

Original Article

## Correlation between Synovial C-Reactive Protein Levels and Clinical Staging of Temporomandibular Joint Internal Derangement: A Prospective Arthroscopic Study

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### ABSTRACT

Discomfort localized to the temporomandibular joint (TMJ) is frequently reported among individuals afflicted with TMD. Unfortunately, the underlying factors that mediate this pain remain insufficiently characterized to allow for targeted therapeutic intervention. For this reason, understanding these mediators and their distinct roles in local inflammation and nociception is of great importance. This study was designed to evaluate the clinical efficacy of visually guided TMJ irrigation in patients with TMDs and to establish a clinical correlation between internal derangement disorders and CRP concentrations measured in synovial lavage fluid. A cohort of 72 individuals presenting with TMJ disorders, diagnosed based on clinical and radiographic findings, was recruited for the investigation. Synovial lavage fluid was collected before arthrocentesis by flushing the joint cavity with saline. These samples were subsequently analyzed for CRP concentrations employing the Nycocard test (a solid-phase sandwich immunometric assay), allowing quantitative measurement. The patients' subjective pain perception was documented using a visual analog scale. Radiographic imaging identified bony alterations in the condyle, while arthroscopic visualization evaluated synovitis. CRP was identified at substantially elevated levels in the TMJ synovial fluid, with concentrations demonstrating a significant relationship to both clinical indicators and arthroscopic observations recorded in the study population. The measured CRP levels (determined by the Nycocard test) averaged 4.50 in the Internal Derangement type II group ( $SD \pm 1.04$ ), contrasting with an average of 9.64 ( $SD \pm 3.08$ ) in the Internal Derangement type III group, yielding a t-value of 1.01. The concentration of CRP in TMJ synovial fluid is a strong indicator of pain intensity and the degree of synovitis, and elevated levels of this protein may serve as a reliable biomarker for degenerative processes within the TMJ.

**Keywords:** Arthralgia, Arthroscopy, C-reactive protein, Internal derangement, Temporomandibular joint disorders, TMD

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### Introduction

The human stomatognathic system constitutes an exceptionally complex and precisely coordinated biological apparatus. As the structural sophistication of the joint system grows, so too does the susceptibility to functional disturbances. Anatomically classified as a diarthrodial joint, the temporomandibular joint (TMJ)

represents a discontinuous articulation between two bony surfaces, its limited motion envelope governed by ligamentous restraints and directed by the associated musculature. It is further characterized as a synovial joint, with its inner surface lined by a specialized endothelium—the synovial membrane—which secretes synovial fluid that occupies both the upper and lower joint spaces [1]. This synovial fluid carries out

two essential biological tasks: (1) serving as a metabolic and nutritional transport medium for the avascular internal joint structures, and (2) providing lubrication between moving articular surfaces during functional activity. Despite the considerable anatomical and functional intricacy of the TMJ, it remarkably performs without incident for the greater part of an individual's life. Throughout history, functional pathologies of the masticatory apparatus have been recognized and assigned a variety of diagnostic labels, among them 'Costen Syndrome', 'temporomandibular joint dysfunction syndrome', 'functional temporomandibular joint disturbances', 'occlusomandibular disturbances', 'myoarthropathy of the temporomandibular joint', 'pain-dysfunction syndrome', 'myofascial pain-dysfunction syndrome', and 'temporomandibular pain dysfunction syndrome'. Disrupted TMJ function commonly manifests through two predominant clinical features: arthralgia (pain) and mechanical dysfunction [2].

