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VOLUME-12,
ISSUE-9,
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Preface

We would like to present, with great pleasure, the volume-12, Issue-9, September 2026, of a scholarly journal, *International Multispeciality Journal of Health*. This journal is part of the AD Publications series *in the field of Medical, Health and Pharmaceutical Research Development*, and is devoted to the gamut of Medical, Health and Pharmaceutical issues, from theoretical aspects to application-dependent studies and the validation of emerging technologies.

This journal was envisioned and founded to represent the growing needs of Medical, Health and Pharmaceutical as an emerging and increasingly vital field, now widely recognized as an integral part of scientific and technical statistics investigations. Its mission is to become a voice of the Medical, Health and Pharmaceutical community, addressing researchers and practitioners in below areas

Clinical Specialty and Super-specialty Medical Science:

It includes articles related to General Medicine, General Surgery, Gynecology & Obstetrics, Pediatrics, Anesthesia, Ophthalmology, Orthopedics, Otorhinolaryngology (ENT), Physical Medicine & Rehabilitation, Dermatology & Venereology, Psychiatry, Radio Diagnosis, Cardiology Medicine, Cardiothoracic Surgery, Neurology Medicine, Neurosurgery, Pediatric Surgery, Plastic Surgery, Gastroenterology, Gastrointestinal Surgery, Pulmonary Medicine, Immunology & Immunogenetics, Transfusion Medicine (Blood Bank), Hematology, Biomedical Engineering, Biophysics, Biostatistics, Biotechnology, Health Administration, Health Planning and Management, Hospital Management, Nephrology, Urology, Endocrinology, Reproductive Biology, Radiotherapy, Oncology and Geriatric Medicine.

Para-clinical Medical Science:

It includes articles related to Pathology, Microbiology, Forensic Medicine and Toxicology, Community Medicine and Pharmacology.

Basic Medical Science:

It includes articles related to Anatomy, Physiology and Biochemistry.

Spiritual Health Science:

It includes articles related to Yoga, Meditation, Pranayam and Chakra-healing.

Each article in this issue provides an example of a concrete industrial application or a case study of the presented methodology to amplify the impact of the contribution. We are very thankful to everybody within that community who supported the idea of creating a new Research with *IMJ Health*. We are certain

that this issue will be followed by many others, reporting new developments in the Medical, Health and Pharmaceutical Research Science field. This issue would not have been possible without the great support of the Reviewer, Editorial Board members and also with our Advisory Board Members, and we would like to express our sincere thanks to all of them. We would also like to express our gratitude to the editorial staff of AD Publications, who supported us at every stage of the project. It is our hope that this fine collection of articles will be a valuable resource for *IMJ Health* readers and will stimulate further research into the vibrant area of Medical, Health and Pharmaceutical Research.



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Recognizing and Managing a Rheumatoid Arthritis Flare: A Comprehensive Step-by-Step Action Plan

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Received:-12 August 2026/ Revised:- 28 August 2026/ Accepted: 08 September 2026/ Published: 18-09-2026

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Non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract— Rheumatoid arthritis (RA) is a systemic, chronic autoimmune disease defined by progressive synovial inflammation, structural joint damage, and widespread systemic complications. Despite significant advances in targeted synthetic and biological disease-modifying antirheumatic drugs (DMARDs), patients frequently experience acute exacerbations of disease activity known as flares. These periods of intensified pain, joint swelling, morning stiffness, and systemic fatigue significantly impair functional capacity, reduce health-related quality of life, and contribute to long-term radiographic joint damage if left unmanaged. This paper provides an evidence-based clinical analysis of the recognition, pathobiological mechanisms, and structured management of RA flares. It proposes a six-step action plan integrating validated disease activity metrics, biomarker monitoring, patient-reported outcome measures (PROMs), pharmacological escalation protocols, non-pharmacological therapies, and self-management strategies. By standardizing flare recognition and clinical response, healthcare providers can mitigate structural damage, optimize patient autonomy, and improve long-term disease outcomes.

Keywords— Rheumatoid arthritis flare, DAS28, CDAI disease activity, Inflammatory synovitis, Corticosteroid bridging therapy, DMARD optimization, Treat-to-Target (T2T) strategy.

I. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterized by persistent inflammation of the synovial membrane (synovitis), leading to cartilage degradation, bone erosions, and systemic extra-articular manifestations [1]. While modern therapeutic paradigms—specifically the "Treat-to-Target" (T2T) approach—have made sustained clinical remission (DAS28<2.6) or low disease activity (DAS28≤3.2) achievable goals, the natural history of RA remains intrinsically episodic [2]. Patients frequently experience acute, unpredictable spikes in disease activity termed "flares."

Flares represent more than temporary discomfort. Uncontrolled disease exacerbations accelerate joint erosion, elevate cardiovascular risk via systemic inflammatory pathways, and cause severe physical disability [3]. Beyond structural and systemic damage, flares inflict a major psychological toll. The unpredictability of flare onset creates anticipatory anxiety, disrupts occupational productivity, and exacerbates illness perception, leading to functional helplessness [4].

Historically, clinical trial endpoints focused primarily on static measures of disease activity at discrete visits, often overlooking the dynamic, transient nature of flares. However, research led by the Outcome Measures in Rheumatology (OMERACT) RA Flare Working Group has established flares as critical primary outcomes in clinical trial design and everyday clinical practice [5].

Despite this recognition, translating flare identification into structured clinical intervention remains challenging. Patients often struggle to distinguish an inflammatory flare from non-inflammatory musculoskeletal pain, such as secondary osteoarthritis or fibromyalgia, leading to either delayed medical presentation or unnecessary escalation of immunosuppressive therapy [6]. Conversely, busy clinical practices may lack formal protocols to rapidly triage and manage patient-reported exacerbations.

This article outlines a comprehensive, step-by-step action plan for recognizing and managing RA flares. Integrating immunologic concepts, clinical assessment tools, pharmacological protocols, and non-pharmacological strategies, this blueprint aims to bridge the gap between patient experience and clinical decision-making.

II. PATHOPHYSIOLOGY AND TRIGGER IDENTIFICATION OF RA FLARES

2.1 Immunological Mechanisms Underlying Flares

An RA flare is not merely a transient increase in symptom perception; it is an active immunologic event characterized by the reactivation of inflammatory pathways within the synovium and systemic circulation. During periods of disease stability or subclinical remission, pathogenic immune cell populations—including memory T cells, plasma cells, and fibroblast-like synoviocytes (FLSs)—remain in a quiescent state, controlled by regulatory T cells (Treg) and therapeutic immunosuppression [7].

An acute flare involves a breakdown of local and systemic immune tolerance. Synovial resident memory CD4⁺ T cells become reactivated, secreting pro-inflammatory cytokines such as:

- Interleukin-17 (IL-17)
- Interferon-gamma (IFN- γ)
- Tumor Necrosis Factor-alpha (TNF- α)

This localized cytokine surge stimulates FLSs and macrophages, triggering an inflammatory cascade. Activated FLSs proliferate, produce matrix metalloproteinases (MMPs), and express Receptor Activator of Nuclear Factor κ B Ligand (RANKL), which recruits and activates osteoclasts, causing focal bone erosions [8]. Concurrently, systemic concentrations of Interleukin-6 (IL-6) rise, driving liver hepatocytes to produce acute-phase reactants, specifically C-reactive protein (CRP) and Erythrocyte Sedimentation Rate (ESR).

