



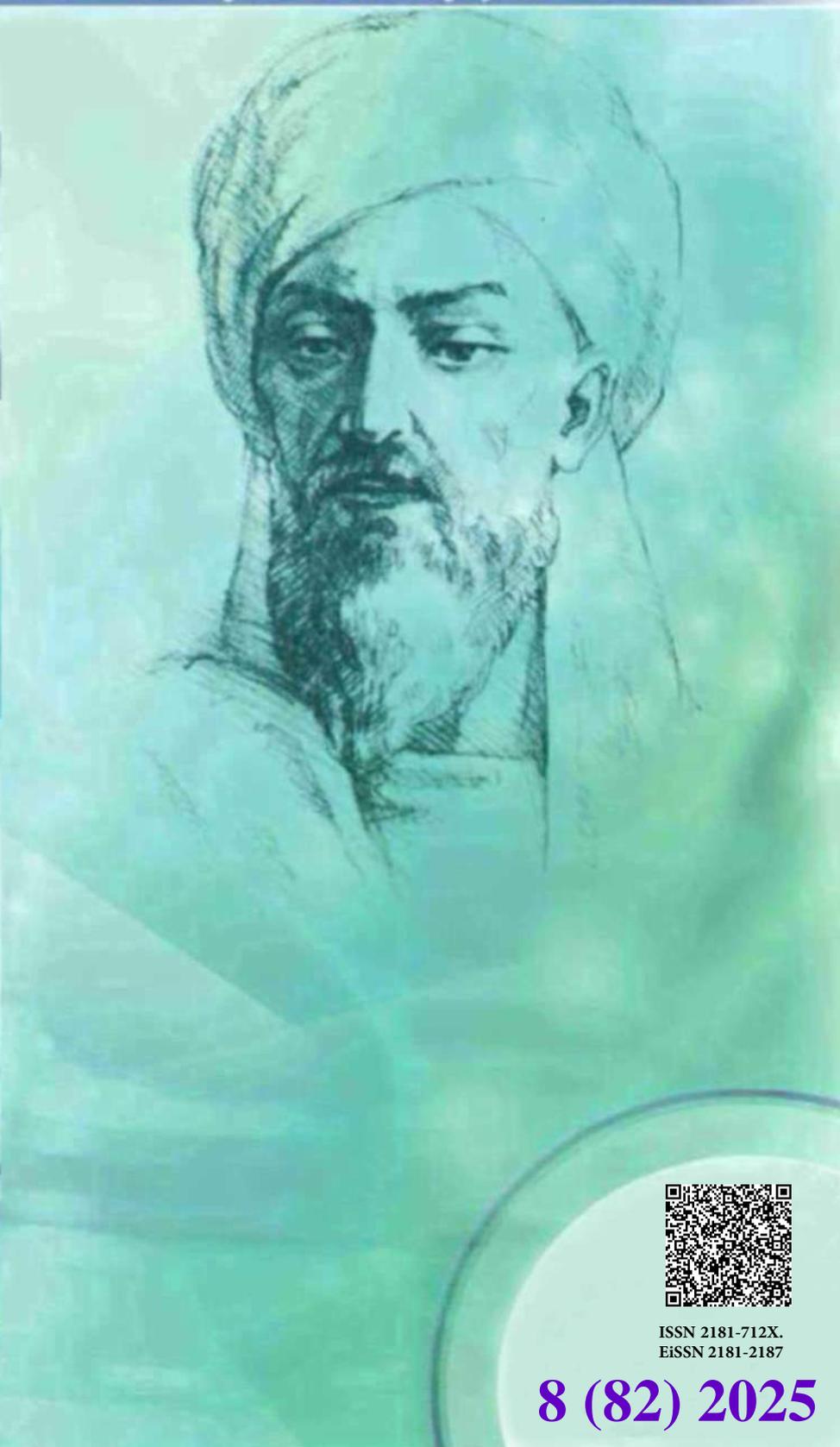
**New Day in Medicine**  
**Новый День в Медицине**

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НОВЫЙ ДЕНЬ В МЕДИЦИНЕ  
NEW DAY IN MEDICINE**

