American Journal of Medicine and Medical Sciences 2025, 15(10): 3624-3627
DOI: 10.5923/j.ajmms.20251510.74

Method of Predicting the Outcomes of Complex Treatment of Hemarthritis in Intra-Articular Fractures of the Lower Extremities

Vakhobov Komilzhon Shakhobidinovich*, Khamdamov Bakhtiyor Zarifovich

Bukhara Medical Institute, Bukhara, Uzbekistan

Abstract The proposed approach to prognostic verification based on immunological dynamics improves the accuracy of risk stratification and opens up opportunities for clinically oriented personalized therapy in patients with hemarthrosis associated with intra-articular fractures.

Keywords Hemarthrosis, Intra-articular fracture, Prognosis

1. Introduction

A modern understanding of traumatic joint injuries is impossible without considering the immunological processes that accompany them. Intra-articular fractures, especially those complicated by GA, represent not only mechanical trauma but also a trigger for a systemic and local inflammatory cascade. This cascade includes activation of innate and adaptive immunity, initiation of the cytokine cascade, production of enzymatic and humoral mediators, and the development of persistent immunopathological changes in the joint cavity [1,3,5].

The appearance of blood in the joint cavity after injury is accompanied by a cascade of activation of innate immune cells: neutrophils, macrophages, NK cells, and then adaptive components—T and B lymphocytes. The expression of cytokines (IL-1β, IL-6, TNF-α), chemokines, and metalloproteinases (especially MMP-9) is stimulated, increasing vascular permeability, promoting matrix degradation, and cartilage destruction. Concurrently, autoantigens are formed, triggering the production of immunoglobulins and circulating immune complexes [7,9,11]. However, the integration of this knowledge into clinical practice remains limited. Immunological parameters are rarely considered as tools for clinical monitoring, much less prognosis [8,10].

Meanwhile, it is the characteristics of the immune response that can determine the rate of reparation, the duration of inflammation, and the risk of chronicity or recurrent effusions. Studying not only the initial values of immunological parameters but also their dynamics during treatment is particularly promising [2,4,6].

Thus, the relevance of a comprehensive clinical and immunological approach to studying HA in intra-articular fractures lies in the need to move from a descriptive traumatological paradigm to a pathogenetically based, immune-stratified patient management model. This is consistent with the priority areas of personalized medicine and creates the basis for the development of new diagnostic and prognostic tools capable of improving the quality of treatment and reducing the risk of disability.

The aim of the study was to identify and substantiate the pathogenetic relationship between clinical and immunological indicators of the inflammatory response and the nature of the outcomes of GA in intra-articular fractures of the extremities, as well as to assess their prognostic significance in the context of complex treatment.

2. Materials and Methods

The total sample size was 150 individuals: 60 patients with GA associated with intra-articular fractures in the main group, 60 in the comparison group with isolated GA without bone pathology, and 30 clinically healthy individuals in the control group. All patients were treated at the Samarkand branch of the Republican Specialized Scientific and Practical Medical Center for Traumatology and Orthopedics from 2021 to 2024.

Patients were selected according to strict inclusion and exclusion criteria. The anatomical location of the injuries (KS and AJ), the time of admission (no more than 48 hours from the time of injury), and the presence of comorbidities were taken into account. The clinical examination was supplemented by radiography, CT or MRI, and in some cases, arthroscopy. The data obtained ensured the homogeneity of the groups and the reliability of the comparative analysis.

* Corresponding author:
komilv9400@mail.ru (Vakhobov Komilzhon Shakhobidinovich)
Received: Oct. 2, 2025; Accepted: Oct. 22, 2025; Published: Oct. 31, 2025
Published online at http://journal.sapub.org/ajmms

During the laboratory examination, an extensive assessment of the immunological status was conducted.

All studies were conducted dynamically (before treatment, on days 7, 14 and 30 of complex treatment) in compliance with biosafety standards and double internal quality control.

