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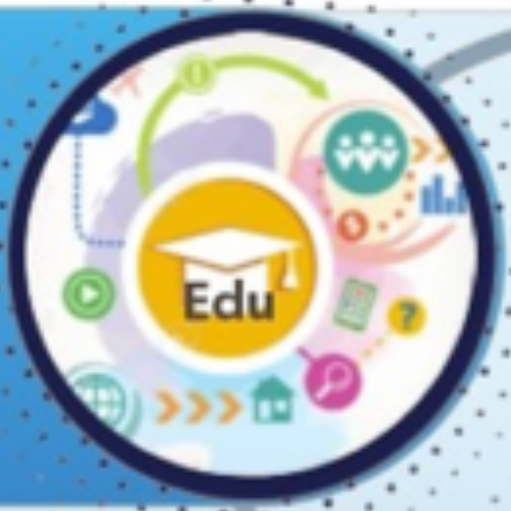

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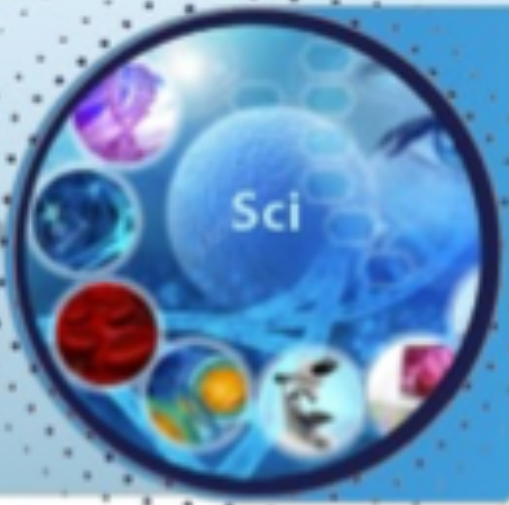

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Development of a Clinical-Immunological Prognostic Model for Adverse Outcomes in Posttraumatic Hemarthrosis Associated with Intra-Articular Fractures

B.Z. Khamdamov[1], K.Sh. Vakhabov[2], K.Kh. Boboev[3]

ABSTRACT

Background. *Posttraumatic hemarthrosis (HA) following intra-articular fractures is a clinically significant condition with variable outcomes ranging from full recovery to persistent joint dysfunction. Early prediction of adverse outcomes remains a challenge. This study aimed to develop and validate an immunologically guided prognostic model based on selected biomarkers.*

Materials and Methods. *A total of 150 individuals were enrolled: 60 patients with HA after intra-articular fractures (main group), 60 with HA without fracture (comparative group), and 30 healthy controls. Serial measurements of $CD4^+$, $CD19^+$, IgG, CIC, IL-6, TNF-α, and phagocytic index (PI) were performed at baseline and on days 10–14 post-injury. Logistic regression and ROC analysis were used to construct a predictive model.*

Results. *Patients with poor clinical outcomes demonstrated negative ΔIL-6 (< –20 pg/mL), low $\Delta CD4^+$ (< +3%), insufficient ΔIgG (< +1.5 g/L), and <15% reduction in CIC. The predictive model including five immune parameters showed excellent performance (AUC = 0.91, sensitivity 87%, specificity 81%). A simplified scoring system was proposed for clinical use.*

Conclusion. *Dynamic immune profiling in the subacute phase of trauma enables early identification of patients at high risk of unfavorable outcomes. The developed model has strong potential for integration into risk stratification protocols in posttraumatic joint care.*

Keywords: *Hemarthrosis, intra-articular fracture, prognosis, immune markers, IL-6, $CD4^+$, CIC, ROC analysis, prediction model.*

[1] Bukhara State Medical Institute, Bukhara, Uzbekistan

[2] Samarkand Branch of the Republican Specialized Scientific-Practical Medical Center of Traumatology and Orthopedics, Samarkand, Uzbekistan

[3] Tashkent Medical Academy, Tashkent, Uzbekistan

INTRODUCTION

Posttraumatic hemarthrosis (HA) is a frequent and disabling complication of intra-articular fractures, associated with synovial inflammation, joint effusion, and potential progression to chronic dysfunction or posttraumatic osteoarthritis [1,2]. While conventional assessment relies heavily on radiological and clinical criteria, these approaches often lack sensitivity for predicting adverse outcomes in the subacute period [3].

Recent studies have emphasized the role of the immune system in modulating joint recovery. Trauma induces both systemic and local inflammatory responses that affect tissue remodeling and regeneration [4]. Key immunological components—such as $CD4^+$ T-helper cells, circulating immune complexes (CIC), immunoglobulins, and proinflammatory cytokines (IL-6, TNF-α)—serve as not only markers of inflammation but also as potential predictors of healing capacity and complication risk [5–7].