2.2 Endogenous and Exogenous Triggers

Although flares can occur without an identifiable catalyst, clinical evidence links many events to distinct endogenous and exogenous triggers:

- **Pharmacological Non-Adherence and Tapering:** Unplanned treatment interruptions, missed DMARD doses, or aggressive dose reduction protocols are major causes of flares. Biologic tapering without close monitoring can induce rebound inflammation due to the clearance of circulating drug levels below therapeutic thresholds [9].
- **Microbial Infections:** Viral or bacterial infections activate pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), on innate immune cells. This systemic inflammatory response triggers bystander activation of autoreactive B and T cells, precipitating a localized synovial flare [10].
- **Psychosocial and Neuroendocrine Stress:** Psychological stress activates the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS). Chronic or acute stress disrupts cortisol signaling and increases pro-inflammatory neuro-peptide release (e.g., Substance P), promoting synovial extravasation of immune cells [11].
- **Environmental Factors and Sleep Disruption:** Cigarette smoke exposure, air pollution, and microclimatic shifts (e.g., changes in barometric pressure and ambient temperature) influence synovial fluid viscosity and inflammatory gene expression. Severe sleep fragmentation suppresses melatonin regulation and disrupts circadian cytokine rhythms, leading to increased early-morning inflammatory activity [12].

TABLE 1
ENDOGENOUS AND EXOGENOUS TRIGGERS OF RA

Trigger Category	Specific Catalyst	Pathophysiologic Mechanism	Relative Frequency
Pharmacological	Medication non-adherence, rapid dose tapering, pharmacy supply delays	Loss of therapeutic serum concentrations; reactivation of suppressed T-cell clones	High (~35–45%)
Infectious	Upper respiratory tract infections, urinary tract infections, periodontal flares	TLR activation; bystander immune stimulation; cross-reactive epitope expansion	Moderate-High (~25–30%)
Psychosocial	Acute emotional trauma, severe occupational stress, burnout	HPA-axis dysfunction; blunted glucocorticoid receptor sensitivity; catecholamine release	High (~40–50%)
Environmental	Tobacco smoke exposure, drastic barometric/temperature drops	Induction of peptidylarginine deiminase (PAD) enzymes; alterations in joint compliance	Moderate (~15–20%)
Physical/Mechanical	Unaccustomed joint overuse, direct physical trauma	Micro-trauma to articular structures; local release of damage-associated molecular patterns (DAMPs)	Moderate (~20–25%)

III. CLINICAL MANIFESTATIONS: INFLAMMATORY VS. NON-INFLAMMATORY PAIN

Accurately managing an RA flare requires distinguishing between inflammatory disease activity and non-inflammatory exacerbations. Treating non-inflammatory pain with immunosuppressive escalation exposes patients to unnecessary medication toxicities without resolving their symptoms.

3.1 Characteristics of an Inflammatory Flare

An inflammatory flare is driven by active synovitis and systemic inflammation. Key signs include:

- **Morning Stiffness:** Stiffness lasting longer than 45–60 minutes, caused by the overnight accumulation of inflammatory cytokines and fluid exudation within the joint capsule (the "gel phenomenon").
- **Symmetrical Joint Swelling:** Soft, boggy, spongy joint enlargement representing synovial hyperplasia and effusion, distinct from the hard, bony enlargements of osteoarthritis.
- **Warmth and Erythema:** Increased local cutaneous temperature over active joints due to synovial hypervascularity and pannus angiogenesis.
- **Systemic Features:** Unexplained physical exhaustion, low-grade pyrexia, weight loss, anorexia, and generalized malaise driven by elevated circulating levels of IL-6 and TNF- α .

3.2 Confounding Non-Inflammatory Etiologies

- **Fibromyalgia (Secondary Central Sensitization):** Up to 20% of RA patients experience secondary fibromyalgia. Central sensitization amplifies pain signaling in the central nervous system without joint inflammation, structural degradation, or elevated CRP/ESR [13].
- **Secondary Osteoarthritis (OA):** Mechanical wear of cartilage damaged by past inflammation causes localized, usage-dependent pain that worsens with activity and improves with rest. Morning stiffness typically resolves within 15–30 minutes.
- **Soft-Tissue Pathology:** Bursitis, tendinopathy, or nerve entrapment syndromes (e.g., carpal tunnel syndrome) cause localized, asymmetric pain that can be mistaken for generalized RA activity.

TABLE 2
CLINICAL MANIFESTATIONS OF RA

Parameter	Inflammatory RA Flare	Secondary Osteoarthritis	Secondary Fibromyalgia
Morning Stiffness	>60 minutes; often lasts hours	<30 minutes ("gelling")	Variable; generalized stiffness without joint restriction
Joint Palpation	Soft, boggy, warm, diffusely tender	Hard, bony (osteophytes), crepitus	Tender at extra-articular enthesal points
Swelling Pattern	Symmetrical, multijoint involvement	Asymmetrical, weight-bearing joints	Absence of true objective joint effusion
Diurnal Variation	Worst in the morning and after rest	Worst in the evening after activity	Worsens unpredictably with fatigue and stress
Acute Phase Reactants	Elevated CRP and/or ESR	Normal	Normal
Response to Steroids	Rapid, dramatic response (<48 hours)	Unresponsive or minimal relief	Unresponsive; risk of adverse central effects

IV. MEASURING DISEASE ACTIVITY AND FLARE METRICS

Relying solely on subjective pain reports risks misclassifying flares. The modern management of RA flares requires validated disease activity scores combining clinical examination, patient-reported outcome measures (PROMs), and acute-phase reactants.

4.1 Validated Clinical Scoring Tools

Disease Activity Score 28 (DAS28): Evaluates 28 specified joints for tenderness and swelling, incorporates the patient's global health assessment (GH) on a Visual Analog Scale (VAS, 0–100 mm), and includes ESR or CRP.

The DAS28-ESR formula is calculated as follows:

$$\text{DAS28-ESR} = 0.56 \times \sqrt{\text{TJC28}} + 0.28 \times \sqrt{\text{SJC28}} + 0.70 \times \ln(\text{ESR}) + 0.014 \times \text{GH} \quad (1)$$

Interpretation of DAS28 scores:

- Remission: <2.6
- Low Disease Activity (LDA): 2.6–3.2
- Moderate Disease Activity (MDA): >3.2–5.1
- High Disease Activity (HDA): >5.1
- Flare Definition: An increase in DAS28 of >1.2, or an increase of >0.6 if the baseline score is ≥ 3.2 [14].

