the end of 2.5 weeks and Grade 2 patients reported VAS score of 1.9 by 5.6 weeks.

Hultman et al. [13] reported reduction in reinjury and lower pain in patients who had minimum 4 visits by 6th month. Van Reijen et al[14] compared exercise-based protocol delivered via phone versus printed booklet. A small reduction in re injury was noted in booklet group which was not statistically significant. Pourkazemi et al[15] noted prevalence of recurrent ankle sprains was 22% in patients who were not regular with exercises.

The duration required to return to activity is influenced by several factors, such as the pre-injury activity level and rehabilitation process. Studies showed average time to return to sports after lateral ankle sprain is 16-25 days [16]. But many athletes experience reinjury or long- term

pain. The recurrent ankle sprain in athletes ranged from 12-47% [17,18]. Lateral ankle sprains can result in proprioceptive disturbances originating from the central nervous system beyond spinal reflexes, which may cause functional instability[19,20]. In this study, among 127 patients with grade I injuries, 45 individuals engaged in recreational sports were able to resume activities by the third week. Our study strictly restricted patient from sports for first 2 weeks even those who were pain free.

Recurrent ankle sprain leads to chronic ankle instability. Chronic ankle instability is an important predictor of post traumatic osteoarthritis.

In our study 54% (145) were females, 32% (88) males and 14% (38) paediatric. All the paediatric ankle sprains happened while playing. 27 children had grade 1 sprain and 11 had grade 2 sprain. All children resumed sports by 11+/- 2 days. Only one child reported twisting injury 4 weeks from the initial injury. The mean weight of the paediatric group was 41.3 kg.

Conclusion

In our cohort we found that C.R.I.E.S protocol in acute ankle sprain led to faster recovery in terms of reduction of pain, full weight bearing and return to sports. There was also very less recurrence noted in our study. We advise supervised exercises and regular follow up in all acute ankle sprains which reduces recurrence and thus future arthritic changes.

Strength and limitation

We tracked 276 patients for at least 6 months, documenting findings and teaching exercises at each visit. One consultant performed all clinical exams. Frequent follow-ups were likely due to our hospital being the only orthopaedic facility for a population of 55,000–60,000. The C.R.I.E.S protocol led to quicker recovery and fewer recurrences of ankle sprains in our experience. No statistical analysis was conducted. All grade 3 ankle sprains were treated conservatively, so we cannot assess the benefits of surgical intervention.

Statements and Declarations

Conflicts of interest

The authors declare that they do not have conflict of interest.

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ORIGINAL ARTICLE

Efficacy of Combined Local Infiltration Anaesthesia and Controlled Anal Dilatation Followed by Conservative Therapy Versus Conservative Therapy Alone in Acute Primary Anal Fissure - A Preliminary Report

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Abstract

Introduction: Anal fissure is a painful anorectal disorder characterized by sphincter spasm and impaired healing due to elevated internal sphincter tone. Conservative management remains the mainstay, but persistent symptoms often progress to chronicity requiring surgical intervention. **Methods:** A prospective study was conducted over 18 months at Nil Ratan Sircar Medical College, Kolkata, involving 40 patients with acute midline anal fissure. Participants were randomized into two equal groups. The test group received local infiltration anaesthesia with 1% lignocaine at four quadrants followed by two-finger controlled anal dilatation (CAD) to a 40 mm anal opening, in addition to standard conservative therapy. The control group received conservative management alone. Outcomes were evaluated at 1, 2, 3, and 6 weeks using the Visual Analogue Scale (VAS) for pain, bleeding, sphincter tone, and associated symptoms. **Results:** Baseline parameters were comparable between groups. The test group showed significantly earlier pain relief ($p < 0.01$), faster cessation of bleeding ($p \approx 0.02$), and normalization of sphincter tone ($p < 0.001$) compared with controls. Improvement in discharge and pruritus was observed but was not statistically significant. No complications, including incontinence, were reported. **Conclusion:** Local anaesthetic-assisted CAD, when combined with conservative therapy, offers superior short-term symptomatic relief and accelerates healing in acute anal fissure without compromising continence. Despite limitations of small sample size and short follow-up, this simple office-based intervention appears to be a safe and effective adjunct to standard care, potentially reducing chronicity and need for surgery.

Keywords: Anal fissure, Controlled anal dilatation, Local infiltration anaesthesia, Conservative management

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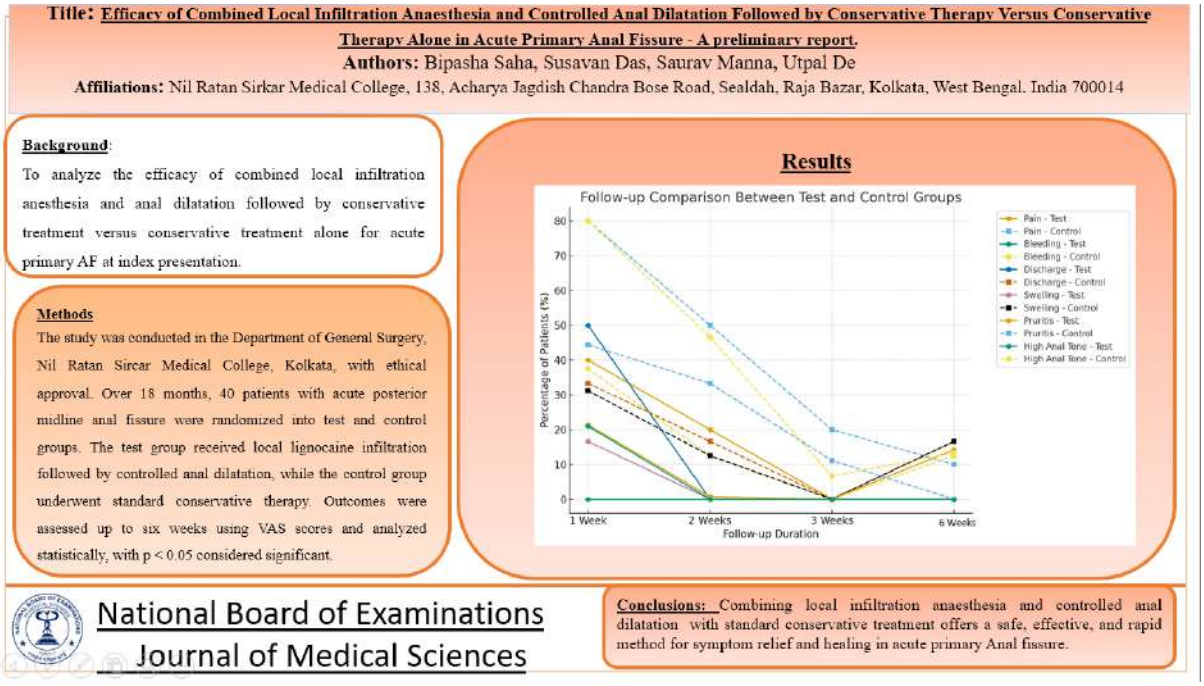
Graphical Abstract



Introduction

Anal fissure (AF) is a longitudinal tear in the anoderm (below the dentate line up to anal verge). Though described as common, the exact incidence is unknown and is comparable to appendectomies with a lifetime risk of 7.8% [1]. It is typically located in posterior midline (90%) and primarily occurs due to excessive straining, constipation, or trauma to the anal canal [1,2]. Females are more commonly affected than males (1.14 vs 1.04 per thousand person-years) [3]. The commonest age of presentation in females is adolescent and young adulthood whereas males are affected in their middle age. Patients typically present with acute pain (throbbing lasting for hours after passage of stool), bright red bleeding (70%), and sphincter spasm, which significantly impact their quality of life [2,4]. Thus, anal fissures pose a unique therapeutic challenge due to increased internal anal sphincter tone and significant patient discomfort.

AF can be acute or superficial or chronic. Chronic AF are those that last for more than six weeks and is associated with fibrous anal polyps, skin tags, induration at the edges, exposed internal sphincter at the floor, infected base and bridged fissure (a post fissure fistula) [1,2,5].

While conservative treatment remains the first-line approach for acute AF, many patients experience persistent symptoms, leading to prolonged suffering and an increased risk of chronicity [6]. This necessitates operative interventions like, fissurectomy, the gold standard internal anal sphincterotomy (LIS), LASER ablation and radiofrequency surgery to enhance healing and symptom relief [3,5,7].

Lord's anal dilatation (LAD), the once conventional treatment practiced for decades fell into disrepute due to higher rate of incontinence (52%) and was abandoned [8]. However, recently standardised anal dilatation or controlled anal dilatation (CAD) has resurfaced with promising

results (healing rate 88%, incontinence 1%) but with limited evidence [8].

Thus, combining local infiltration anaesthesia with CAD may offer a middle ground between conservative and surgical interventions by immediate analgesia, enhancing AF healing, improving patient compliance and overall experience during the initial intervention.

This study aims to analyse the efficacy of combined local infiltration anaesthesia and anal dilatation followed by conservative treatment versus conservative treatment alone for acute primary AF at index presentation.

Methodology

The study was conducted in the Department of General Surgery, Nil Ratan Sircar Medical College and Hospital, Kolkata, after obtaining approval from the Institutional Ethics Committee. It was a longitudinal, descriptive comparative study carried out over 18 months from June 2023 to November 2024, involving both outpatient and inpatient participants. Patients presenting with acute primary posterior midline AF were included. A total of 40 patients were enrolled and divided equally into a test and a control group. The sample size was determined using a standard formula for comparing two proportions, with assumptions based on existing literature showing an expected improvement in outcomes from 36.8% with manual anal dilatation to 60% when combined with local anaesthesia [9]. After accounting for a 10% dropout rate, the total sample size was fixed at 40 participants.

Patients aged 12–80 years with primary acute AF were eligible for inclusion. Those with fissures of secondary etiology, chronic fissures, high-risk conditions such as ischemic heart disease or chronic kidney disease, pregnancy, or unwillingness to undergo examination or follow-up were excluded.

Participants in the control group received conservative management, which included Sitz baths, high-fiber diet, stool softeners, and topical application of 2% lignocaine and nifedipine ointment. The test group underwent a combined approach involving local infiltration anesthesia (LIA) with 5 ml of 1% lignocaine injected at 12, 3, 6, and 9 o'clock positions in the inter-sphincteric plane, followed by a 5-minute interval and controlled two-finger (fore and middle figure) anal stretching in various directions with gradually exerted outward pressure till a 40 mm diameter (vernier caliper) of anal opening was achieved (Figure 1). This was followed by a 5-minute hot compression over the region. Both groups continued the same conservative regimen thereafter for two weeks. The procedure was performed by the same surgeon in all the cases.

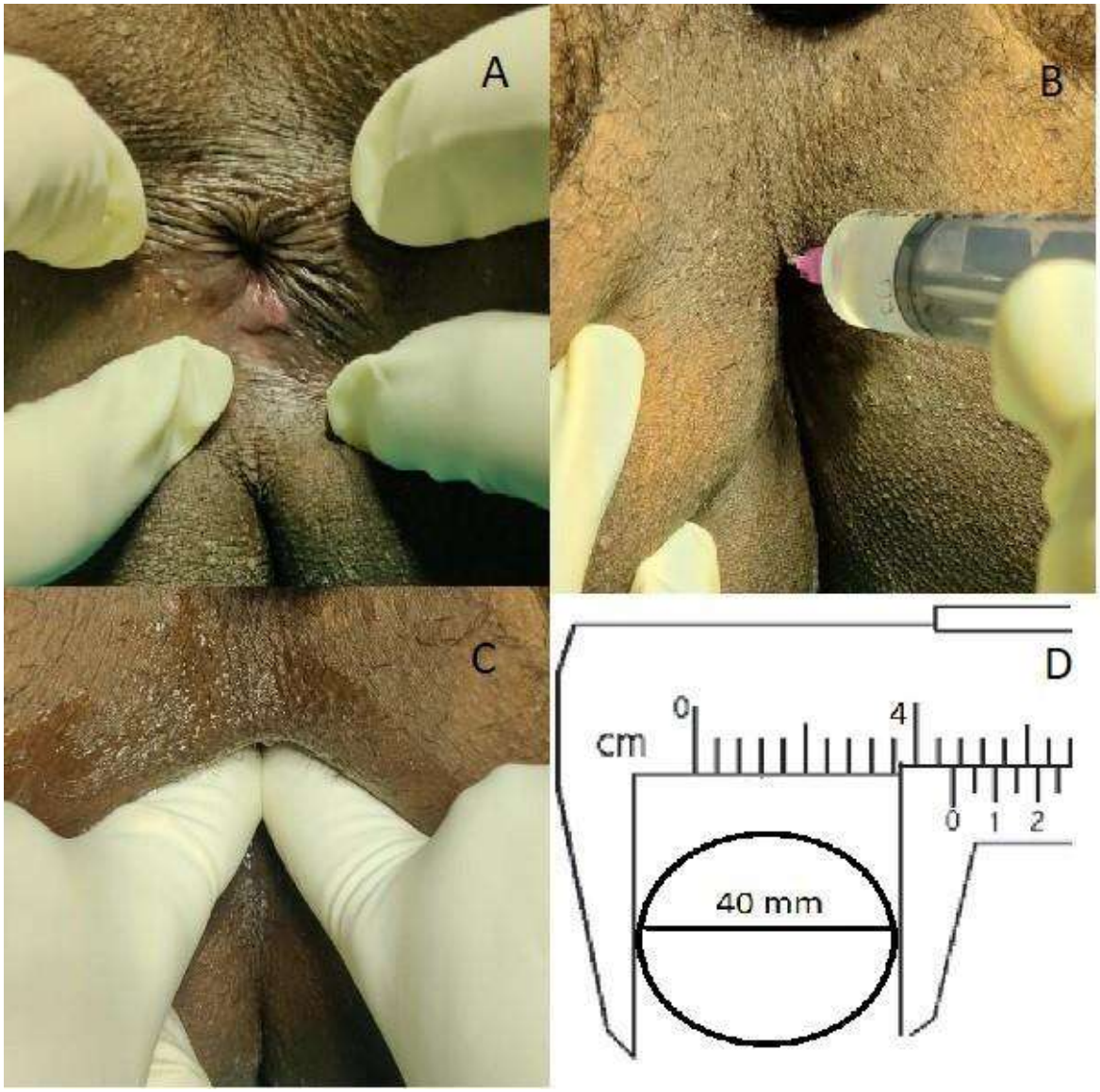


Figure 1. **A**. posterior midline anal fissure, **B**. Local infiltration anaesthesia with 2% lignocaine, **C**. Controlled anal stretching, **D**. Measurement with vernier caliper.

Follow-up was conducted at 1 week, 2 weeks and 3 weeks, with observation extending up to 6 weeks by the same surgeon who performed the procedure. Persistence of symptoms beyond this period or the development of sentinel tags or features of chronic fissure on examination was considered a treatment failure. Data were collected on a structured proforma, including demographic and clinical parameters. Pain intensity was recorded using the Visual Analogue Scale (VAS), along with secondary symptoms such as bleeding, discharge, swelling, pruritus, and anal sphincter tone. Data were tabulated in Microsoft Excel and analyzed using standard statistical software. Descriptive statistics were applied for baseline variables, while categorical data were compared using the Chi-square or Fisher's exact test, with a p-value of less than 0.05 considered statistically significant. Findings were presented using tables and graphical charts for better interpretation.

Results

A total of 40 patients were enrolled, equally divided into Test and Control groups (n=20 each) (Table 1). Baseline demographic, socioeconomic, and clinical parameters were comparable between the groups ($p>0.05$). Both groups showed a similar distribution of age, gender, religion, comorbidities, and socioeconomic status, with most patients belonging to the 31–50-year age range and middle socioeconomic classes. Dietary habits, family type, addiction profile, and place of residence were also evenly distributed, ensuring group comparability.

Table 1. Demographic and Baseline Characteristics of Study Participants (n = 40)

Variable	**Levels**	**Control group**	**Percent**	**Test group**	Percent	P value
Gender	Male	14	70	12	60	0.51
	Female	6	30	8	40	
Age (In Years)	21-30	5	25	4	20	0.87
	31-40	5	25	5	25	
	41-50	7	35	6	30	
	51-60	2	10	2	10	
	61-70	1	5	3	15	
Religion	Hindu	7	35	9	45	0.52
	Muslim	13	65	11		
Comorbidity	HTN	3	15	2	10	0.74
	HTN /T2DM	1	5	3	15	
	T2DM	3	15	1	5	
	HYPO THY	1	5	X		
	COPD	2	10	1	5	
	NIL	10	50	13	65	
SE Status	KS II	2	10	1	5	0.78
	KS III	9	45	11	55	
	KS IV	9	45	9		
Type of Family	Joint	3	15	1	5	0.29
	Nuclear	17	85	19	95	
Dietary Habit	Non-Veg	17	85	18	90	0.67
Addiction	Alcohol	7	35	9	45	0.81
	Tobacco	6	30	5	25	
	NIL	7	35	6	30	
Place of Residence	Rural	6	30	8		0.41
	Semi Urban	2	10	6	30	
	Urban	12	60	6	30	
Total		**20**		**20**		

Clinically, pain was the universal presenting symptom in all patients with comparable mean VAS scores (8 in Test vs. 7 in Control). Associated symptoms such as bleeding, discharge, and pruritus showed no significant intergroup difference (Table 2).

Table 2. Clinical presentation of the patients in Test (20) and Control group (20)

Variable	Gr.	N	%
Pain	PATIENT T	20/20 VAS score (Avg) – 6-10 (8)	100
	PATIENT C	20/20 VAS score (Avg) – 7-10 (7)	100
Pain Affecting Daily Activities	PATIENT T	5/20	25
	PATIENT C	7/20	35
Duration of Pain	PATIENT T	7 – 14 days (Avg – 8 days)	X
	PATIENT C	5 – 16 days (Avg – 6 days)	X
Bleeding	PATIENT T	5/20	25
	PATIENT C	8/20	40
Discharge	PATIENT T	2/20	10
	PATIENT C	6/20	30
Pruritis(Y/N)	PATIENT T	14/20	70
	PATIENT C	9/20	45

Digital rectal examination findings revealed similar local pathology across groups. High anal sphincter tone was slightly more frequent in the Test group (95% vs. 75%), and the canoe-shaped fissure was the predominant type in both. Muscle fibre exposure, bleeding, and pus discharge from the fissure floor were somewhat more frequent in the Test group, though without statistical significance ($p>0.05$) (Table 3).

Table 3. Finding at digital rectal examination in Test (20) and Control group (20)

Variable	Gr.	N	%
Tone of Anal Sphincter (high)	PATIENT T	19/20	95
	PATIENT C	15/20	75
Shape of Fissure Canoe [C] Button Hole [B]	PATIENT T	C – 16/20 B – 4/20	80 20
	PATIENT C	C – 18/20 B – 2/20	90 10
Floor Muscle Fibre (M) Bleeding (B) Pus Discharge (P)	PATIENT T	M – 1/20 B – 12/20 P – 6/20	5 60 30
	PATIENT C	M – 2/20 B – 10/20 P – 2/20	10 50 10
Edges Indurated (I) Non-Indurated (NI)	PATIENT T	I – 18/ 20 NI – 2/20	90 10
	PATIENT C	I -16/20 NI – 4/20	80 20

Follow-up analysis showed a faster and more complete recovery in the Test group. Pain resolved significantly earlier ($p<0.01$), with all Test patients' pain-free by the third week compared to 20% of Controls. Bleeding cessation was complete in the Test group at all follow-ups, while a proportion of Control patients continued to bleed ($p\approx0.02$). Although discharge, swelling, and pruritus showed better trends in the Test group, these did not reach statistical significance. A highly significant improvement was observed in the normalization of anal sphincter tone in the Test group ($p<0.001$). Overall, both groups were comparable at baseline, but the Test group demonstrated faster and statistically significant symptomatic recovery during follow-up (Table 4).

Table 4. Follow-up comparing symptom resolution over time between the Test (T) and Control (C) groups

Variable	Group	1 Week (%)	2 weeks (%)	3 weeks (%)	6 weeks (%)	p value
Pain	PATIENT T	40	20	0	0	< 0.01 (S)
	PATIENT C	80	50	20	10	
Bleeding	PATIENT T	0	0	0	0	0.02 (S)
	PATIENT C	37.5	12.5	0	12.5	

Discharge	PATIENT T	50	0	0	0	> 0.05 (NS)
	PATIENT C	33.3	16.6	0	16.6	
Swelling	PATIENT T	16.6	0	0	0	0.09 (NS)
	PATIENT C	31.2	12.5	0	16.6	
Pruritis	PATIENT T	21.4	0.7	0	0	> 0.05 (NS)
	PATIENT C	44.4	33.3	11.1	14.2	
High anal Tone	PATIENT T	21	0	0	0	< 0.001 (HS)
	PATIENT C	80	46.6	6.6	13.3	

Discussion

The incidence of progression from acute AF to chronicity necessitating operation (LIS) is reported to be 40%. [4,7,9,10]. The main reason being failure of conservative management. LIS the gold standard operation for chronic anal fissure results in a healing rate of 88–100% [3-5,11]. Though LIS has the highest odds ratio of healing compared to other forms of treatment it is associated with significant rate of incontinence (0–44.4%) and wound related complications [10–12]. The reoperation rate following LIS is about 3% [13].

Anal dilatation is an office procedure, easy to perform, and does not require any equipment. It was the procedure of choice in 1960's resulting in healing rate of 95% with early symptom relief. But long-term results showed significant incontinence rates of about 52% [2,7,8,14]. Thus the procedure was abandoned.

Comparable literature, supports CAD as an effective adjunct in acute fissure management, particularly when conservative measures fail with healing rates of 88% and incontinence rate of 1% [13].

The present study was based on the above findings. It evaluated the efficacy of combining local infiltration anaesthesia (LIA) and controlled anal dilatation followed by conservative therapy versus conservative treatment alone in acute primary AF. Both groups were comparable at baseline in terms of demographic and clinical parameters, ensuring unbiased outcome comparison. The results demonstrated a significant advantage of the combined approach in terms of early pain relief, faster cessation of bleeding, and normalization of sphincter tone, indicating enhanced healing dynamics (Figure 2). These findings support the hypothesis that transient reduction of internal sphincter hypertonicity through controlled dilatation improves anodermal perfusion and fissure healing, within three weeks, emphasizing its utility as an intermediate step before surgical intervention.

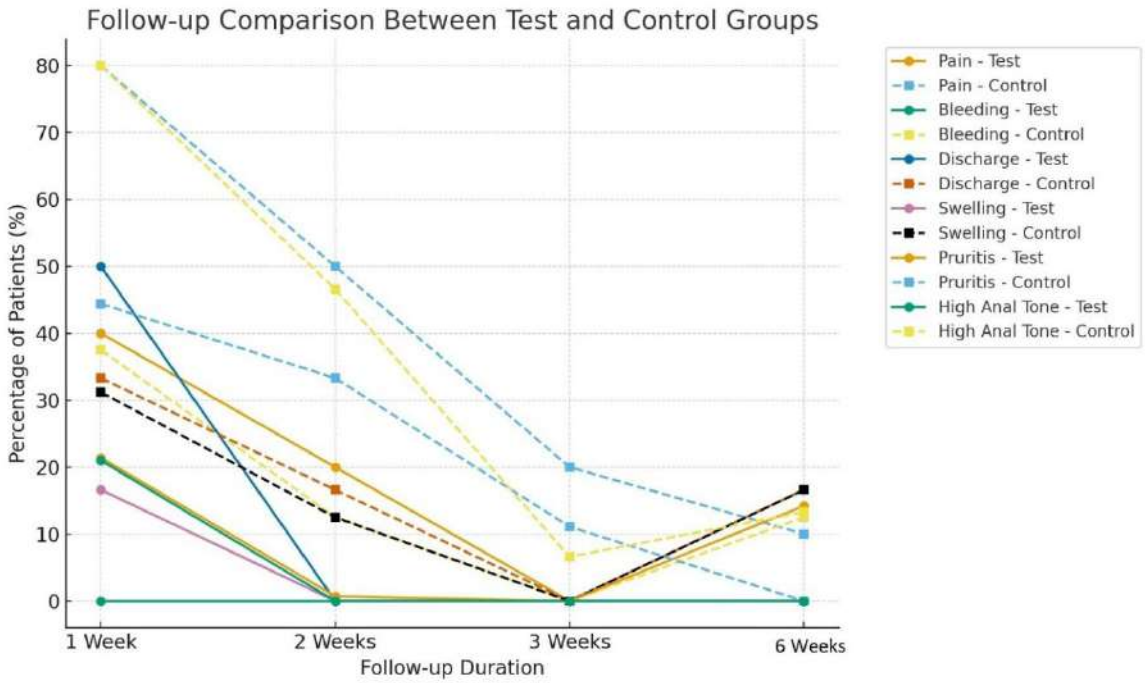


Figure 2. Line diagram comparing symptom resolution over time between the Test (T) and Control (C) groups. The plot clearly shows a faster decline in symptom prevalence across all variables in the Test group, for pain and high anal tone, indicating superior recovery outcomes.

However, absence of significant differences in secondary symptoms such as discharge and pruritus indicates that the primary benefit of this combined approach lies in pain control, restoration of sphincter physiology and mucosal healing effects. (Table 4). Importantly, no major adverse effects such as incontinence were reported, highlighting the safety of the controlled technique employed.

The study was limited by its small sample size and single-centre design, which may restrict generalizability. The short follow-up period of three months precludes long-term recurrence assessment. Additionally, subjective evaluation of pain and sphincter tone may introduce observer bias. Larger, multicentric randomized controlled trials with longer follow-up are recommended to validate these findings and assess durability and recurrence rates.

Conclusion

Combining local infiltration anaesthesia and CAD with standard conservative treatment offers a safe, effective, and rapid method for symptom relief and healing in acute primary AF. The approach bridges the gap between conservative and surgical management, providing a physiologically sound, minimally invasive option for early intervention. Early pain relief, faster bleeding cessation, and improved sphincter relaxation were the key outcomes, making this combined technique a valuable adjunct to conservative therapy.

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I acknowledge the use of ChatGPT (https://chat.openai.com/) to refine the academic language and accuracy of my own work. I submitted my entire essay and

entered the following prompts on 19 October 2025. Improve the academic tone and accuracy of language, including grammatical structures, punctuation and vocabulary

Declarations Conflict of interests

The authors have no competing interests to declare that are relevant to the content of this article.

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ORIGINAL ARTICLE

Association Between Quality of Sleep, Dietary Intake and Obesity Among Adults in Mandya City: A Cross -Sectional Study

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Abstract

Introduction: Sleep is a periodic, reversible physiological condition of unconsciousness that is essential for people's recovery and well being from which a person can be aroused by sufficient stimulus. Sleep problems and obesity are considered an emerging global pandemic. Both the quantity and quality of sleep are crucial for maintaining health and wellbeing. Additionally, one of the main modifiable behavioural risk factors for the development of obesity is an unhealthy diet. **Materials and Methods:** Anthropometric measurements were used to calculate BMI, which was categorized using Indian standards. Sleep quality was assessed using the PSQI and diet using a pre-tested questionnaire. Descriptive statistics, correlation analysis, and visualizations were employed to examine the association between obesity, sleep quality and diet. **Results:** The mean BMI of the participants was 27.46±1.59 kg/m² in males and 27.36±1.57kg/m^2 in females, with all participants classified as obese per Indian BMI guidelines. In this study it was found that age does not correlate significantly with BMI, PSQI, or Diet. Across all four variables (Age, BMI, PSQI, Diet), $p > 0.05$, there are no males and females differ statistically significantly. But BMI, PSQI, and Diet scores are all strongly and positively correlated with each other (r values > 0.97, all $p < 0.001$). This suggests that individuals with higher BMI tend to have higher PSQI (poorer sleep quality) and higher Diet scores (poorer dietary pattern). Thus, this study demonstrated that dietary changes and sleep deprivation cause obesity. **Conclusion:** The findings highlight a significant relationship between obesity and poor sleep quality in young adults in Mandya City. Given the interplay of dietary habits in influencing both factors, targeted interventions focusing on healthy eating and sleep hygiene may be crucial in mitigating obesity-related health risks.

Keywords: Obesity, Body Mass Index (BM), Pittsburgh Sleep Quality Index (PSQI)

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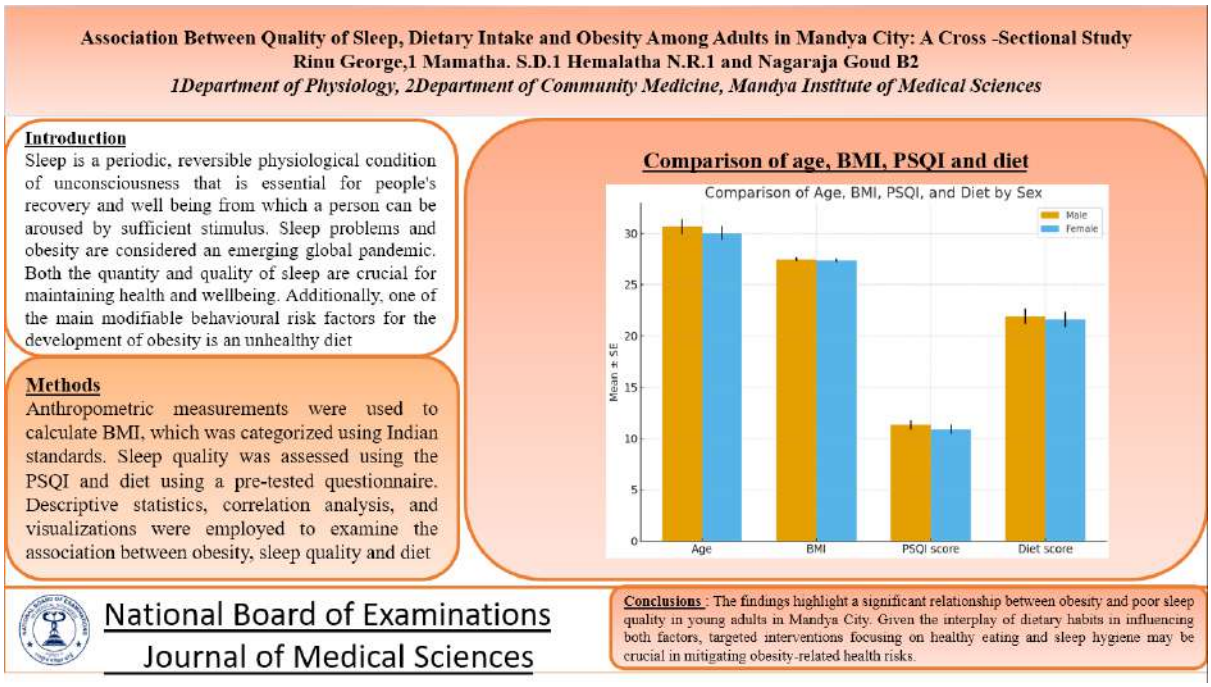
Graphical Abstract



Introduction

Sleep is a periodic, reversible physiological condition of unconsciousness that is essential to people's recovery and wellbeing and can be eliminated with sufficient stimulus. Sleep issues are seen as a new global pandemic [1,2]. Obesity is another global epidemic and short sleep length (6 hours) was linked to a 45% higher risk of obesity compared to regular sleep duration, according to a recent meta-analysis of prospective studies [3,4].