Despite the identification of individual immune parameters associated with poor recovery, integrated models capable of predicting outcomes with high clinical utility remain underdeveloped. Most prior attempts have been limited to single time-point measurements or lacked validation against objective clinical outcomes [8,9].

In this context, dynamic monitoring of immune markers offers a promising strategy. It allows the detection of trajectories associated with failure to resolve inflammation or excessive immune activation, both of which may contribute to joint fibrosis, recurrent effusions, and surgical revision [10].

This study aimed to construct a clinical-immunological model for predicting adverse outcomes in patients with HA secondary to intra-articular fractures. Based on logistic regression of serial immune data, we sought to identify key biomarkers, validate their predictive capacity using ROC analysis, and propose a simplified scoring tool for clinical application.

MATERIALS AND METHODS

This prospective observational study was conducted between 2021 and 2024 at the Samarkand Branch of the Republican Specialized Scientific-Practical Medical Center of Traumatology and Orthopedics. Ethical approval was granted by the Local Ethics Committee of Bukhara State Medical Institute, and written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

The study enrolled 150 participants, divided into three groups: the main group included 60 patients with hemarthrosis (HA) caused by intra-articular fractures of the knee or ankle joints; the comparative group comprised 60 patients with traumatic HA not associated with fractures (confirmed by radiographic and CT imaging); and the control group included 30 clinically healthy volunteers, matched by age and sex. All patients were admitted within 48 hours after injury. Exclusion criteria were the presence of autoimmune or infectious diseases, decompensated diabetes mellitus, chronic hepatic or renal disorders, malignancy, and recent immunosuppressive therapy.

All patients in the main and comparative groups underwent venous blood sampling on day 1–2 (baseline) and again on day 10–14 post-injury. The following immunological parameters were assessed: $CD4^+$ and $CD19^+$ lymphocyte counts (flow cytometry using BD FACSCalibur); serum IgG levels (nephelometry); circulating immune complexes (CIC) (PEG precipitation); cytokines IL-6 and TNF-α (ELISA); and phagocytic index (PI), determined microscopically using latex particle ingestion. For each parameter, delta values (Δ) were calculated as the difference between follow-up and baseline values ($\Delta X = X_{10-14} - X_{1-2}$).

Clinical outcomes were assessed prospectively and categorized as favorable or unfavorable. Unfavorable outcomes included any of the following: recurrent hemarthrosis requiring aspiration, persistent synovitis beyond 14 days, delayed joint function recovery beyond 21 days, or re-hospitalization and surgical revision. Patients were stratified accordingly into two prognostic groups.

Statistical analysis was performed using SPSS 26.0 and MedCalc. The normality of data distribution was tested using the Shapiro–Wilk test. Continuous variables were expressed as mean ± standard deviation and compared using the Student's t-test or Mann–Whitney U test as appropriate. Categorical variables were analyzed using the chi-square test. Logistic regression analysis was applied to identify independent predictors of adverse outcome, with ΔIL-6, $\Delta CD4^+$, ΔIgG, ΔCIC, ΔTNF-α, and ΔPI considered as candidate variables. The final model was selected using backward stepwise elimination ($p<0.05$). Model performance was evaluated using receiver operating characteristic (ROC) analysis with area under the curve (AUC), sensitivity, specificity, and optimal cutoff values reported. Based on regression coefficients, a simplified predictive scoring system was also proposed for clinical use.

RESULTS

A total of 150 participants completed the study. Among them, 60 patients had posttraumatic hemarthrosis (HA) associated with intra-articular fractures (main group), 60 had HA without fractures (comparative group), and 30 healthy individuals comprised the control group. Demographic parameters were comparable between groups ($p > 0.05$). Clinical follow-up revealed that 26 patients (43.3%) in the main group and 9 patients (15%) in the comparative group developed unfavorable outcomes, confirming the higher risk associated with fracture-related HA ($\chi^2 = 10.72$, $p < 0.01$).

Analysis of immune dynamics (Δ-values between days 1–2 and 10–14) revealed significant differences between patients with favorable and unfavorable outcomes. In the unfavorable group, ΔIL-6 was persistently negative, averaging –24.7 ± 8.5 pg/mL, compared to a moderate decline (–9.3 ± 4.7 pg/mL) in the favorable group ($p < 0.001$). Similarly, $\Delta CD4^+$ lymphocytes showed minimal recovery in the unfavorable group (+1.1 ± 0.9%), whereas patients with favorable outcomes exhibited a pronounced increase (+5.2 ± 1.7%, $p < 0.001$). A comparable trend was observed for ΔIgG (+0.7 ± 0.5 g/L vs +2.3 ± 0.8 g/L, $p < 0.001$), and ΔCIC reduction was significantly smaller in the unfavorable group (–8.2 ± 3.4 opt. units vs –17.1 ± 5.6, $p < 0.001$).