Simplified Disease Activity Index (SDAI): A non-weighted numerical sum of TJC28, SJC28, Patient Global Assessment (PGA, 0–10 cm), Evaluator Global Assessment (EGA, 0–10 cm), and serum CRP (mg/dL).

$$\text{SDAI} = \text{TJC28} + \text{SJC28} + \text{PGA} + \text{EGA} + \text{CRP} \quad (2)$$

Interpretation of SDAI scores:

- Remission: ≤ 3.3
- Flare Definition: An increase in SDAI of >4.7 units from the previous stable state [15].

Clinical Disease Activity Index (CDAI): Calculated identically to the SDAI but excludes CRP, making it immediately usable during a clinical visit without waiting for laboratory results.

$$\text{CDAI} = \text{TJC28} + \text{SJC28} + \text{PGA} + \text{EGA} \quad (3)$$

Interpretation of CDAI scores:

- Remission: ≤ 2.8
- Flare Definition: An absolute increase of >12 units, or a shift from remission/LDA to moderate or high disease activity [16].

4.2 Patient-Reported Outcome Measures (PROMs) and OMERACT Criteria

Because clinical visits may not coincide with acute flare episodes, validated self-administered tools are essential for capturing remote or transient exacerbations.

The OMERACT RA Flare Questionnaire (RA-FQ) assesses five domains scored on 0–10 scales over a 7-day recall period:

- Pain
- Physical Function
- Fatigue
- Stiffness Duration
- Stiffness Severity

A cumulative score threshold drop or sustained increase of ≥ 2.5 points across domains reliably differentiates true flares from normal symptom variation [17].

Similarly, the **Routine Assessment of Patient Index Data 3 (RAPID3)** evaluates physical function, pain, and patient global assessment. It can be rapidly calculated in the waiting room, providing a reliable surrogate for clinical disease activity scores [18].

TABLE 3
PROMS AND OMERACT CRITERIA

Diagnostic Index	Variable Composition	Laboratory Component	Remission Cut-off	Flare Delta Threshold
DAS28-ESR	TJC28, SJC28, GH (VAS), ESR	Yes (ESR)	<2.6	$\Delta > 1.2$ (or >0.6 if baseline ≥ 3.2)
DAS28-CRP	TJC28, SJC28, GH (VAS), CRP	Yes (CRP)	<2.6	$\Delta > 1.2$
SDAI	TJC28, SJC28, PGA, EGA, CRP	Yes (CRP)	≤ 3.3	$\Delta > 4.7$
CDAI	TJC28, SJC28, PGA, EGA	None	≤ 2.8	$\Delta > 12.0$
RAPID3	MDHAQ Function, Pain, PGA	None	≤ 3.0	$\Delta > 3.6$
RA-FQ	Pain, Function, Fatigue, Stiffness (2)	None	N/A	Increase of ≥ 2.5 points per domain

V. THE 6-STEP ACTION PLAN FOR RA FLARE MANAGEMENT

Managing an RA flare effectively requires a structured protocol that progresses from patient recognition through clinical triage, targeted intervention, and long-term therapy adjustment.

Step 1: Early Recognition & Self-Assessment

Effective flare management relies on early patient intervention before synovial inflammation causes significant structural damage.

Action Protocols:

- **Symptom Awareness:** Educate patients to monitor for "red-flag" flare symptoms: new or expanding joint swelling, morning stiffness lasting longer than one hour, nocturnal pain that wakes them from sleep, and worsening systemic fatigue.
- **Objective Self-Scoring:** Have the patient complete a structured self-assessment using the RA-FQ or RAPID3 questionnaire.
- **Documentation:** Direct the patient to record the duration, precise joint distribution, and potential triggers (e.g., missed medication doses, stress, recent viral illness) in a paper diary or digital health app.

Step 2: Triage and Differential Screening

Before altering immunosuppressive therapy, clinicians must rule out non-rheumatoid etiologies that mimic flares.

Action Protocols:

- **Infection Screening:** Check for infection before administering glucocorticoid bursts or adjusting DMARDs. Evaluate for fever, dysuria, productive cough, or cutaneous soft-tissue infections.
- **Exclude Septic Arthritis:** If a patient presents with a severe monoarticular flare (e.g., a single swollen, hot knee or wrist) accompanied by fever, perform an immediate diagnostic arthrocentesis to analyze synovial fluid for leukocyte count, Gram stain, and culture.
- **Rule Out Non-Inflammatory Causes:** Assess whether the pain stems from secondary mechanical causes, mechanical joint derangement, or central sensitization (fibromyalgia).

Step 3: Immediate Non-Pharmacological Stabilization

Non-pharmacological measures help soothe inflamed tissues, preserve joint mobility, and reduce pain while pharmacological interventions take effect.

Action Protocols:

- **Thermal Therapy:** Apply cryotherapy (ice packs wrapped in cloth for 15–20 minutes, 3–4 times daily) to acutely swollen, hyperemic joints to induce localized vasoconstriction and slow intra-articular metabolic activity. Reserve thermotherapy (moist heat) for non-swollen, chronically stiff joints.
- **Joint Protection and Orthotics:** Use temporary resting splints (e.g., neutral wrist cock-up splints) to reduce mechanical stress on inflamed synovial membranes.

- **Pacing and Energy Conservation:** Advise patients to practice energy conservation techniques—alternating short periods of activity with scheduled rest—to manage systemic fatigue without becoming completely sedentary.
- **Gentle Range-of-Motion (ROM):** Encourage passive and active-assisted ROM exercises daily to maintain joint flexibility and prevent capsular adhesions, avoiding high-impact resistance training during acute inflammation.

Step 4: Acute Pharmacological Intervention

Acute pharmacological therapy aims to suppress active synovial inflammation rapidly, providing relief while long-term DMARD strategies are evaluated.

Action Protocols:

NSAIDs and COX-2 Inhibitors (Mild/Localized Flares):

- Administer short-term, full-dose nonsteroidal anti-inflammatory drugs (e.g., Naproxen 500 mg BID, Ibuprofen 600–800 mg TID) or COX-2 inhibitors (e.g., Celecoxib 200 mg QD/BID) for 7–14 days.
- **Safety Screen:** Assess renal function, cardiovascular risk factors, and gastrointestinal ulcer history; co-prescribe a proton pump inhibitor (PPI) when indicated.

Systemic Glucocorticoids (Moderate-to-Severe Polyarticular Flares):

- Initiate a short oral prednisone burst (15–20 mg/day) and taper rapidly over 2–3 weeks (e.g., reduce by 5 mg every 5 days) to minimize HPA-axis suppression and adverse metabolic effects [19].
- **Alternative:** Administer a single intramuscular dose of depot methylprednisolone (80–120 mg) for guaranteed adherence and a predictable, self-tapering systemic release curve.

Intra-Articular Glucocorticoid Injections (Monoarticular or Oligoarticular Flares):

- Perform intra-articular injections of long-acting triamcinolone acetonide or hexacetonide (20–40 mg for large joints like knees; 10–20 mg for medium joints like wrists) after ruling out local infection. This delivers targeted local anti-inflammatory action while minimizing systemic side effects.