Research has shown that patterns in sleep issues are similar to those in obesity. Weight gain results from behavioural, metabolic, and endocrine changes brought on by shorter sleep duration and lower sleep quality [3,4]. Additionally, because obese people are more likely to experience sleep apnoea, obesity exacerbates sleep issues [5]. Furthermore, because it is linked to a number of chronic illnesses, including an increased risk of cardiovascular disease, insulin resistance, and hypertension, it continues to be one of the key health concerns [6]. Globally approximately 1.9 million (39%) adults were overweight and 609 million (13%) adults were obese in 2015 according to the World Health Organization [7]. Obesity is also thought to be a strong risk factor elevating the risk of disability and poor overall health among older adults [8]. A chronic pattern of sleep duration of 6 hours a night has been associated with a higher body mass index (BMI) [9]. A meta-analysis of 604509 adults showed obesity for less than (5hrs) of sleep and a dose effect of sleep duration such that for each additional hour of sleep BMI decreased by 0.35kg/m^2 [10].

Sleep takes up 20% to 40% of the day and is a physiological aspect of human life that is mostly regulated by the nervous system. Sleep amount and quality are crucial for maintaining health and wellbeing [11,12]. The recommended sleep duration, according to the National Sleep Foundation is 7 to 9hr for young adults [13].

Reduced consumption of dietary fibre and increased intake of carbs, total sugar, total cholesterol, and total saturated fat are linked to short sleep duration. This increases calorie intake and throws off the equilibrium between energy intake and energy expenditure, which results in obesity [14]. Due to the growing demands of work, school, and leisure activities as well as the widespread use of electronic gadgets and the internet, it is a global phenomenon that both adults and adolescents are sleeping for shorter periods of time than they did a few decades ago [15]. As a result, obesity has become an epidemic on a global scale and significantly increases the burden of chronic illnesses and disabilities.

Additionally, one of the main modifiable behavioural risk factors for the development of obesity is an unhealthy diet [16]. Fast food has been more accessible due to rising urbanization and affluence, which has resulted in numerous modifications over the past few decades. Nutrition has changed quickly as a result of these dietary and lifestyle changes brought on by watching television, using computers, the internet, and smartphones leading to obesity among children, adolescents and adults [17,18]. A variety of dietary recommendation have been proposed to prevent obesity. The major factors contributing to obesity being improper dietary habits like Mealtime irregularities, poor food quality, consuming excessive amounts of junk food, and dining out [17].

According to National Family Health Survey (NFHS-5), India (2019–21) measured population-level estimates: ~24% of women and ~23% of men (age 15–49) are overweight or obese (BMI ≥25), and obesity (BMI ≥30) ~6.4% in women and 4.0% in men. A cross-sectional study among adults in rural Mandya found that 25.9% of participants had hypertension and the study identified obesity (along with a history of diabetes) as a significant risk factor for hypertension in this population [19].

Hence this study was taken up with the primary hypothesis that poor sleep quality (higher PSQI scores) is significantly associated with higher BMI and increased risk of obesity and secondary hypothesis that Unhealthy dietary patterns are significantly associated with higher BMI, poor sleep quality is associated with unhealthy dietary behaviours (e.g., increased caloric intake, poor food choices) and that sleep quality and dietary patterns together have a combined effect on BMI and obesity risk. The objective of the study was to access the association between sleep quality (using PSQI), dietary patterns (using a diet questionnaire), and obesity status (using BMI).

Materials and Methods

This cross-sectional study, was conducted from August 2025 to October 2025 on 209 subjects of age group 20–45 years who are adults with BMI > 25kg/m^2 of Mandya city. The Institutional Ethical committee approved study on August 12, 2025. After obtaining informed consent, data was gathered using a four-part, semi-structured questionnaire.

Socio Demographic Characters

The data shall be recorded using a semi-structured questionnaire which contains 3 parts:

- The first part shall collect details of socio-demographic characteristics like

name, age, sex etc and height and weight of the individual will be measured using stadiometer and a digital weighing scale respectively from which BMI is calculated using Quetelet's index.

- The second part contains The Pittsburgh Sleep Quality Index (PSQI).

Pittsburgh sleep quality index (PQSI)

PSQI has been found to be most effective in terms of reliability and validity. It includes 19 self-rated items, which focus on seven main areas including: subjective sleep quality, sleep latency (time taken to fall asleep), sleep duration, habitual sleep efficiency (the ratio of total sleep time to time in bed), sleep disturbances, the use of sleep-inducing medicines and daytime dysfunction.

PSQI Scoring -The PSQI includes a scoring key for calculating a patient's

seven sub scores, each of which ranges from 0 to 3.

A score of 0 indicates no difficulty.

A score of 3 indicates severe difficulty.

The 7 component scores are then added to make a global score with a range of 0-21

A score of 0 means no difficulty.

A score of 5 or more indicates poor sleep quality.

A score of 21 means severe difficulties in all areas.

(The higher the score, the worse the quality).

- The third part contains details of dietary habits based on a pre-tested questionnaire.[20]

The diet questionnaire contains consists of 11 questions with a global score ranging from 0-34.

(The higher the score, the worse the quality).

Data Collection

Data were collected by convenience sampling technique, among 209 adults of Mandya city. A five minutes briefing session was given to explain the study and various terms which are used in the study, total time of 10 -15 minutes was provided to the adults to fill the questionnaire. They were assured about the confidentiality of their personal information.

Inclusion Criteria

- Adults in Mandya city willing to give informed consent to participate in the study.
- Age group of 20-45 years.
- Adults with BMI >25kg/m^2

Exclusion Criteria

- Adults with a BMI less than 25kg/m^2
- Any physical or mental illness affecting their sleep.
- Any diagnosed psychiatric illness, neurological disorders.
- Adults with history of any endocrinal disorders.
- Adults with habit of smoking, alcohol and drug abuse.

Statistical Analysis

Collected data was entered in Microsoft Excel and analysed using SPSS (Statistical Package for Social Sciences).

Descriptive statistics for categorised data like sex, sleep quality scores, dietary scores etc and for continuous data like age, sleeping hours etc.

Inferential statistics-Chi square test to know association of sleep quality and dietary habits and obesity. Other suitable statistical tests were applied.

Statistical significance was considered if P<0.05.

Results

The total number of participants was 209 with 104 females and 105 males. Group statistics output (descriptive stats for each sex) was done by an independent samples t-test (Figure 1 and Table 1).

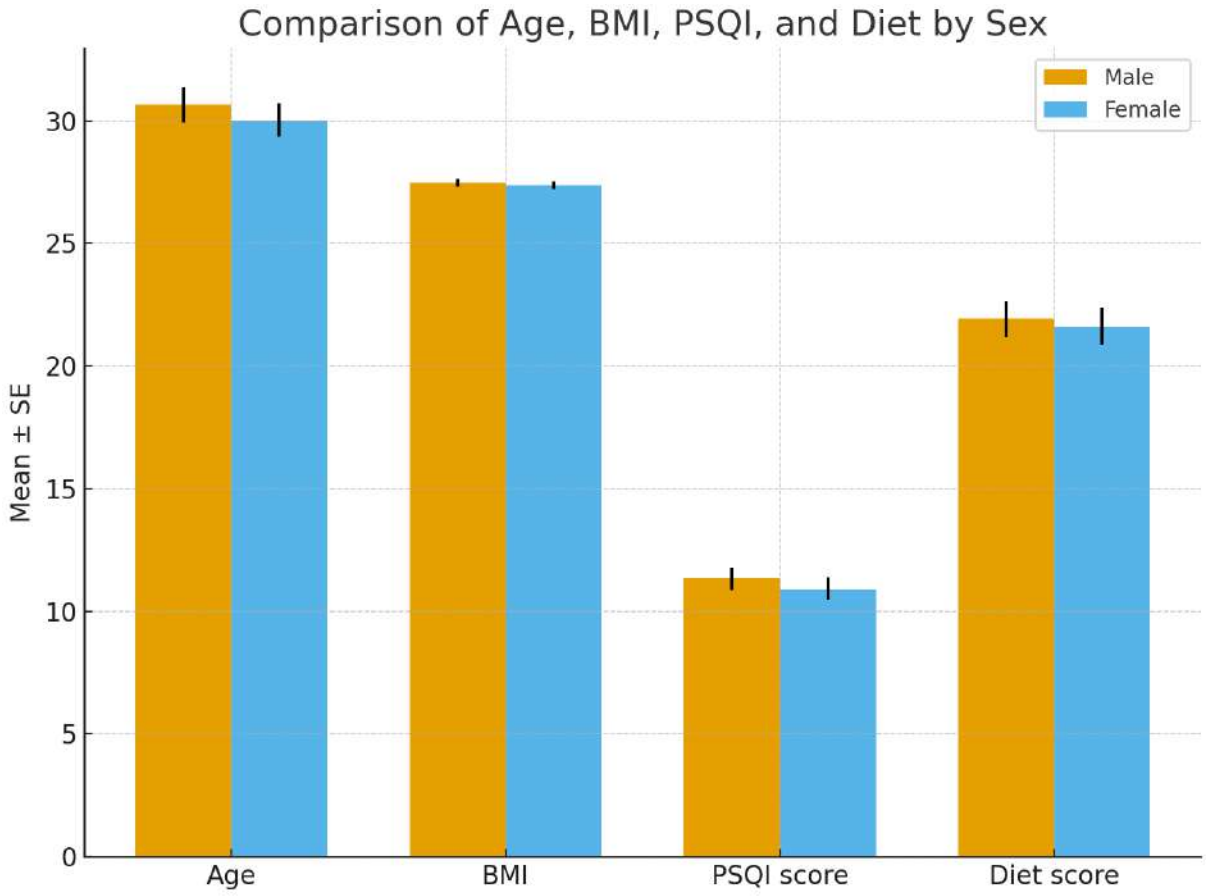


Figure 1. Comparison of age, BMI, PSQI and diet with sex of the individuals

Table 1. Independent sample test for comparison of Age, BMI, PSQI and diet with sex

		Levene's Test for Equality of Variances		t-test for Equality of Means							
						Significance				95% Confidence Interval of the Difference	
		F	Sig.	t	df	One-Sided p	Two-Sided p	Mean Difference	Std. Error Difference	Lower	Upper
Age	Equal variances assumed	.685	.409	.614	207	.270	.540	.619	1.008	-1.369	2.607
	Equal variances not assumed			.614	206.242	.270	.540	.619	1.008	-1.368	2.606
BMI	Equal variances assumed	.040	.842	.459	207	.323	.647	.1004	.2186	-.3306	.5313
	Equal variances not assumed			.459	206.998	.323	.647	.1004	.2186	-.3306	.5313
PSQI score	Equal variances assumed	.017	.896	.645	207	.260	.520	.420	.651	-.864	1.704
	Equal variances not assumed			.645	206.991	.260	.520	.420	.651	-.864	1.704
Diet score	Equal variances assumed	.252	.616	.282	207	.389	.779	.299	1.062	-1.794	2.392
	Equal variances not assumed			.282	206.935	.389	.779	.299	1.062	-1.794	2.392

Across all four variables (Age, BMI, PSQI, Diet), $p > 0.05$, there are no statistically significant differences between males and females (Table 2).

Table 2. Correlation of age, BMI, PSQI score and diet score

		Age	BMI	PSQI score	Diet score
Age	Pearson Correlation	1	.059	.053	.085
	Sig. (2-tailed)		.393	.448	.219
	N	209	209	209	209
BMI	Pearson Correlation	.059	1	.987**	.971**
	Sig. (2-tailed)	.393		<.001	<.001
	N	209	209	209	209
PSQI score	Pearson Correlation	.053	.987**	1	.970**
	Sig. (2-tailed)	.448	<.001		<.001
	N	209	209	209	209
Diet score	Pearson Correlation	.085	.971**	.970**	1
	Sig. (2-tailed)	.219	<.001	<.001	
	N	209	209	209	209

**. Correlation is significant at the 0.01 level (2-tailed).

Age does not correlate significantly with BMI, PSQI, or Diet.

BMI, PSQI, and Diet scores are all strongly and positively correlated with each other (r values > 0.97, all $p < 0.001$).

This suggests that individuals with higher BMI tend to also have higher PSQI (poorer sleep quality) and higher Diet scores.

Discussion

This study showed that higher BMI was associated with poorer quality of sleep and poor dietary habits.

Sleep is a naturally occurring process of mind and body. The National Sleep foundation suggests that healthy adults need 7–9 hours of sleep per night and previous studies showed that sleep loss led to increased ghrelin and decreased leptin levels which has positive correlation with obesity [21]. Ghrelin also known as hunger hormone is secreted mainly by the oxyntic cells of the stomach mucosa and stimulates appetite and food intake. Whereas leptin also known as satiety hormone secreted by adipose tissue suppresses appetite. Inadequate sleep influences food intake, appetite regulation, satiety, and overall

energy balance by altering these hormonal responses [22-24]. Some studies have shown a causal relationship between short sleep duration and the increased consumption of dietary carbohydrates and/or carbohydrate-rich foods, which might lead to an increased risk of obesity [25]. Further the possible mechanism connecting sleep and obesity include reduced physical activity [26,27]. Additionally, poor sleep quality is frequently linked to unhealthy lifestyle patterns, such as increased consumption of high-calorie foods and beverages [28,29].

Normally Ghrelin level decreases in obesity, however regulation fails and hunger persists. Whereas Leptin level increases in obesity but receptors become resistant (Leptin resistance) and satiety signals fail. Although poor sleep health could increase the risk for obesity by increasing appetite and the consumption of a low-quality diet to our knowledge, few studies have examined the relationship between sleep status and obesity in conjunction with dietary intake [30,31].

In the present study PSQI score has shown that the majority of people had disturbances in sleep and inadequate sleep alters the appetite affecting BMI. These alterations affect quality of growth, stress hormones, immune system leading to lifestyle related health problems [32].

The majority of adults worldwide are expected to be obese or overweight by 2030 due to the rising incidence of obesity in many nations. The World Health Organization reports that 340 million children and teenagers between the ages of 5 and 18 were obese in 2016 [33]. The average amount of sleep decreased from 9 hours per night in 1910 to 7.5 hours in 1975 and fewer than 7 hours now due to growing social and professional responsibilities, the introduction of artificial lighting at the turn of the century, and, more recently, the widespread use of computers and other electronic media [34]. Lack of sleep also negatively affects thinking, learning, memory, and recall, which in turn affects one's capability for productive work and unrestricted social interaction. It also leaves one feeling "disconnected" from the outside world. A poor lipid-lipoprotein profile, type 2 diabetes mellitus (DM), hypertension, various cardiovascular diseases (CVD), obesity, and even early death are all linked to sleep deprivation. Long-term poor "Western" eating habits are frequently linked to sleep disturbances [35].

Although many studies have been done in Western countries regarding the same, very few studies have been done in India. Hence this study was taken up.

In this study it was found that age does not correlate significantly with BMI, PSQI, or Diet. But BMI, PSQI, and Diet scores are all strongly and positively correlated with each other (r values > 0.97, all $p < 0.001$). This suggests that individuals with higher BMI tend to also have higher PSQI (poorer sleep quality) and higher Diet scores.

Thus, this study showed strong positive association between poor sleep quality, BMI and poor dietary habits.

Conclusion

Our study concludes that there is a significant association between obesity and poor sleep quality among young adults in Mandya City. Given the interplay of dietary habits in influencing both factors, targeted interventions focusing on healthy eating and sleep hygiene may be crucial in mitigating obesity-related health risks.

Limitations of the Study

- PSQI and diet questionnaires rely on self-report, which may lead to recall bias and social desirability bias (participants underreporting unhealthy food or poor sleep).
- Diet questionnaires may not capture portion sizes correctly, snacking or binge episodes and long-term eating habits.
- Diet and sleep patterns may vary daily or seasonally.
- PSQI measures perceived sleep quality, not objective sleep parameters. Does not include Actigraphy and Polysomnography.

Future Scope of the Study

- Future research can adopt longitudinal designs to track changes in sleep quality, diet, and BMI over time.
- Using tools such as actigraphy, wearable trackers, or polysomnography can provide more accurate and comprehensive sleep data. This helps validate PSQI findings and detect disorders like sleep apnoea.
- Assessing markers such as fasting glucose, lipid profile, insulin resistance (HOMA-IR, inflammatory markers would provide insight into mechanisms linking poor sleep, diet, and obesity.
- Future research can explore emotional eating, stress-related eating and sleep-related behaviour patterns. These may mediate the relationship between sleep quality, diet, and obesity.
- Findings can be used to design sleep–diet–weight management programs for schools, workplaces, and communities.

Key Message

Sleep plays an important role in cognitive and physical functions, in removal of cellular toxins and prevention of various diseases. Higher BMI is significantly linked to poorer sleep quality. Unhealthy diet also leads to obesity. It Emphasizes need for diet, weight, and sleep interventions. Counseling, yoga and meditation may be useful in combating these stress effects and prevent future complications. Future research should explore causal links and dietary patterns.

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Statements and Declarations

Conflicts of interest

The authors declare that they do not have conflict of interest.

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ORIGINAL ARTICLE

Family Burden and Burnout Correlates in Spouses of Persons with Alcohol Dependence, Bipolar Disorder and Schizophrenia

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Abstract

Introduction: Living with a person with major psychiatric illness burdens forcing a unique and predominantly negative experience down spiralling to burnout and chronic psychological morbidity in long-term caregivers. Quantifying the burden and burnout would be useful in screening, early diagnosis and therapy including primordial to tertiary prevention, protecting spousal carers from incarceration. **Aims:** The objective was to estimate burden and burnout correlates of caregiving experience, and study their association with severity of illness, apathy and duration of caregiving, among female spouses of persons with alcohol dependence syndrome, bipolar affective disorder and schizophrenia. **Materials and Methods:** In this cross-sectional, comparative study with consecutive samples of consenting male patients and their spouses 64 pairs in each group attending the Outpatient Psychiatry department at a tertiary care hospital in South India. Apathy inventory, SADDQ, CGI-BP and CGI-SCH, Burden Assessment Schedule, and a composite score from Care-derived Self-esteem subscale of Caregiver Reaction Assessment (CRA) scale, High appreciation subscale of Positive Caregiving Experience scale, and Burnout subscale of Negative Caregiving Experience scale, were used. **Results:** Total burden, and burden in 'spouse's mental health' dimension was higher both in bipolar and schizophrenia groups. Spouses perceiving increased apathy had higher burden scores in schizophrenia group, and lower in alcohol group. As duration of caregiving increased beyond 18 years in carers of alcohol dependents, the initial low burden scores spiked to become on par with other groups. Burnout experience was frequent in alcohol group. There was a positive correlation between burden and positive experience (overcoming burnout) with statistical significance, only in schizophrenia group. Burden and positive experience correlated positively with illness severity in all three groups, the most in alcohol group. **Conclusion:** Increased burden of care and burnout in female spouses are very common and severe in major psychiatric disorders and to similar levels in alcohol dependence syndrome. This warrants spouse-specific psychological treatment approaches to prevent depression in spouses, and improving drug adherence and prognosis in patients.

Keywords: Apathy, Burden, Burnout, Caregiving Experience, Alcohol dependence, Bipolar disorder, Schizophrenia

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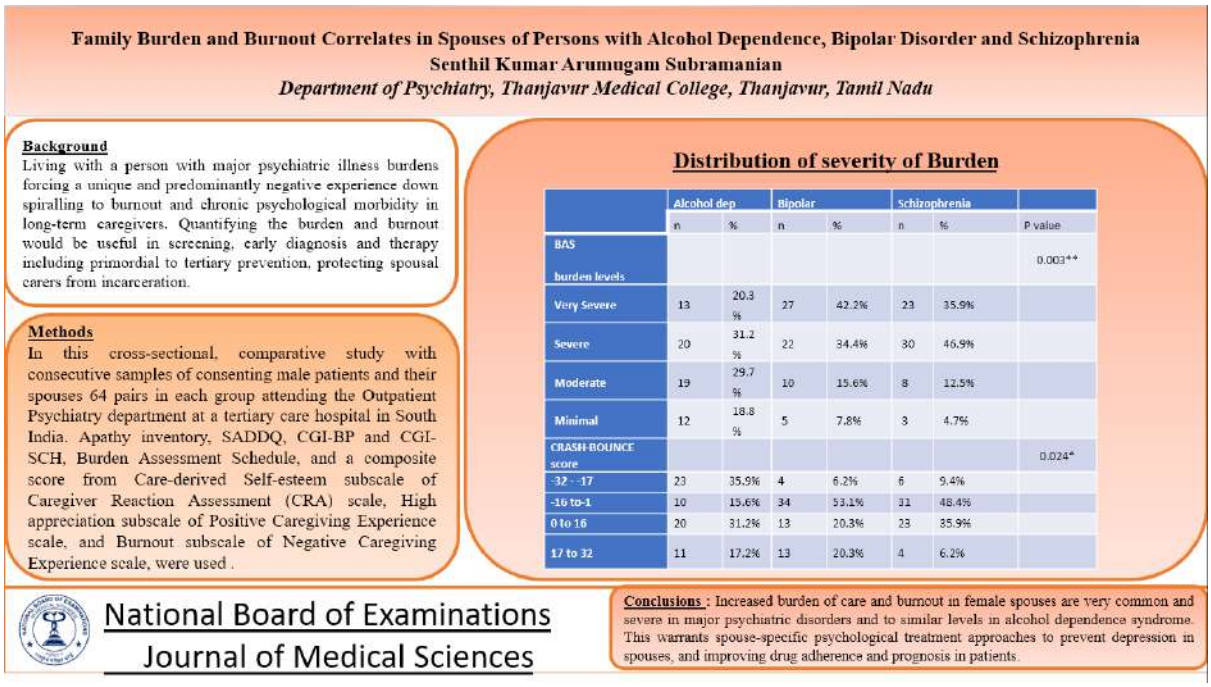
Graphical Abstract



Introduction

Role of family in caregiving is one of the most significant factors in determining the course and outcome in major psychiatric disorders. Spouses as individuals bound with each other by a relationship that is psychological, social and biological. Persons with enduring illness can still be enlivened by eternal and materialistic interdependence, sharing and support, especially offering guidance and solace. A caregiving spouse may encounter more burden in psychological, financial, security and sexual dimensions [1] due to illness, when compared to other caregivers from family.

While a carer provides the skeleton for the patient's progress, burden gives negative caregiving experience invoking social distortions and compulsive adaptations, ultimately reducing the couple's quality of life.

The initial apprehension about the indifference in their eternal companion turns into a prolonged grief, when the spouses gradually becomes aware of the chronicity of the illness. They get puzzled with uncertainty, and sense a curse forbidden with an eternal solitude. They may feel stigmatized, and emote shame, guilt, anger from a sense of having been deceived.

Caregiving disrupts one's personal lifestyle and routine, forcibly alters his or her preferences, dampens enthusiasm and energy in pursuing one's own fantasies and career.

Burden occurring out of privilege or traditional family role, volunteering or compulsion, with altruistic, symbiotic or materialistic facets, evoke a subjective sense of fulfilment as a positive caregiving experience.

Alcohol use disorders and bipolar illness [2] are the second and third leading cause of disability among psychiatric illnesses worldwide. Prognosis worsen drastically with insufficient or inappropriate care, and drug non-compliance [3].

These disorders run a chronic course needing long-term maintenance treatment, and may directly affect patients' personal care, perception of reality, social interaction, functional productivity and personality (aggressive or suicidal behaviour) -often with a hostile reaction towards normal events and innocuous, nonspecific or caring actions of spouses and family members. Overwhelming demands and the resulting embarrassment and interpersonal conflicts increase subjective burden.

In studies by Vohra et al. [4] and Chadda Rakesh et al. [5], both carers of persons with bipolar disorder and schizophrenia felt similar pattern of burden, more in the family routine, finance, leisure and family interaction dimensions. Mueser et al. found more family burden due to manic symptoms than for positive and negative symptoms while comparing carers of patients with bipolar disorder and schizophrenia [6].

Fadden et al reported restricted leisure time increased the burden significantly in the carers who sense doing larger than their fair share in maintaining the marriage [7].

In a study by Perlick et al on 623 caregivers with the baseline data of CATIE, high scores in burden domains like carer routine disruption and resource demands, problematic behaviour, functioning level of activities of daily living and perceived support, were associated with caregiver age and symptom severity, and were the strongest predictors of burden [8], similar to their other study in bipolar disorder [9]. In the latter, misery, irritability, lack of emotional interaction and withdrawal most frequently complicated distressing behaviour in addition.

Indian studies in spouses of persons with schizophrenia found significant association with mental and physical health, especially more fatigue, frustration, anxiety and isolation. Additional financial, treatment, caring routine and social responsibilities over and above the domestic roles added to the excess burden [10]. In addition, self-stigma and level of income determined the high burden in schizophrenia as much as in autism spectrum disorder [11].

Illness severity and patient's apathy

Apathy refers to a reduced interest, involvement in interpersonal relationships, initiative and concern, and flattening of affect. Apathy and other negative symptoms in the patient profoundly contribute to the spouse's perception of appreciation by the patient [12]. It poses difficulties in care, treatment and burden with negative outcomes over time. An interview by Baronet showed poor patient interaction influenced subjective burden the most in carers of mental illnesses [13].

Mueser and Provencher found in carers of persons living with schizophrenia that the negative behaviour like apathy negatively correlated with objective burden [14].

In a study by Mills, odd, disinhibited, or apathetic behaviour, caused more difficulties than daily routine; poor communication in patients was associated with higher burden than express talk [15]. Apathy is typical in depressive phase of bipolar disorder, and chronic schizophrenia. The manic grandiosity, distractibility and disregard dampens the fervour of the carer as does the salience observed in alcohol dependence syndrome. Such apathetic behaviour has a negative impact on motivation for caregiving.

In a study by Pompili et al in primary caregivers over a 48 years period, patients behaviour and patient role deficits caused higher distress in bipolar disorder [3].

Spousal impact in chronic illnesses

Lifespan of unmarried persons with schizophrenia is considerably less compared to that of married persons. This portrays the role of spouses in the prognosis in patients.

Negative symptoms including alogia, avolition, a motivation, flattening of affect, and generalized mental slowing, also tend to frustrate a primary caregiver. This is more so when the latter's subjective burden is not acknowledged, and the patients' repelling nonchalance and delusional behaviour wipes off any lingering resilience. Volunteering as a primary caregiver when the spouse has the option of moving away from the patient doubles the burden up with feelings of frustration from the self-imposed entrapment, overwhelming any gratification from caregiving.

Factors predicting caregiver burden

Other determinants of burden include duration of caregiving, time spent for caregiving, severity of illness, prior hospitalizations, and income [16]. These impact on the carer's innate resiliency, negative caregiving experience, and the propensity for burnout. EPSILON study concluded burden increased with greater duration of caregiving the patients with schizophrenia [17].

Higher burden correlated negatively with emotion-based coping [7] and also drug adherence and treatment outcome in bipolar patients [9]. It was also associated with insufficient self care, lower resilience, higher burnout and enthusiasm in managing emergent problems in alcohol dependents and persons with schizophrenia [8].

Resiliency, vulnerability and factors in burnout

Bouncing back from transient insufficiencies in managing burden is an innate strength denoted by "resiliency". Persistent uncontained burden without any props or channels of de-escalation, dries out caregiver's coping repertoire and gives a sense of insufficiency and vulnerability. When compounded with significant life events, vulnerability lets helplessness in, and the perceived colossal mental fatigue results in a burnout. Resilience was inversely related to the severity of alcohol dependence, history of domestic violence, and severity of depression in wives [18]

Burnout is an acute stress reaction characterized by sense of being overwhelmed, exhaustion, anxiety, depression, and impairment in work performance. This is compensated with immature mechanisms furthering emotional over-involvement, and other expressed emotions, especially critical about patients' unresponsiveness and despise [19].

While gruelling caregiving moulds the fizzed out clayey self into an unhappy, displeased and grumpy personality, better coping and support groups and therapy may be needed to revitalize self-esteem and appreciate life.

Negative experience and burnout

Zarit [20] estimated that 25% to 50% of caregivers meet major depression criteria. Caregivers perceiving extreme stress and burnout are shown ageing prematurely, and reduction of a mean of 10 years from their lifespan [21]. Christakis

and Salaman [22] estimated that in female spouses of patients the mortality risk was increased by 44% while it is 35% in case of male spouses. This risk for extreme ramifications form the rationale for this study.

Aim

To compare the caregiver burden, and net caregiving experience (burnout propensity) between female spouses of males with alcohol dependence syndrome, bipolar affective disorder and schizophrenia. To study the association between severity of illness, duration of caregiving, and apathy as perceived by spouses, and the burden and net caregiving experience/burnout, between these three groups. Primary hypothesis was that there will be no difference in burden and burnout between the caregivers.