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## КЛИНИКО-ИММУНОЛОГИЧЕСКАЯ МОДЕЛЬ ПРОГНОЗИРОВАНИЯ ОСЛОЖНЕНИЙ ПОСЛЕ ПЕРЕЛОМОВ КОСТЕЙ

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### ✓ Резюме

*В результате исследования установлено, что переломы крупных костей (таза, бедра, голени) сопровождаются высоким риском инфекций, тромбозов и некрозов. На основе ретроспективного анализа 284 случаев были определены клинико-иммунологические предикторы осложнений и построена модель риска из 8 переменных (тип травмы, IL-2, TNF-α, D-димер). Проспективное исследование 124 пациентов показало, что использование риск-стратифицированной профилактики, включая CO<sub>2</sub>-терапию, позволило снизить частоту осложнений с 45% до 21,8%, исключить летальные ТЭЛА и ускорить восстановление (Мажед 84 против 68). Разработанная модель обеспечивает достоверную стратификацию риска и создаёт возможности для ранних целевых вмешательств.*

*Ключевые слова: переломы костей; осложнения; прогноз риска; иммунологические маркеры; венозная тромбозия; CO<sub>2</sub>-терапия*

## SUYIK SIRISHLARIDAN KEYINGI ASORATLARNI BASHORATLOVCHI KLINIK VA IMMUNOLOGIK MODEL

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*O'tkazilgan tadqiqot katta suyak sinishlari (tos, son, boldir) yuqori infeksiya, tromboemboliya va bitmaslik xavfi bilan bog'liqligi aniqlandi. 284 holatning retrospektiv tahlilida klinik va immunologik prediktorlar aniqlanib, 8 ta o'zgaruvchidan (shikast turi, IL-2, TNF-α, D-dimer) iborat xavf modeli ishlab chiqildi. 124 bemorda o'tkazilgan prospektiv bosqichda ushbu model asosida shaxsiy profilaktika, jumladan CO<sub>2</sub>-terapiya qo'llanishi asoratlarni 45% dan 21,8% gacha kamaytirdi, o'limga olib keluvchi o'pka emboliyasini oldini oldi va tuzalishni tezlashtirdi (Majeed 84 ga nisbatan 68). Model xavfni ishonchli stratifikatsiya qilib, erta maqsadli choralarni qo'llash imkonini beradi.*

*Kalit so'zlar: suyak sinishlari; asoratlar; xavf prognozi; immunologik markerlar; venoz tromboemboliya; CO<sub>2</sub>-terapiya*

## CLINICAL AND IMMUNOLOGICAL MODEL FOR PREDICTING COMPLICATIONS AFTER LARGE BONE FRACTURES

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✓ *Resume*

*In result, fractures of major bones (pelvis, femur, tibia) were confirmed to carry high risks of infection, thromboembolism, and nonunion. Retrospective analysis of 284 cases identified clinical and immunological predictors, leading to a risk model of 8 variables (injury type, IL-2, TNF- $\alpha$ , D-dimer). In a prospective cohort of 124 patients, applying this model with personalized prophylaxis, including CO<sub>2</sub> therapy, reduced complications from 45% to 21.8%, prevented fatal pulmonary emboli, and improved recovery (Majeed 84 vs 68). The model enables reliable risk stratification and early targeted interventions.*

*Keywords: bone fractures; complications; risk prediction; immunological markers; venous thromboembolism; CO<sub>2</sub> therapy*

### Relevance

Fractures of large bones such as the pelvis, femur, and tibia present a serious problem in traumatology due to their high complication and mortality rates [10; 13]. The incidence of these fractures is steadily rising with urbanization and increasing traffic accidents [17]. Early postoperative mortality ranges from 0.2–4.5%, reaching up to 34.5% within one year in elderly patients [2; 15]. Complications occur in up to 65% of cases and include local issues (osteomyelitis, wound infections, nonunion) and systemic events (deep vein thrombosis (DVT), pulmonary embolism (PE)) [14; 16]. Complications are particularly severe in cases of multiple, open, or unstable fractures, where the risk of infection and thrombosis is highest [18; 21]. The high rate of complications and resultant disability underscores the need for methods of early complication prediction and prevention to individualize treatment.