Step 5: Re-evaluating and Escalating Baseline DMARDs

If flares recur frequently (≥ 2 flares in a 6-month period) or fail to resolve with acute bridging therapy, the baseline disease-modifying strategy must be adjusted.

Action Protocols:

- **Evaluate Adherence:** Confirm that the patient is taking their prescribed background DMARDs consistently before assuming therapeutic failure.
- **Optimize Conventional Synthetic DMARDs (csDMARDs):**
 - If the patient is taking sub-maximal doses of Methotrexate (MTX), escalate the dose up to 25 mg/week orally. If gastrointestinal side effects occur or efficacy plateaus, switch to subcutaneous MTX to improve bioavailability [20].
 - Consider adding second-line csDMARDs to create double or triple therapy (e.g., MTX + Sulfasalazine + Hydroxychloroquine).

- **Escalate to Biologic or Targeted Synthetic DMARDs (b/tsDMARDs):**

- If flares persist despite optimized csDMARD therapy, initiate a biological agent targeting TNF- α (e.g., Adalimumab, Etanercept), IL-6 receptors (e.g., Tocilizumab), or B-cells (e.g., Rituximab), or a Janus Kinase (JAK) inhibitor (e.g., Tofacitinib, Upadacitinib) based on comorbidities and clinical phenotype [2].
- For patients already receiving a b/tsDMARD, evaluate drug trough levels and check for anti-drug antibodies (ADAs). If high titers of neutralising ADAs are present, switch to a drug in a different therapeutic class.

Step 6: Post-Flare Re-evaluation & Treat-to-Target Realignment

Once acute symptoms settle, clinical follow-up ensures that disease activity has returned to baseline and prevents future exacerbations.

Action Protocols:

- **Follow-up Assessment:** Schedule a clinical evaluation 4–6 weeks after flare initiation to measure composite disease activity scores (CDAI, SDAI, or DAS28) and acute-phase reactants (CRP/ESR).
- **Adjust Target Goals:** If post-flare assessments show persistent Moderate or High Disease Activity, adjust the long-term T2T strategy rather than relying on repeated corticosteroid bursts.
- **Update Self-Management Plan:** Review the flare episode with the patient to identify potential triggers, evaluate the effectiveness of the action plan, and refine their self-management strategies for future events.

TABLE 4
ACTION PROTOCOLS FOR CLINICAL INVESTIGATIONS

Step	Core Action	Key Tools / Interventions	Clinical Goal	Target Timeline
1. Recognition	Patient self-identification & scoring	RA-FQ, RAPID3, Symptom Diary	Catch flares early; establish baseline severity	Days 1–2
2. Triage	Screen differential diagnoses	Clinical exam, CRP, Synovial fluid aspirate	Rule out infection, septic arthritis, and non-inflammatory pain	Days 1–2
3. Non-Pharm	Local tissue stabilization	Cryotherapy, splinting, ROM exercises	Reduce mechanical irritation and acute tissue hyperemia	Days 1–7
4. Acute Pharm	Rapid anti-inflammatory control	Oral Prednisone burst, NSAIDs, Steroid injections	Suppress acute cytokine surges and relieve pain	Days 1–21
5. DMARD Adjust	Modify underlying therapy	MTX dose optimization, add/switch b/tsDMARDs	Re-establish long-term immunologic control	Weeks 2–6
6. Realignment	Post-flare T2T follow-up	CDAI, SDAI, DAS28-CRP, ADA therapeutic monitoring	Confirm remission/LDA and update management plan	Weeks 4–8

VI. PHARMACOLOGICAL PROTOCOLS FOR FLARE INTERVENTION

Managing RA flares requires balancing rapid symptom relief with long-term safety. Uncontrolled, chronic exposure to systemic corticosteroids carries significant risks, including osteoporosis, metabolic syndrome, cardiovascular disease, and opportunistic infections [21].

TABLE 5
EVIDENCE-BASED PHARMACOLOGICAL REGIMENS FOR TREATING ACUTE FLARES

Drug Class	Generic Name	Standard Flare Regimen	Mechanism of Action	Critical Monitoring & Contraindications
NSAID (Non-selective)	Naproxen	500 mg PO BID for 7–14 days	Non-selective inhibition of COX-1 and COX-2 enzymes, reducing prostaglandin synthesis	Contraindications: Active peptic ulcer disease, severe CKD (eGFR<30), uncompensated heart failure. Monitor BP and renal function.
NSAID (COX-2 Selective)	Celecoxib	200 mg PO QD or BID for 7–14 days	Selective inhibition of COX-2, reducing gastrointestinal toxicity while controlling inflammation	Contraindications: Ischemic heart disease, post-CABG, stroke history. Lower GI toxicity than non-selective NSAIDs.
Glucocorticoid (Oral Burst)	Prednisone	15–20 mg PO QD for 5 days; taper by 5 mg every 5 days; stop at day 20	Binds glucocorticoid receptor; suppresses NF-κB transcription; downregulates IL-1, IL-6, TNF-α	Side Effects: Hyperglycemia, insomnia, mood disruption, BP spikes. Avoid prolonged bursts (>4 weeks).
Glucocorticoid (IM Depot)	Methylprednisolone Acetate	80–120 mg IM single injection	Depot release delivering sustained systemic glucocorticoid activity over 2–3 weeks	Indications: Ideal for patients with poor oral adherence or GI intolerance. Avoid in suspected systemic infection.
Glucocorticoid (Intra-articular)	Triamcinolone Acetonide	Large joints: 20–40 mg; Small/Medium: 10–20 mg	Localized, high-potency anti-inflammatory suppression within the synovial capsule	Rule out septic arthritis first. Limit to ≤3–4 injections per single joint per year to prevent cartilage atrophy.
csDMARD (Dose Optimization)	Methotrexate	Escalate to 20–25 mg PO/SC weekly + Folic Acid 5 mg/week	Structural analog of folic acid; inhibits DHFR; increases extracellular adenosine	Monitoring: Baseline/periodic LFTs, CBC, serum creatinine. Contraindications: Pregnancy, chronic liver disease, severe alcoholism.
JAK Inhibitor (tsDMARD)	Tofacitinib / Upadacitinib	Tofacitinib 5 mg BID or Upadacitinib 15 mg QD	Reversible intracellular inhibition of JAK1/JAK3 or selective JAK1 pathways, blocking cytokine signaling	Black Box Warnings: Serious infections, thrombosis (VTE/PE), major adverse cardiovascular events (MACE), malignancy screen.

VII. NON-PHARMACOLOGICAL INTERVENTIONS AND PATIENT SELF-MANAGEMENT

While pharmacological therapies target underlying immunologic cascades, non-pharmacological interventions and patient self-management strategies are essential for controlling symptoms, preserving function, and empowering patients during flares.