Materials and Methods

After institutional ethical committee approval, sample for the study was drawn from male patients with female spouses attending the outpatient psychiatry department at Government Stanley Medical College Hospital, Chennai. It was a cross-sectional, comparative study with convenient consecutive sampling of 64 male patients diagnosed with alcohol dependence, 64 with bipolar affective disorder, and 64 with schizophrenia, along with their female spouses who were fulfilling the study criteria, and consented in writing for participation.

Inclusion criteria included males with more than 10 years duration of alcohol dependence or schizophrenia or bipolar affective disorder, satisfying ICD10 criteria for their corresponding diagnoses, along with their female spouses who are providing care for the patients for more than 10 years duration, all with age more than 20 years, and who provided informed consent for the study. Exclusion criteria included patients and spouses with chronic general medical or neurological illness, patients with other psychiatric conditions, and those related by consanguinity.

After obtaining informed consent from the participants, a semistructured proforma was used to collect the relevant sociodemographic details and clinical profile. Severity of illnesses were measured by: Short Alcohol Dependence Data Questionnaire – SADDQ, Clinical Global Impressions - CGI-BP bipolar patients version –severity scale, and Clinical Global Impressions - CGI-SCH schizophrenia – severity scale, for the corresponding patient groups. Spouses were then assessed with Apathy inventory –caregiver version, Burden Assessment Scale BAS. SPSS20.0 was used for statistical analysis.

Short Alcohol Dependence Data Questionnaire, SADDQ [23] is an instrument to measure the severity of alcohol dependence. It has 15 items, with Likert scoring from 0-never to 3-nearly always. A total of 30 and above shows high dependence severity.

Clinical Global Impression CGI-BP [24] and CGI-SCH [25] are used to assess change in severity and improvement, in both clinical and research settings. The CGI-BP, a user-friendly scale for the assessment of bipolar symptoms, and long-term outcome, is a useful tool for the assessment of the efficacy of several treatments. CGI-SCH scale is a valid, reliable instrument to evaluate severity and treatment response in schizophrenia. Correlation between the CGI-SCH and PANSS scores was high (0.75), and was highest for positive and negative symptoms.

Apathy Inventory (IA)[26] is used in the assessment of: emotional blunting, lack of initiative, lack of interest (based on Marin's syndrome criteria). Of the caregiver and patient-based assessments based on the Y/N format, caregiver version was used here. With a total score of 36, it has better reliability than other apathy rating scales (test-retest 0.96, interrater 0.99); it has been validated in Alzheimer's disease and Parkinson's disease, and other neuropsychiatric conditions. It has a concurrent validity comparable with apathy subscale of Neuropsychiatric inventory.

Burden Assessment Schedule (BAS)[27] by Thara et al to assess subjective burden on caregivers of chronic mentally ill. It has nine domains: spouse related, physical and mental health, external support, caregivers routine, support of patient, taking responsibility, other relations, patients behaviour and caregivers strategy. A total of 40 items were rated on a 3-point scale marked 1-3. Severity can be classified into minimum (40-60), moderate (61-80), severe (81-100), and very severe (above 100).

A composite caregiver reaction, experiences and burnout score (CRASH-BOUNCE score) was given to the spouses using the Care-derived Self-esteem subscale of Caregiver Reaction Assessment (CRA-S) scale, Positive Caregiving Experience(H), and the Burnout subscale of Negative caregiving experience (Bou-NCE) (Table 1a,b). Developed by Given et al. [28] CRA has been used in carers of cancer and neuropsychiatric patients, and has good psychometric properties. Burnout is assessed with how exhausted the caregivers are by the time they go to bed, how overwhelmed are they with things to do, how shrunken is their private time, and how pessimistic and stuck is the task despite their hard work. These items used in studies by Ingersoll-Dayton & Raschick [29], and Lin [30]. Positive caregiving experience included how much did the caregiving make them feel good about themselves and appreciate life more. These subscales have good reliability and validity (α = 0.90 and 0.78). A positive CRASH-BOUNCE score is posited to imply positive net caregiving experience, while negative score imply negative experience i.e. burnout in the carers.

Table 1a. A composite utility caregiver burnout-experience score: The CRASH-BOUNCE score

Item no.	**Items of CRA-S: The Caregiver Reaction Assessment scale: Self-esteem – care-derived subscale** (Given et al., 1992)	Cronbach's α=0.73 (Nijboer et al, 1999)
1	Caring for my partner is important to me.	0.54
2	I enjoy caring for my partner.	0.51
3*	Caring for my partner makes me feel good.	0.50
4	I feel privileged to care for my partner.	0.54

5	I resent having to care for my partner.	0.58
6	I really want to care for my partner.	0.51
7	I will never be able to do enough caregiving to repay my partner.	0.83
	Item for H: *H*ighheld-life subscale of Positive Caregiving Experience (Lin, Fee & Wu, 2012)	
1.	Caregiving made me appreciate life more	α = 0.78

Likert scale for each item, 1-2-3-4-5 for1= Strongly disagree, 2= Disagree, 3= Neither disagree nor agree, 4= Agree, and 5= Strongly agree respectively, for CRA-S and H items, 2-4-6-8-10 respectively for BouNCE items. Reverse scoring for items 5&7 in CRA-S subscale.

Table 1b: A composite utility caregiver burnout-experience score: BouNCE score, and Net Caregiving Experience/burnout score calculation

	Items for BouNCE: ***B***urn***ou***t subscale of ***N***egative ***C***aregiving ***E***xperience (Ingersoll-Dayton & Raschick, 2004)	Cronbach's alpha
1	I am exhausted when I go to bed at night.	α = 0.90 (Lin, Fee & Wu, 2012)
2	I have more things to do than I can handle.	
3	I do not have time just for myself.	
4	I work hard as a caregiver but never seem to make any progress.	
Positive Caregiving Experience (***CRA-S***elf-esteem +***H***-PCE), PCE score (max. 40)		
Negative Caregiving Experience (***B***urn***ou***t-***NCE***), NCE score (max. 40)		
Net Caregiver *CRASH-BOUNCE* score, PCE minus NCE (range -32 to +32).		

Results

Mean age of patients was around 36 to 38 yrs and that of spouses was 33 to 34 yrs, in all the groups (Table 2). About two-thirds of the patients across the alcohol, bipolar and schizophrenia groups (59 vs 73 vs 65% respectively) had completed secondary school. All the three groups had almost equal proportions (around 30-35% each) in the three family types *viz.* nuclear, extended and joint. About 61, 64 and 56.3% of patients had an annual family income 120,000 Rupees or more. About 54.6, 46.9 and 57.8% of spouses in the three groups respectively had not completed secondary schooling. The differences between the groups in all the above parameters were not significant. More spouses contributed for half or more of the family income in the bipolar group than others (61 vs 73 and 65%), difference being statistically significant.

Table 2. Distribution of Sociodemographic variables

	Alcohol dependence	Bipolar disorder	Schizophrenia	p value
Age of Patients, mean (SD)	38.44 (5.08)	37.66 (6.36)	36.48 (5.78)	0.159
Age of Spouses, mean (SD)	33.89 (3.99)	34.08 (5.52)	33.64 (4.81)	0.875
Age distribution_ patient, n (%)				
<=35 YRS	25 (39.1)	32 (50)	26 (40.6)	0.113
36-40 YRS	26 (40.6)	20 (31.2)	26 (40.6)	
41-45 YRS	8 (12.5)	5 (7.8)	12 (18.8)	
46-50 YRS	3 (4.7)	3 (4.7)	0 (0)	
> 50 YRS	2 (3.1)	4 (6.2)	0 (0)	
Age_distribution __spouse, n (%)				
<=35 Yrs	36 (56.2)	42 (65.6)	41 (64.1)	0.609
36-40 Yrs	25 (39.1)	14 (21.9)	20 (31.2)	
41-45 yrs	3 (4.7)	5 (7.8)	1 (1.6)	
46-50Yrs	0 (0)	2 (3.1)	1 (1.6)	
>50 Yrs	0 (0)	1 (1.6)	1 (1.6)	
Education, n (%)				
upto Secondary	26 (40.7)	17 (26.6)	22 (34.4)	0.565
High school	30 (46.9)	34 (53.1)	37 (57.8)	
Graduate	8 (12.5)	13 (20.3)	5 (7.8)	
Spouse education, n (%)				
upto Secondary	35 (54.6)	30 (46.9)	37 (57.8)	0.609
High school	15 (23.4)	21 (32.8)	18 (28.1)	
Graduate	14 (21.9)	13 (20.4)	9 (14.1)	
Family type, n (%)				
Nuclear	21 (32.8)	23 (35.9)	24 (37.5)	0.978
Extended	23 (35.9)	22 (34.4)	20 (31.2)	
Joint	20 (31.2)	19 (29.7)	20 (31.2)	

Annual family income, n (%)				
< INR 60,000	12 (18.8)	12 (18.8)	10 (15.6)	0.77
INR 60,000-120,000	13 (20.3)	11 (17.2)	18 (28.1)	
INR 120,000-180,000	22 (34.4)	26 (40.6)	24 (37.5)	
> INR 180,000	17 (26.6)	15 (23.4)	12 (18.8)	
Spouse contribution_income_1yr, n (%)				
<10 %	2 (3.1)	8 (12.5)	8 (12.5)	0.045 *
11-25%	6 (9.4)	0 (0)	0 (0)	sig
26-50%	17 (26.6)	9 (14.1)	14 (21.9)	
51-75%	11(17.2)	16 (25)	12 (18.8)	
Over 75%	28 (43.8)	31 (48.4)	30 (46.9)	

Though spouses in the alcohol group with >18 years of caregiving were more than other groups (28% vs 9 and 20%), the difference was statistically insignificant, and the groups were comparable (Table 3).

Table 3: Caregiving duration and frequency of hospitalizations.

	Alcohol	Bipolar	Schizophrenia	*P* value (*significant if p<0.05)
Duration of caregiving n (%)				
10-13 yrs	37 (57.80)	41 (64.10)	37 (57.80)	0.194
14-17 yrs	9 (14.10)	17 (26.60)	14 (21.90)	
18-21 yrs	12 (18.80)	4 (6.20)	9 (14.10)	
>21 yrs	6 (9.40)	2 (3.10)	4 (6.20)	

Frequency of psychiatric admissions - past 10 yrs				
>6	5 (7.8)	8 (12.5)	13 (20.3)	0.727
5 to 6	19 (29.7)	21 (32.8)	17 (26.6)	
3 to 4	25 (39.1)	22 (34.4)	23 (35.9)	
1 to 2	9 (14.1)	9 (14.1)	7 (10.9)	
0	6 (9.4)	4 (6.2)	4 (6.2)	

The frequency of hospital admissions in past 10 years was high in schizophrenia group (20% vs 8 and 12% having more than six admissions), though it was not statistically significant.

More spouses in bipolar and schizophrenia groups had severe burden levels than alcohol group (76% and 82% vs 51%) and the difference was statistically significant (Table 4).

Table 4. Distribution of severity of Burden, and Burnout-Burnout-Experience (CRASH-BOUNCE scores):

	Alcohol dep		Bipolar		Schizophrenia		
	n	%	n	%	n	%	P value
BAS burden levels							0.003**
Very Severe	13	20.3%	27	42.2%	23	35.9%	
Severe	20	31.2%	22	34.4%	30	46.9%	
Moderate	19	29.7%	10	15.6%	8	12.5%	
Minimal	12	18.8%	5	7.8%	3	4.7%	
CRASH-BOUNCE score							0.024*
-32 - -17	23	35.9%	4	6.2%	6	9.4%	
-16 to-1	10	15.6%	34	53.1%	31	48.4%	
0 to 16	20	31.2%	13	20.3%	23	35.9%	
17 to 32	11	17.2%	13	20.3%	4	6.2%	

Spouses had frequent very severe (-32 to -17) negative experience scores (caregiving reaction/experience minus burnout, the CRASH-BOUNCE scores) in alcohol dependence than other two groups (35% vs 6 and 9%).

Total burden scores, and burden with 'spouse's physical and mental health' dimension was higher both in bipolar and schizophrenia groups (Table 5). Bipolar group had the most burden related to 'patient-related' (marital deficits) dimension. Schizophrenia group had the most burden in 'the taking responsibility' (for financial needs) and 'the other relations' (family stability and affording friendships) dimensions. These findings were statistically significant.

Table 5. Comparison of Burden Domains

Burden domains	Alcohol dep		Bipolar disorder		Schizo-phrenia		
	Mean (SD)	95% C.I.	Mean (SD)	95% C.I.	Mean (SD)	95% C.I.	F
BAS spouse related	8.69 (2.74)	8.00-9.37	13.36 (2.19)	12.81-13.90	11.47 (2.83)	10.76-12.18	52.172***
BAS mental health	12.33 (3.67)	11.41-13.24	16.23 (2.28)	15.66-16.80	16.56 (1.63)	16.15-16.97	49.969*
BAS support	8.08 (2.73)	7.40-8.76	9.77 (2.70)	9.09-10.44	10.09 (2.90)	9.37-10.82	9.681
BAS routine	12.53 (2.43)	11.92-13.14	13.34 (2.21)	12.79-13.90	13.42 (1.48)	13.05-13.79	3.597
BAS pt support	9.48 (2.33)	8.90-10.07	8.98 (2.14)	8.45-9.52	8.39 (2.12)	7.86-8.92	3.967
BAS responsibility	6.78 (2.19)	6.24-7.33	8.75 (2.62)	8.09-9.41	10.91 (1.37)	10.57-11.25	60.408*
BAS other relations	7.16 (1.90)	6.68-7.63	7.52 (1.35)	7.18-7.85	8.27 (1.06)	8.00-8.53	9.432**
BAS pt behavior	8.84 (2.33)	8.26-9.43	9.00 (2.22)	8.45-9.55	10.42 (1.60)	10.02-10.82	11.235
BAS strategy CG	7.66 (2.64)	7.00-8.32	8.20 (2.20)	7.65-8.75	8.61 (2.35)	8.02-9.20	2.534
BAS total	81.55 (16.88)	77.33-85.76	94.17 (15.67)	90.84-98.66	98.20 (14.97)	94.46-101.94	19.663*

significant p value, * $p<0.05$; ** <0.01; *** <0.001

Total burden scores for the female spouse carers increased suddenly after 18 years of duration of caregiving in alcohol group, while the perceived burden eased off substantially after 21 years in bipolar and schizophrenia groups (Table 6). Burden scores progressively increased in all three groups as patients' apathy increased, and were the highest in schizophrenia group, and the lowest in the alcohol group. These ANOVA findings were found to be statistically significant in alcohol

dependence group compared to the other two groups as per Tukey's HSD ad-hoc tests. There was no significant difference between the bipolar and schizophrenia groups. Burden scores were high in schizophrenia, and increased proportionately with increase in severity of illness in all groups; they were more condensed and normal (SD <3 vs 16) in bipolar and schizophrenia groups compared to the alcohol group. These differences in patterns were statistically significant between each of the groups.

Table 6. Burden scores w.r.t. Caregiving duration, apathy, and illness severity

Dependent Variable: BAS total burden score ANOVA								
Duration_of_ caregiving	Alcohol Dep Mean, (n)	SD	Bipolar Mean, (n)	SD	Schizo phrenia Mean (n)	SD	df, F[p]	Tukey HSD Post-Hoc Test#
10-13 Yrs	73.00 (37)	14.88	96.35 (34)	13.17	95.30 (37)	16.81	6 5.67**	a** bs bs
14-17 Yrs	77.14 (9)	14.25	96.88 (16)	13.84	102.07 (14)	8.38		
18-21 Yrs	100.83 (12)	12.91	92.29 (7)	15.87	110.00 (9)	14.67		
>21 Yrs	94.09 (6)	13.27	79.29 (7)	21.55	98.89 (4)	8.76		
Total	82.58 (64)	17.37	94.17 (64)	15.30	98.20 (64)	14.97		
Apathy Inventory								
severe apathy	94.57 (23)	9.40	101.67 (15)	7.55	112.50 (16)	4.60	6 6.59***	a*** bs bs
moderate	83.75 (12)	12.18	91.32 (19)	17.50	99.97 (32)	8.80		
mild	73.95 (22)	16.03	84.45 (20)	13.87	81.64 (11)	10.98		
no apathy	68.29 (7)	24.69	87.81 (10)	2.10	77.60 (5)	20.53		
Total	82.58 (64)	17.37	94.17 (64)	15.30	98.20 (64)	14.97		

Severity_ of_illness§								
High	92.32 (22)	13.47	100.81 (51)	1.94	105.23 (43)	3.75	4 2.76**	a*** b* s*
Medium	80.75 (36)	16.21	77.42 (7)	2.28	89.38 (16)	1.76		
Low	57.83 (6)	5.31	57.33 (6)	0.73	66.20 (5)	1.32		
Total	82.58 (64)	17.37	94.17 (64)	15.30	98.20 (64)	14.97		

§ SADDQ score in alcohol dependence group: High (score 20-45), Medium (10-19), Low (1-9); CGI-BP score in bipolar group, and CGI-SCH score in schizophrenia group: High (score 7,6), Medium (5,4), Low (3,2,1);
# single letter denotes the group is significantly different from the other groups;
"a" alcohol dependence group; "b" bipolar disorder group; "s" schizophrenia group;
^{p} significant p value; * p<0.05; ** <0.01; ***<0.001

Only spouses with schizophrenia patients had moderately positive correlation between their burden and net experience levels (i.e. lower relative burnout) with statistical significance (Table 7). Burden correlated positively with illness severity in all three groups with statistical significance. Net experience more positively correlated with illness severity in the alcohol group, and less positive (higher relative burnout) in other groups.

Table 7. Correlation between Burden, Reaction-Experience-Burnout, and Illness severity

	Alcohol dependence		Bipolar disorder		Schizophrenia	
Correlation coefficient	CRASH-BOUNCE score **τb**	Severity of illness **ρ**	CRASH-BOUNCE score **τb**	Severity of illness **ρ**	CRASH-BOUNCE score **τb**	Severity of illness **ρ**
Burden type	.088 (.45)	.899 (<.001)***	.058 (.64)	.639 (.047)*	.308 (.002)**	.769 (.037)*
CRASH-BOUNCE score	1	.846 (.001)**	1	.545 (.039)*	1	.468 (.036)*

ρ, Spearman **ρ**; **τb**, Kendall's tau-b;
* p<0.05; ** <0.01; ***<0.001, significant p value

In alcohol group, many (10/22) with just moderate burden had very severe net burnout-experience (more scores of -32 to -17), but in bipolar and schizophrenia groups only few (1/27;5/23) with very severe burden had very severe burnout-experience

(-16 to -1) only mostly. Similarly in alcohol group even those (23/35) with medium to high illness severity had very severe burnout-experience, but only few (4/49;6/43) with high illness severity showed very severe burnout in other groups. Both these findings were statistically significant (Table 8).

Table 8a. Distribution of Reaction-Experience-Burnout w.r.t. Illness severity

		Alcohol dep		Bipolar		Schizophrenia	
Illness Severity	CRASH BOUNCE score	n	%	n	%	n	%
High	-17_-32	11	17.19%	4	6.25%	6	9.37%
	-1_-16	7	10.94%	30	46.88%	24	37.5%
	0-16	3	4.69%	6	9.38%	12	18.75%
	17-32	1	1.56%	9	14.06%	1	1.56%
Medium	-17_-32	12	18.75%	0	0.00%	0	0.00%
	-1_-16	3	4.69%	4	6.25%	4	6.25%
	0-16	16	25%	4	6.25%	9	14.06%
	17-32	5	7.81%	2	3.13%	3	4.69%
Low	-17_-32	0	0.00%	0	0.00%	0	0.00%
	-1_-16	0	0.00%	0	0.00%	3	4.69%
	0-16	1	1.56%	3	4.69%	2	3.13%
	17-32	5	7.81%	2	3.13%	0	0.00%
Severity Chi² tests	***(df, X²)***	*df= 6*	*X²= 31.44***	*df=6*	*X²= 13.21**	*df=6*	*X²= 13.37**

* p<0.05; ** <0.01; ***<0.001, significant p value

Table 8b. Distribution of Caregiver-Experience-Burnout w.r.t. Burden severity types

		Alcohol dep		Bipolar		Schizophrenia	
BAS burden severity type	CRASH BOUNCE Score	n	%	n	%	n	%
Very Severe	-17_-32	2	3.13%	1	1.56%	5	7.81%
	-1_-16	2	3.13%	14	21.88%	13	20.31%

	0-16	0	0%	3	4.69%	5	7.81%
	17-32	0	0%	9	14.06%	0	0%
Severe	-17_-32	8	12.5%	3	4.69%	1	1.56%
	-1_-16	6	9.38%	16	25%	13	20.31%
	0-16	11	17.19%	3	4.69%	13	20.31%
	17-32	1	1.56%	0	0%	3	4.69%
Moderate	-17_-32	10	15.63%	0	0%	0	0%
	-1_-16	2	3.13%	4	6.25%	3	4.69%
	0-16	6	9.38%	4	6.25%	4	6.25%
	17-32	4	6.25%	2	3.13%	1	1.56%
Minimal	-17_-32	3	4.69%	0	0%	0	0%
	-1_-16	0	0%	0	0%	2	3.13%
	0-16	3	4.69%	3	4.69%	1	1.56%
	17-32	6	9.38%	2	3.13%	0	0%
BAS type Chi² tests	*(df, X²)*	*df =9*	*X²=21 .23**	*df=9*	*X²=22. 79***	*df=9*	*11.82*

* p<0.05; ** <0.01; ***<0.001, significant p value

Discussion

All three groups had comparable patient and spouse demographic characteristics like age, education, family type, earnings and duration of caregiving, as the differences were statistically non-significant. In caregivers of patients with schizophrenia burnout scores were higher with lack of support during caregiving [31].

In the study about 82% and 76% spouses had severe levels of burden in schizophrenia and bipolar disorder groups, compared to around 51% from alcohol dependence group. These results were identical to those from comparison studies by Swapna et al in South India [32] between alcohol and bipolar (45% and 66% severe burden). Over 80% of the caregivers of persons with schizophrenia showed moderate burden in the study by Liang et al. [33].

Total burden, and burden in 'spouse's mental health' dimension was higher both in bipolar and schizophrenia groups. The higher burden severity in schizophrenia caregivers were comparable to the study by Kumar et al. [10].

The spouses had higher burden levels in 'spouse(patient) related' dimension among bipolar group, while other findings were similar to previous studies [5] where caregivers from bipolar and schizophrenia groups suffered similar levels of burden and had a positive correlation with domains like 'physical and mental health,' 'caregivers' routine,' 'taking responsibility.'

The mean burden score in spouses of persons with schizophrenia was

77.7±1.5, similar to that in the alcohol dependence group (78.4±1.7) in a study by Kumar et al. [34].

Conjugal carers of patients exhibiting increased apathy had burden levels higher in schizophrenia group than alcohol group in the Liang et al study [33]. In a study by van Reekum et al. severity of psychotic symptoms and apathy are related to higher levels of carer burden, and impact drug responses in schizophrenia [35]; in few other studies, burden was higher with such associated factors in bipolar affective disorder [36] than in alcohol dependence syndrome. As duration of caregiving increased beyond 18 years in carers of alcohol dependents, the initial low burden scores spiked to become on par with other groups. Burnout experience was severe and more frequent in alcohol group.

There was a moderate positive correlation between burden and positive experience (overcoming burnout) with statistical significance, only in schizophrenia group. Burden and positive experience correlated positively with illness severity in all three groups, the most in alcohol group. Greater scores of hopefulness and self-esteem in the caregiver correlated with lower family burden perception [37]. Correlation between negative caregiver reaction and higher burnout scores reflected similar results from studies on chronic mental and physical illnesses [28,38].

Conclusion

Though female spouses of persons with schizophrenia and bipolar groups had profound burden of care, more spouses of alcohol dependents showed the highest burnout experience.

Severity of illness significantly correlated with the burden observed in the spouses in all the three groups, while burden increased with perceived apathy in schizophrenia and bipolar groups. Less burden and more burnout scores in alcohol group implied hidden and unexplored detrimental factors worsening the burnout. More burden but lesser burnout levels in schizophrenia and bipolar groups validated higher self-gratification and appreciation from caregiving.

The study differentiated high burden concerns in female spouses of persos with major psychiatric disorders like bipolar disorder and schizophrenia, from severe burnout concerns in alcohol dependence. This warrants family-focused psychological treatment approaches, and targeted economic and social supportive measures for spouses including group support. This would prevent psychiatric morbidity in spouses, and improving treatment adherence and prognosis in patients of alcohol dependence, bipolar disorder and schizophrenia.

Limitations

The authors acknowledge the need to substantiate the findings from this study with larger standardized sample size, including more patients and spouses in above 50 years of age group, and effect of physical constraints due to age on care, peri/post-menopausal physical and psychological factors, and personality traits, on the burden.

Statements and Declarations

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Conflict of interest

The authors declare there were no conflict of interests.

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ORIGINAL ARTICLE

Vitamin D Levels, Lung Function, and Risk Factors in Paediatric Asthma: Evidence from a Case–Control Study

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Abstract

Introduction: Asthma is one of the commonest chronic respiratory disorders in children, influenced by environmental, perinatal, genetic, and nutritional factors. Vitamin D, has essential immunomodulatory functions apart from its role in bone health. Vitamin D has its implications in asthma pathogenesis and control. This study was conducted to assess the serum vitamin D levels in asthmatic and non-asthmatic children, and also to evaluate its correlation with lung function, and the role of associated risk factors. **Materials and Methods:** A hospital-based cross sectional, comparative study was conducted after obtaining Institutional Ethical committee approval. The study was conducted among 50 asthmatics and 50 age- and sex-matched non-asthmatic controls in the age group of 5–16 years. Baseline demographic and anthropometric data were recorded. The environmental risk factors perinatal history, familial history were obtained from the participants. Pulmonary function parameters (FVC, FEV1, FEV1/FVC, PEFR, $FEF_{25–75}$) were measured by spirometry following American Thoracic Society (ATS) guidelines. Serum vitamin D levels were determined using a standard immunoassay. Age-appropriate oral or written assent was obtained from the parents. **Results:** The results showed significantly lower mean vitamin D levels in asthmatic children (15.75 ± 4.46 ng/ml) when compared to controls (18.85 ± 3.98 ng/ml; $p < 0.001$). FEV1 and FEV1/FVC ratios were significantly decreased in asthmatic children ($p < 0.001$). Positive associations with asthma were observed in preterm birth babies ($p = 0.011$), parental history ($p = 0.026$), and passive smoking ($p < 0.001$). There was a significant positive correlation of vitamin D levels with FEV1/FVC ratio overall ($r = 0.473$), in controls ($r = 0.388$), and in cases ($r = 0.333$). **Conclusion:** Positive associations with asthma and lung function were observed with lower vitamin D levels. Addressing the vitamin D deficiency along with modifiable risk factors such as passive smoking may improve the control of asthma. Further research are warranted to establish the therapeutic and preventive role of vitamin D deficiency in childhood asthma.

Keywords: Asthma, Vitamin D, Lung function, Children, Passive smoking

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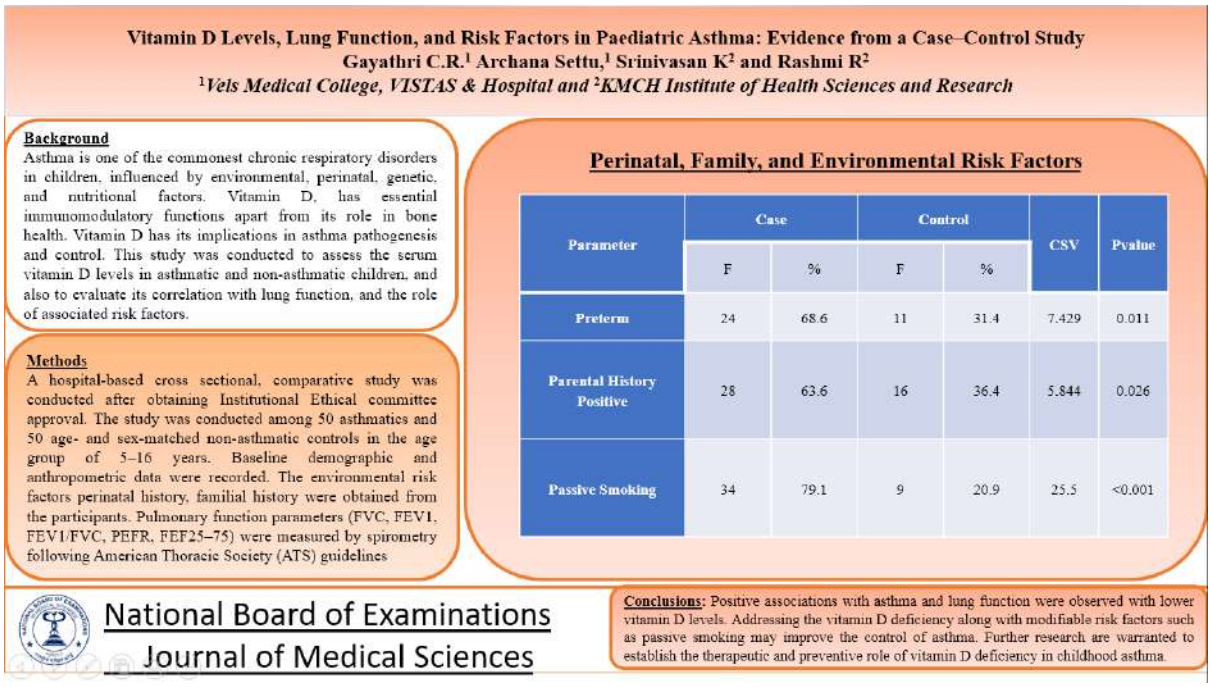
Graphical Abstract



Introduction

Asthma is one of the most prevalent chronic respiratory disorders in children and it has significant public health concern all over the world. It is characterized by the airway obstruction, airway inflammation and bronchial hyperresponsiveness. The prevalence of asthma has been rising recently, mainly among children, leading to severe health morbidity, and impaired quality of life [1,2]. Worldwide, it is estimated that over 300 million people are affected, and childhood asthma contributes substantially to disability-adjusted life years lost due to respiratory disorders [3]. The prevalence of asthma in children ranges between 2–20%, with regional variations, and it has various challenges in early diagnosis, treatment adherence, and environmental risk factor modification [4].