Current protocols for venous thromboembolism prophylaxis after long-bone fractures are based on uniform anticoagulation regimens [11, 19]. However, in severe trauma with systemic inflammation, standard measures may be insufficient or excessive [12, 5]. There is an urgent need for a prognostic model that integrates clinical and immunological parameters to stratify complication risk upon admission [20]. We developed a clinico-immunological model for predicting post-fracture complications (pelvis, femur, tibia), validated it prospectively, and evaluated whether a personalized management strategy guided by this model improves outcomes.

The **aim of the study** is to develop and clinically validate a clinico-immunological model for predicting complications after major long-bone fractures, enabling personalized prophylaxis and improved treatment outcomes.

### Materials and Methods

**Study Design:** We performed a two-stage combined study. In the first, retrospective stage (2018–2022), we reviewed the medical records of 284 patients with fractures of the pelvis (n=94), femur (n=97), or tibia (n=93). Patients with polytrauma, terminal illnesses, or incomplete data were excluded. From this cohort, we identified clinical factors and biomarkers associated with postoperative complications and used them to develop a risk prediction model. In the second, prospective stage (2022–2024), 124 patients (pelvic fractures – 43, femoral – 41, tibial – 40) were treated with guidance from the new model. Inclusion criteria for the prospective group were adult patients with an acute fracture (<72 hours old), no severe comorbidities, and informed consent. All prospective patients were stratified by predicted risk, and management (fixation method, prophylaxis regimen, physiotherapy) was personalized according to calculated risk level.

**Parameters and Model Development:** From the retrospective cohort, we collected data on fracture type and location, injury characteristics (open/closed, stability), presence of shock, time to hospitalization, fixation method, and occurrence of local or systemic complications. Special attention was given to immunological and biochemical markers reflecting inflammation and coagulation: interleukin-2 (IL-2), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), immunoglobulins (IgA, IgG, IgM), and D-dimer, measured in the early post-injury period and at complication onset. Statistical analysis included correlation analysis to identify relationships between biomarkers and complications, and multivariate regression to construct the prognostic model.

Based on retrospective data, we developed a weighted risk score model incorporating **8 predictors**: fracture anatomical site, fracture type (comminuted/oblique/transverse), fracture character

(open/closed), fracture stability (unstable/stable), patient age, IL-2 level, TNF- $\alpha$  level, and D-dimer level. Each factor was assigned a weight proportional to its prognostic importance. The total score **R** represents the risk estimate: **low risk** –  $R \leq 6$ , **moderate** – 7–15, **high risk** –  $R \geq 16$ . For example, an elderly patient with a severe open comminuted femur fracture and high IL-2, TNF- $\alpha$ , D-dimer would score ~23 (high risk). The model was accompanied by treatment recommendations for each risk category: low risk – conservative measures, moderate – standard surgery with short-term prophylaxis, high – urgent surgery, intensive anticoagulation, and mandatory CO<sub>2</sub> therapy. **Carboxytherapy** (local CO<sub>2</sub> infusions) was introduced as a novel adjunct to improve microcirculation and stimulate repair in cases of pronounced systemic inflammation. In the prospective stage, each patient's R-score was calculated; based on risk category and immune status, the VTE prophylaxis was tailored (e.g. mechanical compression vs low-molecular-weight heparin with D-dimer monitoring), the need for CO<sub>2</sub> therapy determined, mobilization timing adjusted, etc., via multidisciplinary decision (trauma surgeon, anesthesiologist, vascular specialist) with ongoing re-evaluation.

**Patient Groups:** The prospective cohort was divided into two main treatment groups. **Group 1** (n=30) received standard care without the predictive algorithm, no formal risk assessment or CO<sub>2</sub> therapy (internal control). **Group 2** (n=94) received model-guided management with clinico-immunological evaluation. Within Group 2, two subgroups were defined: **2a** (n=36) – patients who additionally received carboxytherapy; **2b** (n=58) – patients without CO<sub>2</sub> therapy. We also identified overlapping analytical subgroups irrespective of main group: **Group 3** (n=48) – patients with immune hyperactivation (IL-2 >16 pg/mL, TNF- $\alpha$  >20 pg/mL, D-dimer >1.5 mg/L), and **Group 4** (n=38) – patients with a high risk score ( $R \geq 16$ ). These analytic subgroups were used to examine pathophysiological relationships and to validate model performance, but management decisions primarily depended on assignment to Group 1 vs 2.

