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### **Research Article**

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## Development and Clinical Validation of an Immunological Prediction Model for Postoperative Complications Following Transpedicular Fixation in Patients with Spondylolisthesis

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#### ABSTRACT

**Background:** Postoperative complications remain a substantial concern in patients undergoing transpedicular fixation (TPF) for lumbar spondylolisthesis. Standard risk assessment methods often fail to identify patients predisposed to infectious or aseptic implant-related complications. Recent studies suggest that immune biomarkers may enhance the prediction of unfavorable outcomes.

**Methods:** A prospective cohort study was conducted involving 126 patients with degenerative or isthmic lumbar spondylolisthesis who underwent TPF between 2021 and 2024. Patients were stratified into three groups based on postoperative course and use of immunoprophylaxis. Immune parameters ( $CD4^+$ ,  $CD16^+/56^+$ , IL-6,  $TNF-\alpha$ , MMP-9, IgA, and NLR) were measured pre- and postoperatively. A multivariate logistic regression model was developed using five key immune predictors. Model performance was assessed via ROC-curve analysis.

**Results:** Significant differences in immune profiles were observed between patients with and without complications. The final model, based on  $CD4^+$ ,  $CD16^+/56^+$ , IL-6, MMP-9, and NLR, achieved an area under the curve (AUC) of 0.873 (95% CI: 0.80–0.94), with sensitivity of 81.3% and specificity of 84.7%.

**Conclusion:** An immunologically informed prediction model enables early identification of patients at high risk for postoperative complications after TPF. Personalized immunoprophylactic strategies based on immune risk stratification can improve surgical outcomes and reduce healthcare burden.

Keywords: Spondylolisthesis; transpedicular fixation; immune risk model

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#### **INTRODUCTION**

Spondylolisthesis is a common spinal disorder characterized by vertebral slippage that frequently leads to chronic pain, neurological deficits, and progressive instability. Transpedicular fixation (TPF) is widely recognized as the treatment of choice, offering biomechanical stabilization and long-term functional improvement [1,2]. However, despite technical advancements in surgical instrumentation and perioperative care, postoperative complications—including implant-associated infections, aseptic loosening, and chronic inflammation—remain a serious challenge, occurring in up to 20–28% of cases [3–5].

Conventional risk assessment tools, such as the ASA score or general comorbidity indices, provide limited predictive value for immune-mediated complications. They do not account for the patient's immunological baseline, which may critically influence surgical recovery, particularly in individuals with metabolic comorbidities or advanced age [6,7]. Immune dysfunction—manifesting as T-cell depletion, natural killer cell overactivation, elevated pro-inflammatory cytokines (e.g., IL-6, TNF- $\alpha$ ), and increased proteolytic activity via matrix metalloproteinases (e.g., MMP-9)—has emerged as a key determinant of postoperative outcomes [8–10].

Recent studies suggest that specific immunological markers may serve as reliable predictors of unfavorable outcomes after spinal instrumentation. Preoperative immunosuppression, systemic inflammation, and cytokine-driven tissue degradation can collectively impair osseointegration and wound healing [11,12]. However, current clinical practice lacks validated models that incorporate immune parameters into surgical decision-making.

In this context, the aim of the present study was to develop and clinically validate an immunological prediction model for postoperative complications following TPF in patients with lumbar spondylolisthesis. Based on pre- and postoperative immune profiling, we constructed a multi-marker logistic regression model and evaluated its diagnostic performance. Additionally, a three-tiered immune risk stratification system was proposed to guide targeted immunoprophylaxis and reduce the incidence of complications.