7.1 Physical and Occupational Therapy Modalities

- **Cryotherapy vs. Thermotherapy:** Cryotherapy reduces intra-articular temperature, slows nerve conduction velocity, and inhibits local matrix metalloproteinase activity, making it the preferred modality for acutely inflamed, swollen joints [22]. Thermotherapy should be reserved for chronic muscle tightness and non-swollen joint stiffness.
- **Orthotic Resting Splints:** Custom-molded, neutral-position splints immobilize inflamed joints, reduce mechanical shear stress on fragile synovial tissues, and alleviate pain. Splint use should be balanced with daily passive range-of-motion exercises to prevent capsular tightness and muscle atrophy.
- **Hydrotherapy (Aquatic Therapy):** Warm-water exercise (33–35°C) reduces joint loading through buoyancy, allowing gentle ROM exercises and low-impact muscle activation without stressing inflamed, weight-bearing joints.

7.2 Behavioural, Psychological, and Educational Strategies

Cognitive Behavioural Therapy (CBT) and Mindfulness: Pain catastrophizing exacerbates flare severity by amplifying central pain processing. CBT, mindfulness-based stress reduction (MBSR), and guided imagery help patients reframe pain perception, reduce sympathetic nervous system arousal, and lower circulating stress markers [23].

The "4 Ps" of Energy Conservation:

- **Pacing:** Spreading physical tasks throughout the day rather than rushing through them during brief periods of lower pain.
- **Planning:** Scheduling demanding activities around periods of peak energy and medication coverage.
- **Prioritizing:** Focusing on essential activities and delegating non-essential tasks during acute flares.
- **Positioning:** Using ergonomic tools and joint-sparing techniques (e.g., carrying bags with forearm straps rather than fingers) to minimize articular strain.

Pre-Agreed Written Action Plans: Providing patients with an individualized flare action plan—co-designed by the patient and rheumatology team—empowers early self-management (e.g., initiating temporary NSAIDs or contacting the clinic for pre-authorized steroid bridging) without panic or care delays.

VIII. CLINICAL VIGNETTES AND CASE ANALYSES

The following clinical cases illustrate how to apply the 6-step action plan across different patient presentations.

Case 1: True Polyarticular Inflammatory Flare Secondary to Unsanctioned DMARD Tapering

Patient Profile:

A 54-year-old female with a 7-year history of seropositive RA (Anti-CCP positive, RF positive) achieved sustained clinical remission (CDAI=1.8) on subcutaneous Methotrexate (20 mg/week) and Adalimumab (40 mg every 2 weeks). Prompted by online health forums, she independently discontinued Adalimumab 6 weeks ago. She presents with a 10-day history of worsening bilateral wrist, MCP, and PIP joint pain, severe morning stiffness lasting 2.5 hours, and intense fatigue.

Step-by-Step Action Plan Implementation:

- **Step 1 (Recognition):** The patient recorded an RA-FQ score of 8.2/10 and a RAPID3 score of 22/30, indicating a severe transition from baseline remission to high subjective disease activity.
- **Step 2 (Triage):** Physical examination revealed 10 swollen joints (SJC28 = 10) and 14 tender joints (TJC28 = 14). Vital signs were normal, with no symptoms of infection. Laboratory testing showed elevated CRP (38 mg/L) and ESR (52 mm/hr), confirming a true systemic inflammatory flare secondary to biologic withdrawal.
- **Step 3 (Non-Pharm):** Recommended localized cryotherapy to both wrists for 15 minutes three times daily, temporary volar wrist splinting during task performance, and temporary activity pacing.
- **Step 4 (Acute Pharm):** Initiated an oral Prednisone burst at 20 mg/day for 5 days, tapering by 5 mg every 5 days over 20 days.

- **Step 5 (DMARD Adjust):** Re-instated Adalimumab at 40 mg subcutaneously every 2 weeks. Provided patient education regarding the risks of unsanctioned bDMARD withdrawal.
- **Step 6 (Realignment):** At the 6-week follow-up, the patient's CDAI score dropped to 3.2 (low disease activity), CRP normalized (3.1 mg/L), and full clinical remission was re-established by month 3 without permanent structural joint damage.

Case 2: Monoarticular Flare vs. Septic Arthritis in a Patient on Tofacitinib

Patient Profile:

A 62-year-old male with long-standing erosive RA treated with Tofacitinib (5 mg BID) and Methotrexate (15 mg/week) presents to the emergency department with acute severe pain, swelling, and inability to bear weight on his left knee. Symptoms began abruptly 24 hours prior. He reports mild fever and chills. He has a history of type 2 diabetes.

Step-by-Step Action Plan Implementation:

- **Step 1 (Recognition):** The patient identified a severe localized flare in his left knee (Pain VAS=9/10).
- **Step 2 (Triage - Critical Branching):** Physical examination revealed a large, hot, hyperemic, severely tender left knee effusion. Systemic temperature was 38.4°C. Other joints were quiescent (SJC28=1, TJC28=1).

Immediate Diagnostic Procedure: Arthrocentesis yielded 35 mL of purulent synovial fluid. Synovial WBC count was 88,000/μL with 92% neutrophils. Gram stain revealed Gram-positive cocci in clusters, subsequently identified as *Staphylococcus aureus*.

Diagnosis: Septic Arthritis mimicking a monoarticular RA flare.

- **Step 3 & 4 (Pharm/Non-Pharm Modification):**
 - Tofacitinib and Methotrexate were immediately held due to active infection and systemic immunosuppression.
 - Systemic steroid bursts and intra-articular steroid injections were strictly contraindicated.
 - The patient underwent urgent arthroscopic joint debridement and lavage, followed by IV Cefazolin based on sensitivity testing.
- **Step 5 & 6 (DMARD Realignment):** Controlled orthopedic drainage and a 6-week course of targeted IV antibiotics successfully cleared the infection. Targeted synthetic DMARD therapy was carefully resumed under combined rheumatological and infectious disease supervision only after complete resolution of the infection.

Case 3: Pseudoflare Driven by Secondary Central Sensitization and Life Stress

Patient Profile:

A 41-year-old female with seronegative RA managed with Leflunomide (20 mg/day) presents reporting a "massive flare-up of RA everywhere" over the past month. She reports widespread joint pain (10/10), constant fatigue, and non-restorative sleep following a high-stress divorce.

Step-by-Step Action Plan Implementation:

- **Step 1 (Recognition):** The patient logged elevated scores across all RAPID3 domains (RAPID3=24/30).
- **Step 2 (Triage):** Physical examination revealed diffuse tenderness over muscle beds, entheses, and joint margins, but zero swollen joints (SJC28=0, TJC28=18). Ultrasound imaging of hands, wrists, and knees showed no active synovial thickening or Doppler hypervascularity. Acute-phase reactants were normal (CRP=1.2 mg/L, ESR=11 mm/hr).

Diagnosis: Secondary Fibromyalgia Exacerbation / Central Sensitization, not an inflammatory RA flare.

- **Step 3 (Non-Pharm Stabilization):** Educated the patient on the distinction between inflammatory joint damage and central pain amplification. Initiated sleep hygiene interventions, low-impact aerobic conditioning (aquatic walking), and referred her for Cognitive Behavioral Therapy (CBT).