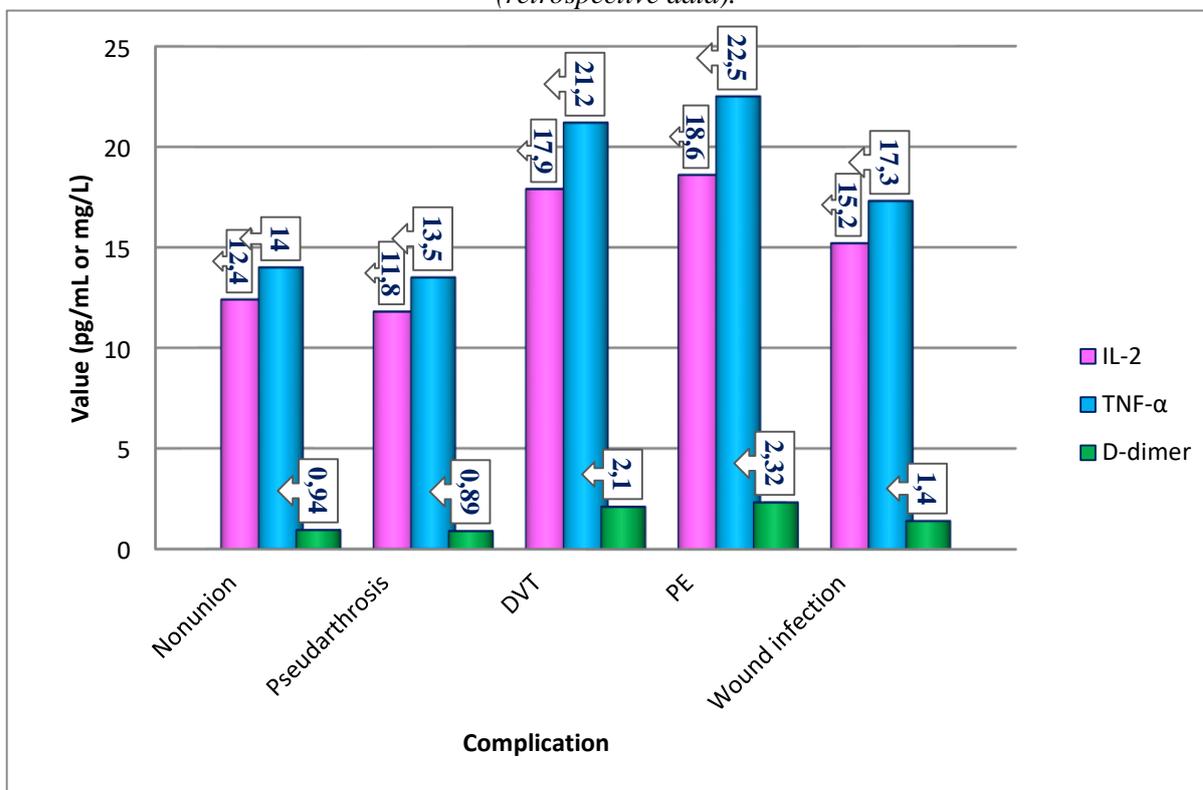
## Result and discussions

**Retrospective Analysis of Complications:** Among 284 retrospective patients, a large proportion experienced complications. **Local (orthopedic) complications** included fracture **nonunion**, pseudarthrosis (false joint formation), and osteosynthesis site infections. The overall incidence of local complications reached ~40% of patients, and some patients had more than one complication (338 total local complications in 284 patients). The most common were pseudarthroses (41.2% of all local complications), followed by nonunions (32%) and malunions (26.8%). Soft-tissue infections (purulent wound complications) occurred in 19.0% of patients (54 cases). **Systemic complications** occurred in ~30% of patients (135 events) and included: deep vein thrombosis in 13.0%, hypostatic pneumonia in 10.2%, decompensation of chronic conditions (e.g. heart failure) in 12.0%, pressure sores in 6.7%, and pulmonary embolism in 5.6%. Nearly all systemic complications were observed in patients who also had local complications (prolonged immobilization, multiple surgeries, etc., predisposed to systemic problems). The most dangerous complication was PE: although relatively infrequent (16 patients, 5.6%), PE had a 25% mortality (4 deaths despite treatment). Thus, the retrospective data confirmed that greater initial injury severity and the presence of local complications substantially increase the risk of life-threatening systemic complications.