3. Results and Discussion

A comparative analysis of the clinical course of traumatic HA in patients with and without fractures revealed statistically significant differences in a number of parameters. In patients in the main group (with intra-articular fractures), HA volumes exceeded those in the comparative group by more than 40% ($p < 0.01$), and the incidence of severe effusion requiring evacuation was up to 78.3% of cases versus 51.7% in the group without fractures. The frequency of repeated punctures in the main group was 2.3±1.0 times, while in the comparative group it was 1.4±0.6 times ($p < 0.01$). The duration of hospitalization was also longer: 14.2±3.6 versus 9.8±2.7 days ($p < 0.01$). This reflects both the need for longer observation and the complexity of recovery when bone structures are involved.

Additionally, the proportion of patients undergoing arthroscopic intervention was higher in the study group – 21.7% versus 5% ($p < 0.01$), which is explained not only by the volume of HA but also by concomitant damage to intra-articular elements. Open surgery (including osteosynthesis) was performed in 35% of patients in the study group, while such interventions were not performed in the comparison group ($p < 0.001$). Repeat surgery was required in 10% of patients in the study group, compared to 1.7% in the second group ($p = 0.042$), highlighting the high rate of complications in the presence of fractures. An analysis of clinical differences by anatomical location revealed that patients with knee fractures had the largest effusion volume and the most severe pain (VAS score: 7.2 ±1.1 points versus 6.4 ±1.0 points for AJ injuries, $p < 0.05$), while AJ injuries were more likely to have edema, contracture, and disruption of the stabilizing ligaments. The length of hospital stay for bone fractures in the knee was 2 days longer than for AJ fractures ($p < 0.05$), and the need for punctures was 25% higher.

These indicators collectively confirm a more severe course and a higher risk of complications in the presence of an intra-articular fracture, especially in the knee joint area. They emphasize the need for early diagnosis, dynamic observation, and proactive management of patients with osteoarticular trauma. A primary study of cellular and humoral immunity in the study group revealed a significant suppression of the adaptive immune response compared to patients who had sustained a fracture-free injury. The average $CD3^+$ lymphocyte count was 52.4±6.8%, compared to 58.2±5.9% in the comparison group ($p=0.036$), indicating a general decrease in the T-cell population. A more pronounced decrease was recorded in the $CD4^+$ count: 27.6±4.3% in the study group versus 32.1±4% ($p=0.021$), and in the $CD8^+$ count: 21.4±3.9% versus 26.3±3.7% ($p=0.042$). These data indicate profound suppression of both the effector and suppressive components of the T-cell response, especially against the background of increased activation of the humoral component of inflammation. One of the most indicative humoral markers of inflammation was the level of circulating immune complexes (CIC). Elevated CIC concentrations indicate pronounced activation of the humoral immune system and may indicate the development of immune complex-mediated damage to intra-articular tissues.

Proinflammatory mediators, detected both in the systemic and local circulation, deserve special attention. The average IL-6 level in patients with fractures was 74.2±18.6 pg/ml versus 52.8±16.4 pg/ml in the comparison group ($p <0.001$). This increase reflects the activity of the systemic inflammatory cascade and is an indirect indicator of injury severity. IL-6 is known to act not only as an inflammatory mediator but also as a key factor in regulating the acute phase response, modulating phagocytes, and stimulating the production of acute phase proteins in the liver.

Equally significant was the level of MMP-9, which is responsible for the degradation of the extracellular matrix. In patients with intra-articular fractures, MMP-9 concentrations reached 232.4±42.1 ng/ml, compared to 168.9±35.7 ng/ml ($p <0.001$) in the non-fractured group. Elevated MMP-9 levels are associated with impaired regenerative processes and the development of chronic synovitis and osteoarthritis.

The combination of these changes (decreased cellular immunity, increased proinflammatory and tissue-destructive mediators, and activation of humoral inflammation) suggests complex immune decompensation in patients with intra-articular fractures.

A comparative analysis of clinical and immunological parameters demonstrated a consistent relationship between the severity of HA and osteoarticular damage and the severity of immunological changes. Arthritis with an intra-articular fracture is associated not only with a more severe clinical course but also with dysregulation of both cellular and humoral immunity. The results indicate that bone involvement triggers a cascade of proinflammatory mediators, primarily IL-6 and TNF-α, and leads to an imbalance between $CD4^+$ and $CD8^+$ lymphocytes. The resulting immune profile is unstable and associated with a risk of complications.