A binary logistic regression analysis identified four Δ-indicators as independent predictors of unfavorable outcomes: ΔIL-6 < –20 pg/mL (OR = 4.65; 95% CI: 2.01–10.78), $\Delta CD4^+ < +3\%$ (OR = 3.74; 95% CI: 1.66–8.46), ΔIgG < +1.5 g/L (OR = 3.92; 95% CI: 1.71–9.00), and ΔCIC reduction < 15 units (OR = 3.58; 95% CI: 1.59–8.09). ΔTNF-α and ΔPI did not retain significance in the final multivariate model ($p > 0.05$).

The predictive model incorporating these four variables demonstrated high discriminative ability, with ROC analysis yielding an AUC of 0.91 (95% CI: 0.86–0.96). At the optimal cutoff, the model achieved 87% sensitivity and 81% specificity for predicting adverse outcomes. A simplified scoring system was derived, assigning one point for each high-risk Δ-indicator. Patients scoring 3–4 points had a 78% probability of developing complications, while those with 0–1 points had less than 10% risk.

The model was internally validated using bootstrapping (1000 iterations), which confirmed its robustness (corrected AUC: 0.89).

DISCUSSION

The present study demonstrates that dynamic monitoring of selected immune parameters can provide clinically meaningful prognostic information in patients with hemarthrosis (HA) following intra-articular fractures. Our findings suggest that specific patterns of immune recovery—or failure thereof—are closely linked to the development of unfavorable outcomes, including persistent synovitis, delayed functional recovery, and repeated effusions.

One of the key findings was the significant prognostic value of IL-6 dynamics. A persistent elevation or insufficient decline of IL-6 (ΔIL-6 < –20 pg/mL) was the strongest individual predictor of adverse outcome. This aligns with prior studies that have identified IL-6 as a reliable marker of systemic inflammatory response and tissue damage following trauma [1,2]. While acute elevation of IL-6 may be appropriate in the early inflammatory phase, its sustained production is associated with ongoing synovial activation and joint matrix degradation [3].

Similarly, $\Delta CD4^+$ lymphocyte count emerged as a powerful immunological marker. Patients with inadequate restoration of $CD4^+$ levels within two weeks post-injury were significantly more likely to experience complications. $CD4^+$ T cells play a central role in orchestrating immune resolution and tissue repair [4]; thus, their persistent deficiency may reflect post-traumatic immunosuppression or regulatory failure. These observations are consistent with previous data on $CD4^+$ dysfunction in polytrauma and sepsis [5].

Immunoglobulin G (IgG) recovery also proved predictive. A ΔIgG below +1.5 g/L was independently associated with poor outcomes, suggesting that humoral immune exhaustion contributes to impaired joint homeostasis. While IgG is classically involved in pathogen defense, it also participates in clearance of immune complexes and supports tissue repair [6].

The role of circulating immune complexes (CIC) in posttraumatic inflammation has been highlighted in both experimental and clinical literature [7]. Our study confirms that insufficient reduction of CIC over time is linked to delayed resolution of inflammation, possibly due to ongoing antigen exposure or defective clearance mechanisms. Elevated CIC levels may perpetuate synovial irritation and complement activation, further exacerbating joint injury [8].

Interestingly, although TNF-α and the phagocytic index (PI) showed significant differences between groups in univariate analysis, they did not retain statistical significance in the final model. This suggests that their prognostic utility may be limited in the presence of stronger markers such as IL-6 and $CD4^+$.

The resulting four-parameter model demonstrated excellent diagnostic performance, with an AUC of 0.91. This level of accuracy is comparable to or superior to existing orthopedic scoring systems, many of which lack immunological integration [9]. Importantly, our model is based on simple and widely available laboratory assays, which increases its feasibility for clinical adoption.

From a practical perspective, the derived point-based scale allows for stratification of patients into high- and low-risk groups using a straightforward scoring algorithm. This may facilitate early identification of patients requiring closer follow-up, immunological consultation, or tailored therapeutic approaches such as intensified physical therapy or anti-inflammatory interventions.

Limitations of this study include the single-country setting and relatively short follow-up period. Further multicenter validation is warranted to confirm external applicability. Nonetheless, the robustness of the model under internal validation suggests that its core components are biologically relevant and clinically useful.

CONCLUSION

This study presents a novel clinical-immunological model for predicting adverse outcomes in patients with posttraumatic hemarthrosis following intra-articular fractures. By evaluating the dynamics of key immune indicators—specifically ΔIL-6, $\Delta CD4^+$, ΔIgG, and ΔCIC—we were able to identify patients at high risk for prolonged inflammation, functional limitations, and surgical complications. The proposed model demonstrated high diagnostic accuracy and internal validity, and can be easily implemented using standard laboratory tools.