**Clinico-Immunological Correlations:** Our analysis revealed two fundamentally different patterns of inflammatory response in complicated courses (illustrated in Figure 1). The first is a relatively **localized inflammatory reaction** associated with orthopedic complications (nonunion, pseudarthrosis), characterized by moderate cytokine elevations (IL-2 ~11–12 pg/mL, TNF- $\alpha$  ~13–14 pg/mL) and minor changes in D-dimer. The second pattern is **systemic inflammation** accompanying general complications (infections, thromboses, PE), in which IL-2 and TNF- $\alpha$  levels more than doubled (reaching ~18–19 pg/mL and ~22–25 pg/mL, respectively) and D-dimer rose to 1.8–2.3 mg/L. For example, in cases of pulmonary embolism, mean IL-2 was  $18.6 \pm 3.6$  pg/mL, TNF- $\alpha$   $22.5 \pm 4.1$  pg/mL, D-dimer  $2.32 \pm 0.45$  mg/L, whereas in fracture nonunion IL-2 averaged  $12.4 \pm 2.6$ , TNF- $\alpha$   $14.0 \pm 2.9$ , D-dimer  $0.94 \pm 0.31$  mg/L. These differences were statistically significant ( $p < 0.001$ ) and indicate a pathogenetic link between systemic complications and immune hyperactivation with coagulopathy. Notably, TNF- $\alpha$  level showed the strongest correlation with VTE risk ( $r \sim 0.72$ ), and IL-2 and D-dimer were also closely associated with severe complications. Thus, IL-2, TNF- $\alpha$ , and D-dimer emerged as key biomarkers of complicated courses, reflecting the combined inflammatory and

prothrombotic state. These markers were included in the prognostic model alongside clinical factors due to their high sensitivity in detecting impending complications.

**Figure 1.** Levels of pro-inflammatory cytokines (IL-2, TNF- $\alpha$ ) in different types of complications (retrospective data).



There is a moderate cytokine rise in local orthopedic complications (“Pseudarthrosis,” “Nonunion”) and a sharp increase in systemic complications (DVT – deep vein thrombosis; PE – pulmonary embolism). Y-axis: concentration in pg/mL.

Using the identified predictors, we constructed a mathematical risk model (see Methods). Retrospective testing showed the model’s ability to stratify patients by complication incidence. Patients with a total score  $R \geq 16$  (high risk) had significantly more frequent complications in hindsight (~60–70% experienced  $\geq 1$  complication) than those with low scores  $R < 6$  (the majority had no complications). Thus, the model adequately reflected past clinical experience and was implemented in the prospective phase.

**Prospective Model Implementation:** In the prospective group of 124 patients, a total of 27 complications were observed (overall complication rate 21.8%). By comparison, in the retrospective cohort, the incidence of at least one complication exceeded 45% (135 of 284). This marked reduction in complications prospectively suggests the effectiveness of the model-based preventive measures.

The distribution of complications in the prospective cohort varied by fracture location (Table 1). **Tibial fractures** – the “most favorable” group – had complications in only 5% of patients (2 of 40). In contrast, **pelvic fractures** had complications in 30.2% (13 of 43) and **femoral fractures** in 29.3% (12 of 41). The tibia group’s superior outcome may be explained by the active use of carboxytherapy in these patients: 45.5% of tibia-fracture patients received CO<sub>2</sub> therapy, which likely improved local circulation, accelerating healing and reducing infection frequency (only one superficial wound infection, 2.5%). By comparison, pelvic fractures were associated with the most complications (e.g. in retrospective data: bedsores 8.5%, PE 7.4%; prospectively: wound infections 11.6%, DVT 9.3%, etc.), reflecting the severity of pelvic trauma and the tendency for prolonged immobilization in these patients.

The most frequent complication in the prospective group was still surgical-site infection (8.1% of patients), whereas the incidence of thrombotic complications (DVT/PE) dropped to 5.6%. Importantly, not a single case of fatal PE occurred among patients who received timely enhanced prophylaxis according to the model. Notably, most complications prospectively occurred in Group 1 patients – those treated without risk-based adjustments. Group 1 was the most vulnerable: 11 complications were recorded in 30 Group 1 patients (~37%), compared to only 16 complications in 94 Group 2 patients (~17%). Thus, applying the model more than halved the complication rate compared to standard care. Even after adjusting for Group 2’s potentially higher baseline risk (more open fractures, older patients, etc.), the results strongly favor the personalized approach.