Vitamin D is known for its role in calcium and bone metabolism, and it has recently gained attention for its immunomodulatory properties. The receptors of Vitamin D are widely expressed on T lymphocytes, B lymphocytes, macrophages, and dendritic cells, suggesting its influence on both adaptive and innate immunity [5]. Recent researchers have proved that vitamin D may decrease the airway inflammation, improve epithelial integrity, and enhance regulatory T-cell function, which are relevant to the pathogenesis of asthma [6,7]. Vitamin D deficiency has been linked with increased risk to respiratory infections, wheezing, and lesser asthma control in children [8].

Various studies have suggested an association between low serum vitamin D levels and increased asthma severity, its exacerbations, and decreased pulmonary function parameters, particularly FEV1 and FEV1/FVC ratios [9,10]. Vitamin D deficiency has also been linked with elevated steroid resistance in asthmatics, highlighting its role in influencing the treatment outcomes [11]. There are evidences which prove this association, but there is a paucity of regional studies from India, where both asthma and vitamin D deficiency are highly prevalent due to

different lifestyles, limited sun exposure an urbanization.[12].

The current study was undertaken to assess the serum vitamin D levels in asthmatic and non-asthmatic children and to evaluate their association with lung function parameters. The study also explored perinatal, familial, and environmental risk factors for asthma, with an emphasis on the role of parental history, passive smoking, and preterm birth. These associations may provide insights into the interplay between nutritional status of children and asthma. This may help in building preventive and therapeutic strategies for Indian asthmatic children.

Aim and Objectives

1. To compare the pulmonary function parameters, and Vitamin D levels between Asthmatic and Non-Asthmatic Children
2. To correlate the serum Vitamin D levels with FEV1/FVC ratio in cases and controls
3. To evaluate the association of perinatal, family, and environmental risk factors with childhood asthma.

Materials and Methods

This hospital-based cross sectional, comparative study was conducted after obtaining Institutional Ethical committee approval. The study was conducted among 50 asthmatics and 50 age- and sex-matched non-asthmatic controls in the age group of 5–16 years. The cases were identified in the inpatient department and paediatric outpatient after taking spirometry, confirmation of asthma based on clinical history, physical examination in accordance with GINA guidelines. The controls were age- and sex-matched healthy children without a history of asthma or other respiratory disorders. Exclusion criteria include children receiving long-term steroids for conditions other than asthma, chronic systemic illnesses or those with congenital anomalies.

For children below 7 years of age, only *parental/guardian consent* was obtained prior to recruitment, as they were considered too young to provide meaningful assent. For those aged 7–11 years, *oral assent* was obtained in addition to parental consent, while for children aged 12 years and above, *written assent* was taken along with parental consent.

Basic demographic and anthropometric details like age, sex, weight, height and body mass index (BMI), were obtained from the participants. Family history of asthma, perinatal history, environmental exposures such as passive smoking were recorded.

Lung function parameters were assessed using spirometry in accordance with American Thoracic Society (ATS) recommendations. The parameters measured included Forced Vital Capacity (FVC), Forced Expiratory Volume in the first second (FEV1), FEV1/FVC ratio, Forced Expiratory Flow between 25–75% of vital capacity (FEF25–75) and Peak Expiratory Flow Rate (PEFR) were recorded. The best of three reproducible manoeuvres was taken from each participant, and calibration of the spirometer was performed daily.

Under aseptic precautions, venous blood samples were collected for estimating serum vitamin D levels in the participants. Chemiluminescent immunoassay (CLIA) or equivalent validated methods, was used as a standard immunoassay method and adherence to internal quality control protocols was ensured in the institution's central laboratory [13,14].

All the data were entered into a database and analysed using standard statistical methods. Continuous variables (age, BMI, lung function parameters, vitamin D levels) were expressed as mean ± standard deviation. It was then used to compare the cases and controls using independent sample T-tests. Chi-square test was used to assess the categorical variables (preterm birth, parental history, passive smoking exposure). Pearson's correlation coefficient was used to evaluate the correlation between serum vitamin D levels and pulmonary function indices. p-value <0.05 was considered statistically significant (Figure 1).

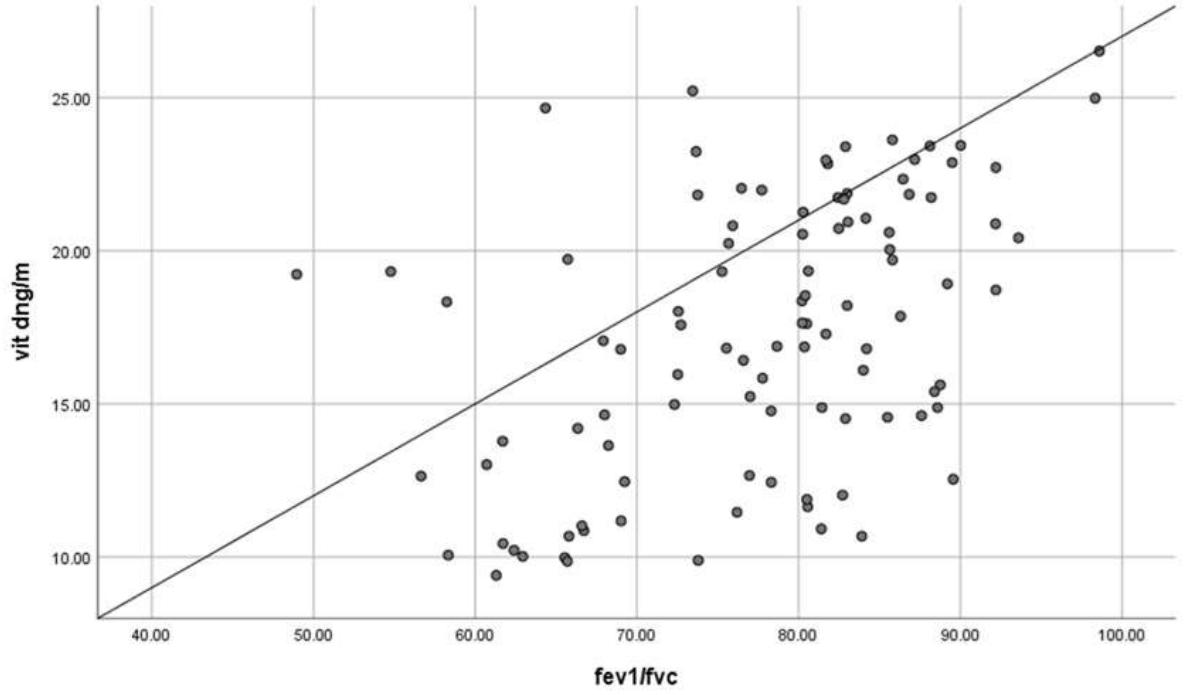


Figure 1. Correlation of Serum Vitamin D Levels with FEV1/FVC Ratio in Cases and Controls

Results

The study included 50 asthmatics (cases) and 50 non-asthmatics (controls). The mean age of the participants was 10.28 ± 2.73 years, with no significant difference between the cases (10.14 ± 2.88) and the controls (10.42 ± 2.58). Similarly, height and weight did not differ significantly across groups. However, the mean Body Mass Index (BMI) was found to be significantly higher among the cases (19.50 ± 2.13) when compared to the non-asthmatics (18.27 ± 2.86), with a mean difference of 1.23 (p = 0.02).

Spirometry revealed that FVC values were comparable between groups. In contrast, FEV1 values were markedly decreased in the asthmatics (1.48 ± 0.42) compared to the non-asthmatics (1.84 ± 0.49), which was significant (p < 0.001) statistically. The FEV1/FVC ratio showed a pronounced difference, with asthmatic children demonstrating much lower ratios (69.87 ± 7.68) compared to controls (85.54 ± 4.58), giving a significant difference (p < 0.001). Peak Expiratory Flow Rate (PEFR) was also significantly decreased in asthmatics (2.81 ± 0.57) than in controls (3.39 ± 0.95) (p < 0.001). But, the mean values of

FEF25–75 were not significantly different between cases and controls. Serum vitamin D levels were considerably lesser among the cases (15.75 ± 4.46 ng/ml) when compared to controls (18.85 ± 3.98 ng/ml), with a mean difference of 3.10, which was considered to be highly significant ($p < 0.001$) statistically (Table 1).

Table 1. Comparison of General Characteristics, Pulmonary Function Parameters, and Vitamin D Levels between Asthmatic and Non-Asthmatic Children

Parameter	Overall				Case		Control		MD	t Value	P Value
	Min	MaX	Mean	SD	Mean	SD	Mean	SD			
Age	5	16	10.28	2.73	10.14	2.88	10.42	2.58	0.28	0.511	0.28
Height	107	170	139.34	15.04	138.70	16.27	139.98	13.85	1.28	0.424	0.67
Weight	18	64	37.61	10.90	36.56	10.51	38.66	11.29	2.10	-0.963	0.34
BMI	14.40	24.40	18.88	2.59	19.50	2.14	18.27	2.86	1.23	-2.438	0.02
FVC	1.030	4.230	2.15	0.61	2.15	0.65	2.16	0.58	0.01	0.083	0.93
FEV1	0.86	2.77	1.66	0.49	1.48	0.42	1.84	0.49	0.37	3.984	<0.001
FEV1/ FVC	48.96	98.60	77.70	10.08	69.87	7.69	85.54	4.58	15.67	12.379	<0.001
PEFR	1.16	5.24	3.10	0.83	2.81	0.57	3.39	0.95	0.58	3.729	<0.001
FEF 25-75	0.700	3.880	1.99	0.58	2.01	0.66	1.97	0.49	0.04	-0.349	0.728
Vit D ng/mL	9.40	26.52	17.30	4.49	15.75	4.46	18.85	3.98	3.10	3.657	<0.001

Associated risk factors also faced significant differences between cases and controls. Preterm birth was more commonly observed among the cases, with 68.6% of cases reporting a preterm history as against only 31.4% of controls, a difference that was statistically significant ($\chi^2 = 7.429$, $p = 0.011$).

A positive parental history of asthma was also more common in asthmatics (63.6%) compared to non-asthmatics (36.4%) ($\chi^2 = 5.844$, $p = 0.026$). While looking at the environmental risk factors, the exposure to passive smoking was found to be higher in the cases, with 79.1% whereas only 20.9% of controls were exposed. This association was highly significant ($\chi^2 = 25.5$, $p < 0.001$). These findings highlight that perinatal factors, family history, and passive smoking act as strong contributors to the development of asthma in children (Table 2).

Table 2. Association of Perinatal, Family, and Environmental Risk Factors with Asthma

Parameter	Case		Control		CSV	Pvalue
	F	%	F	%		
Preterm	24	68.6	11	31.4	7.429	0.011
Parental History Positive	28	63.6	16	36.4	5.844	0.026
Passive Smoking	34	79.1	9	20.9	25.5	<0.001

The correlation analysis between pulmonary function and serum vitamin D levels, measured by the FEV1/FVC ratio, showed a significant positive relationship. In this research, the correlation coefficient was r = 0.473, indicates a moderate positive correlation. When analysed separately, the correlation remained statistically significant in both groups, though with varying strength. Among the non-asthmatics, the correlation was r = 0.388, whereas among the asthmatics, it was r = 0.333. This positively suggest that the higher vitamin D levels are associated with better pulmonary function across all paediatric age group, and that this positive link is seen in asthma as well.

Discussion

In the current research, the children with asthma had significantly lesser serum vitamin D levels compared to non-asthmatic controls. This is similar with various earlier reports that proved a strong relationship between hypovitaminosis D and asthma susceptibility in children [8–10]. Vitamin D has a pivotal role in immunomodulation, particularly in regulating T-cell proliferation, epithelial barrier integrity, and dendritic cell activity. [5–7]. Vit D deficiency may lead to airway inflammation, increased severity by causing bronchospasm, thereby explaining the lesser vit D levels observed among the cases.

The Spirometry parameters revealed that FEV1 and FEV1/FVC ratios reduction in cases compared to controls, with expected pathophysiological changes in the obstructive airway disease [1–3]. Serum vit D levels showed a positive association with pulmonary function indices (overall r = 0.473), implying that adequate vit D may help to maintain the lung function. Similar findings were reported by Gupta et al. [10], who showed that lower vit D levels were associated with more airway remodelling and lessened lung function in asthmatic group. Brehm et al. [8] also emphasized that vit D deficiency was associated with increased risk of severe asthma exacerbations, proving the protective role of vit D in respiratory health. Also, Fedora et al. [15] in a meta-analysis reported that vit D supplementation lessens the asthma exacerbations in children and may cause improvements in FEV1, further strengthening the clinical relevance of our findings.

There exists significant association of asthma with factors such as preterm birth, positive parental history of asthma, perinatal history, and passive smoking. Preterm babies are known to have under developed lungs and altered immune responses, predisposing them to chronic respiratory illness like asthma [2,4]. A positive family history suggests the genetic predisposition, while exposure to passive smoking suggests the contribution of modifiable environmental triggers [3,4]. Our study agrees with the past researches which stated that family history and environmental exposures play an essential role in determining the asthma risk in children [4,12].

The immunological basis of relationship between the vit D deficiency and asthma is further supported by the studies showing that vitamin D role in regulatory T- cell function and reduces airway hyperresponsiveness [5,6]. Pfeffer and Hawrylowicz [7] reported the importance of vit D in maintaining pulmonary health, particularly in children with a high prevalence of vit D deficiency. Searing et al. [11], reported that the decreased vit D levels have been linked to poor response to corticosteroid therapy, which proves the asthmatic children with low vitamin D have poorer control and more frequent exacerbations. Recent

systematic reviews and expert opinions continue to emphasize this dual role. In the Cochrane review, during the year 2023 by Williamson et al. [16], the vitamin D supplementation may decrease the risk of severe exacerbations, although heterogenous results were obtained world wide. Devulapalli [17] had showed in a 2025 study, that supplementation can be beneficial in some children, but it does not consistently improve the pulmonary function across all populations.

The results of our study underscore the multifactorial nature of paediatric asthma, involving the genetic susceptibility, environmental exposures, perinatal influences, and nutritional status. The current study adds to the fact that the role of vit D in the pathophysiology of asthma, highlights the need for routine evaluation of vitamin D levels in asthmatic children, especially in developing countries like India where vit D deficiency is common [12]. Treatment of vit D deficiency, with avoidance of passive smoke exposure and careful monitoring of preterm children or with positive parental history, could provide a more comprehensive strategy for the prevention and management of asthma. Further researches, ie., randomized trials in children, must be initiated to begin vitamin D supplementation for improved clinical outcomes in pediatric asthma, which is evident from recent systematic reviews [15–17].

Conclusion

The current study showed that the asthmatic children had significantly lesser serum vit D levels compared to non-asthmatics. The decreased vitamin D levels was positively correlated with impaired pulmonary function tests, particularly FEV1 and the FEV1/FVC ratio. The perinatal and environmental risk factors like preterm birth, positive parental history of asthma, and passive smoking were found to be positively associated with asthma. These findings show the multifactorial involvement of paediatric asthma, where both environmental and genetic determinants interact with nutritional status to influence the asthmatic disease expression.

The results highlight the role of vitamin D as a modifiable risk factor in paediatric asthma. Routine screening for vit D deficiency, dietary supplementation or lifestyle interventions, and by preventing environmental triggers such as passive smoking may together contribute to better control and prevention of paediatric asthma. Further interventional and longitudinal studies are needed to establish whether the targeted vitamin D supplementation can improve clinical outcomes and pulmonary function in children with asthma.

Statements and Declarations

Conflicts of interest

The authors declare that they do not have conflict of interest.

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ORIGINAL ARTICLE

Reliability of Admission Cardiotocography with and without Amniotic Fluid Index in Predicting Maternal and Fetal Outcomes: A Comparative Observational Study

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Abstract

Background: Intrapartum fetal problems remain an important cause of illness and death around birth, especially in low-resource settings. Admission CTG is commonly used to quickly check fetal well-being, but its ability to predict problems varies. AFI, which reflects placental function and long-term fetal condition, may improve this assessment. **Objectives:** To assess the reliability of admission CTG alone and CTG+AFI in predicting fetal distress, maternal outcomes, and neonatal outcomes. **Methods:** This comparative descriptive study was carried out at CSI Kalyani Multispecialty Hospital, Chennai, over two years (October 2012–October 2014). A total of 150 term pregnant women in labour were included and divided into two equal groups: Group I—CTG alone, and Group II—CTG+AFI. CTG tracings were labelled as normal, suspicious, or abnormal. AFI was grouped as oligohydramnios (≤5 cm), borderline (5.1–8 cm), and normal (8.1–20 cm). Outcomes studied were fetal distress, type of delivery, Apgar scores, and need for NICU admission. **Results:** Normal CTG was seen in most women—88% in Group I and 89.3% in Group II. Oligohydramnios was present in 11% of cases. Abnormal CTG had a strong link with fetal distress (50%), LSCS (100%), and NICU admission (50%). When both CTG and AFI were abnormal, prediction improved further: fetal distress was seen in 75% and NICU admission in 50%. Specificity was high (98%) and NPV was good (91.8%), but sensitivity stayed low (37.5%). **Conclusion:** Admission CTG is a useful screening tool with high specificity to rule out fetal compromise. Adding AFI improves the ability to predict fetal distress and the need for maternal intervention. However, abnormal CTG or AFI patterns also lead to more operative deliveries without a matching improvement in newborn outcomes. Careful interpretation is needed to avoid unnecessary interventions.

Keywords: Cardiotocography, Admission Test, Amniotic Fluid Index, Fetal Distress, Neonatal Outcome, MBPP

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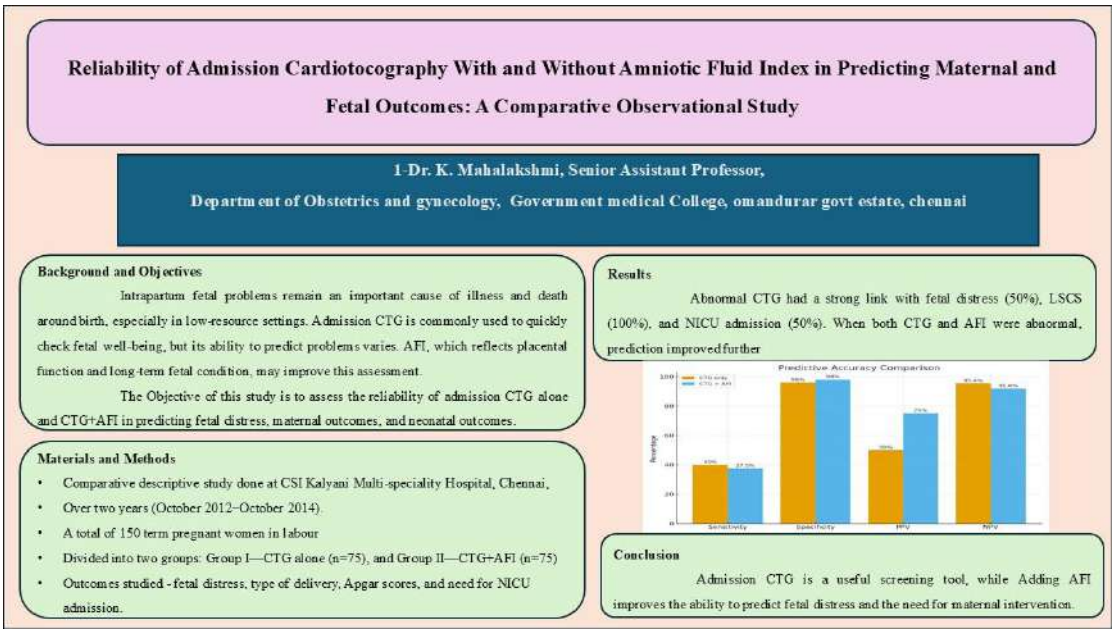
Graphical Abstract



Introduction

Intrapartum hypoxia is still one of the main preventable causes of illness and death around the time of birth in developing countries [1]. Even when women are assessed as low risk during pregnancy, about 20% can develop problems during labour [2]. For this reason, continuous fetal monitoring with cardiotocography (CTG) has been used worldwide since the mid-20th century to pick up early signs of fetal hypoxia [3]. The admission test (AT) is a 20-minute CTG done when the woman is admitted to the labour ward. Its purpose is to quickly identify fetuses who may develop distress during labour [4]. A normal CTG at admission is usually reassuring for the next 1–2 hours, whereas suspicious or abnormal tracings indicate the need for closer monitoring or intervention [5].

However, CTG alone has a high false-positive rate, which may lead to an increased number of unnecessary operative deliveries [6]. CTG patterns can also be influenced by other factors such as maternal fever, drugs, fetal sleep, and prematurity [7]. The amniotic fluid index (AFI) is a well-known marker of long-term placental function. Low amniotic fluid (oligohydramnios, AFI ≤5 cm) is linked to more frequent fetal heart rate abnormalities, cord compression, meconium-stained liquor, and a higher chance of operative delivery for fetal distress [8,9]. Using AFI together with CTG may therefore help to better identify women who are truly at risk.

In India, many labour wards are busy and have limited staff, so the admission test is still widely used as a triage tool. However, only a few studies have compared the effectiveness of CTG alone with CTG plus AFI in Indian women.

Objectives

To assess the reliability of admission CTG alone and CTG+AFI in predicting fetal distress, maternal outcomes, and neonatal outcomes.

Materials and Methods

This comparative descriptive study was conducted in the Department of Obstetrics and Gynaecology at CSI Kalyani Multispeciality Hospital, Mylapore, Chennai, over a two-year period from October 2012 to October 2014. The required sample size was calculated using the standard formula for estimating a single proportion, $n=Z\alpha/_2p(1-p)/d^2$. Considering the hospital statistics, A prevalence of fetal distress (p) of 0.11, an absolute precision (d) of 0.05, and a 95% confidence level corresponding to a Z-value of 1.96 were applied. Based on these parameters, the estimated sample size was 150.4, and the final sample size was rounded to 150 participants.

Eligible participants included women with term pregnancies (≥37 weeks), carrying a singleton fetus in cephalic presentation, and in spontaneous or induced labour. High-risk pregnancies such as gestational diabetes mellitus, hypothyroidism, preeclampsia, anaemia, premature rupture of membranes, bad obstetric history, and intrauterine growth restriction were also included. Exclusion criteria comprised gestational age <36 weeks, multiple gestation, non-cephalic presentations, previous lower-segment caesarean section, acute obstetric emergencies requiring immediate operative intervention (such as abruption or severe fetal bradycardia), and fetuses with lethal congenital anomalies.

Participants were allocated into two study groups: Group I (n = 75), in which cardiotocography (CTG) alone was assessed, and Group II (n = 75), in which CTG was evaluated in combination with amniotic fluid index (AFI). CTG tracings were interpreted according to the NICE guidelines, classifying patterns as normal, suspicious, or abnormal. AFI was measured using the four-quadrant Phelan method and categorised as oligohydramnios (≤5 cm), borderline (5.1–8 cm), or normal (8.1–20 cm).

Outcomes assessed included maternal outcomes such as mode of delivery, fetal outcomes including evidence of fetal distress, and neonatal outcomes such as Apgar scores and need for NICU admission. Data were analysed using SPSS version 16. The Chi-square test was used to examine associations between variables, and diagnostic performance was evaluated using sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). A p-value <0.05 was considered statistically significant. Institutional Ethics Committee approval was obtained and written informed consent was taken from the study participants before the start of the study.

Results

The baseline characteristics were comparable between the two groups. There was no statistically significant difference in age distribution (p=0.119) or parity (p=0.954) between Group I (CTG only) and Group II (CTG+AFI). The proportion of low-risk and high-risk pregnancies was similar across groups (p=1.000). Among high-risk categories—including preeclampsia, GDM, anaemia, PROM, hypothyroidism, and multiple risk factors—none showed significant differences between the groups, although PROM (p=0.067) and multiple risk factors (p=0.080) showed borderline variation. Overall, both groups were comparable with respect to maternal demographic and risk characteristics.

In both groups, most women had a normal CTG pattern. However, when the amniotic fluid was low (oligohydramnios, AFI ≤5 cm), abnormal CTG was much more common (50%) compared with women whose AFI was more than 5 cm (only 6% abnormal CTG). This difference was statistically significant (p = 0.0001). These findings show that AFI provides additional useful information and improves the ability of the admission CTG to predict fetal distress. Tables 1-3 present the distribution of baseline characteristics.

Table 1. Baseline Maternal Characteristics (N = 150)

Variable	**Group I (CTG only) n=75**	**%**	**Group II (CTG + AFI) n=75**	**%**
Age (years)				
15–20	0	0	3	4
21–25	32	43	25	33
26–30	30	40	24	32
31–35	11	15	20	27
>35	2	3	3	4
Parity				
Primigravida	39	52	42	56
Gravida 2	22	29	15	20
Gravida 3	10	13	12	16
Gravida 4+	4	5	6	8
Risk status				
Low risk cases	39	52%	38	50.7%
High risk cases	36	48%	37	49.3%
High risk cases				
Preeclampsia	2	6%	2	5.4%
GDM	15	42%	13	35.1%
Anaemia	2	6%	2	5.4%
PROM	5	14%	13	35.1%
Hypothyroid	4	11%	5	13.5%
Others (Multiple combination of risk factors)	8	22%	2	5.4%
AFI (Group II)	—	—		
≤ 5 cm	—	—	8	11

Variable	Group I (CTG only) n=75	%	Group II (CTG + AFI) n=75	%
5.1–8 cm	—	—	24	32
8.1–20 cm	—	—	43	57

Table 2. Admission Test Findings (CTG and AFI)

Parameter	Group I (CTG only)	%	Group II (CTG + AFI)	%
CTG Pattern				
Normal	66	88	67	89.3
Suspicious	5	7	5	6.7
Abnormal	4	5	3	4
Correlation between CTG & AFI (Group II)				
AFI >5 cm + Normal CTG	63	94	—	—
AFI >5 cm + Abnormal CTG	4	6	—	—
AFI ≤5 cm + Normal CTG	4	50	—	—
AFI ≤5 cm + Abnormal CTG	4	50	—	—
p-value	**0.0001** (significant association)			

Table 3. Maternal and Neonatal Outcomes vs Admission Test Findings

Test Category	Normal Delivery	LSCS	Instrumental	Fetal Distress	NICU Admission
CTG – Normal (n=66)	56	6	4	Low	Very low
CTG – Suspicious (n=5)	0	3	2	Moderate	Moderate
CTG – Abnormal (n=4)	0	4	0	High	High (50%)
CTG+AFI – Both Normal (n=61)	52	6	3	Minimal	Minimal
CTG+AFI – Both Abnormal (n=4)	0	3	1	Very high (75%)	High (50%)
Normal CTG +	2	3	1	Moderate	Moderate

Test Category	Normal Delivery	LSCS	Instrumental	Fetal Distress	NICU Admission
Abnormal AFI (n=6)					
Abnormal CTG + Normal AFI (n=4)	1	2	1	Moderate–High	Moderate

Abnormal CTG was very strongly linked to caesarean delivery (LSCS), with all such cases ending in LSCS (100%), and it was also associated with more fetal distress and NICU admissions. When both CTG and AFI were abnormal, the ability to predict poor outcomes became much better: 75% of these babies had fetal distress and 50% required NICU admission. The specificity of the test improved from 96% with CTG alone to 98% with the combined CTG+AFI, and the positive predictive value (PPV) increased from 50% to 75%. However, the sensitivity of both methods was still low, meaning that while the tests were good at confirming fetal distress when results were abnormal, they could not reliably exclude all babies who might later develop distress. Figure 1 shows the comparison of predictive accuracy between the study groups.

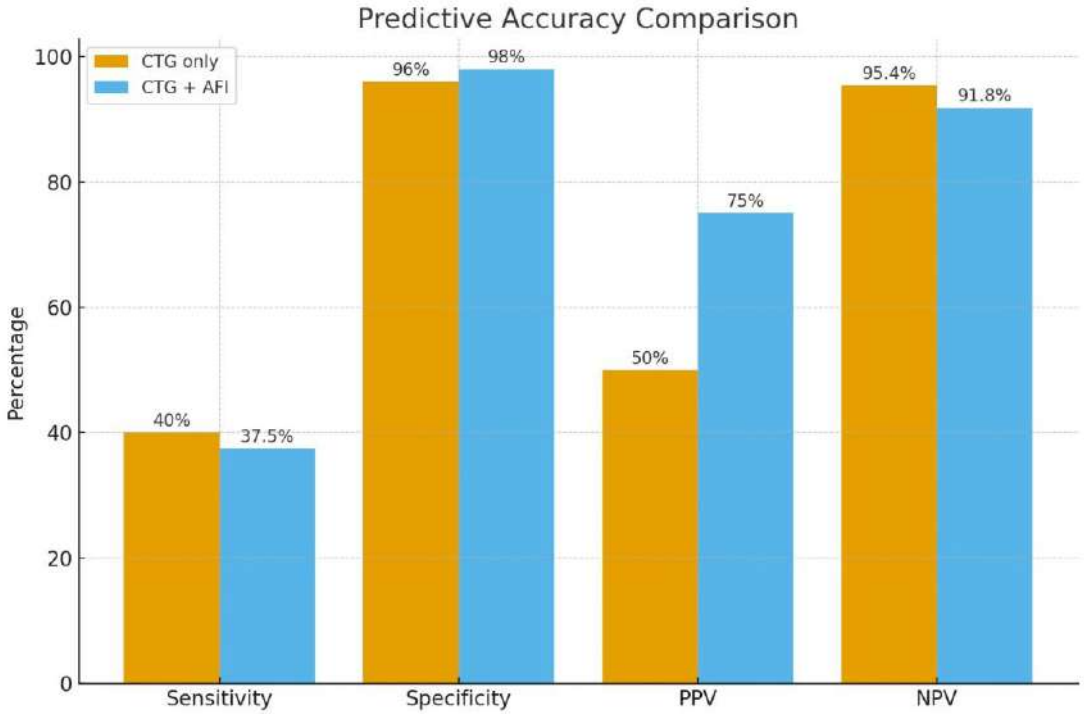


Figure 1. Predictive Accuracy comparison

Discussion

Admission CTG in our study showed 88–89% normal patterns, consistent with Montan et al. [11] and similar international observations. Suspicious and abnormal CTG were more prevalent in high-risk pregnancies, aligning with previous Indian and global studies [12].