Thus, the data obtained confirm the possibility of using immunological parameters as benchmarks for the early assessment of the severity of the inflammatory response.

In the main group, by days 14-30 of treatment, a significant increase in the level of $CD3^+$ lymphocytes was observed from 52.4±6.8% to 58.7±7.1% ($p <0.01$), $CD4^+$ - from 27.6±4.3% to 32.4±4.6% ($p <0.01$), as well as normalization of $CD8^+$. The immunoregulatory index increased from 1.29 to 1.45 ($p <0.05$), indicating the restoration of the functional activity of the T-cell link. In the comparative group, similar dynamics were less pronounced and statistically significant only for $CD4^+$ ($p = 0.047$).

Humoral immunity also showed recovery: IgM and IgG levels increased in patients in the study group by day 30, while CIC concentrations decreased from 93.5±12.4 optical

units to 71.2 ±10.5 optical units ($p < 0.01$), possibly indicating the elimination of immune complexes from the bloodstream. Complement C3 and C4 levels increased by 10-15% from baseline, while lysozyme increased from 0.64 ±0.09 mg/L to 0.91 ±0.11 mg/L ($p < 0.01$), reflecting the activation of innate defense mechanisms.

The cytokine profile demonstrated the most pronounced dynamics. In the study group, IL-6 levels decreased from 74.2 ±18.6 pg/ml to 38.4 ±13.5 pg/ml ($p < 0.001$), TNF-α from 49.3 ±11.4 pg/ml to 31.7 ±9.9 pg/ml ($p < 0.001$), and IL-1β and IL-10 to levels approaching physiological values. In the comparison group, a decrease in IL-6 and TNF-α was also observed, but was less pronounced and statistically significant only by day 30. In the SF, IL-6 and MMP-9 decreased by 1.5-1.8 times from baseline values, especially in patients with CL injury.

Along with the described changes, patients demonstrating positive clinical dynamics also showed stabilization of immunological parameters, accompanied by an improvement in their general condition. A significant reduction in pain (by more than 3 points on the VAS scale), a decrease in the frequency of repeat intra-articular punctures (by 1.7 times in patients with positive dynamics), and restoration of joint range of motion occurred in parallel with normalization of cytokine levels and humoral parameters.

Thus, immunological parameters can be considered not only as a reflection of treatment effectiveness but also as a guide for assessing the timeliness and necessity of repeat drainage procedures.

A comparative analysis of patients with GA depending on the injured joint shows that the rate and severity of immunological changes are closely linked to the ability to control local inflammation. A more pronounced reduction in inflammatory mediators with frequent and timely punctures into the joint emphasizes the role of this intervention not only as a symptomatic but also as a pathogenetically significant one. This opens the prospect of more active use of punctures not only for exudate removal but also as a method for controlling the inflammatory load in the joint, especially in fractures accompanied by massive GA.

A dynamic reduction in concentrations of key inflammatory and enzymatic markers (IL-6, TNF-α, MMP-9, circulating immune complexes), as well as normalization of IL-1β and IL-10, is accompanied by clinical improvement in patients' condition, a reduction in pain, and a decrease in the frequency of AA relapses. These changes occur against the background of a significant increase in $CD3^+$, $CD4^+$, and $CD8^+$ lymphocytes, an increase in IgM and IgG levels, and activation of innate defenses (increased lysozyme levels). This shift in the immunological profile reflects the restoration of a regulatory balance between proinflammatory, adaptive, and innate components of the immune response and can be considered a biological marker of a favorable course of post-traumatic inflammation.

Stabilization of the immune response by day 30 of treatment, especially with timely punctures and consistent clinical and laboratory monitoring, emphasizes the need for comprehensive monitoring of not only the clinical condition but also the dynamics of immunological parameters. IL-6, TNF-α, circulating immune complexes (CIC), $CD4^+$, $CD19^+$, IgG, and FI proved to be the most sensitive and informative markers in this process, reliably reflecting clinical dynamics and treatment outcome. Using these markers in a sequential monitoring mode not only allows for an objective assessment of treatment effectiveness but also for early stratification of the risk of an unfavorable course, forming the basis for developing prognostic algorithms.