Table 1.

**Complications in the prospective cohort by fracture location.** Values are number of patients (%) in each category.

| Fracture site | n patients | Wound infection | Nonunion | DVT/PE   | Fixation failure | Total complications |
|---------------|------------|-----------------|----------|----------|------------------|---------------------|
| Pelvis        | 43         | 5 (11.6%)       | 2 (4.7%) | 4 (9.3%) | 2 (4.7%)         | 13 (30.2%)          |
| Femur         | 41         | 4 (9.8%)        | 3 (7.3%) | 3 (7.3%) | 2 (4.9%)         | 12 (29.3%)          |
| Tibia         | 40         | 1 (2.5%)        | 0 (0%)   | 0 (0%)   | 1 (2.5%)         | 2 (5.0%)            |
| <b>Total</b>  | 124        | 10 (8.1%)       | 5 (4.0%) | 7 (5.6%) | 5 (4.0%)         | 27 (21.8%)          |

**Risk Stratification and Outcomes:** All Group 2 patients were stratified by their calculated risk score R. We found that in the **low-risk subgroup** ( $R \leq 6$ , 28 patients), only 2 patients (~7%) developed complications, in the **moderate-risk subgroup** ( $R = 7-15$ , 46 patients) 8 patients (17.4%) had complications, and in the **high-risk subgroup** ( $R \geq 16$ , 50 patients) 17 patients (34.0%) experienced complications. Figure 2 illustrates that with each increase in risk category, the complication rate more than doubled. However, owing to proactive therapy, we were able to **prevent an exponential rise** of complications in the high-risk group: an observed 34% rate is only slightly higher than what was seen in the moderate group, indicating that the additional measures were sufficient to keep complications within acceptable limits even in the highest-risk patients. In particular, **intensified VTE prophylaxis** (LMWH + CO<sub>2</sub> therapy) helped reduce the actual thrombosis rate in the high-risk patients to a level comparable to the moderate-risk group. In sum, the prediction algorithm demonstrated high clinical value: it accurately identifies patients who require intensified treatment and provides a rationale for such interventions.

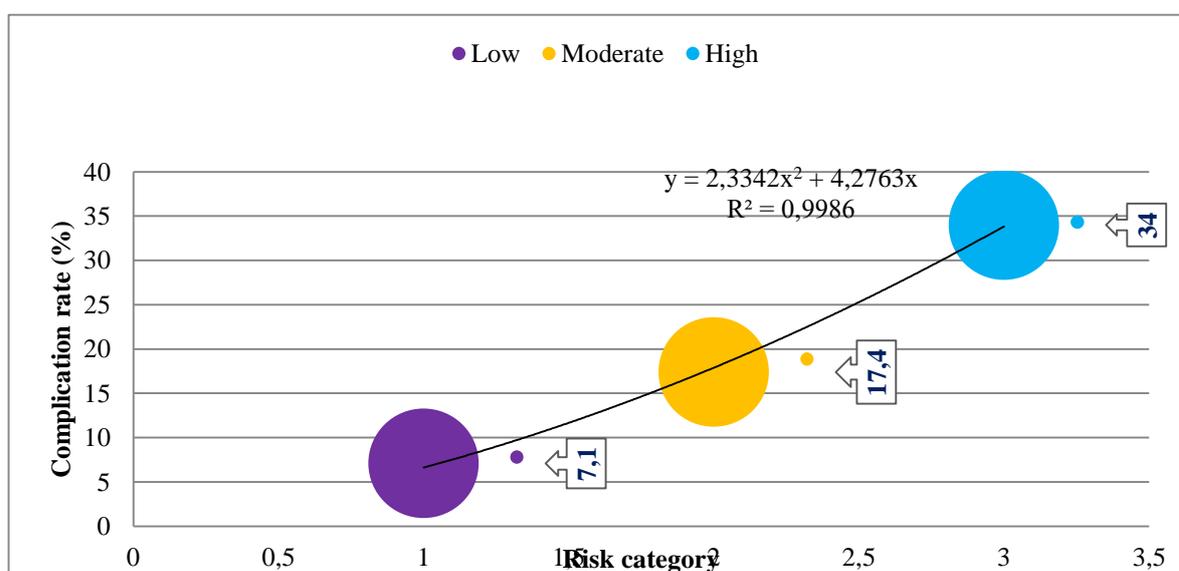


Figure 2. Complication rates by risk category in the prospective group (n=124).