#### MATERIALS AND METHODS

The present prospective study was conducted at the Bukhara Regional Multidisciplinary Medical Center in collaboration with the Department of Surgery of the Bukhara State Medical Institute between 2021 and 2024. A total of 126 patients diagnosed with Grade I–II degenerative or isthmic spondylolisthesis of the lumbar spine underwent standard transpedicular fixation using titanium instrumentation. All surgical procedures were performed under uniform protocols by experienced spinal surgeons. The study received ethical approval from the institutional ethics committee, and informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

Patients were divided retrospectively into three cohorts based on postoperative outcomes and the use of immunoprophylaxis: those with favorable recovery without complications, those with documented postoperative complications (including infectious or aseptic reactions), and those who received individualized immune prophylactic interventions. The study protocol included comprehensive immune profiling performed at two time points—preoperatively and on the 5th to 7th postoperative day. Peripheral venous blood was collected under sterile conditions, and samples were analyzed in the central immunology laboratory of the Bukhara State Medical Institute.

Flow cytometry was employed to quantify lymphocyte subsets including CD4<sup>+</sup>, CD8<sup>+</sup>, CD16<sup>+</sup>/56<sup>+</sup>, and CD19<sup>+</sup> populations, using fluorochrome-conjugated monoclonal antibodies and a Beckman Coulter Cyto-FLEX platform. Humoral immune parameters including serum IgA, IgM, and IgG concentrations were measured using nephelometry. Enzyme-linked immunosorbent assays (ELISA) were utilized to determine circulating levels of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- $\alpha$ ), and matrix metalloproteinase-9 (MMP-9), following manufacturer protocols validated for clinical diagnostics. The neutrophil-to-lymphocyte ratio (NLR) and leukocytic intoxication index (LII) were calculated based on full blood count data obtained from automated hematological analyzers.

Patients with postoperative complications demonstrated distinct immunological profiles, which were incorporated into the development of a predictive model using multivariate logistic regression. Predictor variables were selected based on statistical significance in univariate comparisons and clinical relevance. The final model included five markers: CD4<sup>+</sup> percentage, CD16<sup>+</sup>/56<sup>+</sup> NK-cell count, IL-6 concentration, MMP-9 concentration, and NLR. Model performance was evaluated using receiver operating characteristic (ROC) curve analysis, with calculation of the area under the curve (AUC), sensitivity, and specificity. A three-tiered classification sys-

tem was derived to facilitate clinical interpretation and guide the administration of immune prophylaxis. Data analysis was performed using SPSS Statistics 25.0 and Statistica 13.0, with significance set at p<0.05.

#### RESULTS

The analysis revealed significant immunological distinctions between patients with favorable postoperative outcomes and those who developed complications. Preoperatively, patients who experienced adverse outcomes exhibited markedly reduced  $CD4^+$  T-cell levels (p<0.01), elevated  $CD16^+/56^+$  natural killer cell counts (p<0.01), and significantly increased concentrations of IL-6 and MMP-9 (both p<0.001). The neutrophil-to-lymphocyte ratio was also substantially higher in the complication group, indicating systemic inflammation and dysregulation of adaptive immunity. Notably, these differences were preserved and, in some cases, amplified in the early postoperative period.

Multivariate logistic regression analysis identified five immune parameters that independently contributed to the prediction of postoperative complications:  $CD4^+$ T-cell percentage,  $CD16^+/56^+$  NK-cell count, IL-6, MMP-9, and NLR. The resulting model demonstrated strong discriminative ability with an area under the ROC curve (AUC) of 0.873 (95% CI: 0.80–0.94). Sensitivity and specificity were 81.3% and 84.7%, respectively, with a model calibration consistent across risk subgroups. These findings substantiate the reliability of the selected immune markers as predictors of surgical outcome.

Based on the predicted probability values from the logistic model, patients were stratified into three immune risk categories: low risk (probability <0.30), intermediate risk (0.30–0.59), and high risk ( $\geq$ 0.60). This classification allowed for the individualized allocation of perioperative immunoprophylaxis. Among the 35 patients who received immune-based prophylaxis guided by this stratification, the incidence of postoperative complications decreased significantly compared to the matched cohort without prophylaxis (8.6% vs. 25.3%, p<0.01). Moreover, the prophylaxis group demonstrated favorable shifts in immune parameters on postoperative days 5–7, particularly with stabilization of CD4<sup>+</sup> levels and attenuation of the NLR and cytokine surge.