Pain originating from the TMJ stands as a widespread symptom for patients suffering from TMJ disorders. Regrettably, the mechanistic drivers of pain are inadequately understood, hindering the development of etiology-specific treatments. Accordingly, closing the knowledge gap concerning the identity of these mediators and their precise influence on local tissue inflammation and pain generation is critically needed. Diverse molecular mediators, notably serotonin, cytokines, and reactive oxygen species, have been implicated in the regional inflammatory cascade, contributing to the generation of pain, hyperalgesia, and allodynia. In this phenomenon, an otherwise innocuous stimulus elicits a painful response [3]. The synovial lining is a principal source of eicosanoids (bioactive arachidonic acid derivatives encompassing prostaglandins, thromboxane, and leukotrienes) within joint fluid, and a host of triggers, such as trauma and inflammation, markedly upregulate their biosynthesis [3]. Cytokines are polypeptide signaling molecules that orchestrate immune and inflammatory responses. These molecules are presumed to participate in both tissue remodeling and the degenerative cascades that impact the TMJ. Kaneyama *et al.* [4] documented an array of cytokines—including IL-1 $\beta$ , tumor necrosis factor- $\alpha$ , IL-6, and IL-8—in symptomatic joints. This pronounced cytokine profile is hypothesized to reflect the disease processes driving temporomandibular disorders [5].

The liver parenchymal cells (hepatocytes) are responsible for the synthesis of C-reactive protein (CRP), an acute-phase protein detectable in circulating plasma. Serum CRP concentrations have been correlated with plasma titers of IL-1 $\beta$ , a cytokine

known to stimulate hepatic production of acute-phase reactants like CRP and serum amyloidextrin-A, in addition to triggering the synthesis and secretion of prostaglandins from connective tissue elements residing within the synovial tissue [6, 7]. This represents the key molecular signal for protein synthesis, originating from macrophage populations activated at sites of tissue injury. While prior investigations have established a link between pro-inflammatory cytokine expression and the severity of intracapsular TMJ derangements, knowledge remains scarce regarding CRP expression patterns in the TMD patient population, including conditions such as rheumatoid arthritis, osteoarthritis, and other arthropathies. A rigorous analysis of the biochemical constituents of synovial fluid in the context of TMJ disorders is essential to form robust conclusions and yield novel perspectives on the etiology and clinical management of these pathologies. Stemming from this paradigm shift, the primary management philosophy has shifted away from open arthrotomy procedures designed to reconstruct the functional anatomy of the TMJ toward more conservative, minimally invasive approaches centered on intracapsular lavage and adhesion lysis [8].

The technique of TMJ arthroscopy entails the introduction of a purpose-built fiberoptic endoscope into the joint space, serving a dual diagnostic and therapeutic function. It yields a magnified, high-resolution view of the synovial membrane, enabling direct observation of tissue responses to traumatic injury or other pathological conditions. This minimally invasive surgical modality also allows the surgeon to aspirate synovial fluid for subsequent laboratory assessment [9]. The diagnostic insight provided by this intra-articular arthroscopic approach, combined with the concomitant analysis of synovial fluid markers, has reshaped surgical thinking, leading many clinicians to curtail the use of open-joint arthroplasties and reduce the risk of associated adverse sequelae. This study was designed to evaluate the clinical efficacy of visually guided TMJ irrigation in patients with TMDs and to establish a clinical correlation between internal derangement disorders and CRP concentrations measured in synovial lavage fluid.

## Materials and Methods

The research was executed in conformity with established ethical principles, having secured clearance from the institutional ethical committee (EC/NEW/INST/2020/1244) at Santosh Deemed to be University, Ghaziabad, NCR Delhi, referenced by letter number SF/JAN/23/2021.

### Study design

Prospective case series.

### Study settings

The present work was carried out at the outpatient unit of Oral and Maxillofacial Surgery at Santosh Dental College and Hospital, Ghaziabad, Uttar Pradesh, India. Informed by a pilot investigation, the anticipated effect size was set at  $\approx 2$ ; with a statistical power of 80% and a significance threshold of  $P = 0.05$ , the computed minimum sample size was 60. With an acceptable dropout rate of 20%, 72 participants were ultimately enrolled.