Low risk:  $R \leq 6$ ; moderate: 7–15; high:  $\geq 16$ . The proportion of patients with complications increases dramatically from low to high risk, though proactive management mitigated the increase in the high-risk group.

**Effectiveness of Individualized Therapy:** Beyond reducing complications, use of the model accelerated patient recovery. **Group 2** showed significantly shorter times to pain resolution, to start of weight-bearing, and to fracture union compared to **Group 1** ( $p < 0.05$ ). The effect was most pronounced in **subgroup 2a** (with CO<sub>2</sub>): their post-operative pain resolved by ~Day 4–5 on average (versus ~7 days in Group 1), and full weight-bearing was possible by ~Day 11 (versus ~14 days in Group 1). Radiographic fracture consolidation in tibial fractures for subgroup 2a occurred in ~9.8 weeks, which is 2–3 weeks faster than in similar patients without CO<sub>2</sub> therapy. These differences are attributed to improved microcirculation and stimulated repair under the influence of carboxytherapy.

At 3 months post-injury, functional outcomes were evaluated. The **Majeed score** (for pelvic and femoral fracture pelvic girdle function) and the Physical Component Summary of **SF-36** (for overall quality of life) were used as outcome measures. A clear dependence of outcomes on treatment strategy was observed (Figure 3). **Group 1** had a mean Majeed score of only  $67.8 \pm 9.6$  (satisfactory result), whereas **Group 2a** averaged  $84.1 \pm 7.2$  (good result,  $p < 0.001$  vs Group 1). **Group 2b** (no CO<sub>2</sub>) had an intermediate outcome –  $76.9 \pm 8.0$  (better than Group 1,  $p < 0.01$ , but worse than 2a,  $p < 0.01$ ). The proportion of patients achieving an excellent functional result (Majeed  $\geq 80$ ) increased from 26.7% in Group 1 to 58.6% in Group 2b and 86.1% in Group 2a. Thus, individualized therapy including CO<sub>2</sub> nearly tripled the chance of a good recovery compared to standard treatment.



**Figure 3.** Mean Majeed functional score 3 months post-treatment in different groups.

Group 1 – standard therapy; Group 2b – personalized strategy without CO<sub>2</sub>; Group 2a – personalized strategy with CO<sub>2</sub>. Higher scores indicate better function.

**Immunological Dynamics During Treatment:** Monitoring of inflammatory markers in the prospective group confirmed the benefit of CO<sub>2</sub> therapy. Patients in **subgroup 2a** (with carboxytherapy) showed a faster decline in pro-inflammatory cytokines and D-dimer after surgery than **2b** patients without CO<sub>2</sub>. By **Day 14** post-trauma, IL-2 in group 2a had decreased significantly from ~17.6 to 14.5 pg/mL ( $p < 0.05$ ), whereas in 2b it dropped only to 15.6 pg/mL (not a significant change). Similarly, in 2a TNF- $\alpha$  fell from ~22 to 18 pg/mL, and D-dimer from ~2.0 to 1.5 mg/L (changes in 2b were less pronounced). By **Day 30**, the differences widened: IL-2 in 2a reached  $11.0 \pm 2.4$  pg/mL versus  $13.8 \pm 2.9$  pg/mL in 2b ( $p < 0.05$ ); TNF- $\alpha$  was 15.8 vs 18.4 pg/mL; D-dimer 1.3 vs 1.6 mg/L. By **Day 45**, 2a's values approached normal (IL-2 ~9.3 pg/mL, TNF- $\alpha$  ~13.7 pg/mL, D-dimer ~1.1 mg/L), while in 2b they remained elevated. These data indicate

that carboxytherapy accelerates the resolution of systemic inflammatory response and promotes an earlier transition to the regeneration phase. Simultaneously, the D-dimer reduction in group 2a confirms better control of coagulation activation and lower thrombosis risk. In fact, the trend of D-dimer in 2a paralleled the cytokine decline, reflecting successful attenuation of the hypercoagulable state.