To assess these relationships, the degree of reduction in cytokines, immune cells, and humoral components was compared with the recorded dynamics of clinical parameters, such as the duration of hospitalization, the frequency of GA recurrence, the need for repeat punctures, and residual joint dysfunction.

Patients who achieved a favorable clinical outcome showed significant improvement in key immunological parameters by day 30. The IL-6 level decreased from 74.2 ±18.6 pg/ml to 38.4 ±13.5 pg/ml, TNF-α - from 49.3 ±11.4 pg/ml to 31.7 ±9.9 pg/ml, CIC - from 93.5 ±12.4 optical units to 71.2 ±10.5 optical units. The $CD4^+$ and $CD19^+$ indicators increased by 17.4% and 21.7%, respectively, IgG increased from 9.4 ±0.88 g/l to 11.3 ±1.1 g/l, and FI increased by 18.6%.

Correlation analysis revealed that the highest prognostic value was shown by the rates of decline in IL-6 ($r = -0.683$), TNF-α ($r = -0.592$), and MMP-9 ($r = -0.538$), as well as increases in $CD4^+$ ($r = 0.514$), $CD19^+$ ($r = 0.497$), IgG ($r = 0.481$), and FI ($r = 0.461$), allowing these parameters to be used as integral indicators of therapy effectiveness and predictors of the risk of complications.

Subgroup analysis based on injury location revealed that IL-6 and MMP-9 in the SF had the greatest prognostic value in patients with GA CS, with levels above the median values significantly associated with GA recurrence, prolonged recovery, and repeat interventions. Markers such as CIC and lysozyme also demonstrated additional value, but their contribution was less pronounced.

In the final stage of the analysis, a prognostic model was constructed based on logistic regression, incorporating the most sensitive and specific dynamic immunological parameters. The resulting model demonstrated high prognostic accuracy and enabled risk stratification at the early stages of follow-up.

The resulting prognostic model included seven dynamic immunological parameters: IL-6, TNF-α, CIC, $CD4^+$, $CD19^+$, IgG, and FI. The dynamics of IL-6, CIC, and $CD4^+$ contributed the most to risk differentiation. According to the results of the ROC analysis, the model demonstrated moderate prognostic accuracy: the area under the curve (AUC) was 0.621, with a threshold of 0.530, sensitivity reached 39.3%, and specificity reached 84.4%. These indicators confirm the feasibility of using immunological changes as a prognostic basis for early stratification of patients at risk for complicated disease progression.

The developed scale allows for the identification of patients at high, moderate, and low risk based on the combined dynamics of these indicators. The model can be

used to inform treatment planning and clinical monitoring.

Thus, the proposed approach to prognostic verification based on immunological dynamics improves the accuracy of risk stratification and opens up opportunities for clinically oriented personalized therapy in patients with AA associated with intra-articular fractures.

4. Conclusions

1. Hemarthrosis in patients with intra-articular fractures is more severe: the volume of effusion is statistically higher, pain is more severe, the number of punctures is more than 1.5 times higher, and the duration of hospitalization is 4.4 days longer than in patients without fractures. Recurrent hemarthrosis, reactive synovitis, and the need for surgical intervention are recorded 4-6 times more often.
2. Analysis of the relationships between immunological parameters revealed statistically significant correlations between the components of the inflammatory and immune responses. IL-6 levels decreased with an increase in $CD4^+$ lymphocytes, $CD19^+$, lysozyme, and FI, reflecting the activation of regulatory mechanisms of immune compensation. Conversely, an increase in MMP-9 was accompanied by an increase in circulating immune complexes (r=0.482) and a decrease in IgG (r=-0.401), indicating an increase in the humoral component of inflammation with suppression of the specific response.
3. Identification of typical patterns of deviation from the recovery dynamics at the early stage of observation creates the basis for an objective assessment of the risk of an adverse outcome, including the possibility of personalized planning of further monitoring and rehabilitation.

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