Joint Diseases and Related Surgery

Jt Dis Relat Surg
2025;36(2):415-419

ORIGINAL ARTICLE

The role of inflammatory markers in the differential diagnosis of stiff shoulder disease

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ABSTRACT

Objectives: The aim of this study was to assess the diagnostic value of pre-treatment inflammatory markers, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR), in distinguishing frozen shoulder (idiopathic stiff shoulder) from secondary stiff shoulder caused by shoulder pathologies.

Patients and methods: Between February 2008 and August 2021, a total of 176 patients (64 males, 112 females; mean age: 54.0±9.9 years; range, 24 to 82 years) were retrospectively analyzed. The patients underwent analysis of surgical video recordings. Seventy-one patients with rotator cuff pathology were classified as having secondary stiff shoulders, while 105 patients without a history of trauma or cuff pathology were classified as having frozen shoulder (primary stiff shoulder). Demographic and preoperative laboratory data, including white blood cell count (WBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), neutrophil, lymphocyte, monocyte, platelet counts, along with NLR, PLR, and LMR values, were evaluated.

Results: Significantly higher levels of WBC, neutrophils, and NLR were observed in patients with secondary stiff shoulder ($p<0.001$ for all). In contrast, LMR ($p=0.013$) and platelet values ($p=0.046$) were found to be significantly higher in the frozen shoulder group. No statistically significant differences were observed between the groups regarding CRP, ESR, lymphocyte count, monocyte count, or PLR ($p>0.05$).

Conclusion: The NLR and LMR values have diagnostic utility in differentiating primary and secondary stiff shoulder. Elevated NLR values are associated with more acute inflammatory responses typical of secondary stiff shoulder, while higher LMR and platelet levels are linked to chronic and fibrotic processes observed in frozen shoulder.

Keywords: Frozen shoulder, inflammatory markers, lymphocyte to monocyte ratio, neutrophil to lymphocyte ratio.

Frozen shoulder is a common musculoskeletal condition characterized by gradually increasing pain and progressive restriction of shoulder movements in all directions.[1] Originally described as a challenging disorder marked by muscle spasms and the development of adhesions around the joint, the condition has been redefined over time. More recent classifications describe frozen shoulder as an idiopathic condition with no identifiable cause, while stiffness resulting from known factors such as trauma, surgery, or other shoulder pathologies is referred to as secondary stiff shoulder.[2,3]

Frozen shoulder affects approximately 2 to 5% of the general population, with a higher prevalence among women, particularly between the fifth and sixth decades of life.[4,5] Clinically, the condition progresses through three distinct stages. The first stage, known as the painful stage, is characterized by

Received: November 13, 2024
Accepted: March 24, 2025
Published online: April 05, 2025

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Doi: 10.52312/jdrs.2025.2000

Citation: Tosun MF, Çiçeklidağ M, Bircan R, Yaş S, Can MM, Baymurat AC, et al. The role of inflammatory markers in the differential diagnosis of stiff shoulder disease. Jt Dis Relat Surg 2025;36(2):415-419. doi: 10.52312/jdrs.2025.2000.

significant pain with minimal limitation of motion. The second stage, or freezing stage, is marked by persistent pain accompanied by progressive restriction of movement. The final stage, referred to as the thawing or resolution phase, involves gradual improvement in both range of motion and pain.[6] Diagnosis is typically made based on clinical examination, as imaging studies usually do not reveal specific findings. Treatment options range from conservative methods such as medications, corticosteroid injections, and physiotherapy to more invasive interventions, including manipulation under anesthesia, open capsular release, and arthroscopic capsular release.[7]

Despite its frequency, the etiology, pathophysiology, natural course, and optimal management of stiff shoulders remain subjects of debate. Although the underlying pathogenesis is not fully understood, it is widely believed that the condition begins with an inflammatory process, eventually leading to fibrosis and capsular contracture.[8,9] Conservative management remains the first-line treatment for frozen shoulder, whereas in secondary stiff shoulder, identification and management of the underlying pathology are crucial.[3] Therefore, distinguishing between primary and secondary stiff shoulders is of significant clinical importance. Given the central role of inflammation in the disease process, inflammatory markers may serve as useful diagnostic tools for differentiating these two entities, similar to their use in other chronic inflammatory conditions. Based on that hypothesis, in the present study, we aimed to investigate the diagnostic utility of pre-treatment inflammatory markers, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR), in differentiating frozen shoulder from secondary stiff shoulder associated with shoulder pathologies.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Gazi University Faculty of Medicine, Department of Orthopedics and Traumatology between February 2008 and August 2021. Patients who underwent shoulder arthroscopy with a diagnosis of stiff shoulder or frozen shoulder were included. Patients with elevated C-reactive protein (CRP) levels or known hematological, infectious, or rheumatic diseases that could affect inflammatory parameters, as well as those with incomplete medical records, were excluded from the study. Initially, a total of 284 patients were evaluated, of whom 108 were excluded due to incomplete records or not meeting the inclusion criteria. Finally, a total of 176 patients (64 males, 112 females; mean age: 54.0±9.9 years; range, 24 to 82 years) were recruited. The patients underwent analysis of surgical video recordings. Seventy-one patients with rotator cuff pathology were classified as having secondary stiff shoulders, while 105 patients without a history of trauma or cuff pathology were classified as having frozen shoulder (primary stiff shoulder). A written informed consent was obtained from each patient. The study protocol was approved by the Gazi University Clinical Research Ethics Committee (date: 09.01.2023, no: 07). The study was conducted in accordance with the principles of the Declaration of Helsinki.