### Study participants

Following the established inclusion criteria, individuals aged 16 through 60 years who reported a history of localized discomfort and functional impairment of the TMJ region persisting for at least 1 month, exhibited tenderness upon lateral or posterior palpation of the joint, and demonstrated readiness to adhere to the follow-up schedule were recruited. Meanwhile, individuals whose TMJ pain originated from pathology in other structures of the stomatognathic complex, such as dental pain, myalgia, or neuralgia, were excluded.

### Preoperative evaluation and planning

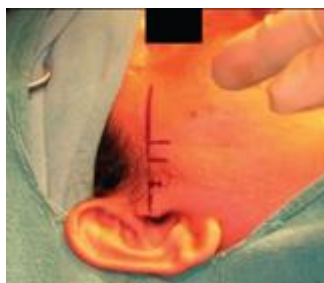
All enrolled participants underwent a thorough preoperative workup comprising a detailed case history, clinical photographic documentation, orthopantomographic imaging, and blood analyses (a complete hemogram along with random blood glucose measurement). Each patient was evaluated for inter-incisal mouth opening, the range of mandibular movements associated with pain (excursive, protrusive, and vertical motions), the occurrence of clicking or crepitus, and joint tenderness across three distinct anatomical points (the lateral condylar pole; the base of the retrodepression, felt with the fingertip

placed in that hollow with the mouth agape; and the posterior surface of the condyle as it is drawn anteriorly under load). In advance of the arthroscopic and arthrocentesis procedures, every subject rated their pain experience on a 'Visual Analogue Scale' (VAS) anchored from 0 to 10 points.

### Intervention and surgical technique

The operative field was cleansed using betadine solution, and the patient was draped while rigorous aseptic technique was maintained. The intervention was conducted under anesthesia (local or general) employing 2% lignocaine hydrochloride containing epinephrine at a 1:200,000 dilution. The external auditory meatus was packed with cotton saturated in mineral oil. The cutaneous entry site was marked following the landmark protocol outlined by McCain *et al.* [10] for arthroscopic access.

Upon creating a stab incision, the sharp trocar fitted inside the arthroscopic sleeve was propelled to traverse the skin and enter the joint capsule. The trocar was backed out at the moment the sensation of tissue resistance dissipated. The cannula was then seated into the joint space after the sharp trocar had been introduced. The capsule was subsequently expanded using irrigating fluid. The cannula was then advanced, and the blunt obturator was removed to permit fluid egress. The joint chamber was flushed with 2 mL of normal saline, which was instilled via the second marked access point. A synovial fluid specimen (1 ml) was drawn off through the outflow into a sterile collection container. Joint lavage was then performed to clear blood or debris from the puncture site, using repeated irrigation with normal saline. A luer-loc connector paired with a stopcock valve was utilized to regulate both inflow and outflow. The arthroscope was then inserted, the joint interior was examined, and to conclude, an intra-articular dose of 1 ml DepoMedrol (methyl prednisolone 40 mg/ml) was delivered (Figures 1a–1f).



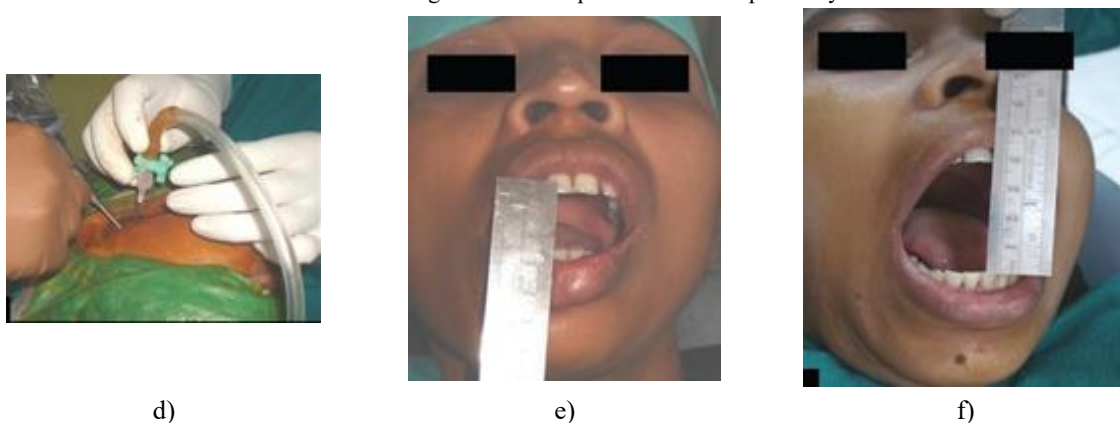
a)