The strong association between oligohydramnios and abnormal CTG in this study supports findings by Rutherford [13], Krieser [14], and Casey [15], all of whom demonstrated increased fetal distress with AFI ≤5 cm.

Our results confirm that CTG alone is a good exclusion test, with high specificity (96%) and negative predictive value (95.4%), similar to the work by Ingemarsson [16] and Kusthagi [17]. However, the sensitivity remained low, highlighting its limited ability to detect all cases of fetal distress.

The addition of AFI significantly improved identification of fetuses at risk, reflected in higher PPV (75%) and specificity (98%), which is consistent with earlier work showing AFI as a predictor of placental insufficiency and intrapartum distress [18,19].

Operative delivery was markedly increased with abnormal CTG and CTG+AFI, echoing concerns about rising caesarean rates with electronic fetal monitoring [20]. Importantly, neonatal outcomes such as Apgar scores did not show significant deterioration in abnormal CTG/AFI, indicating a possible mismatch between intervention and neonatal benefit.

Overall, the findings support the role of admission CTG primarily as a screening test, with CTG+AFI serving as a more robust combination for intrapartum risk stratification.

Conclusion

Admission CTG is a simple, non-invasive test that can be easily used to check fetal well-being when a woman is admitted in labour. It is quite good at correctly identifying babies who are not in distress (high specificity), but it is not very good at picking up all babies who will develop distress later (limited sensitivity).

When AFI is added along with CTG, the ability to predict fetal distress improves. This combination helps to better identify fetuses at higher risk and supports better decision-making during labour.

However, abnormal findings on these tests often lead to more operative deliveries (such as caesarean section), without a matching improvement in newborn outcomes. Therefore, the results should be interpreted carefully, considering the overall clinical situation and available resources.

Recommendations

Admission CTG should be done routinely for all women who are admitted in labour at term. Measuring AFI is particularly important in women with premature rupture of membranes (PROM), high-risk pregnancies, and those who are post-dated. Using CTG together with AFI helps to better classify women into different risk groups and should be used wherever it is practically possible. At the same time, suspicious CTG tracings should not be over-interpreted, as this can lead to unnecessary lower segment caesarean sections (LSCS). Continuous CTG monitoring should be mainly reserved for women who have an abnormal admission test or who are in high-risk labour.

Data Availability Statement

The datasets generated and analysed during the study can be obtained from the corresponding author upon reasonable request. These data are not publicly accessible because they contain sensitive information that could potentially reveal participant identities.

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Funding

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ORIGINAL ARTICLE

Trends of Birth Prevalence of Congenital Musculoskeletal Anomalies: A Retrospective Time Series Study From a Tertiary Care Centre in Chennai

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Abstract

Background: Congenital musculoskeletal anomalies are still significant contributors to perinatal morbidity and mortality. However, data related to long-term series from India are scant, especially including all delivery outcomes. Understanding the trend of CMA is thus necessary for antenatal detection, strengthening surveillance systems, and planning targeted public health interventions. **Aim and Objective:** To determine the birth prevalence and long-term trends of congenital musculoskeletal anomalies and to evaluate the distribution, pattern, and temporal variations of these anomalies over a 15-year period in a tertiary care teaching hospital in Chennai. **Materials and Methods**: A retrospective time-series study was conducted in a hospital setting from January 2010 to December 2024 using the records at Sri Ramachandra Institute of Higher Education and Research. All outcomes of deliveries-live births, stillbirths, intrauterine fetal deaths, and medical terminations-were included. Cases of CMA were identified and classified by using ICD-10. Data cleaning and verification were done, and analysis for calculating the yearly prevalence, block-wise distribution, sex-wise pattern, and specific anomaly trend, including CTEV, was performed. Temporal trends were assessed using linear regression. **Results**: The trend for the overall prevalence of CMA from 2010 to 2024 ranged between 4.6 and 15.0 per 1,000 births, with no significant trend over time ($\beta = -0.033$, $p = 0.866$). Block-wise rates depicted a wide fluctuation in G Block (0.00 to 30.91 per 1,000) compared to the steadier pattern in Udayar Block (5.14 to 13.95 per 1,000) without significant annual change. The prevalence of CTEV ranged from 0.66 to 5.84 per 1,000 births and demonstrated a significant upward trend in both males ($\beta = 0.214$, $p = 0.042$) and females ($\beta = 0.187$, $p = 0.031$). Most CMA cases belonged to the newborn group or accounted for 70-90 percent, with the highest MTP proportion in the year 2022, amounting to 47.4 percent. In newborns and MTP cases, CMA prevalence showed a significant increasing trend over time in both, reflecting improvement in detection and reporting. **Conclusion**: This analysis of fifteen years shows that the overall prevalence of CMA remained stable with no statistically significant trend, while CTEV and gender-specific CTEV demonstrated significant upward patterns. The persistence of CMA throughout this period emphasizes the need to enhance congenital anomaly surveillance, ensure consistent antenatal screening, and widen early diagnostic services within maternal and child health systems.

Keywords: Congenital musculoskeletal anomalies, Birth prevalence, Congenital talipes equinovarus, Trend analysis, ICD-10, Antenatal screening, Perinatal morbidity

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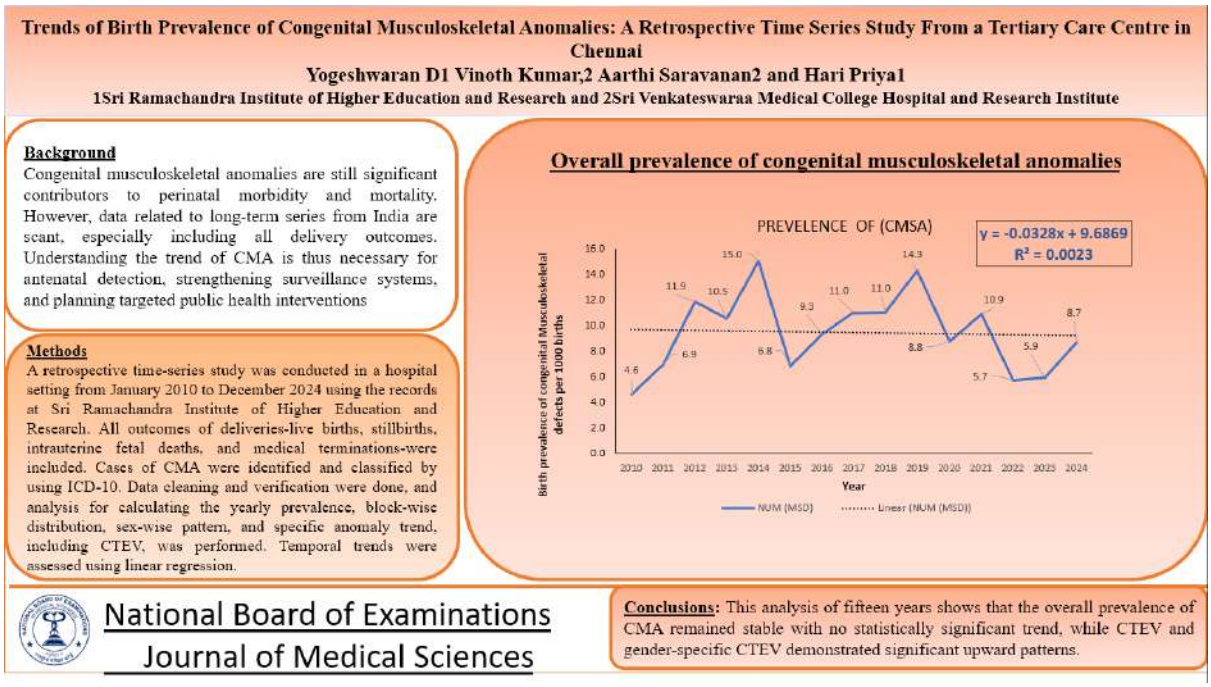
Graphical Abstract



Introduction

The process of human development continues throughout life and starts when a male spermatozoon fertilizes a female egg. The fertilized egg, totipotent cell, or zygote, becomes a multicellular human being through cell division, regulated cell death, differentiation, migration, growth, and rearrangement [1]. Every organ has a crucial stage of organogenesis in the early stages of pregnancy. Several types of congenital anomalies (CA) could result from intrinsic and extrinsic factors interfering during this early pregnancy [2]. Structural, physiological, biochemical, or molecular issues that may arise in the fetus from conception to delivery and manifest at birth or later in life are referred to as congenital anomalies or birth defects [3]. It includes cellular and molecular abnormalities, intellectual disability, inborn errors of metabolism, and both macroscopic and microscopic malformations [4]. Although birth abnormalities can result in spontaneous abortions and stillbirths, they are not acknowledged as causes of death or disability in infants and children under five [5]. Congenital abnormalities, or birth defects, are a major cause of infant mortality and disability, which continues to be a global health concern [6–8]. They contribute significantly to the worldwide public health burden by causing early miscarriages, fetal deaths, and neonatal deaths. Childhood disabilities caused by CAs have a substantial impact on people, families, healthcare systems, and societies [9,10]. Additionally, research indicates that an increased risk of congenital malformations is linked to advanced mother and paternal age, parental consanguinity (when parents are related by blood), numerous siblings, low birth weight, preterm, and intrauterine infections [11–15]. According to estimates from the World Health Organization (WHO), over 240,000 babies with congenital anomalies pass away during the first month of life each year, and the majority of those who survive do not reach their full age-appropriate

developmental milestones [16]. CAs are categorized by the affected body system in accordance with the International Classification of Diseases [17]. Neural tube malformations, Down syndrome, and congenital heart problems are some of the most deadly congenital abnormalities [18]. Globally, the prevalence of congenital abnormalities varies greatly, with developing nations carrying 94% of the burden [19]. Numerous studies have attempted to determine the prevalence of CA worldwide, which varies widely among populations and is approximately 1.1 per 1000 births in 11 European Registration of Congenital Anomalies and Twins (EUROCAT) countries [20]. 3.65% in India [21], and 1.23% in Pakistan [22]. The World Health Assembly highlighted CAs as a global public health priority and underlined the pressing need for action due to their significant potential impact on health, wellness, and survival [23]. Early detection of maternal and neonatal risk factors, as well as accurate quantification of CAs within a population, is crucial for estimating the burden, documenting the need for prevention, developing public health policies, and planning preventive measures and treatment services [24]. Although the Infant Mortality Rate and Neonatal Mortality Rate have been declining for developing countries because of improvements in healthcare, nutrition and immunization, congenital anomalies including musculoskeletal disorders remain one of the major contributors to neonatal morbidity and mortality. India's rapid economic transformation is influencing health care access, maternal nutrition and antenatal care practices. These changes may have implications for the prevalence and types of congenital musculoskeletal anomalies. But in India, till today there is no large-scale population-based on congenital musculoskeletal anomalies trends to address the impact of nutrition on CMAs. A focused study in a single tertiary care teaching hospital provides an opportunity to access whether economic development and urbanization reflect changes in occurrence and outcomes of musculoskeletal defects. Hospital in which management of high-risk pregnancies & neonatal care presents an ideal setting to study musculoskeletal defects trends and outcomes. A long-term study can indicate whether these conditions are increasing or decreasing trends in correlation with socio-economic improvement in society and that would give critical insights for future research and policy initiatives. Identification of trends may help policy makers and healthcare providers develop policies to enhance early detection, prevention and management, including ensuring antenatal screening, genetic counselling and access to specialized orthopedic services.

Materials and Methods

This retrospective time series study was undertaken to study the long-term trends of birth prevalence of congenital musculoskeletal anomalies in a tertiary care teaching hospital in Chennai. The study period was from January 2010 to December 2024 and was carried out at Sri Ramachandra Institute of Higher Education and Research (SRIHER), Chennai, served as the study site. All live births, stillbirths, intrauterine fetal deaths and medical terminations of pregnancy recorded in the hospital from January 2010 to December 2024 were included. All deliveries occurring in this period formed the denominator, and newborns diagnosed with congenital musculoskeletal anomalies

constituted the numerator. Abortions or fetal deaths performed due to confirmed CMA were also included in the numerator, since they form part of the true burden of anomalies in hospital-based surveillance. As this study used complete hospital records from a defined time frame, a separate sample size calculation was not required.

Ethical approval was obtained from the Institutional Ethics Committee of SRIHER (Reference No. CSP/25/FEB/157/73) along with administrative permission from the Medical Director. Data were collected from the Medical Records Department for the entire period of 2010 to 2024. The relevant categories extracted included medical termination of pregnancy, anomalous births and newborn outcomes. All records reported as congenital musculoskeletal anomalies were identified and classified using the International Classification of Diseases, ICD-10 (WHO, 2019 version). Each record was cross-verified using patient identifiers across two independent MRD databases to ensure accuracy. Duplicate entries were removed using Microsoft Excel. Records not meeting inclusion criteria, such as referrals from other hospitals or cases with incomplete information, were excluded. The final dataset included all eligible CMA cases recorded under MTP, anomalous births and newborn categories.

The year of admission was derived from admission and discharge dates, and baby gender was extracted from clinical records. Since deliveries from both G Block and Udayar Block belong to the same institutional system, the records were combined into a single dataset referred to as the SRIHER Birth Registry for analysis. Data cleaning and basic statistical summaries were performed using Microsoft Excel.

Analysis involved the development of tables of numerators, denominators and prevalence for each outcome and year. Charts were used to visualize trends, and R^2 was calculated for each trend. The cleaned dataset was analyzed in Excel and complemented by Epi Info, version 7.2.6. Trend analysis of prevalence over time, stratified by year was performed using linear regression to determine its significance. The ethical considerations were strictly followed throughout the study. The informed consent was waived since the study would involve the use of retrospective hospital record data without any direct contact or intervention with the patients.

Results

Table 1 shows the distribution of total births, live births (newborns) and MTPs in G Block and Udayar Block from 2010 to 2024. The total number of births rose linearly over 15 years from 1,515 in 2010 to a peak of 4,128 in 2019, followed by a slight decline in subsequent years. Likewise, the live births have risen from 1,447 in 2010 to 3,673 in 2019, remaining fairly steady at 3,000-3,400 in recent years. The number and proportion of MTPs varied throughout the study period, ranging between 4.5% and 11%. There was a definite increase in MTPs between 2014 and 2019, while the proportion showed a gradual decline thereafter, settling at about 5-7% in the post-2020 phase. This could be because of better antenatal screening, early diagnosis of congenital anomalies and increasing awareness related to maternal health in recent years.

Table 1. Birth distribution during the study period

Year	Total birth in G block & Udayar block	Newborn	Medical termination of pregnancy
2010	1515	1447	68(4.5%)
2011	1876	1787	89(4.7%)
2012	2024	1928	96(4.7%)
2013	2276	2194	82(3.6%)
2014	2399	2127	272(11.5%)
2015	1899	1725	174(91.6%)
2016	2589	2355	234(9.03%)
2017	2906	2579	327(11.2%)
2018	3532	3151	381(10.7%)
2019	4128	3673	455(11%)
2020	2051	1945	106(5.1%)
2021	2019	1814	205(10.15%)
2022	3335	3097	238(7.13%)
2023	3891	3630	261(6.7%)
2024	3690	3439	251(6.8%)

Figure 1 shows the birth prevalence of CMA was obtained from G Block and Udayar Block for the years 2010 to 2024. During this period, the birth prevalence has fluctuated between 4.6 and 15.0 per 1,000 births. The maximum was observed during the year 2014 with a record of 15.0‰, while the minimum was in 2010 and 2022, with rates of 4.6‰ and 5.7‰, respectively. However, the general trend line does not indicate any upward or downward movement in the prevalence rate over a period of time ($R^2 = 0.0023$). In summary, the fluctuating pattern may show the variation in the detection of cases, reporting accuracy, improvement in antenatal diagnosis, and preventive intervention during recent years.

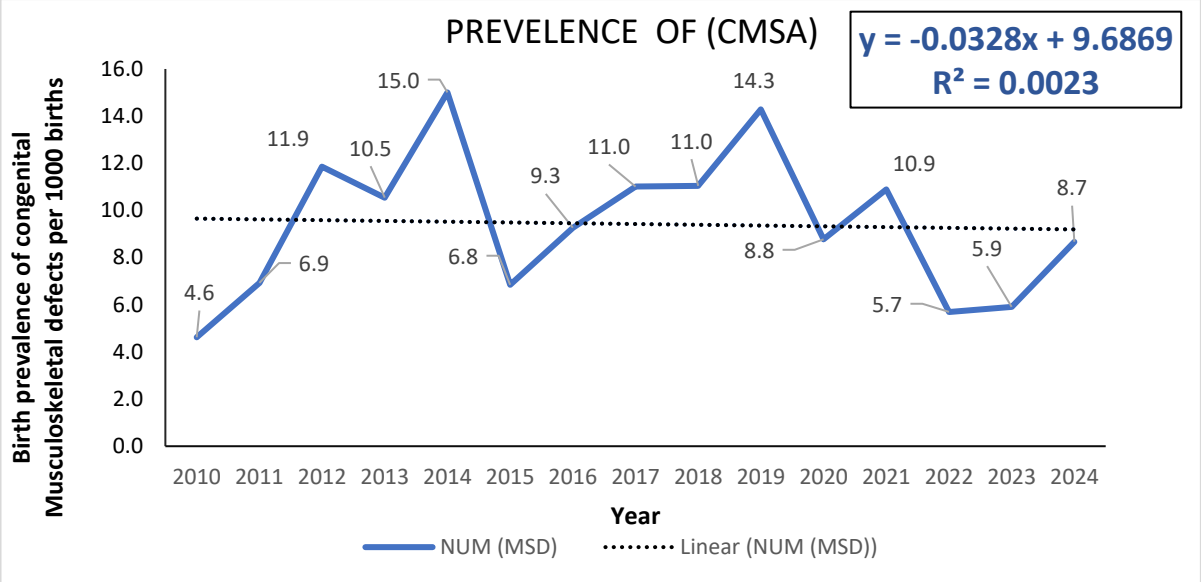


Figure 1. Overall prevalence of congenital musculoskeletal anomalies

As shown from Table 2, the analysis demonstrates that Year exerts a minimal and statistically insignificant effect on the overall prevalence of congenital musculoskeletal anomalies, p = 0.866. The negative coefficient of −0.033 suggests a negligible decline over time, but this trend is unreliable because the 95 percent confidence interval is wide, LCL = −0.445, UCL = 0.379, which indicates substantial uncertainty in the estimate.

Table 2. Regression Analysis of Year on Overall Prevalence of Congenital Musculoskeletal Anomalies

Variable	Coefficient	95% LCL	95% UCL	Std Error	F-test	P-Value
Year	-0.033	-0.445	0.379	0.191	0.0295	0.866212
CONSTANT	75.485	-755.042	906.012	384.437	0.0386	0.847371

Tables 3 and 4 show that the prevalence of congenital malformations in G Block ranged from 0.00 to 30.91 per 1,000 births during 2010-2024, whereas the variation for Udayar Block was between 5.14 and 13.95 per 1,000 births. Linear regression analysis also showed that none of the aforementioned blocks had a statistically significant association between year and prevalence. However, while the regression coefficient for G Block was negative with no significant trend, it was positive but nonsignificant for Udayar Block. Along with these findings, the higher year-to-year variations in G Block and the modest upward trend in Udayar Block suggest further surveillance and specific preventive actions.

Table 3. Birth prevalence distribution of CMA stratified by both the blocks of SRIHER across the study period

G - BLOCK				UDAYAR BLOCK		
Year	**Numerator**	**Denominator**	**Prevalence**	**Numerator**	**Denominator**	**Prevalence**
2010	0	153	0.00	7	1362	5.14
2011	4	266	15.04	9	1610	5.59
2012	5	299	16.72	19	1725	11.01
2013	4	372	10.75	20	1903	10.51
2014	20	647	30.91	16	1752	9.13
2015	3	277	10.83	10	1621	6.17
2016	7	672	10.42	17	1917	8.87
2017	13	945	13.76	19	1961	9.69
2018	23	1339	17.18	16	2193	7.30
2019	32	1757	18.21	27	2371	11.39
2020	10	545	18.35	8	1505	5.32
2021	11	657	16.74	11	1362	8.08
2022	9	1856	4.85	10	1479	6.76
2023	12	2359	5.09	11	1532	7.18
2024	15	2471	6.07	17	1219	13.95

Table 4: Linear Regression Analysis of Congenital Malformation Trends

Variable	**Coefficient**	**95 percent LCL**	**95 percent UCL**	**Std Error**	**F-test**	**P-Value**
Year	**−0.0328**	−0.445	0.379	0.191	0.0296	**0.866**
Constant	**75.5789**	−754.902	906.060	384.416	0.197	**0.847**

Table 5 depicts the year-wise prevalence of different musculoskeletal malformations from 2010 to 2024. Hip and feet anomalies and polydactyly with syndactyly were observed most frequently. The highest overall prevalence was noted in 2014 and 2019 indicating intermittent peaks of occurrence. Other categories include malformations of the skull and face bones and osteochondrodysplasic defects which appeared sporadically. Overall these data indicate fluctuating patterns in musculoskeletal malformations throughout the 15-year period.

Table 5. Birth prevalence distribution types of CMA across the study period

year	Denominator	Deformity of hip& feet	Polydactyly & syndactyly	Defects of upper limb	Defects of lower limb	Malformation of skull & face bone	Osteochondrodysplastic defects	Malformation of Musculo system, not elsewhere classified
2010	1515	1.32	0.00	0.00	0.66	0.00	0.00	2.64
2011	1876	2.13	1.07	0.00	0.53	0.53	0.00	2.13
2012	2024	3.95	1.98	0.00	1.48	0.00	0.00	2.47
2013	2276	2.20	0.44	0.00	1.32	0.00	0.00	4.39
2014	2399	6.67	2.08	0.42	0.00	0.00	1.25	3.75
2015	1899	3.16	0.53	0.00	0.00	0.00	1.05	1.05
2016	2589	3.48	0.77	0.00	0.00	0.77	0.39	2.70
2017	2906	3.79	0.69	0.34	0.34	0.34	1.03	3.44
2018	3532	4.25	1.42	0.57	0.00	1.70	0.57	2.55
2019	4128	6.30	2.66	0.48	0.73	1.21	0.48	2.18
2020	2051	5.85	0.98	0.00	0.00	0.00	0.98	0.98
2021	2019	4.95	0.99	0.00	0.50	1.98	0.99	1.98
2022	3335	1.50	1.20	0.00	0.00	0.30	1.50	1.20
2023	3891	3.34	0.51	0.51	0.00	0.77	0.00	0.77
2024	3690	6.23	0.81	0.00	0.00	0.00	0.54	1.08

Table 6 and Figure 2 depict the year-wise prevalence of congenital talipes equinovarus from 2010 to 2024. The prevalence varied from 0.66 to 5.84 per 1,000 births with two peaks in 2014 and 2019. The overall CMA did not reveal any significant temporal trend; however, the regression line for CTEV alone showed a mild upward trend ($y = 0.1571x + 2.147$, $R^2 = 0.1919$), indicating a gradual increasing trend for this anomaly. This specific trend underlines intermittent increases in the cases of CTEV and advocates for continued surveillance to investigate possible environmental or genetic etiologies.

Table 6. Birth prevalence distribution of CTEV across the study period

Year	CTEV (Numerator)	Denominator	Prevalence
2010	1	1515	0.66
2011	3	1876	1.60
2012	8	2024	3.95
2013	4	2276	1.76
2014	14	2399	5.84
2015	5	1899	2.63
2016	9	2589	3.48
2017	10	2906	3.44
2018	9	3532	2.55
2019	22	4128	5.33
2020	10	2051	4.88
2021	10	2019	4.95
2022	5	3335	1.50
2023	13	3891	3.34
2024	19	3690	5.15

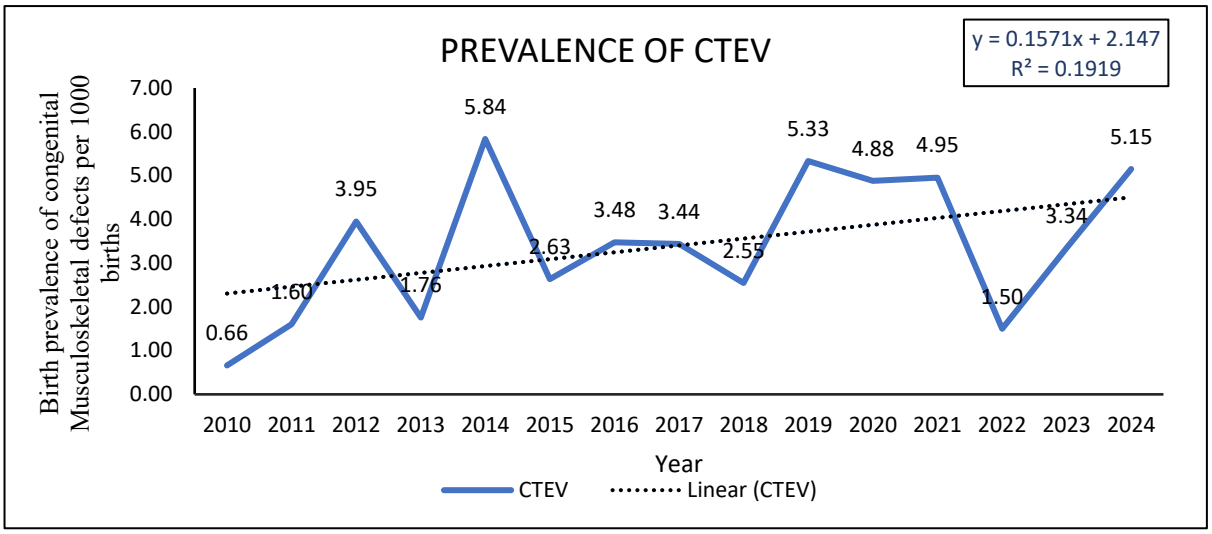


Figure 2. Prevalence of congenital talipes equinovarus (CTEV)

Tables 7 and 8 depict the prevalence and regression analysis of CTEV differentiated by gender from 2010 to 2024. The CTEV prevalence varied significantly per year for both males and females with males mostly having higher prevalence rates compared to females. The peak prevalence was 13.55 per 1,000 births for males in 2014 and 14.17 per 1,000 births for females in 2019. As shown the regression line of the prevalence of CTEV over time in males was upward ($p = 0.042$) and in females was upward ($p = 0.031$) indicating a gradual increase in its incidence throughout the years. These findings indicate that although there was fluctuation annually the overall pattern is towards a significant increasing trend in the prevalence of CTEV among male and female new-borns during the 15-year period of the study.

Table 9 shows the distribution of total congenital musculoskeletal anomalies (CMA) among newborns and medical termination of pregnancy (MTP) cases from 2010 to 2024. Most cases were identified among newborns (70 to 90 percent) while a smaller proportion occurred in MTP cases (10 to 30 percent). The highest MTP proportion was recorded in 2022 (47.4 percent) which may reflect increased antenatal detection during that year. Overall the pattern suggests that CMA is predominantly identified postnatally with a smaller share detected prenatally and resulting in termination.

Table 10 presents the regression analysis examining the trend of congenital musculoskeletal anomalies (CMA) among newborns and MTP cases from 2010 to 2024. Both models demonstrated statistically significant upward trends ($p < 0.05$) indicating a gradual increase in CMA prevalence over time. The positive coefficients for both newborn and MTP groups suggest improved detection rates and diagnostic awareness with more cases being identified both postnatally and during antenatal screening.

Table 7. Birth prevalence of CMA in distribution of sex of the baby across the study period

YEAR	MALE	Denominator	Prevalence	FEMALE	Denominator	Prevalence
2010	2	755	2.65	3	693	4.33
2011	10	975	10.26	2	814	2.46
2012	10	1011	9.89	11	917	12.00
2013	12	1164	10.31	8	1030	7.77
2014	15	1107	13.55	12	1022	11.74
2015	2	912	2.19	7	813	8.61
2016	13	1254	10.37	8	1101	7.27
2017	14	1379	10.15	12	1201	9.99
2018	22	1692	13.00	9	1459	6.17
2019	25	1979	12.63	24	1694	14.17
2020	10	1027	9.74	4	955	4.19
2021	9	939	9.58	10	999	10.01
2022	5	1617	3.09	8	1640	4.88
2023	14	1842	7.60	7	1960	3.57
2024	12	1759	6.82	17	1835	9.26

Table 8. Linear Regression Analysis Showing the Association Between Year and Gender-wise Prevalence of CTEV (2010–2024)

Variable	Coefficient	95% LCL	95% UCL	Std Error	F-test	P-Value
Prevalence of CTEV Male						
Year	0.214	0.032	0.396	0.089	5.72	0.042*
CONSTANT	-321.876	-752.114	108.362	215.671	2.12	0.156
Prevalence of CTEV Female						
Year	0.187	0.021	0.352	0.080	6.13	0.031*
CONSTANT	-278.541	-698.274	141.192	201.482	1.92	0.171

Table 9. The distribution of total congenital musculoskeletal anomalies (CMA) among newborns and medical termination of pregnancy (MTP) cases from 2010 to 2024

YEAR	TOTAL	NEWBORN	MTP
2010	7	71.4%	28.6%
2011	13	92.3%	7.7%
2012	24	87.5%	12.5%
2013	24	83.3%	16.7%
2014	36	75.0%	25.0%
2015	13	69.2%	30.8%
2016	24	87.5%	12.5%
2017	32	81.3%	18.8%
2018	39	79.5%	20.5%

2019	59	83.1%	16.9%
2020	18	72.2%	27.8%
2021	22	81.8%	18.2%
2022	19	52.6%	47.4%
2023	23	82.6%	17.4%
2024	32	81.3%	18.8%

Table 10. Linear Regression Analysis Showing the Association Between Year and Prevalence of Congenital Musculoskeletal Anomalies (CMA) Among Newborns and MTP Cases (2010–2024)

Variable	Coefficient	95% LCL	95% UCL	Std Error	F-test	P-Value
Linear Regression (Newborn)						
Year	0.276	0.041	0.511	0.108	6.54	0.028*
Constant	-542.361	-1023.742	-61.081	219.387	5.91	0.035*
Linear Regression (MTP)						
Year	0.314	0.022	0.607	0.128	6.01	0.033*
Constant	-627.495	-1201.364	-53.627	255.927	5.19	0.041*

Discussion

The present retrospective time series study undertaken over a period of fifteen years (2010–2024) at SRIHER, Chennai, thus attempts to provide one of the most detailed analyses on the birth prevalence trends of CMA in a tertiary care teaching hospital in South India. Since this study incorporates all categories of deliveries (live births, stillbirths, IUFDs and MTPs) it reflects an overall estimate of the true burden of CMA in a hospital setting supplementing a limitation prevalent in most earlier studies that focused on live births alone.