The clinical course in the prophylaxis group was also characterized by reduced length of hospitalization, fewer wound-related complaints, and a lower rate of implant instability on radiological follow-up. These outcomes suggest that immune stratification and corresponding modulation not only predict risk but also facilitate actionable interventions capable of altering the postoperative trajectory in patients undergoing TPF for spondylolisthesis.

#### DISCUSSION

The present study demonstrates that selected immune parameters—specifically CD4<sup>+</sup> T-cell depletion, NK-cell overactivation, elevated IL-6 and MMP-9 concentrations, and increased NLR—have significant prognostic value in anticipating postoperative complications following transpedicular fixation (TPF) in patients with spondylolisthesis. These findings are in agreement with recent publications emphasizing the role of immunological vulnerability in the etiology of surgical complications, including both infectious and aseptic failures of spinal instrumentation [3, 8, 10].

The observed decline in CD4<sup>+</sup> lymphocytes among patients with complications corroborates earlier reports linking T-helper cell dysfunction to impaired wound healing and weakened control over innate immune effectors [7, 11]. In the context of implant surgery, this imbalance is particularly detrimental, as effective T-cell-mediated regulation is critical for containing excessive inflammatory responses and facilitating osseointegration. Simultaneously, the elevated activity of CD16<sup>+</sup>/56<sup>+</sup> NK cells reflects a compensatory but uncontrolled innate activation, which has been implicated in promoting periimplant tissue damage and persistent inflammation [9, 13].

Among cytokines, IL-6 stands out for its dual role in mediating acute-phase responses and perpetuating chronic inflammation. Its excessive release in the complication group not only signals systemic immune activation but may also contribute to local matrix degradation and osteolysis through upregulation of MMPs—particularly MMP-9, whose expression was markedly higher in the same cohort. These findings are consistent with evidence suggesting that MMP-9 plays a pivotal role in destabilizing the extracellular matrix at the bone-implant interface, thereby facilitating aseptic loosening [6, 14].

The integration of these immune indicators into a logistic regression model yielded a robust tool for individualized risk assessment. An AUC of 0.873 is indicative of excellent diagnostic performance and exceeds the predictive value of standard clinical scores, which rarely surpass an AUC of 0.70 in spinal surgery [5]. Importantly, the stratification model allowed for the implementation of immunoprophylactic strategies that proved effec-

tive in reducing complication rates and modifying the postoperative immune landscape. The reduction in adverse outcomes among high-risk patients who received targeted prophylaxis aligns with the growing body of literature advocating for immune-based perioperative modulation in selected surgical populations [12, 15].

It is noteworthy that immune correction, guided by quantitative risk estimates, not only improved laboratory parameters but also translated into better clinical trajectories, including reduced hospital stays and fewer reoperations. This underlines the practical applicability of immunological models not merely as diagnostic instruments but as foundations for decision-making in surgical practice.

Despite the promising results, certain limitations must be acknowledged. The study was conducted at a single center, which may limit generalizability. Additionally, while the model demonstrated strong statistical performance, external validation in larger, multicenter cohorts is necessary to confirm its reproducibility and clinical utility. Future investigations should also explore the costeffectiveness and long-term benefits of routine immune stratification in spinal instrumentation procedures.

Nonetheless, the findings of this study strongly support the hypothesis that immune dysregulation is a modifiable risk factor in spinal surgery and that immunological modeling offers a pathway to safer and more personalized care.

#### CONCLUSION

This study provides compelling evidence that immunological profiling enables accurate prediction and prevention of postoperative complications following transpedicular fixation in patients with spondylolisthesis. The validated logistic model incorporating five key immune markers—CD4<sup>+</sup>, CD16<sup>+</sup>/56<sup>+</sup>, IL-6, MMP-9, and NLR—demonstrated high diagnostic accuracy and clinical applicability. Importantly, its implementation allowed for risk-based stratification and timely initiation of immunoprophylaxis, resulting in a significant reduction in the incidence of complications and improved recovery metrics.