b)



c)



**Figure 1.** (a) Insertion points marked for the insertion of the arthroscope, (b, c) Arthroscopic sheath inserted, (d) Arthroscope-assisted lavage is being done, (e) Preoperative mouth opening, and (f) Postoperative mouth opening.

#### *Postoperative management*

The puncture site was dressed with a topical antibiotic ointment and secured with small adhesive strips and a tab. Diclomol 100 mg (a combination of diclofenac sodium and paracetamol) was directed to be taken three times daily over a 5-day course. An oral cephalosporin was routinely administered after an intraoperative IV bolus of 1 g of cephalosporin. Patients were instructed in a jaw exercise regimen consisting of mouth opening, lateral excursions to both sides, and mandibular protrusion; each movement was to be performed 10 times, with 10 daily repetitions, for a minimum of 10 days (the Rule of 10's).

#### *Examination of the synovial fluid*

The harvested synovial fluid specimen was stored at  $-4^{\circ}\text{C}$ . When turbidity became evident, the sample was centrifuged at 1000 rpm before storage. The Nycocard test (a solid-phase sandwich immunometric assay) was used to quantify CRP levels.

#### *Study variables*

The association between the synovial fluid concentration of the inflammatory biomarker (CRP) and the clinical staging of TMDs was explored by stratifying patients according to internal derangement stages. The resulting groups were subsequently compared to identify any association between CRP concentrations and the graded severity of TMJ internal derangement, and efforts were made to reconcile each subject's arthroscopic observations with their respective derangement stage. The clinical parameters—namely, pain severity as per the Visual Analog Scale (VAS), Maximal Incisal Mouth Opening (MIO), mandibular range of motion, preauricular tenderness, clicking (on opening and closing), arthroscopic features, and CRP concentrations—were documented at both the preoperative and postoperative

time points to gauge the clinical efficacy of arthroscope-guided lysis and lavage.

#### *Methods of record keeping and statistical analysis*

The gathered information was logged using pre-printed structured case record forms and then exported to STATA for statistical treatment. The data's distributional normality was verified using the Kolmogorov-Smirnov test. Descriptive results were reported as count (percentage) and mean  $\pm$  SD. Inferential comparisons were made using the Chi-square test and Student's t-test.

#### **Results and Discussion**

The mean age calculated across the study cohort was  $30.6 \pm 2.82$  years ( $P = 0.6$ , Student's t-test). Regarding baseline characteristics of the 72 enrolled subjects, 10 had unilateral anterior disc displacement with reduction, 32 had unilateral anterior disc displacement without reduction, and 30 had bilateral anterior disc displacement without reduction. Of the total 72 participants, 54 were female and 18 were male, yielding a female-to-male ratio of 4:1. The preoperative mean pain rating (**Table 1**) was recorded at 6.63 (SD:  $\pm 2.0$ ); this figure dropped to 1.32 (SD:  $\pm 0.22$ ) postoperatively, generating a statistically significant t-value of 10.60 and underscoring the capacity of the treatment to alleviate pain. The mean Maximal Interincisal Opening showed a notable improvement after the intervention, increasing from 26.06 mm (SD:  $\pm 6.28$ ) to 35.81 mm (SD:  $\pm 4.23$ ), with a corresponding t-value of 5.68. An evaluation was performed on the painful mandibular movements following arthroscope-assisted lysis and lavage, specifically tallying the number of voluntary jaw actions—mouth opening, lateral excursion to each side, and protrusion—that triggered discomfort. For this