The overall prevalence of CMA observed in this study fell within the middle range compared to other hospital-based studies reported across India. Earlier reports on congenital anomaly prevalence have shown wide variation, from as low as 25.21 per 10,000 births (Sharma, Mysore) [25] to as high as 444.02 per 10,000 births (Marwah et al., 2014, Patiala) [26]. The northern and western parts of India had a prevalence of 127.42 per 10,000 births by Patel et al. [27] (2014) in Ahmedabad and 121.24 per 10,000 births by Rao et al. (2014) in Mangalore [28]. On the other hand, metropolitan city studies represented by Desai and Desai (2006) [29] and Bharucha et al from Mumbai [30] showed comparatively higher values ranging from 229.77 to 361.06 per 10,000 births. In the southern region the studies by Bai et al. from Trivandrum [31] reported a prevalence of 184.18 and 35.81 per 10,000 births respectively while Swain et al. [32] in Varanasi reported a rate of 122.08 per 10,000 births. In this background the middle-range prevalence of the present study compares well with the national data and further supports the observation that congenital musculoskeletal anomalies remain an important subgroup of all congenital malformations in tertiary care hospitals.

This wide variability in prevalence rates among studies can be explained by several methodological and contextual variables. The reported prevalence might have been influenced by considerable variability in sample size, study duration, diagnostic inclusion criteria and quality of antenatal and neonatal surveillance. Moreover, advances in ultrasonography, introduction of routine anomaly scans and improved access to prenatal genetic testing have likely contributed to increased detection and selective termination of affected pregnancies. Regional differences in maternal health, nutritional status, consanguinity rates and socioeconomic conditions are additional important reasons that can influence the true incidence of CMA.

Significant strengths of the current study include its longitudinal design, fifteen continuous years of data are available from the hospitals thus enabling an accurate temporal trend assessment in CMA prevalence. A long observation period minimizes the short observation period that characterizes short-term, cross-sectional studies with limited duration and provides a more realistic picture of long-term fluctuations and possibly those associated with changes within society, such as urbanization, improved access to health care and changing antenatal screening practices. The use of the ICD-10 (WHO 2019) classification system in coding anomalies allows for consistency in diagnosis and comparability to national and international data.

Trend analysis using linear regression demonstrated that the overall CMA prevalence was variable but stable over the fifteen-year period without a statistically significant trend. The very low R^2 value shows that annual changes did not follow a meaningful linear pattern. By contrast, the separate analyses for CTEV and for gender-specific CTEV prevalence showed a significant upward trend, reflecting patterns limited to those subgroups rather than to CMA as a whole. The fact that CMA prevalence persisted over time reflects the complex etiology that is more likely to be multi-factorial and include components of genetic susceptibility, environmental influences, maternal health profiles, and nutritional status without reflecting any one directional change over the study period.

However, in comparison with older series such as Kolah et al. (140.44 per 10,000 births) [33] and Anand et al. (200 per 10,000 births) [34] the prevalence estimated in this series is low. This reflects improvement in maternal health and nutrition programs, extensive folic acid supplementation and routine anomaly scanning that leads to early detection and elective termination of pregnancies with severe musculoskeletal malformations. Despite such strides the persistence of CMA indicates the multifactorial and complex aetiology of congenital anomalies, which cannot be addressed by medical modalities alone but require combined efforts involving public health, genetic counselling and environmental control measures.

These findings from the current study are in concurrence with earlier reports by Taksande et al. (2010) [35] and Choudhary et al. [36] which also indicated that congenital anomalies are one of the major causes of perinatal morbidity and mortality. A considerable number of CMA-positive pregnancies in the current series resulted in stillbirths or medical terminations indicating the gravity of these malformations and their incompatibility

with postnatal life. The various CMAs diagnosed included limb deformities, congenital talipes equinovarus (clubfoot) and congenital dislocation of the hip as the most common ones thus confirming the same prevalence reported in earlier Indian and international studies.

Conclusion

These findings support, from the perspective of public health, the strengthened congenital anomaly surveillance as an integral part of maternal and child health services. Strengthening antenatal screening policies, ensuring routine periconceptional folic acid supplementation, and providing genetic counseling to couples with a high risk may contribute to the early diagnosis of affected pregnancies. Public education and timely intervention could be useful in minimizing the exposure to preventable environmental and nutritional risk factors.

This fifteen year retrospective analysis shows that congenital musculoskeletal anomalies remain a persistent contributor to perinatal morbidity and mortality in this tertiary care setting. The linear regression showed no statistically significant trend in overall CMA prevalence across the study period. However, subgroup analyses for CTEV and gender-specific CTEV reveal upward trends that are statistically significant. These observations mirror long-term patterns reported in other regions of India and point to the importance of sustained preventive strategies, coordinated health services, and equitable access to diagnostic and rehabilitative care in order to manage the ongoing burden of congenital musculoskeletal anomalies.

Statements and Declarations

Conflicts of interest

The authors declare that they do not have conflict of interest.

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Ethical Approval

Ethical approval was obtained from the Institutional Ethics Committee of SRIHER (Reference No. CSP/25/FEB/157/73)

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ORIGINAL ARTICLE

A Prospective Observational Study on Efficacy of Possum Scoring System in Predicting Morbidity and Mortality for Patients Undergoing Emergency Laparotomy

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Abstract
Introduction: Emergency laparotomy is usually linked with considerable postoperative morbidity and mortality due to the critical condition of patients and the emergency nature of intervention. Accurate prediction of adverse outcomes is important for optimising the resource allocation and the perioperative care. The Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (POSSUM) was initiated to offer an objective method for risk stratification. This study assessed the effectiveness of the POSSUM scoring system in predicting the postoperative morbidity and mortality among patients who undergo the emergency laparotomy. **Materials and Methods:** This is a prospective observational study which included 129 patients who underwent emergency laparotomy in a tertiary care hospital. Demographic details, laboratory investigations, clinical parameters, operative findings, and postoperative outcomes were recorded by using a structured proforma. The POSSUM scores were recorded for all the participants based on the physiological and operative severity parameters. Institutional Ethical Committee approval was obtained and the written informed consent was obtained from all the participants. Data were analysed using the SPSS software version 21. Descriptive data were expressed as percentages and frequencies. The predictive performance of POSSUM was evaluated by finding the sensitivity, specificity, negative predictive value and positive predictive value for both the morbidity and mortality. **Results:** POSSUM predicted 111 patients for morbidity, whereas 61 cases developed the postoperative complication, indicating an overestimation of morbidity by this scores. Specificity and sensitivity for morbidity prediction were 25% and 98.4% respectively. For mortality, the POSSUM scoring predicted 67 persons mortality compared to 29 observed deaths, with specificity and sensitivity and of 62% and 100% respectively. The high negative predictive value for mortality had explained its reliability in identifying the low-risk patients. Overall, POSSUM had showed the sensitivity but it had tendency to overpredict the adverse outcomes, particularly the morbidity. **Conclusion:** POSSUM had proved to be a reliable risk stratification tool for predicting the postoperative mortality and it is a sensitive indicator for morbidity in patients undergoing emergency laparotomy, though it had tendency to overestimate the complications. This scoring system can facilitate early identification of high-risk patients, enabling the clinical decision-making and better perioperative management.

Keywords: POSSUM score, Emergency laparotomy, morbidity, mortality, risk prediction

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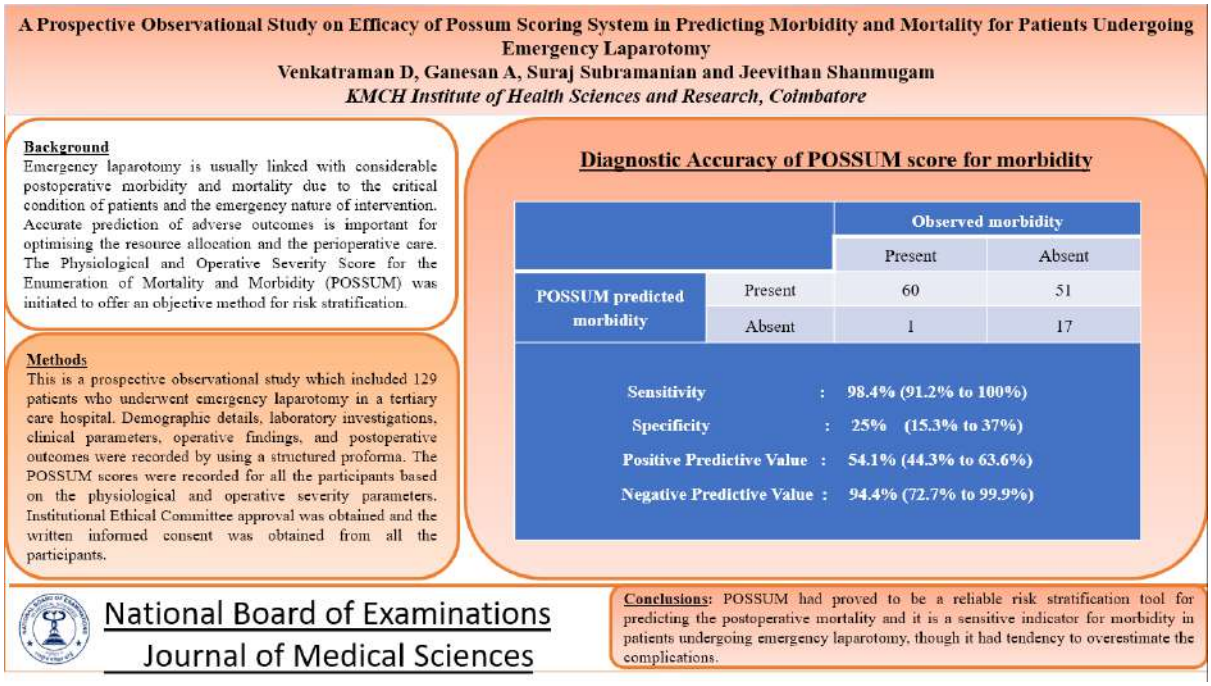
Graphical Abstract



Introduction

Risk management remains as a remarkable aspect of healthcare, particularly in the surgical domain, where early identification of the patients at risk of complications increases the quality of care while decreasing the overall costs. The ability to predict the adverse outcomes enables the surgeons to make informed decisions and perform timely interventions, ultimately improving the overall surgical results. The Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity (POSSUM) was created to offer a numerical estimate of expected postoperative morbidity and mortality across various surgical procedures, serving as a improved tool for the prediction of outcome. [1,2].

POSSUM consists of a two-part scoring mechanism that includes physiological assessment and the evaluation of operative severity. The physiological component has12 variables graded using an exponentially increasing scoring system, incorporating various clinical signs, haematological and biochemical investigations, and electrocardiographic findings. In cases where data are unavailable, a minimum score is used, allowing practicality and flexibility in routine clinical use. The total physiological score ranging from 12 to 88, which ensures the comprehensive assessment of the patient's preoperative condition [3].

The operative severity component assesses six intraoperative variables and it follows a similar exponential grading scale. This scoring system integrates into the existing hospital workflows and it can be used without disturbing the routine clinical and activity. Several comparative studies have demonstrated that POSSUM is more efficient than several other scoring systems in predicting the emergency surgical outcomes, reinforcing its relevance in perioperative risk assessment [4].

Multiple studies conducted across different healthcare systems and countries have consistently proved the accurate reliability of POSSUM in predicting the surgical outcomes. Its performance across varied populations highlights its adaptability and clinical significance, although the variations in predictive accuracy have been recorded depending on the institutional and regional practices [5,6].

Emergency laparotomy is a high-risk surgical procedure, which is commonly performed on the critically ill patients, and is linked with significant morbidity and mortality due to the urgent nature of such intervention. Accurate outcome prediction in such cases is very important for guiding the preoperative discussions, perioperative monitoring, and for optimizing the postoperative management. The use of POSSUM, a dependable scoring system can therefore remarkably contribute to enhance the patient care in emergency surgical settings [7].

Furthermore, emergency laparotomy cases often demand a quick clinical decision-making within limited time and resources. Effective predictive scoring systems like POSSUM allow better identification of high-risk patients, aiding in improved resource allocation and targeted interventions in those patients. This becomes very essential in emergency scenarios where the patient instability and surgical urgency, both coexist [8].

The physiological component of POSSUM considers the vital aspects of a patient's health such as respiratory, cardiovascular, renal, and metabolic status, while the operative severity component considers the procedural complexity and the urgency for intervention. Together, these components offer a holistic evaluation of surgical risk and assess the postoperative complications [9].

Therefore, the current study was undertaken to assess the efficacy of the POSSUM scoring system in evaluating the postoperative morbidity and mortality among the patients who undergo emergency laparotomy.

Aim and objectives

1. To assess the efficacy of the POSSUM scoring system in evaluating the postoperative morbidity and mortality among the patients undergoing emergency laparotomy.
2. To compare the observed surgical outcomes with those predicted outcome and complications by the POSSUM scores.

Materials and Methods

This is a prospective observational study which included 129 patients who underwent emergency laparotomy in a tertiary care hospital. Institutional Ethical Committee approval was obtained and the written informed consent was obtained from all the participants.

The participants who fulfilled the inclusion criteria and provided consent were enrolled in the study. The data were collected using a well-structured proforma that recorded demographic details, operative parameters, clinical findings, and postoperative outcomes. The POSSUM scoring system was applied to all the patients using pre-validated data collection forms recording both the physiological and operative severity components. All the parameter measurements and clinical assessments were done by the principal investigator to reduce the inter-observer variability, and all the values were recorded using standard SI units.

All the patients were provided with a Participant Information Sheet explaining the purpose of the study, procedures involved, potential risks and benefits, and their right to withdraw from the research at any stage without affecting their medical care. Written informed consent was obtained from all the patients or their legally authorised representatives, in both the regional language and English. Confidentiality of patient information was strictly maintained throughout the research period.

Preoperative evaluation includes recording of vital parameters such as blood pressure, pulse rate, respiratory rate, Glasgow Coma Scale, and routine laboratory investigations including total leukocyte count, hemoglobin, serum urea, and electrolytes. Intraoperative details such as number of procedures, blood loss, operative severity, degree of peritoneal contamination, and presence of malignancy were monitored. Postoperative outcomes were recorded until the discharge or death, and the occurrence of morbidity and mortality was recorded accordingly.

Data were entered into Microsoft Excel and analysed using the SPSS software (version 21). The descriptive data were expressed as frequencies and percentages (F and %). Diagnostic accuracy of the POSSUM scoring system was evaluated by comparing the predicted outcomes with observed morbidity and mortality. Specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV) were measured to evaluate its performance in predicting the postoperative morbidity and mortality.

Results

Most of the patients undergoing emergency laparotomy were elderly, with the highest proportion (34.9%) belonging to the age group ≥ 61 years, followed by the even representation across the remaining age groups. This highlights the more susceptibility of elderly patients to acute abdominal emergencies requiring surgical intervention. The pronounced male predominance (68.99%) suggests that the older males were more frequently affected in this cohort, possibly correlating the gender-related differences in exposure to the risk factors or healthcare utilisation patterns. Procedural characteristics further indicate that most of the surgeries were classified as major procedures (98.4%), with majority of patients undergoing a single operative intervention (86%), reflecting a relatively uniform surgical severity profile. Complications like blood loss was predominantly seen between 101–500 ml in 63.5% of cases, while peritoneal soiling was not seen in 36.3% but it is present in the remaining patients in various forms, suggesting significant intra-abdominal contamination in them. The low prevalence of malignancy (12.4%) proves that most emergency laparotomies were done for non-malignant acute conditions (Table 1).

Table 1. Socio Demographic and Clinical Characteristics of the study participants

Category	Sub classification	Number	%
Age	≤30 years	23	17.80
	31-30 years	21	16.30
	41-50 years	19	14.70
	51-60 years	21	16.30
	≥61 years	45	34.90
Sex	Males	89	68.99
	Females	40	30.01
Procedural Details			
Operative severity	Major	127	98.4
	Major +	2	1.6
Number of procedures	1	111	86
	2	14	10.9
	3	4	3.1
Blood loss	<100 ml	21	16.3
	101-500 ml	82	63.5
	501-1000 ml	13	10.1
	>1000 ml	13	10.1
Peritonieal Soiling	None	47	36.3
	Local pus	12	9.2
	Bowel contents	32	24.8
	Blood	18	13.9
Malignancy	None	113	87.6
	Primary alone	15	11.6
	Nodal spread	1	0.8

POSSUM scoring system had demonstrated very high sensitivity (98.4%) in predicting the postoperative morbidity, indicating that it was highly efficient in identifying patients who may develop complications following emergency laparotomy. However, the specificity was low (25%), indicating that the system tended to overpredict the morbidity by incorrectly classifying many of the patients as high risk who did not develop the complications. The positive predictive value of 54.1% indicating moderate accuracy in confirming the morbidity when predicted, while the high negative predictive value of 94.4% correctly

reassures that patients identified as low risk were unlikely to experience postoperative complications. Thus, these findings suggest that POSSUM scoring system is more effective as a sensitive screening tool for morbidity risk assessment rather than a precise predictor of complication occurrence (Table 2).

Table 2. Diagnostic Accuracy of POSSUM score for morbidity.

		Observed morbidity	
		Present	**Absent**
POSSUM predicted morbidity	Present	60	51
	Absent	1	17
Sensitivity : 98.4% (91.2% to 100%)			
Specificity : 25% (15.3% to 37%)			
Positive Predictive Value : 54.1% (44.3% to 63.6%)			
Negative Predictive Value : 94.4% (72.7% to 99.9%)			

POSSUM demonstrated excellent predictive performance for mortality assessment, with a sensitivity of 100%, indicating that all patients who died postoperatively had been correctly identified as high risk. The specificity of 62% shows moderate accuracy in identifying patients who would survive. The positive predictive value of 43.3% reflects some degree of overprediction, while the negative predictive value of 100% confirms that no patient predicted as low risk died during the study period. These findings highlight the strong reliability of the POSSUM scoring system in predicting the mortality following emergency laparotomy (Table 3).

Table 3. Diagnostic Accuracy of POSSUM score for mortality.

Variable		**Observed mortality**	
		Present	**Absent**
POSSUM predicted mortality	Present	29	38
	Absent	0	62
Sensitivity : 100% (82.8% to 100%)			
Specificity : 62% (51.7% to 71.5%)			
Positive Predictive Value : 43.3% (31.2% to 56%)			
Negative Predictive Value : 100% (91.5% to 100%)			

Discussion

The POSSUM (Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity) and its variants such as P-POSSUM are the effective tools for predicting postoperative morbidity and mortality worldwide. In the current study, the POSSUM scoring system was applied to evaluate its predictive accuracy among the participants undergoing the emergency laparotomy. The findings confirm its relevance as a risk stratification tool, particularly in high-risk surgeries where the accurate prediction of outcomes can significantly influence the perioperative decision-making and patient management.

The participants predominantly comprised of elderly patients for with emergency laparotomy, consistent with the demographic profile. Similar age distributions were reported by Mzoughi et al. [10] and Cao et al. [11], highlighted on geriatric populations undergoing emergency laparotomy. Imaoka Y et al. [12] also reported the vulnerability of very elderly patients to emergency abdominal conditions, reinforcing the observed age-related susceptibility noted in the present study.

A male predominance was observed clearly in the present cohort, with a male-to-female ratio of 2:1 approximately. This finding was consistent with Simpson et al. [13] who reported a similar pattern in an older population undergoing the emergency laparotomy, and Chen et al. [14] who reported comparable male predominance in hepatobiliary surgical patients. These trends may suggest the gender-based differences in disease burden and healthcare utilisation of the society.

The prevalence of comorbidities such as diabetes mellitus and hypertension played an essential role in influencing the postoperative outcomes. Wang et al. [15] proved the preoperative biochemical parameters as key predictors of adverse outcomes, while Imaoka et al. [12] and Mzoughi et al. [10] proved that the increased physiological scores correlated strongly with the increased morbidity and mortality. This reflects the current study's observation that underlying systemic illnesses contribute to the postoperative complications and poor outcomes significantly.

POSSUM scoring system demonstrated high sensitivity for both morbidity and mortality prediction, though it tended to overestimate the outcomes, particularly morbidity This pattern aligns with various other studies worldwide that have highlighted POSSUM’s tendency to overpredict complications while maintaining the strong ability to point the high-risk patients. Despite this limitation, its application remains clinically valuable for finding the patients requiring continuous monitoring and preoperative optimisation, thus supporting its continued use in emergency surgical laparotomy settings

Conclusion

This study highlighted that the POSSUM scoring system is an essential, valuable, and sensitive tool for predicting the postoperative outcomes in patients undergoing emergency laparotomy, particularly in identifying the patients at risk of mortality. While POSSUM showed good sensitivity and negative predictive value for mortality prediction, its lower specificity and tendency to overestimate the morbidity reflects that it may overpredict the complications, especially in high-risk patients. Despite this limitation, POSSUM

remains clinically significant as a risk stratification tool that aids in early identification of vulnerable patients, aids in informed clinical decision-making, and supports appropriate allocation of perioperative resources. The findings demonstrates the importance of combining POSSUM scoring with clinical assessment to optimise the patient care and improve surgical outcomes in emergency settings.

Statements and Declarations

Conflicts of interest

The authors declare that they do not have conflict of interest.

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ORIGINAL ARTICLE

Placental Laterality as a Predictor of Pre-Eclampsia: A Prospective Comparative Study From a Tertiary Care Centre in South India

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Abstract

Background: Pre-eclampsia, a multisystem disorder marked by new-onset hypertension after 20 weeks, affects 2–8% of pregnancies and remains a major cause of maternal mortality in low- and middle-income countries. Mid-trimester placental laterality on ultrasound is suggested as a predictor of impaired placentation and future pre-eclampsia. Simple, low-cost predictive tools are crucial for early detection, especially in resource-limited settings. **Aims and objectives:** To evaluate whether placental laterality detected at 18–24 weeks' gestation predicts the subsequent development of pre-eclampsia. **Materials and Methods:** A prospective longitudinal study was conducted among 200 pregnant women whose gestational age is between 18–24 weeks and attending the antenatal clinic of a tertiary care hospital in Madurai. Women presented with pre-existing medical or obstetric comorbidities were excluded. Ultrasonography was used to classify placental location as central or lateral. Participants were followed until delivery for development of pre-eclampsia. Collected data were compiled using MS Excel software, and statistical analysis included Chi-square test, independent t-test, sensitivity–specificity indices, and odds ratios with 95% CI. **Results**: In our study the central placentation was observed in 81% and lateral placentation in 19% of participants. Pre-eclampsia was developed in 32.5% of the study participants. It was also reported that among women with lateral placentation, 60.5% developed pre-eclampsia compared with 26% with central placentation. Lateral placentation was associated with a significantly increased risk of pre-eclampsia (OR 4.38, 95% CI: 2.03–9.41, $p < 0.001$). Blood pressure measurements demonstrated a significant rise in both systolic and diastolic pressures for the lateral placenta group by the fourth visit ($p = 0.001$). **Conclusion**: Lateral placental implantation detected during the mid-trimester through ultrasound is strongly associated with an increased risk of developing pre-eclampsia. Routine reporting of placental laterality during anomaly scans may enable early risk stratification and closer surveillance of susceptible women.

Keywords: Pre-eclampsia, Placental laterality, Mid-trimester ultrasound, Hypertensive disorders, Predictive factors

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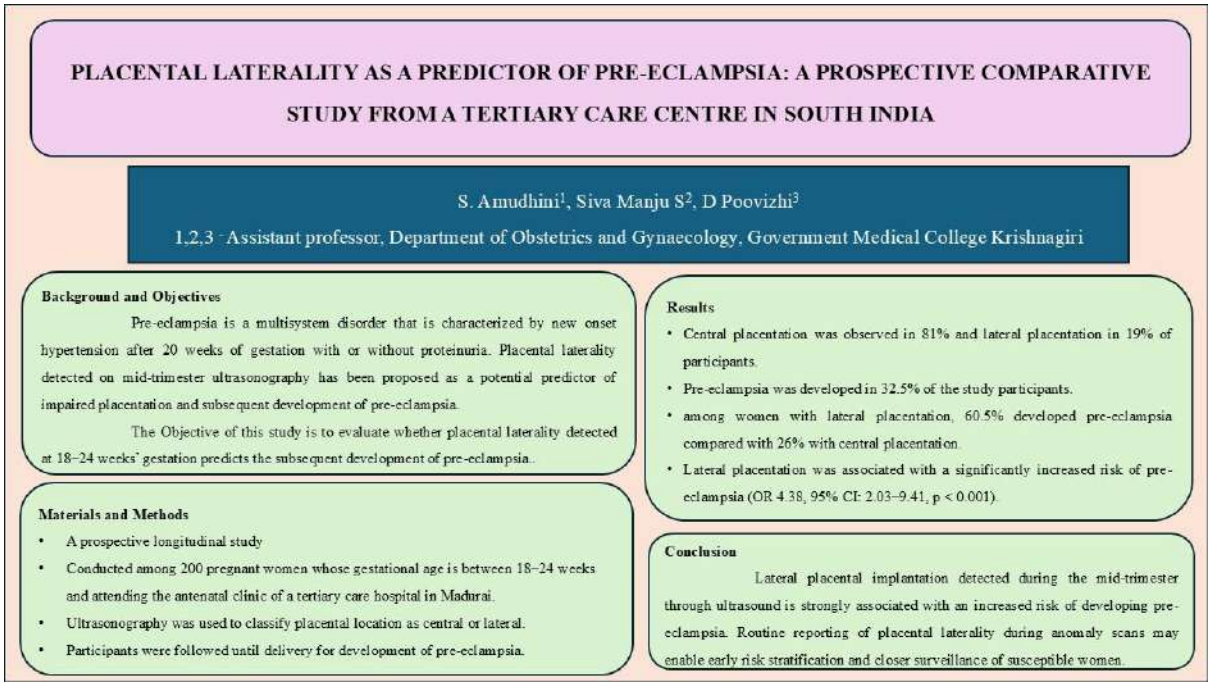
Graphical Abstract



Introduction

Hypertensive disorders of pregnancy (HDP) were among the most common and significant medical complications that occurs during pregnancy globally and it significantly contributes to the maternal and perinatal morbidity and mortality. Pre-eclampsia is a multisystem disorder that can be characterised by new-onset hypertension after 20 weeks of gestation with or without proteinuria, affects approximately 2–8% of pregnancies globally. It is also the leading direct cause of maternal mortality in low- and middle-income countries [1,2]. In India, pre-eclampsia and eclampsia together account for nearly 5–7% of maternal deaths, underscoring the need for early prediction and prevention strategies [3].

The clinical manifestations usually appear in the second trimester of pregnancy but the pathogenesis of pre-eclampsia begins even before that. Impaired trophoblastic invasion, defective remodelling of spiral arteries, and resultant high-resistance uteroplacental blood flow are central pathophysiological events that is associated with pre-eclampsia [4,5]. These abnormalities may lead to experience placental hypoxia, oxidative stress, release of anti-angiogenic factors, and widespread maternal endothelial dysfunction, which combined together can produce the clinical syndrome of pre-eclampsia [4].

Identifying this condition at an early stage with reliable, and cost-effective predictors for pre-eclampsia is considered as a public health priority. Placental laterality is recognised as a predictor and it can be assessed on mid-trimester ultrasonography. A centrally located placenta generally receives balanced perfusion from both uterine arteries, whereas a laterally implanted placenta depends predominantly on one uterine artery, resulting in asymmetrical blood supply and higher uterine artery resistance [6]. This hemodynamic discrepancy may predispose to impaired placentation and subsequent development of pre-eclampsia.

Many research articles have reported that laterally located placentas are significantly associated with a higher incidence of pre-eclampsia and intrauterine growth restriction (IUGR) [6-9]. A meta-analysis by Naik et al. demonstrated nearly a 3.5-fold increased risk of pre-eclampsia among women with lateral placentation on second-trimester ultrasound [9]. Given that anomaly scans are universally performed between 18–24 weeks even in resource-limited settings, placental laterality offers an inexpensive, non-invasive adjunctive screening tool.

The present study, conducted at a tertiary care centre in South India, evaluates whether placental laterality detected during the second trimester can predict the development of pre-eclampsia, thereby aiding early risk stratification and targeted surveillance.

Aim and Objective

To find whether placental laterality as determined by ultrasound done between 18–24 weeks can be used as a predictor for the development of pre-eclampsia.

Methodology

Study design and setting

This was a prospective comparative study conducted in the Department of Obstetrics and Gynaecology, Government Rajaji Hospital and Madurai Medical College, Madurai, Tamil Nadu. The study was carried out over a period of one year among pregnant women attending the antenatal clinic both as outpatient and inpatient at the hospital.

Study population

The study population comprised pregnant women between 18 and 24 weeks of gestation with singleton pregnancies attending the antenatal clinic during the study period.