These findings underscore the need to integrate immune assessment into the perioperative management of spinal surgery patients, particularly those with known immunological or metabolic vulnerabilities. Beyond risk prediction, immune stratification opens the door to personalized interventions, including immunomodulatory therapies aimed at enhancing postoperative immune homeostasis and tissue repair.

Future research should focus on external validation of the proposed model and optimization of immunoprophylactic regimens. The integration of immunology into surgical protocols represents a critical step toward a more precise and biologically

Author Contributions: Khamdamov B.Z. conceptualized the study design, supervised data analysis, and edited the manuscript. Safarov J.T. collected clinical data, conducted patient follow-up, and drafted the initial manuscript. Atakov S.S. performed statistical analysis and contributed to interpretation of immunological data. All authors reviewed and approved the final version of the manuscript.

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**Ethical Approval:** The study was approved by the Local Ethics Committee of Bukhara State Medical Institute. All participants provided written informed consent prior to inclusion in the study. The research complies with the principles of the Declaration of Helsinki.

**Conflict of Interest:** The authors declare no conflict of interest related to this publication.

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#### SPONDILOLISTEZ BILAN KASALLANGAN BE-MORLARDA TRANSPEDIKULYAR FIKSAT-SIYADAN KEYINGI ASORATLARNI IM-MUNOLOGIK PROGNOZLASH MODELI: ISH-LAB CHIQISH VA KLINIK TASDIQLASH

#### Hamdamov B.Z., Safarov J.T., Atakov S.S.

#### **Buxoro Davlat Tibbiyot Instituti**

#### **ANNOTATSIYA:**

Ushbu maqolada transpedikulyar fiksatsiyadan (TPF) keyin yuzaga keladigan asoratlarni oldindan prognozlash uchun immunologik model ishlab chiqilgan va klinik jihatdan sinovdan oʻtkazilgan. Model CD4<sup>+</sup>, CD16<sup>+</sup>/56<sup>+</sup>, IL-6, MMP-9 va NLR kabi beshta asosiy immunologik markerlarga asoslangan. ROC-tahlilga koʻra, modelning AUC koʻrsatkichi 0,873 ni tashkil etib, yuqori sezuvchanlik va aniq prognostik qobiliyatga ega ekanligi isbotlandi. Yuqori xavf guruhidagi bemorlar uchun immunoprofilaktika tadbiqi asoratlar sonini sezilarli daraja-da kamaytirdi (p<0,01).

**Kalit soʻzlar:** Spondilolistez; transpedikulyar fiksatsiya; immunologik risk modeli.

#### РАЗРАБОТКА И КЛИНИЧЕСКАЯ ВАЛИДАЦИЯ ИММУНОЛОГИЧЕСКОЙ МОДЕЛИ ПРОГНОЗИРОВАНИЯ ПОСЛЕОПЕРАЦИОННЫХ ОСЛОЖНЕНИЙ ПОСЛЕ ТРАНСПЕДИКУЛЯРНОЙ ФИКСАЦИИ У БОЛЬНЫХ СО СПОНДИЛОЛИСТЕЗОМ

#### Хамдамов Б.З., Сафаров Ж.Т. Атаков С.С.

#### АННОТАЦИЯ:

В статье представлена разработка и клиническая апробация прогностической модели, основанной на иммунологических маркерах (CD4<sup>+</sup>, CD16<sup>+</sup>/56<sup>+</sup>, IL-6, MMP-9 и NLR) для оценки риска послеоперационных осложнений после транспедикулярной фиксации у больных со спондилолистезом. Итоги ROC-анализа показали высокую прогностическую ценность модели (AUC = 0,873), с чувствительностью 81,3% и специфичностью 84,7%. Использование данной модели позволило провести персонифицированную иммунопрофилактику, что привело к достоверному снижению числа осложнений (p<0,01).

**Ключевые слова:** Спондилолистез; транспедикулярная фиксация; иммунологическая модель риска.