assessment, a maximal score of 4 was assigned to each motion; preoperatively, the mean score per motion was 2.75 (SD: ± 1.13), decreasing to a postoperative mean of 1.25 (SD: ± 0.86), with a t-value of 5.81. Further documentation of improvements in clinical indicators, such as preauricular tenderness and joint clicking, was made following the procedure. Preauricular tenderness

was encountered in 62.50% of subjects before the operation, a proportion that decreased to 25% afterward. In comparison, clicking was initially detected in 37.50% of subjects and decreased to 18.70% postoperatively, once again highlighting the favorable influence of TMJ lysis and lavage among the patients investigated.

**Table 1.** Comparative evaluation of variables.

Variable	Significance (P-value)	t-value*	Postoperative SD	Postoperative mean	Preoperative SD	Preoperative mean
Pain scores (VAS)	0.00	10.60	0.22	1.32	2.00	6.63
Mouth opening	0.00	5.69	4.23	35.81	6.28	26.06
Total number of painful movements	0.00	5.81	0.86	1.25	1.13	2.75
Arthroscopic findings – FA	0.00	0.00	0.00	0.00	0.00	0.00
Arthroscopic findings – AS	0.12	-1.70*	0.40	0.82	0.58	0.33

In the present study, average CRP concentrations were 4.50 in individuals with Internal Derangement type II (SD: ± 1.04). In contrast, those categorized as Internal Derangement type III had a value of 9.64 (SD: ± 3.08), yielding a t-value of 1.01 (**Table 2**). The values differed substantially across the two disease stages, and the t-value was statistically significant. Arthroscopic visualization of the joints was performed to assess synovial hyperemia, the appearance of the synovial lining (SL), and fibrous adhesion formation, to map the relationship between clinical staging and diagnostic arthroscopic findings. Among the joints scoped, a majority displayed notable hyperemia (vascularity score of 2 on a 0–3 scale), 18 joints had mild hyperemia

(vascularity score of 1), and 12 joints were free of hyperemia. The assessment of SL hyperemia yielded a mean of 1.00 (SD: ± 0.00) in stage II subjects and 0.91 (SD: ± 0.54) in stage III subjects, with a t-value of 4.38 that was statistically significant. Hence, a definitive association was established between the extent of synovitis and the disease stage. The mean extent of articular surface (AS) changes documented in stage II subjects was 0.33 (SD: ± 0.57), compared to 0.82 (SD: ± 0.40) in stage III subjects. The associated t-value was 7.43, also statistically significant, thereby permitting a clear inference that arthroscopic observations correlate with TMJ functional disorder staging.

**Table 2.** Evaluation of CRP levels in the lavage fluid.

Dimension	Sig. level	t-value*	Treatment groups			
			Stage-III (n = 11)		Stage-II (n = 3)	
			SD	Mean	SD	Mean
CRP levels	0.33	1.02*	3.08	5.64	0.00	7.50

SD = standard deviation. Unpaired t-test.

In this body of work, we initiated a thorough examination to address TMJ disorders by quantifying CRP levels in synovial fluid collected during arthroscopy-assisted lavage and correlating CRP concentrations with arthroscopic findings and clinical staging of TMDs. The deliberate selection of synovial lavage fluid over synovial tissue specimens was motivated largely by evidence that inflammatory activity within the TMJ manifests in the synovia and that synovial fluid likely serves as a reservoir of both locally elaborated and distally sourced proteins that have pooled in the joint space [11, 12]. Viewed from this angle, synovial lavage fluid may convey a more nuanced impression of the degree of ongoing inflammation. Additionally, when considering patient

experience and procedural ease, harvesting synovial lavage fluid is a less invasive, technically simpler maneuver.