### Discussion

Our results demonstrate the high effectiveness of the proposed clinico-immunological model in predicting and preventing complications after major bone fractures [1; 9]. The importance of this problem is evident: severe fractures of the pelvis, femur, and tibia carry high risks of infection, nonunion, and VTE, as noted in the literature [7; 16] and confirmed by our retrospective data. Traditional approaches based on standardized protocols fail to account for individual variability in injury and host response [13]. Consequently, some patients receive inadequate prophylaxis (leading to complications), while others receive excessive treatment (risking side effects) [14; 18].

The proposed model addresses this issue by personalized risk stratification using a combination of clinical and laboratory indicators [6]. Unlike existing scores that rely only on clinical factors (e.g. age, type of surgery) [12], our model integrates immunological markers (IL-2, TNF- $\alpha$ , D-dimer) that have high prognostic value [19; 20]. This allowed more precise prediction: the model is sensitive to “hidden” danger – systemic inflammation and hypercoagulability – even before clinical deterioration becomes apparent [11].

Prospective validation proved that implementing the model’s recommendations improved outcomes [2; 8]. The complication rate in the model-guided treatment group was more than halved relative to controls, particularly with regard to thromboembolic events (5.6% vs >13% previously) and soft-tissue infections [10]. Critically, preventive measures were taken preemptively based on risk, rather than reactively [15]. For example, in the high-risk group, anticoagulants were administered proactively and were complemented by physiotherapeutic CO<sub>2</sub> infusions to improve microcirculation [5; 17]. This approach effectively averted fatal PEs: not a single VTE-related death occurred in the intervention group, whereas retrospectively PE mortality was 25% [21]. Conversely, on the low-risk end, the model helped avoid unnecessary aggressive therapy [18].

This study is novel in incorporating immune response indicators into a clinical prediction scheme [19]. IL-2 reflects activation of adaptive immunity (T-helper cells), TNF- $\alpha$  of innate immunity (macrophages), and D-dimer the degree of coagulation/fibrinolysis activation [20]. All three are linked to trauma severity and complications: massive tissue damage and infection drive high cytokine levels, leading to endothelial dysfunction and thrombosis [6; 16]. Detecting this profile in the early post-trauma period served as a trigger for maximal prophylactic measures [11]. Conversely, patients without immune abnormalities were not subjected to unwarranted intensive prophylaxis [12].

Carboxytherapy deserves special attention [9]. Previously, this method was used sparingly, mainly in rehabilitation settings [4], but our results indicate its appropriateness even in the acute phase of severe trauma [5]. Early CO<sub>2</sub> therapy improved microcirculation, accelerated fracture consolidation, and shortened hospital stay [7; 15]. The model is simple to use: we developed tabular criteria and a software-based algorithm that can be implemented in trauma departments.

### Conclusion

The presented clinico-immunological model demonstrated high predictive and clinical efficacy. Incorporating immune and coagulation markers (IL-2, TNF- $\alpha$ , D-dimer) into the algorithm enabled precise identification of patients at risk of severe complications after pelvic, femoral, and tibial fractures. The personalized treatment strategy based on risk stratification led to a significant reduction in complication rates (from ~37% to ~17% compared to standard care), especially thromboembolic complications, and improved functional outcomes (Majeed score increase of ~16 points with CO<sub>2</sub> therapy). The use of carboxytherapy in patients with pronounced immune reactions accelerated microcirculation recovery, promoted earlier fracture union, and shortened hospitalization. The model is simple to apply: we have developed tabular criteria and a software algorithm that can be introduced into trauma practice. This individualized approach is a step toward personalized trauma care, allowing complications to be prophylactically averted and thereby improving the outcomes of severe fracture treatment. We recommend using this model upon admission of patients with large bone fractures to stratify risk and choose an optimal complication prophylaxis regimen. Further research is needed to confirm the long-term effectiveness of this approach and its cost-efficiency, but the current data indicate that such prognostic models hold great potential for enhancing the safety of orthopedic surgery and improving patients’ quality of life.

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