Inclusion criteria

- Pregnant women at 18–24 weeks of gestation
- Singleton pregnancy
- No identifiable high-risk factors at recruitment

Exclusion criteria

- Chronic/essential hypertension
- Diabetes mellitus
- Thyrotoxicosis
- Renal disease
- Severe anaemia
- Connective tissue disorders or positive lupus anticoagulant/anticardiolipin antibodies
- Rh incompatibility
- Multiple gestation
- Positive VDRL test

Sample size and sampling

The minimum required sample size was calculated as 198, based on the reported prevalence of pregnancy-induced hypertension among women with lateral placentation of 48.5% [10], using the standard formula $n = Z^2pq/d^2$ with 95% confidence level ($\alpha = 0.05$) and 7% absolute precision. The sample size was rounded off to 200 participants. A simple random sampling method was used to recruit eligible women.

Assessment of placental location

All eligible women underwent an ultrasonographic examination between 18 and 24 weeks of gestation to determine placental location. Placental position was classified as:

- Central placenta – placental tissue approximately equally distributed on

both right and left sides of the uterine midline, irrespective of anterior, posterior or fundal attachment.

- Lateral placenta – ≥75% of the placental mass situated on one side of the uterine midline [9].

Based on this, women were grouped into:

- Central placentation group (non-exposed)
- Lateral placentation group (exposed)

Assessment of the Primary Outcome

All enrolled women were followed throughout pregnancy for the development of signs and symptoms of pre-eclampsia at each antenatal visit. Pre-Eclampsia was defined and categorised as per the diagnostic criteria of ACOG Practice bulletin [11].

Results

A total of 200 pregnant women between 18 and 24 weeks of gestation were enrolled. Based on mid-trimester ultrasonography, 162 women (81%) had centrally located placenta and 38 women (19%) had laterally located placenta as shown in Table 1.

Table 1. Distribution of participants by placental location

Placenta	**Frequency (N)**	**Percentage (%)**
Lateral	38	19.0
Central	162	81.0
Total	200	100

Participants were grouped based on their placental position, and both the groups were similar with respect to the baseline variables like Age, Parity and family history of hypertension ($p<0.05$).

Among the 200 pregnant women studied, 59 (29.5%) developed pre-eclampsia, 4 (2%) had severe pre-eclampsia, and 2 (1%) progressed to eclampsia, as shown in Table 2. Among women with lateral placentation (n=38), 18 (47.4%) developed pre-eclampsia, 3 (7.9%) developed severe pre-eclampsia, and 2 (5.3%) developed eclampsia. In contrast, among those with central placentation (n=162), the majority were normotensive, with lower proportions of pre-eclampsia (24.7%), severe pre-eclampsia (0.6%), and no cases of eclampsia. These findings indicate that lateral placentation is associated with a substantially higher risk and greater severity of hypertensive disorders of pregnancy compared to central placentation as shown in Table 3 and 4.

Table 2. Distribution of study participants based on development of hypertension

Pregnancy induced hypertension (PIH)	**Frequency (N)**	**Percentage (%)**
Yes	65	32.5
No	135	67.5
Total	200	100

Table 3. Distribution of study participants based on severity of Pre-eclampsia

Pre-Eclampsia	**Frequency (N)**	**Percentage (%)**
Pre-Eclampsia	59	29.5
Severe – Pre Eclampsia	4	2.0
Eclampsia	2	1.0
Nil	135	67.5
Total	200	100

Table 4. Placental Location across the categories of Pre-Eclampsia

Placenta	**Pre- Eclampsia**	**Severe Pre-Eclampsia**	**Eclampsia**	**Total**
Lateral	18	3	2	38
Central	40	1	0	162
Total	59	4	2	200

A strong association was observed between placental laterality and the development of pre-eclampsia. Among those with lateral placentation, 23 out of 38 women (60.5%) developed pre-eclampsia, whereas among those with central placentation, only 42 out of 162 women (26%) developed pre-eclampsia. This association was statistically significant (p = 0.0001). The calculated odds ratio was 4.38, indicating that women with lateral placentation were 4.38 times more likely to develop pre-eclampsia than those with central placentation as shown in Table 5.

Table 5. Comparison of Placental Location and the development of Pre-Eclampsia

Placenta	**Pre-Eclampsia**		**OR (95% CI)**	**P-value**
	Yes (n)	**No (n)**		
Lateral	23	15	4.3810	0.0001
Central	42	120		

Blood pressure trends further supported this association. By the fourth follow-up visit, women with lateral placentation showed a significantly higher mean systolic blood pressure (132.1 ± 18.8 mmHg) compared to those with central placentation (120.7 ± 14.2 mmHg) (p = 0.001). Similarly, the mean diastolic blood pressure was significantly higher in the lateral placenta group (87.4 ± 12.9 mmHg) compared to the central placenta group (79.4 ± 10.2 mmHg) (p = 0.001) as shown in Table 6.

Table 6. Blood pressure values during follow-up visits

Visit	**Placental Location**	**Mean Systolic BP (mmHg)**	**p-value (Systolic)**	**Mean Diastolic BP (mmHg)**	**p-value (Diastolic)**
2nd Trimester (1st visit)	**Lateral**	117.6 ± 4.3	0.630	77.9 ± 4.7	0.364
	Central	118.1 ± 4.6		77.0 ± 5.3	
2nd Visit	**Lateral**	117.6 ± 7.1	0.406	75.3 ± 6.5	0.367

	Central	116.8 ± 5.2		76.2 ± 5.3	
3rd Visit	**Lateral**	118.2 ± 10.9	0.037	77.1 ± 6.9	0.141
	Central	115.2 ± 7.0		75.2 ± 7.0	
4th Visit	**Lateral**	132.1 ± 18.8	0.001	87.4 ± 12.9	0.001
	Central	120.7 ± 14.2		79.4 ± 10.2	

Discussion

In our prospective comparative study that was conducted among 200 pregnant women between 18 and 24 weeks of gestation, a significant association was observed between placental laterality and the subsequent development of pre-eclampsia. Lateral placentation was identified in 19% of the study population, while 81% exhibited central implantation. Among women with lateral placenta, 60.5% developed pre-eclampsia, compared with 26% among those with central placentation, reflecting an odds ratio of 4.38, demonstrating that women with lateral placenta have four times more chances to develop pre-eclampsia compared to central placentation group. These findings strongly indicate that placental laterality, as detected on routine mid-trimester ultrasonography, can serve as an efficient and low-cost early predictor for the disorder.

The results corroborate earlier reports describing the relationship between abnormal placentation and hypertensive disorders of pregnancy. Yousuf et al. showed that lateral placenta, when combined with abnormal uterine artery Doppler indices, significantly increased the likelihood of pregnancy-induced hypertension, with more than half of lateral placenta cases progressing to pre-eclampsia [6]. Dagklis et al. similarly demonstrated that lateral placentation was associated with elevated uterine artery resistance indices and a higher incidence of pre-eclampsia and fetal growth restriction [7]. Faizi et al. also reported that laterally located placentas had increased rates of pre-eclampsia compared to centrally placed placentas [8]. Moreover, the meta-analysis by Naik et al., reviewing 16 studies, confirmed a consistent association, estimating a 3.48-fold increase in risk of pre-eclampsia among women with lateral placentation [9]. The magnitude of risk in the present study (OR 4.38) is congruent with these previously published findings.

A centrally implanted placenta typically receives balanced perfusion from both uterine arteries, whereas a placenta situated laterally is predominantly supplied by a single uterine artery. This asymmetric blood flow results in increased placental vascular resistance, greater susceptibility to ischemia, and shallower trophoblast invasion factors collectively central to the development of the hypertensive phenotype of pre-eclampsia [5,6,12].

Our study further demonstrated that blood pressure patterns across gestation reflected this impaired placentation. While systolic and diastolic pressures in both groups were similar during mid-pregnancy, significant differences emerged later, with women in the lateral placenta group showing markedly higher blood pressure levels at the fourth visit (mean systolic 132.1 mmHg vs. 120.7 mmHg; mean diastolic 87.4 mmHg vs. 79.4 mmHg; p = 0.001 for both). This late-pregnancy escalation is consistent with the classical temporal progression of pre-eclampsia described in pathophysiological and clinical studies [2,4,11].

Overall, the findings of this study reinforce the growing evidence that placental laterality is an important and clinically meaningful predictor of pre-eclampsia. As a simple and widely accessible tool, placental location assessment should be considered an essential component of mid-trimester ultrasonography, especially in settings where advanced predictive modalities such as biochemical markers or uterine artery Doppler assessment are not routinely available.

Conclusion

This prospective study reports that placental laterality identified on mid-trimester ultrasonography is a significant predictor of pre-eclampsia. Women with lateral placentation had more than a fourfold increased risk of developing pre-eclampsia compared with those with centrally located placenta, and they exhibited a greater rise in both systolic and diastolic blood pressure as pregnancy advanced. These findings correlated with the physiological association between asymmetric uteroplacental perfusion and impaired placentation.

Author Contributions

SA contributed to the conceptualization and definition of the intellectual content of the manuscript. SM was responsible for the design of the study, data analysis, and statistical analysis, and contributed to the definition of intellectual content. DP and played a key role in literature search, data acquisition, manuscript editing, and manuscript review. SM will serve as the corresponding author /guarantor of the manuscript

Data availability statement

Access to the study data can be provided by the corresponding author upon request. Public sharing is restricted to protect participant confidentiality, as the dataset includes potentially identifiable information.

Statements and Declarations

Conflicts of interest

The authors declare that they do not have conflict of interest.

Funding

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ORIGINAL ARTICLE

Gender Differences in Physiological Cardiovascular Reactivity to Cold Pressor Stress Test: A Cross-Sectional Study

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Abstract
Background/Introduction: The Cold Pressor Test (CPT) is a recognized method for assessing autonomic function by evaluating cardiovascular responses to cold-induced stress. Understanding gender-specific variations in autonomic reactivity, particularly changes in blood pressure and pulse rate, is an important area of physiological research. **Aims and Objective:** This study aimed to examine and compare the physiological responses to the cold pressor test between healthy adult males and females, focusing on systolic and diastolic blood pressure (SBP and DBP), as well as pulse rate at various time intervals. **Materials and Methods:** A cross-sectional study was carried out among 30 healthy individuals (15 males and 15 females) aged 18 to 40 years. SBP, DBP, and pulse rate were recorded at baseline (pre-test), during the CPT, and post-test at 1 minute and 5 minutes. Data were analysed using descriptive statistics, and comparisons between the sexes were made using independent t-tests. The results were expressed as mean ± standard deviation, and p-values < 0.05 were considered statistically significant. **Results:** Male participants exhibited significantly higher SBP and DBP compared to females at all time points. For example, during the test, males showed an SBP of 131.87 ± 4.53 mmHg versus 113.07 ± 5.62 mmHg in females ($p < 0.001$). Diastolic pressures were similarly elevated ($p < 0.001$). Pulse rate was also higher in males, especially during the test (90.27 ± 3.89 vs. 87.00 ± 6.59; $p = 0.048$). Although values declined toward baseline at 5 minutes post-test, males consistently maintained higher readings. **Conclusion:** This study highlights significant gender differences in cardiovascular autonomic responses to the cold pressor test. Males demonstrated a more pronounced increase in SBP, DBP, and pulse rate, suggesting greater sympathetic activation in response to cold-induced stress. These findings underscore the need to consider sex-specific variations when interpreting autonomic function tests and probability of higher cardiovascular risk in males and lower risk in females due to the role of female hormones.

Keywords: Autonomic Stress, Cold pressor test (CPT), Left ventricular function, Cold stressor, sympathetic nervous system

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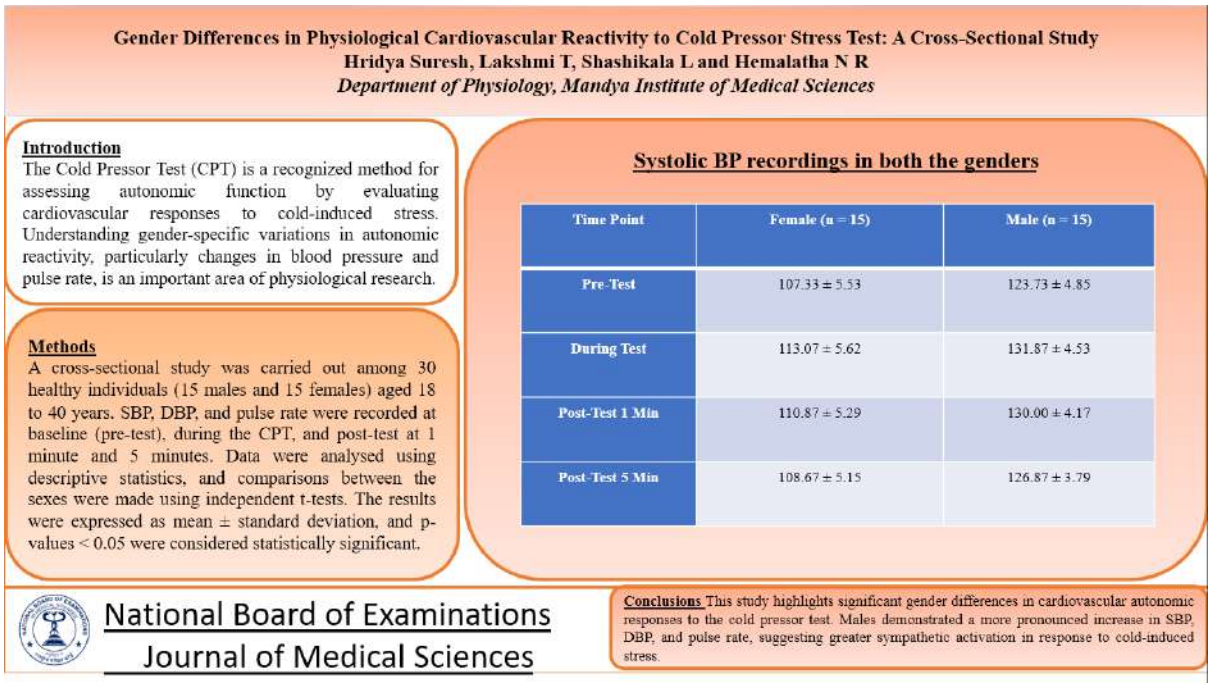
Graphical Abstract



Introduction

The cold pressor test (CPT) is a well-established method for evaluating sympathetic nervous system reactivity. In this procedure, an individual immerses a hand or foot into cold water maintained at 3–5°C for 1–3 minutes while blood pressure (BP) and heart rate are continuously recorded [1]. The intense cold stimulus activates cutaneous afferents and triggers a reflex increase in sympathetic outflow, producing a rise in BP that is independent of baroreflex mechanisms. Because of this direct sympathetic activation, the CPT has been widely used in both clinical and research settings to assess autonomic integrity and vasomotor responsiveness [1].

In everyday life, individuals are exposed to multiple physical and psychological stressors, all of which can influence cardiovascular regulation. Sympathetic activation during stress elevates BP and heart rate, and exaggerated responses have been repeatedly associated with a higher risk of developing hypertension later in life [2]. The CPT offers a standardized, non-invasive way to quantify this reactivity, making it a useful screening tool for identifying normotensive individuals who may be predisposed to future cardiovascular disease [3].

Sex-based differences in cardiovascular physiology are well documented. Variations in endothelial function, vascular tone, and autonomic regulation contribute to the differing patterns of hypertension and coronary artery disease observed between men and women [4]. Estrogen-mediated endothelial protection has been proposed as an important factor underlying the lower incidence of cardiovascular disease in premenopausal women [5,6]. However, the extent to which these physiological differences translate into divergent CPT responses remains incompletely understood.

Despite the widespread use of CPT internationally, there is limited data from

Indian populations, and even fewer studies have directly compared male and female responses using standardized protocols. Understanding whether sex influences BP and heart rate reactivity during CPT may help identify early deviations in autonomic or vascular function, contributing to more refined cardiovascular risk prediction.

Therefore, the present study was undertaken to compare the cardiovascular responses to the cold pressor test between healthy young adult males and females, and to explore whether sex-related differences in sympathetic reactivity can be identified through this simple, non-invasive assessment.

Materials and Method of Study

Ethical committee approval was received from Institutional Ethics Committee – Mandya Institute of Medical Sciences, Mandya on 29.01.2025, and the data was collected as mentioned below :

Study Participants

Healthy young adults aged 18–35 years were recruited for the study. Eligible participants were normotensive (resting BP <140/90 mmHg), nonsmokers, non-alcohol users, and provided written informed consent.

Inclusion Criteria

- Age 18–35 years
- Resting BP <140/90 mmHg
- Nonsmokers and non-alcohol consumers
- Voluntary consent to participate

Exclusion Criteria

Participants with a history of:

- Cardiovascular disease
- Endocrine disorders
- Renal disease
- Neurological dysfunction
- Hypertension
- Cold intolerance or sweating disorders were excluded from the study.

Sample Recruitment and Representativeness

Participants were recruited from attendants of various departments in the medical college and from patient attendants in outpatient areas. Because this sampling was based on convenience rather than random selection, the study population may not fully represent the broader young adult population. This limitation is acknowledged, as the findings may not be generalizable beyond similar institutional settings.

Sample Size Considerations

A total of 30 participants (15 males and 15 females) were included. No formal power analysis was performed before recruitment.

Pre-Test Preparation

Participants were instructed to:

- Avoid caffeine-containing beverages and exercise for at least 4 hours prior to testing
- Consume only a light breakfast on the day of assessment

All participants rested quietly for 10 minutes before measurements were taken. The procedure was explained in detail before initiating the test.

Sociodemographic and Health Information

Baseline information was obtained using a semi-structured questionnaire, including:

- Name
- Age
- Sex
- Addictive habits (if any)
- Family history of hypertension
- Past medical or surgical history
- Current medication use

Cold Pressor Test Procedure

Participants immersed their left hand up to the wrist in ice-cold water maintained at 3–5°C for 1 minute. Blood pressure (BP) was measured in the right arm.

Blood Pressure Measurement

BP was recorded using a calibrated mercury sphygmomanometer (Elkometer 0983369) with participants in a seated position.

1. *Resting BP:*

After 10 minutes of rest, three BP readings were taken at 5-minute intervals. The average of these values was considered the resting BP.

2. *During CPT:*

A second BP reading was recorded immediately after the participant immersed the hand in cold water.

3. *Post-CPT Recovery*:

Two additional readings were taken—one at 1 minute and another at 5 minutes after hand withdrawal.

Statistical Analysis

The data collected was entered in Microsoft Excel and analysed using SPSS trail version 22.0 (Statistical Package for Social Sciences).

- Descriptive statistics

1. For categorised data (like sex)
2. For continuous data (like age, Blood pressure and heart rate)

- Inferential statistics
  1. Chi^2 test (to know the association of HR, SBP with cold pressor test)
  2. t test (to know the differential means like SBP and Cold pressor test)

Statistical significance will be considered if $p < 0.05$.

Results

Table 1. Showing participants distribution and mean age of the subjects

Sex	Number of Subjects	Mean Age (years)	SD of Age
Female	15	27.93	8.37
Male	15	26.40	8.72

A total of 30 subjects participated in the study, with equal representation of males and females (15 each). The mean age of the female participants was 27.93 ± 8.37 years, while that of the male participants was 26.40 ± 8.72 years. The close similarity in mean ages and standard deviations between the two groups suggests that the study population was age-matched, thereby minimizing age-related bias in the analysis (Tables 1 and 2).

Table 2. Systolic BP recordings in both the genders

Time Point	Female (n = 15) (in mmHg)	Male (n = 15) (in mmHg)
Pre-Test	107.33 ± 5.53	123.73 ± 4.85
During Test	113.07 ± 5.62	131.87 ± 4.53
Post-Test 1 Min	110.87 ± 5.29	130.00 ± 4.17
Post-Test 5 Min	108.67 ± 5.15	126.87 ± 3.79

At baseline (pre-test), males exhibited a higher mean systolic blood pressure (123.73 ± 4.85 mmHg) compared to females (107.33 ± 5.53 mmHg). During the test, both groups showed an increase in systolic pressure, with males reaching 131.87 ± 4.53 mmHg and females 113.07 ± 5.62 mmHg. One minute after the test, the systolic BP declined in both groups but remained higher than baseline. By 5 minutes post-test, near-resting values were observed in both genders, though males continued to demonstrate consistently higher systolic pressures than females at all time points. This indicates greater cardiovascular reactivity among males compared to females (Table 3).

Table 3. Pulse rate recordings in both the genders

Time Point	Female (n = 15) (in mmHg)	Male (n = 15) (in mmHg)
Pre-Test	76.27 ± 6.62	77.73 ± 3.96
During Test	87.00 ± 6.59	90.27 ± 3.89
Post-Test 1 Min	83.27 ± 5.23	86.67 ± 2.94
Post-Test 5 Min	76.13 ± 6.51	80.33 ± 3.81

At baseline, the mean pulse rate was comparable between females (76.27 ± 6.62 bpm) and males (77.73 ± 3.96 bpm). During the test, a marked rise in pulse rate was observed in both groups, with males reaching 90.27 ± 3.89 bpm and females 87.00 ± 6.59 bpm, indicating sympathetic activation. At one minute post-test, pulse rates decreased but remained elevated compared to pre-test levels. By five minutes post-test, pulse rates in females almost returned to baseline, whereas males maintained slightly higher values than their initial readings. These findings suggest that although both genders exhibit autonomic reactivity, males tend to show a more sustained elevation in pulse rate following stress (Table 4).

Table 4. Diastolic BP recording in both the genders

Time Point	Female (n = 15) (in mmHg)	Male (n = 15) (in mmHg)
Pre-Test	71.00 ± 7.17	84.80 ± 4.12
During Test	74.13 ± 6.52	89.33 ± 3.51
Post-Test 1 Min	73.20 ± 6.08	87.47 ± 3.31
Post-Test 5 Min	70.87 ± 5.71	84.13 ± 3.32

At baseline, males demonstrated a significantly higher mean diastolic blood pressure (84.80 ± 4.12 mmHg) compared to females (71.00 ± 7.17 mmHg). During the test, both genders showed an elevation in diastolic pressure, with males reaching 89.33 ± 3.51 mmHg and females 74.13 ± 6.52 mmHg. At one minute post-test, diastolic values began to decline but remained above baseline in both groups. By five minutes post-test, females returned nearly to their initial values, while males maintained slightly higher pressures compared to baseline. This trend indicates that males not only had higher diastolic pressures at all time points but also exhibited more sustained vascular reactivity following stress.

Discussion

The present cross-sectional study demonstrated distinct sex-related differences in cardiovascular reactivity during the cold pressor test, with males exhibiting stronger and more persistent increases in systolic and diastolic blood pressures compared with females. Although both sexes showed significant systolic elevation during the cold exposure, the magnitude and duration of the pressor response were markedly greater in males, indicating a higher degree of sympathetic activation and vascular reactivity. These findings align with earlier evidence showing amplified sympathetic vasoconstrictor responses in men during cold- or pain-induced stressors [7,8]. The

prolonged elevation of diastolic pressure observed in men suggests sustained peripheral vasoconstriction after removal of the cold stimulus, reflecting delayed sympathetic withdrawal and reduced endothelial counter-regulation.

Heart rate responses followed a similar pattern. Both genders demonstrated a rise in pulse rate during cold stress, yet males showed slightly higher peak values and a slower return to resting levels. This indicates that the reactivation of parasympathetic tone occurred more rapidly in females, consistent with their higher baseline vagal modulation. These observations are supported by previous reports indicating that males exhibit a relatively greater sympathetic–parasympathetic imbalance during autonomic challenges [9], and that stress-induced sympathetic surges tend to be more exaggerated and persistent in men compared with women [10,11]. Together, these physiological tendencies create a profile of heightened cardiovascular responsiveness in men during acute stress.

The mechanisms underlying these sex-based differences are deeply rooted in hormonal regulation and endothelial physiology. Estrogen plays a central protective role in females by acting through ERα, ERβ, and G-protein–coupled estrogen receptors (GPER), which activate PI3K/Akt signaling and enhance eNOS phosphorylation. This increases nitric oxide (NO) synthesis and promotes potent vasodilation, thereby buffering the vasoconstriction triggered by sympathetic stimulation [12–14]. Estrogen also limits L-type calcium influx into vascular smooth muscle cells, reducing intracellular calcium availability and preventing excessive contraction [15]. By decreasing α-adrenergic vasoconstrictor sensitivity and enhancing β-adrenergic–mediated vasodilation, estrogen supports a vascular environment characterized by lower resistance and diminished stress reactivity [16]. These molecular effects explain the distinctly moderated blood pressure and heart rate responses observed in female participants.

Progesterone complements these actions by antagonizing mineralocorticoid receptor–mediated sodium retention, promoting NO release, suppressing endothelin-1 synthesis, and modulating vascular ion channels to reduce stiffness and sympathetic sensitivity [17,18]. Although progesterone can transiently elevate sympathetic tone through thermogenic modulation of hypothalamic centers, its aggregate impact remains predominantly vasodilatory and partially sympathoinhibitory, especially during the luteal phase [19]. Consequently, female participants benefit from dual-hormonal protection against excessive vasoconstriction during cold stress.

In contrast, testosterone-driven androgen receptor activation predisposes males to heightened stress reactivity. Testosterone increases peripheral sympathetic nerve activity, enhances α-adrenergic receptor responsiveness, augments renin–angiotensin system signaling, and reduces baroreflex gain—all of which intensify vasoconstriction during noxious stimuli [20–22]. These actions create a physiological milieu in which vascular tone amplifies rapidly during sympathetic activation. Our findings are consistent with these hormonal influences, as males consistently exhibited stronger and more sustained pressor responses.

Beyond hormonal effects, intrinsic vascular and neural differences between sexes further reinforce the stronger male

response. Men generally exhibit greater baseline arterial stiffness, reduced nitric oxide bioavailability, and higher total peripheral resistance, which magnify blood pressure increase during sympathetic activation [23,24]. Studies also show higher sympathetic nerve firing rates and greater catecholamine surges in men when exposed to cold or pain stimuli [25], closely matching the exaggerated responses observed in our male participants.

Our results also correspond closely with findings from studies such as those by Jones et al. [32], who demonstrated significantly greater increases in muscle sympathetic nerve activity in males during cold pressor testing. Their work confirms a mechanistic basis for the heightened male pressor response: greater sympathetic outflow and slower sympathetic withdrawal. Similarly, Usselman et al. [33] reported that females exhibit stronger cardiac vagal reactivation following stress, allowing faster normalization of heart rate and blood pressure—precisely reflected in our observation of quicker recovery patterns among women. In another study, Hart et al. [34] found that the cold pressor test elicits higher total peripheral resistance in males compared with females due to sex differences in adrenergic receptor sensitivity. Their conclusions reinforce the physiological explanation that men rely more heavily on vasoconstrictor pathways during autonomic challenges, contributing to the larger and more persistent blood pressure elevations observed in the present study.

Central autonomic regulation also contributes significantly to these sex differences. Females often possess stronger vagal modulation, enhanced baroreceptor sensitivity, and more effective cardiovascular buffering during acute stress exposure [26]. These features facilitate early parasympathetic reactivation and faster stabilization of cardiovascular parameters. In contrast, males tend to exhibit lower vagal tone and greater reliance on sympathetic efferent pathways, resulting in an overall pattern of exaggerated reactivity and delayed recovery [27]. These central autonomic differences provide a cohesive explanation for the divergent blood pressure and pulse rate trajectories documented in our sample.

Taken together, the combined influence of endothelial signaling, sex hormone receptor activity, adrenergic responsiveness, neurohumoral regulation, and autonomic balance renders males more prone to intense cardiovascular responses during cold pressor stress. Estrogen-mediated nitric oxide release and reduced vasoconstrictor sensitivity offer females substantial protection from excessive autonomic surges, whereas testosterone-associated sympathetic stimulation and vascular stiffness predispose males to stronger and more prolonged stress responses. These findings are in agreement with earlier studies documenting sex-specific cardiovascular reactivity patterns during sympathetic provocation [28], and the additional research incorporated here further reinforces the consistency of these physiological differences across multiple populations.

Clinical Implications

The sex-related differences observed in this study carry important clinical implications. A heightened pressor response to the cold pressor test has been associated with future development of hypertension, endothelial dysfunction, and increased cardiovascular risk. Because males demonstrated a consistently larger

and more persistent rise in blood pressure during cold stress, young men may represent a subgroup with greater susceptibility to early vascular dysregulation and later-life hypertension. Identifying such exaggerated sympathetic reactivity at a young age could allow earlier lifestyle counselling, targeted stress-reduction strategies, and closer monitoring in routine clinical practice.

In females, the blunted and faster-recovering cardiovascular response suggests greater autonomic resilience during reproductive years, largely driven by estrogen-mediated endothelial protection. However, the decline in estrogen after menopause eliminates this advantage, potentially shifting women toward a more "male-like" hemodynamic profile. Understanding these sex-specific trajectories may help clinicians interpret stress tests differently in men and women, anticipate blood pressure patterns across the lifespan, and tailor preventive strategies accordingly.

Furthermore, the CPT may serve as a simple adjunct tool in assessing autonomic balance and vascular reactivity in normotensive individuals, particularly those with a family history of hypertension or early vascular disease. Incorporating knowledge of sex differences can refine risk stratification models, improve diagnostic accuracy, and inform individualized approaches to cardiovascular prevention and stress management.

Conclusion

The findings of this study highlight distinct gender differences in cardiovascular reactivity to stress. Males consistently demonstrated higher baseline systolic and diastolic blood pressures compared to females, and their responses during and after the stress test showed a more pronounced and sustained elevation. Pulse rate recordings also revealed that while both genders exhibited sympathetic activation during stress, males showed a comparatively greater rise with a delayed return to baseline, suggesting prolonged autonomic arousal. These observations indicate that males have heightened sympathetic activity and vascular reactivity, whereas females display faster recovery, possibly due to the modulatory effects of estrogen, progesterone and other protective mechanisms.

Such gender-related variations in autonomic function have important clinical implications. Understanding these differences may contribute to better prediction of cardiovascular risk and more individualized preventive strategies.