The diagnosis of stiff shoulder was made by a single senior surgeon based on the presence of insidious onset of shoulder pain, night pain, and restricted passive range of motion, defined as forward elevation less than 100° and external rotation less than 50% of the normal range.[10] Surgical intervention was recommended for patients who experienced persistent pain and restricted motion for at least six months despite receiving comprehensive conservative treatment, including pharmacological therapy, physiotherapy, and intra-articular injections.

Data of the patients were retrieved from the hospital database. No additional interventions were performed beyond routine clinical management. Demographic data including age, sex, surgical side, and preoperative laboratory values, were recorded. Laboratory data included CRP, white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), neutrophil count, lymphocyte count, monocyte count, platelet (PLT) count, and calculated ratios of PLR, NLR, and LMR.

Statistical analysis

Statistical analysis was performed using IBM SPSS version 27.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency, where applicable. Non-parametric methods were applied for variables that did not follow a normal distribution. Comparisons between two independent groups were made using the Mann-Whitney U test. The Pearson chi-square (test was used to evaluate relationships between independent categorical variables. A p value of <0.05 was considered statistically significant.

TABLE I
Demographic and clinical characteristics of patients

Variables	Frozen group (n=105) n	Frozen group (n=105) %	Stiff group (n=71) n	Stiff group (n=71) %	Statistical analysis* Probability χ^2	Statistical analysis* Probability *p*
Sex						
Male	31	29.5	33	46.5	5.262	**0.022**
Female	74	70.5	38	53.5		
Side						
Right	58	55.2	45	63.4	1.157	0.282
Left	47	44.8	26	36.6		

* "Pearson-χ^2" cross tables.

TABLE II
Comparison of age and biochemical findings by groups

Variables	Frozen group (n=105) Mean±SD	Frozen group (n=105) Median	Frozen group (n=105) Min-Max	Stiff group (n=71) Mean±SD	Stiff group (n=71) Median	Stiff group (n=71) Min-Max	Statistical analysis* χ^2	Statistical analysis* *p*
Age (year)	51.64±9.53	51.0	24.0-82.0	57.58±9.48	56.0	35.0-77.0	–3.823	**<0.001**
CRP	5.08±5.61	3.1	1.0-39.4	6.01±5.86	3.9	1.0-28.3	–1.439	0.150
Sedimentation	17.90±12.32	14.0	2.0-74.0	19.54±16.63	13.0	1.0-87.0	–0.169	0.866
WBC	7.96±5.35	7.3	3.1-57.6	8.61±2.16	8.8	4.3-15.8	–3.527	**<0.001**
Neutrophil	4.37±1.71	4.1	1.6-14.6	5.50±1.93	5.3	2.5-13.6	–4.222	**<0.001**
Lymphocyte	2.86±4.77	2.5	1.0-50.6	2.26±0.64	2.3	1.0-5.2	–1.211	0.226
Monocyte	0.54±0.16	0.51	0.2-1.0	0.59±0.17	0.56	0.3-1.2	–1.733	0.083
PLT	285.25±63.34	279.0	179.0-441.0	268.02±71.53	258.0	123.0-51.0	1.992	**0.046**
NLR	1.91±0.77	1.76	0.1-3.9	2.92±1.73	2.56	1.1-13.6	–5.004	**<0.001**
LMR	5.36±7.28	4.41	1.3-77.9	4.09±1.32	4.14	1.1-7.2	–2.493	**0.013**
PLR	128.89±48.01	117.8	4.9-294.9	125.59±44.75	119.3	51.3-265.0	–0.394	0.694

SD: Standard deviation; * For data not having a normal distribution, "Mann-Whitney U" test (Z-table value) statistics were used to compare the measurement values of two independent groups.

RESULTS

There was a statistically significant difference in the sex distribution between the groups (p=0.022). Female predominance was observed in the frozen shoulder group (70.5%), whereas male predominance was noted in the secondary stiff shoulder group (46.5%) (Table I). In addition, the mean age was significantly higher in the secondary stiff shoulder group compared to the frozen shoulder group (p<0.001). However, no significant differences were found between the groups regarding CRP levels, ESR, lymphocyte count, monocyte count, or PLR values (p>0.05 for all). The WBC counts demonstrated a significant difference between the two groups (p<0.001), with elevated values observed in the secondary stiff shoulder group.