A conspicuous female predominance (4:1) was observed in this study, a finding supported by the existing literature. In synovial tissue from individuals with TMJ pathology, female patients were observed to have substantially elevated concentrations of inflammatory biomarkers [13, 14]. The disproportionate sex representation evident in TMDs progressing to surgical treatment may be reflected in differential CRP concentrations, an issue deserving of deeper exploration [15]. Age at presentation has been identified as a predictive factor in TMJ disorders, with older subjects (≥ 50 years) demonstrating markedly

more favorable outcomes than younger individuals ( $\geq 30$  years). When age categories were juxtaposed rather than analyzing mean age alone, no differences in surgical outcomes emerged. Consistent with other reports in the field, patient age did not exert a detectable influence on postoperative outcomes. In a separate investigation, an unadjusted analysis revealed that older age at the time of surgery also strongly predicted success for TMJ procedures [16]. A comparable incidence pattern was registered in our own dataset. Taken alongside earlier work, this study suggests that a patient's chronological age may be a reliable predictor of surgical intervention.

The capacity of visually directed arthroscopic lavage to produce clinical benefit was gauged by documenting the gains observed in a set of clinical variables employed within our work. The indices used to classify subjects into the various stages of TMJ internal derangement comprised Pain scores on the VAS, Maximal Incisal Opening (MIO), the arc of mandibular excursions, preauricular tenderness, and joint clicking (on mouth opening and closing). Each participant rated the severity of their pain using a subjective 'Visual Analogue Scale' (VAS). Alstergren and Kopp [17] and Kaneyama *et al.* [4] applied the same criteria in their respective investigations to link TMJ pain intensity to PGE2 concentrations. Mandibular mobility was also measured; the available range was scored on a 0–4 scale based on the degree of discomfort accompanying protrusion, laterotrusion toward either side, and mouth opening. One point was tallied for every movement that posed difficulty (maximum achievable score = 4). For this particular indicator—one that reflects the success of joint irrigation—a statistically significant t-value of 5.81 was calculated. The presence or absence of a click was recorded to categorize participants as +ve (positive) or -ve (negative). Since the preoperative and postoperative clicking data were categorical rather than numerical, we could only derive percentage-based improvement for this variable and observed a meaningful gain of close to 38.4%. Preauricular tenderness was likewise charted in a +ve/-ve fashion, meaning that progress with respect to this measure also had to be expressed as a percentage, dropping from 62.50% preoperatively to 5% postoperatively—a relative improvement of 90%. Indeed, 90% of the subjects in this study attained relief from clicking after arthroscopy. Although these ameliorated figures are not remarkably elevated, they remain encouraging and hold clinical significance. They demonstrate that lysis and lavage are effective at reducing clinical symptoms, a finding that is all the more noteworthy given that these results stem from a minimally invasive approach

rather than major surgery. Statistically significant gains were observed across all five clinical indicators, an outcome that aligns with earlier accounts by Gulen *et al.* [18] and Nitzan *et al.* [19].

In the current study, we linked CRP levels measured in synovial lavage fluid to radiological morphology, clinical morbidity, or both in the TMJ using a solid-phase sandwich immunometric assay. We noted that subjects with anterior disc displacement without reduction harbored markedly elevated CRP concentrations [20]. According to Alkan and Etöz [21], individuals with restricted mouth opening had synovial fluid with a significantly diminished biomarker profile compared with those without such restrictions. Our data led us to parallel conclusions and reinforced the earlier report's observations. When synthesizing these two bodies of evidence, we conclude that TMJs with disc displacement exhibit higher CRP titers than those without displacement. The inflammatory biomarker was measured in lavage fluid specimens, and the values were subsequently linked to detailed radiographic alterations and arthroscopic findings within the TMJ. In the majority of patients, anchored discs were identified within the superior joint recess, and every patient presenting with a closed lock likewise had an anchored disc and notably elevated CRP levels. These findings hint that the initiation of early TMJ disease may follow superficial injury to the articular tissue, which could then progress to articular fibrillation and eventually culminate in disc anchorage. Patients with locked joints and limited mouth opening are at greater risk of developing adhesions, and advancing internal derangement is associated with more severe adhesive grading within the TMJ [22]. An array of inflammatory mediators generated within the intra-articular environment by a mechanically overburdened TMJ can trigger synovial inflammation. It has also been pointed out that, because the synovial membrane is ordinarily impermeable to proteins, CRP was not identifiable in the synovial fluid of healthy joint cavities [22]. The buildup of CRP in synovial fluid results from increased permeability of the synovium to plasma proteins, a condition provoked by synovial inflammation. Our study confirmed that elevated CRP levels in the intra-articular space are a consequence of intense mechanical stress and the liberation of inflammatory mediators [23, 24].