Limitations

While the findings are consistent with existing literature, several limitations must be acknowledged:

1. **Small Sample Size**

   Each group consisted of only 15 participants. This limited sample reduces statistical power and restricts the ability to generalize the findings to the broader population. Larger cohorts may reveal subtler sex-related differences or identify interacting variables that were not detectable in this study.

2. **Menstrual Cycle Not Controlled**

   Female participants were not screened or grouped based on menstrual cycle phase. Fluctuations in oestrogen and progesterone across the cycle can significantly alter vascular tone, endothelial NO activity, and sympathetic responsiveness. The absence of cycle-phase

control may have attenuated or exaggerated the observed female responses.

3. **Potential Confounders**

Several variables were not controlled for and may have influenced cardiovascular reactivity:

- **Time of day:** Autonomic tone and vascular responsiveness vary diurnally.
- **Dietary factors:** Salt intake, hydration status, and recent meals may affect sympathetic activity.
- **Medication use:** Although major drug use was screened, minor or over-the-counter agents could alter autonomic responses.
- **Physical activity before testing:** Variations in activity levels earlier the same day might modify baseline autonomic tone.

These factors should be controlled or documented in future studies.

Future Research

In future studies, we can do modifications like expanding the sample size to improve statistical power and enhance the reliability of sex-related comparisons. We can also control for menstrual cycle phase or include hormonal measurements to more precisely evaluate the influence of estrogen and progesterone on cardiovascular reactivity in female participants. Additional modifications may include incorporating detailed hormonal profiling in both sexes, examining different age groups such as adolescents, postmenopausal women, and older adults, and studying individuals with prehypertension or metabolic conditions to understand how cold pressor responses vary across populations. We can also extend the design to longitudinal follow-up, allowing us to determine whether exaggerated cold pressor responses truly predict later development of hypertension or cardiovascular disease.

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Statements and Declarations

Conflicts of interest

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CASE REPORT

A Case Report and Literature Review on oral Verruciform Xanthoma

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Abstract

Oral verruciform xanthoma (OVX) is a rare, benign mucocutaneous lesion occurring within the oral cavity. Clinically, it manifests as a soft, slightly elevated lesion with a rough or granular surface and may appear yellowish or reddish in color. The size typically ranges from about 0.2 cm to 2.0 cm in diameter. Histologically, the lesion displays parakeratinized stratified squamous epithelium showing papillary or verrucous surface projections and thin rete ridges. The connective tissue papillae extend toward the epithelial surface and are filled with numerous foam cells, also known as xanthoma cells. These foam cells represent lipid-laden macrophages. Surgical excision is the preferred treatment method, and the prognosis is excellent, as recurrence is uncommon.

Keywords: Oral Verruciform Xanthoma, benign mucocutaneous lesion, oral cavity, xanthoma cells

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Introduction

Oral verruciform xanthoma is a benign lesion of the oral mucosa that was first reported by Shafer in 1971 [1]. The lesion is relatively uncommon, with an incidence ranging from 0.025% to 0.094% among all benign mucocutaneous lesions of the oral cavity [2]. It shows a higher occurrence in males and usually presents clinically as a sessile or pedunculated mass [3,4]. The present case report describes a case of oral verruciform xanthoma and includes a review of the relevant literature.

Case Report

A 26-year-old female presented with a complaint of swelling in the gingiva accompanied by pain and bleeding for the past one month. Intraoral examination revealed an exophytic growth on the buccal mucosa adjacent to tooth number 42. The inflammatory gingival lesion measured approximately 3 × 4 mm and extended over the vestibular surface of the clinical crown. Clinically, the lesion appeared soft, lobulated, and irregular in texture, with bleeding elicited upon stimulation. The patient's medical, surgical, and dental history were unremarkable.An excisional biopsy of the soft tissue mass was performed. Histopathological examination revealed hyperparakeratotic stratified squamous epithelium exhibiting focal spongiosis and keratin plug formation between acanthotic and elongated rete ridges. The underlying lamina propria was expanded and contained numerous collections of foamy macrophages (xanthomatous cells), which were also seen extending into the epithelium both singly and in clusters. Focal areas of the overlying epithelium displayed a basal granular layer. No granulomatous inflammation or evidence of malignancy was observed in the examined sections. Based on these histopathological findings, a diagnosis of verruciform xanthoma of the oral cavity was established (Figure 1).

Discussion

Oral verruciform xanthoma is a rare benign lesion of the oral cavity. It typically occurs in individuals between 38 and 54 years of age; however, in the present case, the lesion was identified in a 26-year-old patient. According to literature, chronic irritation resulting from factors such as alcohol consumption, tobacco use, certain medications, allergic agents, trauma, microbial infections, and dental materials may act as potential triggers for the lesion [5,6]. In the present study, local trauma within the oral cavity caused epithelial injury, and the resulting inflammatory response, accompanied by the infiltration of lipid-laden macrophages at the site of damage, was considered the predisposing factor for the development of the lesion.

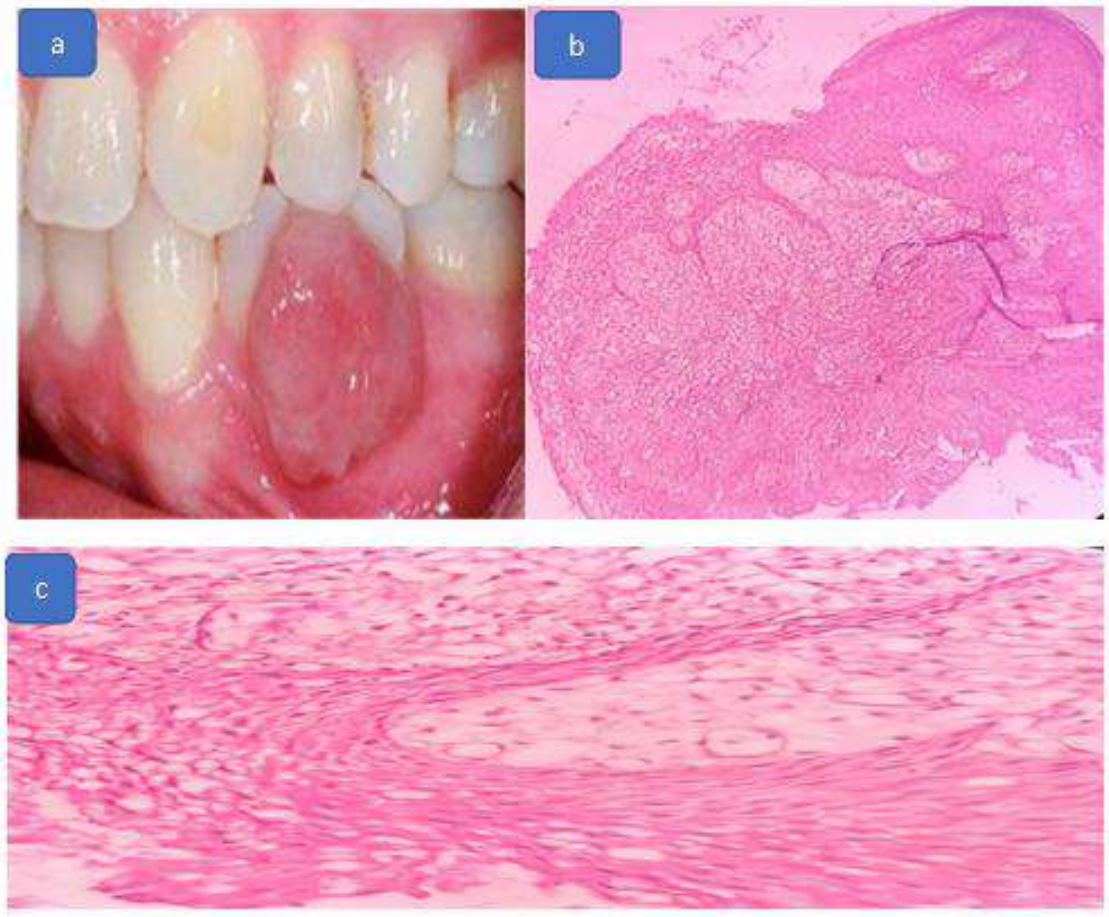

Figure 1. a) Clinical photography showing the exophytic lesion in the gingiva. b) Epithelial hyperplasia with parakeratosis and elongated rete pegs. Haematoxylin and Eosin (H&E,10X) c) Eosinophilic granular cytoplasm with eccentrically placed nuclei and are called foam cells or xanthoma cells. Haematoxylin and Eosin (H&E,40X)

Oral verruciform xanthoma usually presents as an isolated lesion, although in some cases it has been strongly associated with conditions such as discoid lupus erythematosus, dystrophic epidermolysis bullosa, pemphigus vulgaris, lichen sclerosus, congenital epidermal nevi, chronic or congenital lymphedema, graft-versus-host disease, and carcinoma in situ [7,8].

This lesion primarily affects the masticatory mucosa of the oral cavity. Commonly involved sites include the hard palate, tongue, buccal mucosa, floor of the mouth, soft palate, and the junction between the hard and soft palate. Clinically, oral verruciform xanthoma appears as a single papule or plaque with a verrucous or papillomatous surface and varies in color from reddish-pink to gray. Because of its appearance, it is often misdiagnosed as a viral wart or mistaken for premalignant and malignant lesions of the oral cavity such as verruca vulgaris, squamous papilloma, or verrucous carcinoma [9,10]. In the present case, the lesion was observed as an exophytic growth on the buccal mucosa, measuring approximately 3 × 4 mm, situated adjacent to tooth number 42. It extended onto the vestibular aspect of the clinical crown and appeared soft, lobulated, and irregular in texture. The lesion was noted to bleed

upon provocation or slight mechanical stimulation.

Histopathological features of oral verruciform xanthoma are variable and typically include a papillary or verrucous growth pattern of stratified squamous epithelium. The epithelium commonly exhibits parakeratosis, acanthosis, and hyperkeratosis. The rete ridges are thin and elongated, often extending toward the surface. The connective tissue papillae characteristically contain numerous xanthoma cells. These xanthoma cells are round to oval in shape, possess foamy cytoplasm due to lipid accumulation, and have round, regular, eccentrically placed nuclei.

In the present study, similar histopathological features were observed. The lesion showed parakeratinized stratified squamous epithelium with an underlying connective tissue stroma. The papillae extended between the epithelial strands up to the surface, covered by a thin epithelial layer. The connective tissue contained numerous foam or xanthoma cells.

Special staining with Periodic Acid–Schiff (PAS) was used to demonstrate the presence of xanthoma cells, while immunohistochemical staining with CD68 confirmed strong positivity for macrophages. In the present case, both special staining and immunohistochemical analysis were performed to confirm the diagnosis of verruciform xanthoma.

Surgical excision remains the treatment of choice. The differential diagnoses include squamous papilloma, verruca vulgaris, verrucous carcinoma, and squamous cell carcinoma [10].

Conclusion

Verruciform xanthoma is an uncommon lesion that typically occurs on the gingival mucosa. Because its clinical appearance is not distinctive, it should be considered in the differential diagnosis of verrucous or papillary oral lesions.

Statements and Declarations

Conflicts of interest

The authors declare that they do not have conflict of interest.

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CASE REPORT

Fatal Amitraz Poisoning: A Case Report

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Abstract

Amitraz is insecticide and acaricide derived from formamidine which is commonly used in veterinary and agricultural practice, which has a significant risk of accidental, occupational, or intentional exposure. Even though, Amitraz poisoning is very rare clinical presentation, it can mimic organophosphate poisoning due to overlapping features such as bradycardia, hypotension, and respiratory depression, increasing the risk of misdiagnosis. In this article, we report a fatal case of Amitraz poisoning in a 25-year-old female who ingested the compound with suicidal intent. She developed severe toxic symptoms and died approximately 36 hours post-ingestion. Autopsy revealed 100 ml of greenish-brown, pungent gastric contents, congestion of the gastric mucosa and internal organs, and chemical analysis confirmed Amitraz in viscera. Histopathology showed focal sinusoidal dilation, mild steatohepatitis, zone-3 necrosis, and inflammatory infiltrates in the liver; acute tubular necrosis and degenerative changes in the kidneys; and diffuse alveolar hemorrhages, pulmonary oedema, and thickened alveolar septa in the lungs. To distinguish Amitraz poisoning from organophosphate poisoning, clinicians should note the absence of a hypersecretory state, the presence of hypothermia, frequent hyperglycaemia, and normal serum cholinesterase levels in Amitraz poisoning. Early recognition of these differences is essential to ensure correct diagnosis and prompt, appropriate treatment.

Keywords: Amitraz, Acaricide, Suicide, Autopsy

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Introduction

Amitraz (CAS No: 33089-61-1) is an formamidine pesticide (1,5 di(2,4-dimethylphenyl)/3-methyl-1,3,5 triazapenta-1,4-diene) that acts on α-2 adrenergic receptors as α-2 agonist and is used worldwide to control ticks in animals [1]. The clinical toxidrome seen in amitraz poisoning cases is somewhat similar to that of cholinesterase inhibitor poisoning and sometimes had been misdiagnosed as poisoning due to organophosphates (OP) and clonidine. As a result, many patients receive an incorrect treatment due to an erroneous diagnosis [2]. This, along with underreporting, further complicates the identification and documentation of such cases in India [3].

From 2014 through 2016 New South Wales Poison Information Centre (NSWPIC, Australia's largest poisons information centre) received 2655 calls regarding exposure to veterinary pharmaceutical products which amounts to 11.72 human exposures to veterinary pharmaceuticals per 1000 PIC (Poison Information Centre) initial contact exposure calls (Confidence Interval, CI: 10.95–12.49) per year. The vast majority of exposures were with products intended for companion animals, particularly of the class "antiparasitic products, insecticides and repellents" [4]. This indicates a global concern about accidental poisoning from veterinary care products.

In India, the National Poisons Information Centre and studies conducted at several tertiary care hospitals have noted a rising trend in pesticide poisonings, with amitraz accounting for a small yet significant fraction of these cases. A 2019 retrospective study from a South Indian tertiary care centre reported that amitraz was responsible for approximately 1.5–2% of all pesticide poisonings over a five-year period. In fact, the true incidence may be higher due to frequent misclassification of this substance under a more commonly used pesticide or unknown poison categories[5]. This case report brings forth a rare but fatal outcome of amitraz ingestion in an adult patient.

Case details

A 25-year-old female was referred to our institute with an alleged history of deliberate ingestion of an insecticide (later confirmed to be Amitraz). Despite continuous treatment, the patient succumbed to poisoning after a survival period of approximately 36 hours. On postmortem examination, no external injuries were noted. Internal examination revealed approximately 100 ml of greenish-brown fluid with a pungent odour in the stomach, with congestion of the gastric mucosa. The internal organs, including the brain, lungs, liver, and kidneys, appeared grossly congested. No other gross pathological findings were observed. Viscera including stomach and its contents, small intestine and its contents, one half of each kidney and liver were preserved and sent for chemical analysis. The forensic science laboratory report confirmed the presence of Amitraz, establishing the diagnosis of Amitraz poisoning. In addition, tissue samples from the lungs, liver, and kidneys were sent for gross and histopathological examination.

The Lung sections showed diffuse alveolar haemorrhage, pulmonary oedema and infiltration of inflammatory infiltrates with alveolar septal wall thickening (Figures 1 and 2), Liver showed focal sinusoidal dilation, mild steatohepatitis, zone-3 necrosis, lobular and periportal inflammatory infiltrates (Figures 3 and 4), Kidney showed degeneration of tubular

epithelium (Acute tubular necrosis), some tubules show atrophic changes, some show dilatation with granular casts and chronic inflammatory infiltrates (Figures 5 and 6). These findings were supportive of multi-organ toxicity associated with Amitraz ingestion. The cause of death in this case was opined as multi organ dysfunction syndrome as a complication of amitraz poisoning.

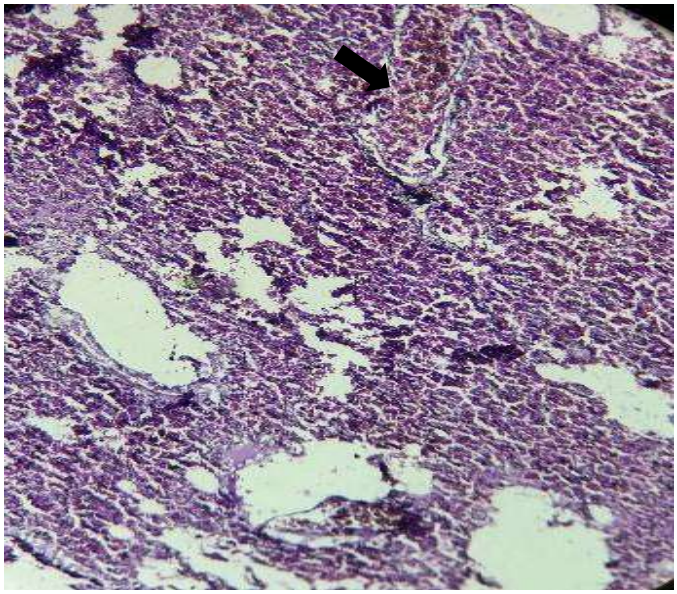

Figure 1. Alveolar haemorrhage (High power 40x, H&E)

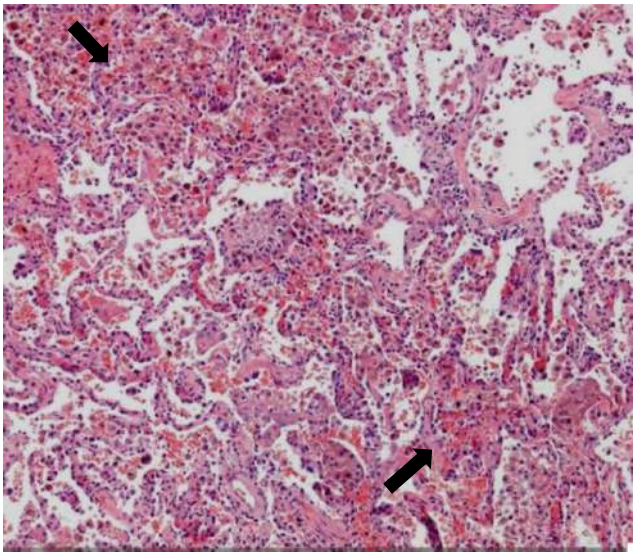

Figure 2. Capillary congestion, diffuse alveolar haemorrhage and pulmonary oedema. Alveolar spaces and interstitium are infiltrated by numerous inflammatory cells. (40x, H&E)

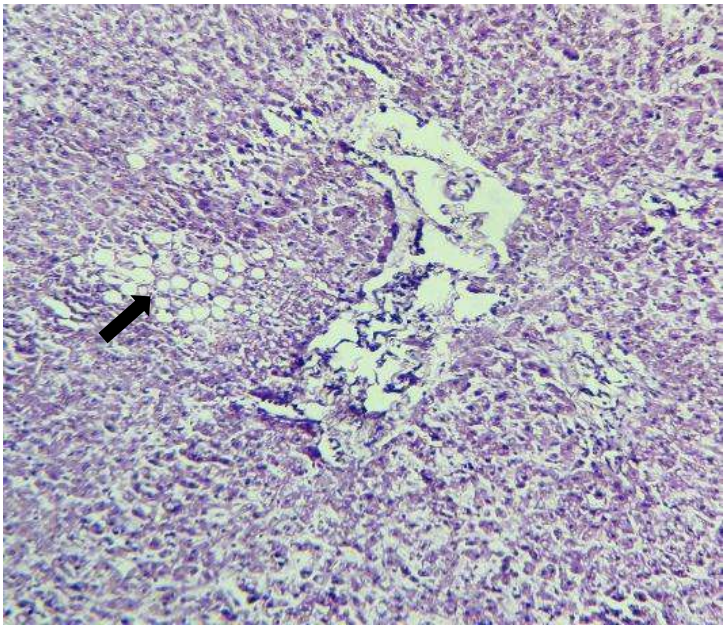

Figure 3. Mild steatohepatitis (H&E staining, 10X)

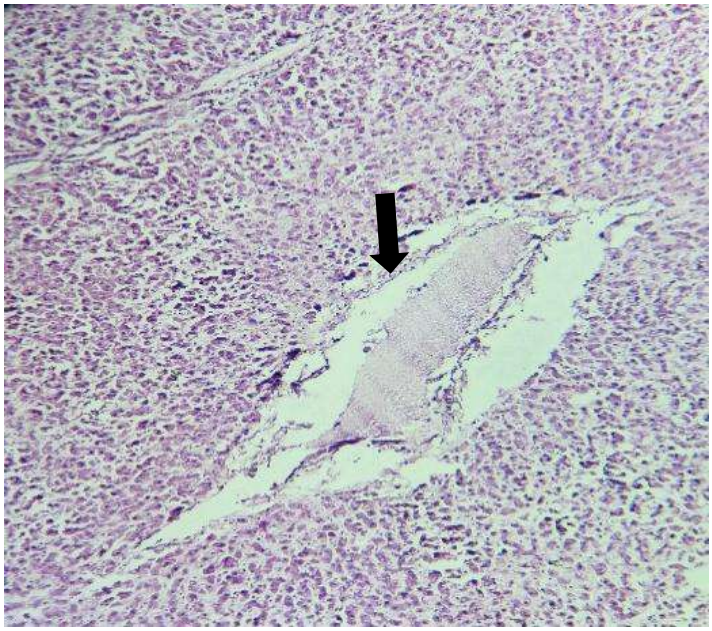

Figure 4. Zone-3 necrosis (H&E staining, 10X)

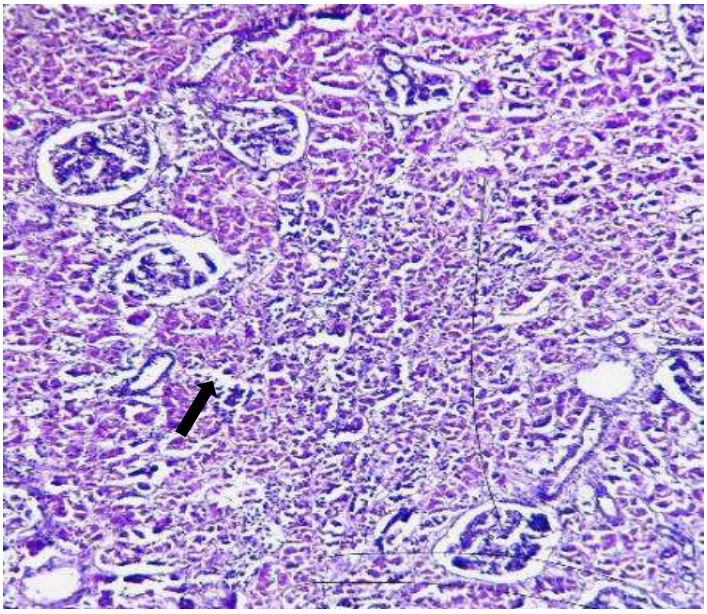

Figure 5. Inflammatory infiltrates and eosinophilic proteinaceous casts in tubules (H&E staining, 10X)

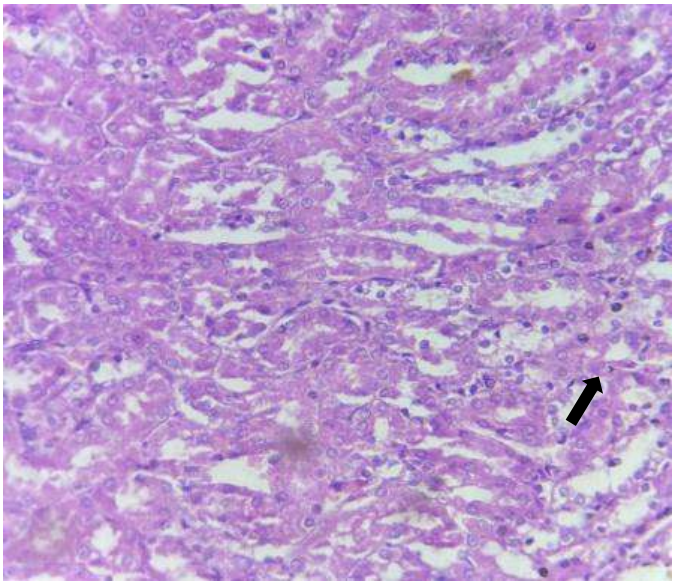

Figure 6. Acute tubular necrosis, (H&E staining, 40X)

Discussion

Amitraz is a commonly used insecticide, veterinary medicine, and antiparasitic agent used in the agricultural practices and pet management. Amitraz belongs to the formamidine class of pesticides and is chemically known as 1,5-di-(2,4-dimethylphenyl)-3-methyl-1,3,5-triaza-penta-1,4-diene [2].

Amitraz can be absorbed through oral, dermal, and inhalational routes. Oral ingestion is more common in suicidal cases, while dermal exposure can occur in veterinary and agricultural settings during spraying and topical application to animals. Absorption is rapid and depends on the solvent used. Amitraz is lipophilic and is well distributed in fatty tissues. It can cross

the blood–brain barrier, causing CNS effects. Amitraz is metabolized in the liver by microsomal enzymes, undergoing hydrolysis into its active metabolite, N-2,4-dimethylphenyl-N′-methylformamidine, and 2,4-dimethylaniline (2,4-DMA). It is excreted mainly in urine, with a small portion excreted in bile and faeces [2,3].

Amitraz has been banned for agricultural use in the European Union; for example, countries like Germany, Austria, and Switzerland do not authorize any pesticide products containing this compound [6]. In the United States, the Environmental Protection Agency (EPA) classifies Amitraz as slightly toxic when ingested (Class III) and lists it as a Group C; 'possible' human carcinogen. As a result, it is not approved for use on crops there but continues to be permitted for certain veterinary treatments [7]. In Canada, agricultural uses of Amitraz have been discontinued, and its use in veterinary products is currently under re-evaluation [8]. Even though amitraz has multiple uses in several aspects in agriculture and veterinary field, there are many alternatives such as synthetic pyrethroids, isoxazolines and organophosphates which are relatively safer [9]. It is always advisable to shift to less toxic alternatives wherever possible.

Accidental and suicidal poisonings with this substance are more common than homicidal poisoning instances as per available literature. The chances of criminal poisoning with amitraz are less as it has a strong pungent odour, bitter and sharp taste, and strong brown colour that renders it difficult to poison food or drinks with it[7].
Amitraz acts like clonidine by stimulating α-2 adrenergic receptors in the nervous system, which produces effects like bradycardia, miosis, hypotension, and shortness of breath. It can also cause hypothermia and hyperglycaemia. At low doses, it usually causes pupil constriction, but at higher doses, the pupils may dilate. Amitraz can cause hyperglycaemia by reducing insulin in the body. It can affect the liver, though liver function often returns to normal within a couple of days in non-fatal cases. The common solvent used with Amitraz, xylene, can add to its toxicity by causing problems like dizziness, lack of coordination, and even coma[3,7,10]. In the present case, amitraz ingestion caused death with evident multi system involvement. The amount of ingestion remains unknown, and the blood levels of the substance were not evaluated. The most possible cause of the lethal toxicity in the present case could be high-dose ingestion. The primary target organs in Amitraz poisoning are the CNS and CVS. It can cause death due to respiratory failure and cardiac complications such as bradycardia, hypotension, and arrhythmias.

The clinical features associated with amitraz are similar to Organo Phosphorous (OP) poisoning, as a result often can lead to misdiagnosis. Therefore, the point of care physicians should make it a priority to obtain the container of the poison and identify the active ingredient involved if possible. The most frequent symptoms of this poisoning are altered mental status, constricted pupils, and bradycardia. These signs can often cause confusion, leading physicians to mistakenly diagnose it as OP poisoning. Features such as hyperglycaemia, hypothermia, and paralytic ileus are more typical of Amitraz. Patients with Amitraz poisoning may also have a noticeable solvent-like or mothball odour, whereas OP poisoning is more often linked to a characteristic garlic-like smell. Investigations such as RBC and Serum cholinesterase levels estimation can be used to distinguish between the two, normal

levels are seen in amitraz cases whereases low levels are seen in OP poisoning, [3,7].

Gas chromatography–mass spectrometry and gas–liquid chromatography are useful for qualitative and quantitative analysis of Amitraz and its metabolites in serum and urine [7]. There are no specific histo-pathological findings which differentiates amitraz and op poisoning, however the findings which are observed in this case more or less correlate with those findings observed in the OP poisoning or a systemic multi organ failure noticed in poisoning cases.

Symptomatic and supportive care is the mainstay of treatment for Amitraz poisoning. Management includes hemodynamic stabilization, gastric lavage, administration of activated charcoal to limit further absorption, and dialysis if needed. Amitraz has very little mortality rate even though it exerts potent acute toxicity and can cause extended hospitalisation. Correct diagnosis of Amitraz poisoning is crucial, as there have been reported deaths caused by repeated doses of atropine given due to an initial misdiagnosis as organophosphate poisoning [3,10].

Conclusion

Amitraz is widely used in agropastoralism because it serves multiple purposes and is economical. Apart from suicidal ingestion, accidental exposure to amitraz is common, with reported cases of dermal and inhalational poisoning occurring during the spraying of pesticides and insecticides [11]. The majority of deaths due to amitraz poisoning occur as a result of its misdiagnosis as organophosphate poisoning; therefore, immediate identification and prompt treatment are crucial to prevent fatalities. There is an immediate necessity of developing bed side tests to differentiate amitraz poisoning from other common forms of poisoning encountered in practice.

The development of a safer and more effective antidote is one way to help prevent these deaths although the lethality associated with amitraz poisoning is relatively less. The risk of accidental exposure to amitraz can be reduced by providing personal protective equipment (PPE) and educating farmers about the safe use of pesticides and insecticides. Suicidal ingestion of such dangerous pesticides can be curbed only by implementing strict laws and procedures for their purchase. Mandatory purchase licensing for farmers, veterinarians, and people who own pets and livestock should be enforced.

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Not applicable.

Conflict of interest

None to declare.

Ethics approval

Consent for autopsy in this case was obtained from the appropriate law enforcement authorities. All ethical considerations have been duly addressed by the authors.

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