- **Step 4 & 5 (Pharmacological Modifications):** Avoided corticosteroid bursts and DMARD escalation, preventing exposure to unnecessary immunosuppression. Initiated Duloxetine (30 mg QD, titrated to 60 mg QD) to address central sensitization, neuropathic pain pathways, and co-existing affective stress.
- **Step 6 (Realignment):** At her 8-week evaluation, the patient reported a 50% reduction in global pain scores, improved sleep quality, and maintained stability of her underlying RA without changing her base DMARD regimen.

IX. CONCLUSION

Managing rheumatoid arthritis flares effectively is essential for preventing structural joint damage, preserving functional independence, and maintaining quality of life. Modern rheumatology has advanced beyond treating flares with ad-hoc corticosteroid bursts. Optimal outcomes require a structured, evidence-based approach that combines validated disease metrics, clinical evaluation, targeted pharmacological escalation, and non-pharmacological therapies.

By implementing this step-by-step action plan, clinicians and patients can work together to systematically recognize, triage, and manage acute exacerbations. Differentiating true inflammatory flares from infectious mimics or central pain sensitization ensures that immunosuppressive adjustments are applied safely and effectively. Equipping patients with self-assessment tools, clear protocols, and non-pharmacological coping strategies restores autonomy, reduces anxiety, and supports long-term disease control.

LIMITATIONS

This review is based on published literature and clinical guidelines; the proposed action plan has not been formally validated in prospective studies. Implementation may vary based on local resources, healthcare infrastructure, and patient populations. The pharmacological protocols presented are general recommendations and should be individualized based on patient comorbidities, drug interactions, and shared decision-making.

FUTURE RESEARCH DIRECTIONS

Prospective studies should evaluate the effectiveness of standardized flare protocols on patient outcomes, including structural damage progression, quality of life, and healthcare utilization. Implementation science research is needed to identify barriers and facilitators to protocol adoption in diverse clinical settings. Additionally, comparative effectiveness studies of different flare management strategies would help optimize care pathways. As targeted biological and synthetic therapies continue to evolve, integrating standardized flare protocols into everyday clinical practice will remain a cornerstone of effective RA management—ensuring that transient spikes in disease activity do not lead to permanent disability.

DECLARATION OF INTEREST STATEMENT

The authors declare no conflicts of interest related to this work.

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Coronary Artery Variation Phenotypes and Associated Clinical Characteristics in a Libyan Adult Cohort: A Multicentre Imaging Analysis

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Received:-24 August 2026/ Revised:- 02 September 2026/ Accepted: 12 September 2026/ Published: 18-09-2026

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Abstract—

Background: Coronary artery variations encompass a heterogeneous group of developmental and morphological phenotypes whose clinical expression may differ according to subtype and patient characteristics. Population-specific data from North Africa remain limited.

Methods: This multicentre retrospective cross-sectional study analysed 200 Libyan adults aged 26–85 years who underwent coronary assessment at three referral centres. Coronary artery variation status and phenotype were abstracted from coronary imaging reports together with demographic, anthropometric, cardiovascular risk, and symptom data. Descriptive statistics, chi-square tests, Monte Carlo procedures for sparse contingency tables, Cramér's V, and one-way analysis of variance were used as appropriate.

Results: Coronary artery variations were identified in 87/200 participants (43.5%). Among variation-positive cases, anomalous origin/ostial variants were most frequent (33/87, 37.9%), followed by other/unspecified patterns (17.2%), branching/length variants (14.9%), ectasia/aneurysm (13.8%), myocardial bridging (10.3%), and interarterial/intramural courses (5.7%). Phenotype distribution differed by sex (Monte Carlo $p=0.004$), whereas no significant association was observed with age band (Monte Carlo $p=0.243$). Palpitations occurred more frequently in participants with a coronary variation than in those without one (19.5% vs 8.8%; $\chi^2=4.811$, $p=0.028$; $V=0.155$), although the effect size was small. Mean body mass index did not differ across variation phenotypes ($F(5,81)=0.483$, $p=0.788$).

Conclusion: Coronary artery variation phenotypes were common in this clinically referred Libyan cohort and showed distinct sex-related patterns and a modest association with palpitations. Phenotype-level anatomical reporting may add clinically useful information beyond recording the presence or absence of a coronary variation.

Keywords— coronary artery variations; coronary anomalies; coronary anatomy; Libya; coronary imaging; myocardial bridging; palpitations.

I. INTRODUCTION

Coronary artery variations and anomalies comprise deviations in coronary origin, ostial position, course, branching, length, termination, or vessel morphology, and are commonly classified according to anatomical subtype to aid clinical and imaging interpretation [1,2]. Many are incidental, but selected phenotypes can influence myocardial perfusion, complicate catheter

engagement or surgery, and alter procedural planning. Contemporary guidelines therefore emphasize accurate anatomical definition when a clinically relevant anomalous origin or course is suspected [3,4].

Reported prevalence varies markedly according to the population studied, imaging modality, and—critically—the definition used. Large angiographic and CT-based series restricted to congenital anomalies of origin and course generally report prevalence in the low single digits [5,6], whereas broader frameworks that include myocardial bridging, ectasia, branching patterns, and other coronary variants yield substantially higher estimates [7–10]. This definitional heterogeneity makes direct comparison between populations difficult and supports reporting individual phenotypes rather than a single pooled anomaly rate.

Coronary CT angiography (CCTA) provides three-dimensional assessment of coronary origin and course and is particularly useful for defining relationships with the aorta and pulmonary artery. Invasive coronary angiography remains central to the assessment and treatment of obstructive coronary disease but may be less informative for some three-dimensional anatomical relationships [3,4,11]. The increasing use of coronary imaging has consequently expanded recognition of anatomical phenotypes that were previously under-reported.

Evidence describing coronary variation phenotypes in North African populations is limited [12]. The present analysis was designed to characterise the phenotype distribution of coronary artery variations in a multicentre Libyan adult cohort and to examine selected demographic and clinical correlates. To maintain a distinct clinical-anatomical focus, the primary analyses address phenotype, sex, age, body mass index (BMI), and palpitations rather than comparative diagnostic performance between imaging modalities or multivariable prediction of coronary artery disease.

II. METHODOLOGY

This was a multicentre retrospective cross-sectional analysis of routinely collected coronary imaging and clinical data from three Libyan referral centres—Tripoli Medical Center, Benghazi Medical Center, and Tajoura Heart Center—reported in accordance with the STROBE guidelines for observational studies [13]. The analytical cohort comprised 200 adults aged 26–85 years who underwent coronary assessment. Duplicate records and paediatric cases were removed during data cleaning. Records with insufficient information for the required variables and patients whose native coronary anatomy could not be reliably classified were excluded.

Data were abstracted using a structured collection instrument. Variables included age, sex, BMI, cardiovascular history and risk indicators, presenting symptoms, imaging modality, presence of a coronary artery variation, and anatomical phenotype. Coronary phenotypes were grouped as: anomalous origin/ostial variants; branching/length variants; ectasia/aneurysm; interarterial/intramural course; myocardial bridging; and other/unspecified variations. These groups were selected to preserve clinically meaningful anatomical distinctions while allowing statistical comparison.