Incorporation of this model into clinical practice may improve early risk stratification, guide personalized treatment strategies, and ultimately enhance outcomes in the management of joint trauma. Further multicenter studies are warranted to externally validate and refine this approach across broader patient populations.

Ethical Approval:

This study was approved by the Local Ethics Committee of Bukhara State Medical Institute. All participants signed written informed consent prior to enrollment, in accordance with the Declaration of Helsinki (2013 revision).

Conflict of Interest:

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

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Author Contributions:

Khamdamov B.Z. – Conceptual design, supervision, critical revision of the manuscript.

Vakhabov K.Sh. – Patient enrollment, immunological testing, statistical analysis, drafting of the manuscript.

Boboev K.Kh. – Laboratory quality control, interpretation of immunological data, editing and coordination.

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TRAVMATIK GEMARTROZLI BEMORLARDA NOQULAY KLINIK NATIJALARNI BASHORAT QILISH UCHUN KLINIKO-IMMUNOLOGIK MODELNI ISHLAB CHIQISH

Hamdamov B.Z.[1], Vahobov K.Sh.[2], Boboyev K.X.[3]

[1] Buxoro Davlat Tibbiyot Instituti, Buxoro, O‘zbekiston
[2] Respublika ixtisoslashtirilgan travmatologiya va ortopediya ilmiy-amaliy tibbiyot markazi, Samarqand filiali
[3] Toshkent Tibbiyot Akademiyasi, Toshkent, O‘zbekiston

ANNOTATSIYA:

Ichki bo‘g‘im sinishlari bilan kechuvchi travmatik gemartrozdan so‘ng noqulay natijalarni erta aniqlash dolzarb klinik vazifadir. Ushbu tadqiqotning maqsadi — IL-6, $CD4^+$ limfotsitlar, IgG, tsirkulyatsiyalovchi immun komplekslar (TsIK) kabi asosiy immun ko‘rsatkichlar dinamikasiga asoslangan bashorat modelini ishlab chiqish va baholashdan iborat bo‘ldi. Tadqiqotda 150 nafar ishtirokchi qatnashdi. 10–14 kun oralig‘idagi o‘zgarishlar (Δ) hisoblandi va logistik regressiya asosida to‘rt ko‘rsatkichli prognoz modeli yaratildi. Natijalar ΔIL-6 < –20 pg/ml, $\Delta CD4^+$ < +3%, ΔIgG < +1.5 g/l va ΔTsIK < –15 birlik bo‘lgan bemorlar orasida asoratlar xavfi yuqoriligini ko‘rsatdi. ROC tahlilga ko‘ra, modelning aniqligi (AUC = 0.91) yuqori bo‘lib, tavsiya etilgan ballik tizim klinik qo‘llash uchun mos deb topildi.

Kalit so‘zlar: Gemartroz, bo‘g‘im sinishi, immunologik markerlar, IL-6, TsIK, $CD4^+$, prognoz modeli, ROC.

РАЗРАБОТКА КЛИНИКО-ИММУНОЛОГИЧЕСКОЙ МОДЕЛИ ПРОГНОЗИРОВАНИЯ НЕБЛАГОПРИЯТНОГО ИСХОДА У ПАЦИЕНТОВ С ПОСТТРАВМАТИЧЕСКИМ ГЕМАРТРОЗОМ, АССОЦИИРОВАННЫМ С ВНУТРИСУСТАВНЫМИ ПЕРЕЛОМАМИ

Хамдамов Б.З.[1], Вахобов К.Ш.[2], Бобоев К.Х.[3]

[1] Бухарский государственный медицинский институт, г. Бухара, Республика Узбекистан
[2] Самаркандский филиал Республиканского специализированного научно-практического медицинского центра травматологии и ортопедии
[3] Ташкентская медицинская академия, г. Ташкент, Республика Узбекистан

АННОТАЦИЯ:

Ранняя идентификация пациентов с высоким риском неблагоприятного исхода после травматического гемартроза остаётся актуальной клинической задачей. Целью данного исследования явилась разработка и валидация прогностической модели на основе динамики иммунологических показателей — IL-6, $CD4^+$-лимфоцитов, IgG и циркулирующих иммунных комплексов (ЦИК). В исследование были включены 150 пациентов. Оценивалась разница значений на 10–14 сутки после травмы (Δ). Построенная логистическая модель продемонстрировала высокую диагностическую точность (AUC = 0.91). Установлено, что значения ΔIL-6 < –20 пг/мл, $\Delta CD4^+$ < +3%, ΔIgG < +1,5 г/л и снижение ЦИК < 15 опт. ед. достоверно ассоциированы с осложнённым течением. Разработанная балльная шкала позволяет проводить раннюю стратификацию риска и может быть использована в клинической практике.

Ключевые слова: Гемартроз, внутрисуставной перелом, иммунные маркеры, IL-6, ЦИК, $CD4^+$, модель прогноза, ROC-анализ.