Similarly, neutrophil counts were significantly higher in the secondary stiff shoulder group (p<0.001). In contrast, PLT count was significantly higher in the frozen shoulder group (p=0.046). The analysis of NLR values revealed a statistically significant elevation in the secondary stiff shoulder group compared to the frozen shoulder group (p<0.001). Additionally, LMR values were found to be significantly higher in the frozen shoulder group (p=0.013), indicating a potential distinction between the inflammatory profiles of the two conditions (Table II).

DISCUSSION

In the present study, we investigated the diagnostic utility of pre-treatment inflammatory markers in differentiating frozen shoulder from secondary stiff shoulder associated with shoulder pathologies. Our study results demonstrated that WBC, neutrophil counts, and NLR values were significantly higher in patients with secondary stiff shoulder, whereas elevated LMR and PLT levels were observed in those with frozen shoulder. To date, no previous studies have specifically focused on distinguishing between these two conditions using inflammatory markers, making the present study the first to suggest that variations in neutrophil, lymphocyte, and monocyte counts may contribute to differential diagnosis. These findings imply that the inflammatory processes underlying primary and secondary stiff shoulder likely follow distinct pathophysiological mechanisms.

It is well established that inflammation plays a key role in the pathogenesis of frozen shoulder. Previous studies have reported elevated expression of inflammatory mediators contributing to abnormal tissue repair and subsequent fibrosis in affected patients.[11-13] The cascade of inflammatory events leading to fibrotic changes has been clearly demonstrated in the literature.[14] Additionally, simple hematological parameters such as NLR, LMR, and PLR have increasingly been recognized as prognostic indicators in various inflammatory and neoplastic conditions.[15-17] However, there is limited evidence regarding how these markers differ between frozen shoulders and secondary stiff shoulders. The significant elevation of neutrophil counts and WBC levels in secondary stiff shoulder observed in the current study supports the notion of a more acute and robust inflammatory response, which is consistent with the etiology of secondary stiff shoulder involving prior trauma, surgical interventions, or underlying shoulder pathologies.

The higher LMR values observed in patients with frozen shoulder may reflect the role of monocytes in tissue repair and fibrotic processes.[18,19] Similarly, elevated PLT levels in that group suggest a contribution of PLTs to tissue fibrosis, given their ability to release growth factors and cytokines that promote healing and fibrotic tissue formation,[9,20] These observations indicate that frozen shoulder is characterized by a prolonged, lower-intensity inflammatory process, whereas secondary stiff shoulder appears to involve a more acute and intense inflammatory response.

In addition, the underlying pathology in secondary stiff shoulders is not always detectable through clinical examination or imaging studies. This highlights the need for alternative diagnostic methods. The present findings suggest that readily available markers such as NLR and LMR, obtained through routine blood tests, may provide valuable support in the differential diagnosis of stiff shoulder subtypes and may assist in treatment planning.

In the current study, demographic differences were also identified, with the frozen shoulder group consisting predominantly of female patients, and the secondary stiff shoulder group showing male predominance. Furthermore, the secondary stiff shoulder group had a significantly higher mean age, consistent with the existing literature.[4,5]

Nonetheless, there are several limitations to this study, including its single-center, retrospective design, which may have restricted the generalizability of the findings. Additionally, blood cell counts were known to fluctuate and can be influenced by various external factors, and only a single pre-treatment measurement was evaluated without accounting for disease stage. Despite these limitations, the main strengths of this study include the exclusion of patients with pre-existing infectious, hematological, or rheumatological conditions that may have influenced inflammatory parameters. Moreover, the use of routine complete blood counts ensured that the evaluated markers, NLR and LMR, were simple, reproducible, and cost-effective tools for clinical assessment.

In conclusion, our study results indicate that NLR and LMR values have a diagnostic value in differentiating between frozen shoulder and secondary stiff shoulder. These findings suggest that inflammatory markers may serve as useful adjuncts in clinical practice, aiding in the distinction between these two conditions and potentially contributing to more accurate diagnosis and appropriate treatment strategies.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept and design: M.F.T., M.Ç., U.K.; Data collection and/or processing: S.Y.,M.M.C.; Analysis and/or interpretation and control/supervision: M.F.T.,R.B., A.C.B., M.A.T.; Literature review: S.Y., M.M.C.; Writing the article: M.F.T., M.Ç., M.M.C.; Critical review: M.F.T., M.Ç., M.A.T., U.K.; References and fundings: R.B., S.Y.; Materials: M.F.T., A.C.B.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

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