Imaging modalities included coronary CT angiography (CCTA) and invasive coronary angiography (ICA). Imaging reports were abstracted by trained research personnel under the supervision of a cardiologist, with discrepancies resolved by consensus. Phenotypes were classified according to a standardised classification system based on the original imaging reports.

Age was grouped as 26–39, 40–49, 50–59, 60–69, and ≥ 70 years for phenotype summaries. BMI was analysed as a continuous measure when comparing variation phenotypes. Palpitations were treated as a binary clinical symptom. Statistical analyses were performed using IBM SPSS Statistics version 27, with the Monte Carlo procedures conducted in SciPy 1.17. Categorical variables are reported as frequencies and percentages. Pearson's chi-square test assessed associations between categorical variables, with Cramér's V used to quantify association strength where expected cell counts were adequate. One-way analysis of variance assessed mean BMI across phenotype groups. Because of sparse expected cell counts in the sex-by-phenotype and age-band-by-phenotype contingency tables, statistical significance for both comparisons was assessed using a Monte Carlo procedure based on 100,000 simulated tables with fixed row and column margins (Patefield's algorithm; fixed random seed for reproducibility). The Pearson chi-square statistic is reported for each comparison, while the Monte Carlo estimate was used for inference. Two-sided $p < 0.05$ was considered statistically significant. Missing data were handled using complete case analysis, as the proportion of missing data was low.

The "other/unspecified" phenotype category was a residual classification retained for imaging-reported coronary variations that could not be confidently assigned to one of the five explicitly defined subtypes (anomalous origin/ostial, branching/length, ectasia/aneurysm, interarterial/intramural course, or myocardial bridging) at the level of anatomical detail documented in the original imaging reports. This category is acknowledged as a limitation of the underlying source data (see Discussion).

All data used for analysis were anonymised. Ethical approval was granted by the responsible institutional research ethics committee (Approval No. LUC-REC/2024/078; 20 May 2024). Administrative permissions were obtained from Tripoli Medical Center, Benghazi Medical Center, and Tajoura Heart Center. Only anonymised retrospective clinical and imaging data were analysed, and patient confidentiality was maintained throughout the study.

AI-assisted tools were used during manuscript preparation for language editing, structural refinement, and reference formatting. ChatGPT (OpenAI; GPT-5.6 Sol) was used for these purposes. All scientific content, statistical results, citations, and interpretations were reviewed and verified by the authors, who take full responsibility for the final manuscript.

III. RESULTS

The final cohort included 200 adults. Men represented 84.5% (n=169) and women 15.5% (n=31). Mean BMI was 27.03±2.31 kg/m². Cardiovascular risk indicators were frequent: hypertension was documented in 83.0%, diabetes mellitus in 43.0%, hyperlipidaemia in 89.0%, and sedentary activity in 78.5%. Chest pain was reported in 95.5%, shortness of breath in 74.5%, and palpitations in 13.5%.

TABLE 1
BASELINE CLINICAL CHARACTERISTICS OF THE STUDY COHORT (N=200)

Characteristic	n	%
Male sex	169	84.5
Female sex	31	15.5
Hypertension	166	83
Diabetes mellitus	86	43
Hyperlipidaemia	178	89
Sedentary activity	157	78.5
Current smoking	64	32
Former smoking	47	23.5
Family history of CAD (1st/2nd degree)	104	52
Chest pain	191	95.5
Shortness of breath	149	74.5
Palpitations	27	13.5

Coronary artery variations were present in 87 participants (43.5%). Among variation-positive cases, anomalous origin/ostial variants constituted the largest group (37.9%). The remaining distribution is shown in Table 2.

TABLE 2
DISTRIBUTION OF CORONARY ARTERY VARIATION PHENOTYPES AMONG VARIATION-POSITIVE CASES (N=87)

Phenotype	n	% of variation-positive cases
Anomalous origin/ostial variants	33	37.9
Other/unspecified	15	17.2
Branching/length variants	13	14.9
Ectasia/aneurysm	12	13.8
Myocardial bridging	9	10.3
Interarterial/intramural course	5	5.7

Phenotype distribution differed significantly by sex (Pearson $\chi^2=16.833$, df=5; Monte Carlo p=0.004). Because 6 of 12 cells (50.0%) had expected counts <5 (minimum ≈ 1.38), inference was based on the Monte Carlo procedure rather than the asymptotic Pearson p-value. Myocardial bridging was observed only among men in this dataset (9/63 male variation-positive cases, 14.3%, versus 0/24 female variation-positive cases, 0.0%), whereas the other/unspecified category represented a larger

proportion of variation-positive women (10/24, 41.7%) than men (5/63, 7.9%), as shown in Table 3. Because several phenotype-by-sex cells were small, these findings should be interpreted as descriptive and hypothesis-generating.

TABLE 3
CORONARY ARTERY VARIATION PHENOTYPE BY SEX AMONG VARIATION-POSITIVE CASES (N=87)

Phenotype	Female, n (%)	Male, n (%)
Anomalous origin/ostial variants	6 (25.0)	27 (42.9)
Branching/length variants	3 (12.5)	10 (15.9)
Ectasia/aneurysm	4 (16.7)	8 (12.7)
Interarterial/intramural course	1 (4.2)	4 (6.3)
Myocardial bridging	0 (0.0)	9 (14.3)
Other/unspecified	10 (41.7)	5 (7.9)
Total variation-positive cases	24	63

Note: Cells are small; interpretation should be cautious. The "other/unspecified" category is a residual classification for variations that could not be confidently assigned to a specific phenotype based on the available imaging reports.

Coronary artery variation phenotype was not significantly associated with age band (Pearson $\chi^2=23.857$, $df=20$; Monte Carlo $p=0.243$). Because 26 of 30 cells (86.7%) had expected counts <5 , inference was based on the Monte Carlo procedure rather than the asymptotic Pearson p -value. Anomalous origin/ostial variants remained prominent in the older age bands, while myocardial bridging was concentrated in the 40–69-year groups; however, small subgroup counts limit inference regarding age-specific patterns.

TABLE 4
CORONARY ARTERY VARIATION PHENOTYPE BY AGE BAND AMONG VARIATION-POSITIVE CASES (N=87)

Phenotype	26–39	40–49	50–59	60–69	≥ 70
Anomalous origin/ostial	2	1	10	13	7
Branching/length	0	1	6	5	1
Ectasia/aneurysm	1	2	1	4	4
Interarterial/intramural	0	1	2	2	0
Myocardial bridging	0	4	2	3	0
Other/unspecified	0	4	6	3	2

Note: Cells are small; interpretation should be cautious.

Palpitations were reported by 17 of 87 participants with a coronary variation (19.5%) compared with 10 of 113 participants without a variation (8.8%). This association was statistically significant but small in magnitude ($\chi^2=4.811$, $df=1$, $p=0.028$; Cramér's $V=0.155$). In contrast, BMI did not differ significantly across variation phenotypes ($F(5,81)=0.483$, $p=0.788$), suggesting that overall adiposity did not distinguish anatomical phenotype within the variation-positive subgroup.