Subjective TMJ discomfort, captured via a VAS, is among the most frequently used metrics for assessing TMJ pathology, second only to MIO. Moreover, TMJ discomfort has been scrutinized as a possible harbinger of surgical outcome. While some lines of inquiry have established a connection between raised preoperative

TMJ pain and a less favorable prognosis, others have not replicated this link [25, 26]. Despite this divergence, our univariate analysis revealed a positive association among the preoperative pain VAS score, CRP concentrations, and arthroscopic observations. Earlier work has documented a meaningful association between pain comorbidities and TMD; therefore, this easily modifiable variable may carry prognostic weight [27].

To substantiate the association, the patients enrolled in this investigation were scored along three dimensions when the joint interior was visualized through the arthroscope. These dimensions comprised fibrous adhesions, the synovial lining (SL), and the articular surface (AS). Each of these three features was assigned a score ranging from 0 to 2, anchored to the arthroscopically determined severity of adhesions, hyperemia, or fibrillation. Thereafter, a robust association between these scores and the stages of internal derangement disorders emerged. In the current study, we documented a largely analogous relationship between CRP concentrations and arthroscopic findings, clinical signs, and symptoms, including pain. In their work, McCain *et al.* [10] found that TMJs containing non-reducing discs displayed greater synovial hypervascularity than those with reducing discs. Before the introduction of TMJ arthroscopy, the significance of inflammatory processes within the TMJ went largely unrecognized [25]. Hallmarks of inflammation, such as erythema and hypervascularity, are commonly identified and have been shown to correlate with pain severity. Comparable patterns emerged from our data, showing a positive correlation between the arthroscopic picture and the escalating severity of the condition. Based on arthroscopic findings from our investigation, we hypothesized that CRP levels would correlate with the extent of degenerative changes in the TMJ.

To elaborate on the study's constraints, it is worth noting that the generalizability of the findings may be limited by the single-center design. The single-center framework may have limited the diversity of patient demographics, fracture configurations, and operative techniques, potentially limiting the extent to which the conclusions can be generalized to other patient cohorts. Furthermore, bias may be propagated and study outcomes skewed by discrepancies in institutional workflows, surgical proficiency, and patient management practices operating within a single facility. The condensed follow-up interval also poses a considerable limitation. When evaluating TMJ arthralgia, the VAS, along with the pain questionnaire applied in our study, may prove somewhat overly

generic. Still, augmented levels of inflammatory mediators constitute one facet of inflammation-mediated pain, in line with the CRP pain mechanism. A particularly noteworthy observation from this research was a significant association between the ratio of degenerative change scores recorded during arthroscopy and CRP levels. While statistical significance was reached, additional investigation is required to corroborate the underlying biological relationship.

## Conclusion

The body of evidence generated by this study indicates that a positive correlation prevails among CRP levels in synovial lavage fluid, arthroscopic findings, and the clinical staging of TMJ internal derangement. Synovial lavage fluid may provide a more refined depiction of the prevailing inflammatory state; moreover, from the patient's perspective, its procurement is a minimally invasive, technically simpler undertaking.

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**Conflict of Interest:** None

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**Ethics Statement:** None

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