TABLE 5
ASSOCIATION BETWEEN CORONARY ARTERY VARIATION STATUS AND PALPITATIONS (N=200)

Variation status	Palpitations absent	Palpitations present	Total
Absent	103	10	113
Present	70	17	87
Total	173	27	200

IV. DISCUSSION

This multicentre analysis demonstrates substantial anatomical heterogeneity among Libyan adults referred for coronary assessment. The broad variation prevalence of 43.5% should not be interpreted as the prevalence of rare congenital coronary anomalies in the general population. Rather, it reflects a clinically referred cohort and an intentionally broad phenotype definition that includes ostial/origin patterns, branching and length variants, ectasia/aneurysm, myocardial bridging, interarterial/intramural courses, and other reported variations. Published prevalence estimates vary considerably when broader

anatomical variants are included, reinforcing the importance of transparent definitions [7–10]. Contemporary regional and international imaging series have reported widely varying prevalence estimates depending on the population studied, imaging modality, and anatomical definitions applied [14–17].

Anomalous origin/ostial variants formed the largest phenotype group in the present cohort. These findings are clinically relevant because ostial configuration, proximal course, and relationships to the great vessels may affect ischaemic risk and procedural strategy, particularly for anomalies with an interarterial course or other high-risk anatomic features that have previously been linked to exertional symptoms and, rarely, sudden cardiac death [18,19]. Current adult congenital heart disease guidance recommends anatomical confirmation with CCTA or magnetic resonance angiography when anomalous coronary origin is suspected, with CCTA generally favoured for spatial definition [3,4].

The observed sex-related difference in phenotype distribution is noteworthy but requires cautious interpretation. Myocardial bridging occurred only among men in this dataset, while women were relatively over-represented in the residual other/unspecified category. Previous imaging studies have shown substantial variability in the frequency of myocardial bridging and other coronary variants according to population and ascertainment method [7–10,22]. Sex-related differences in the frequency and pattern of coronary artery anomalies have been reported elsewhere, though the direction of the effect varies across series and imaging modalities [20,21]. The small number of women and sparse subtype cells in our cohort preclude a firm biological conclusion; larger sex-balanced datasets are needed. Additionally, the disproportionate representation of women in the "other/unspecified" category may reflect differences in imaging modality, image quality, or reporting practices rather than true biological differences. This should be considered when interpreting the sex-related findings.

Age-band analysis did not demonstrate a significant overall association with phenotype. This is plausible because many coronary variations are developmental anatomical traits rather than acquired abnormalities. Nevertheless, their clinical expression may change with age as atherosclerotic burden, myocardial demand, and comorbid disease accumulate. The absence of a statistically significant age association in the present cohort should therefore not be interpreted as evidence that age is irrelevant to clinical risk.

Palpitations were approximately twice as frequent among participants with a coronary variation as among those without one. The effect size was small, and the cross-sectional design does not establish causality. Still, selected phenotypes—particularly myocardial bridging, ectatic segments, and haemodynamically important anomalous courses—can be associated with transient ischaemia or arrhythmic symptoms in susceptible patients [23–25]. This finding supports careful symptom correlation when a coronary variation is identified rather than treating every anatomical observation as an incidental imaging label. However, palpitations may also be influenced by other factors such as anxiety, arrhythmias, or medication effects, which were not systematically assessed in this study.

Comparison with data from other North African and Middle Eastern populations is limited by the lack of published studies using comparable phenotype definitions. A Tunisian study of coronary anomalies reported prevalence estimates restricted to congenital anomalies of origin and course [12], which are not directly comparable to the broader phenotype framework used in this study. Larger, prospective studies using standardised definitions are needed to establish population-specific prevalence estimates across the region.

4.1 Limitations

Several limitations should be acknowledged:

- 1) **Retrospective hospital-based cohort:** This was a retrospective hospital-based cohort enriched for patients undergoing coronary assessment and therefore cannot provide population prevalence.
- 2) **Male predominance:** Men predominated (84.5%), limiting sex-specific inference. The disproportionate representation of women in the "other/unspecified" category further complicates the interpretation of sex-related findings.
- 3) **Imaging protocol variation:** Imaging was performed in routine clinical pathways rather than under a single prospective imaging protocol, and the distribution of imaging modalities was not uniform across centres.
- 4) **Broad phenotype framework:** The broad phenotype framework increases anatomical capture but complicates comparison with studies restricted to congenital anomalies of origin and course.

- 5) **Symptom ascertainment:** Symptom associations may be influenced by referral patterns and coexisting coronary disease. Palpitations were not systematically characterised in terms of frequency, duration, or triggers.
- 6) **Residual category:** The "other/unspecified" category is a residual classification that may mask important anatomical distinctions and affect the interpretation of sex-related findings.
- 7) **Missing data:** Missing data were handled using complete case analysis; the potential impact of missingness on the findings cannot be fully excluded.
- 8) **Cross-sectional design:** The cross-sectional design evaluates associations at a single time point and cannot establish causality.

The strength of the study is its multicentre design and phenotype-level reporting in a population for which published coronary anatomical data remain scarce. External validation in independent cohorts with standardised imaging protocols and more balanced sex distribution is needed to confirm these findings.

V. CONCLUSION

Coronary artery variations were frequently documented in this clinically referred Libyan adult cohort, with anomalous origin/ostial patterns forming the largest phenotype group. Variation phenotype differed by sex but not significantly by age band, and palpitations were more common among participants with a documented variation. These findings support phenotype-level reporting of coronary anatomy and careful integration of anatomical findings with the patient's clinical presentation.

Larger prospective, sex-balanced studies using standardised coronary variation definitions are needed to establish population-specific prevalence and clinical risk. Future research should also address the limitations identified in this study, particularly the need for standardised imaging protocols, complete anatomical characterisation, and systematic symptom assessment.

DECLARATIONS

Ethical approval: Ethical approval was granted by the responsible institutional research ethics committee (Approval No. LUC-REC/2024/078; 20 May 2024). Administrative permissions were obtained from Tripoli Medical Center, Benghazi Medical Center, and Tajoura Heart Center.

Informed consent: The study used retrospective, de-identified records, and the requirement for written informed consent was waived.

Funding: No external funding was received for this study.

Conflict of interest: The authors declare no conflict of interest.

Data availability: De-identified data supporting the findings are held within the doctoral research dataset and may be made available on reasonable request, subject to institutional and ethical restrictions.

Author contributions: Yaseen Ahmad Muhammad Wafi: Conceptualization, Methodology, Data curation, Formal analysis, Writing – original draft. Emad M.N. Abdelwahab, Lubna Shirin, and Mohammed S. Kabir: Supervision, Validation, Writing – review & editing. All authors reviewed and approved the final manuscript.

AI use disclosure: AI-assisted tools were used during manuscript preparation for language editing, structural refinement, and reference formatting. ChatGPT (OpenAI; GPT-5.6 Sol) was used for these purposes. All scientific content, statistical results, citations, and interpretations were reviewed and verified by the authors, who take full responsibility for the final manuscript.

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