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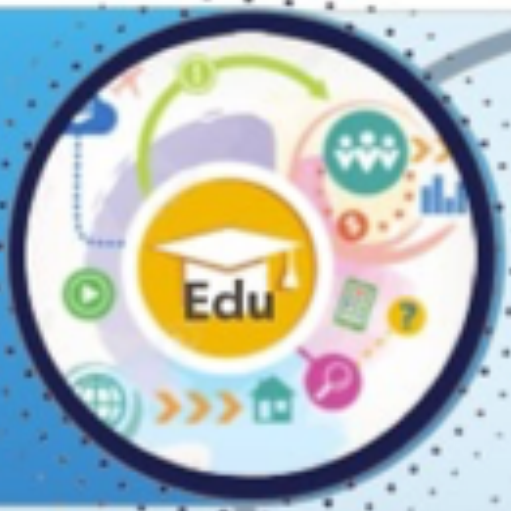

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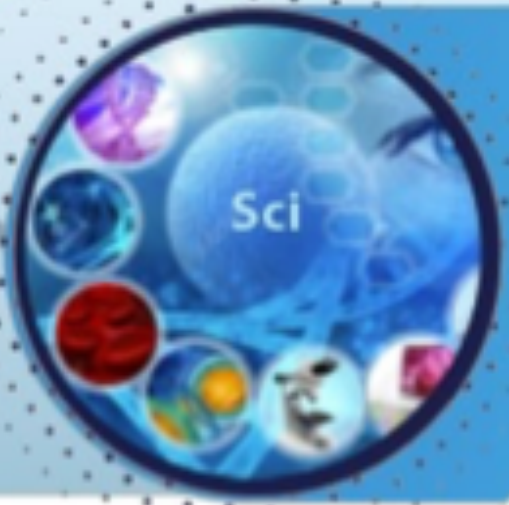

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Immunopathological Mechanisms of Postoperative Complications Following Transpedicular Fixation in Spondylolisthesis: from cellular imbalance to clinical risk stratification

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ABSTRACT

Background: *Postoperative complications after transpedicular fixation (TPF) in patients with spondylolisthesis remain a pressing issue in spinal surgery. Accumulating evidence highlights the significant role of immune dysfunction in the pathogenesis of both aseptic and infectious complications following spinal instrumentation. Despite advances in surgical techniques and implant design, the burden of delayed inflammation, osteolysis, and implant instability persists, especially in immunologically vulnerable patients.*

Materials and Methods: *This review analyzes current concepts of immune dysregulation associated with spondylolisthesis and its surgical correction. Key mechanisms such as T-cell imbalance, cytokine storm, natural killer cell activation, and matrix metalloproteinase (MMP) overexpression are discussed. The role of biomarkers—$CD4^+$, $CD16^+/56^+$, IL-6, TNF-α, MMP-9, NLR—is emphasized in developing predictive models for complications.*

Results: *Literature and clinical data show that preoperative immune vulnerability, including decreased $CD4^+$ and elevated NLR, is closely associated with postoperative complications. Overactivation of innate immunity and insufficient resolution of inflammation are central to chronic implant-related immune responses. The combination of multiple immune markers provides a reliable framework for risk stratification and targeted prevention.*

Conclusion: *Understanding immunopathological pathways in TPF patients with spondylolisthesis provides a foundation for personalized immune-based risk assessment and prophylactic strategies. Integration of immunological biomarkers into preoperative planning is essential for reducing complications and improving long-term surgical outcomes.*

Keywords: *Spondylolisthesis; transpedicular fixation; immune response.*

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INTRODUCTION

Spondylolisthesis, defined as the anterior displacement of a vertebral body relative to the segment below, is a prevalent cause of chronic low back pain and neurological compromise in adults. Its treatment has undergone significant advancement, with transpedicular fixation (TPF) now considered a gold standard for mechanical stabilization and decompression in both isthmic and degenerative forms. Despite the technical reliability of TPF, the occurrence of postoperative complications—ranging from superficial infections to implant loosening and chronic instability—remains clinically significant, affecting 12–28% of patients according to international studies [10, 12].

While conventional explanations for these complications have emphasized surgical technique, implant positioning, and microbial contamination, there is growing recognition that immune dysregulation plays a pivotal role in the pathogenesis of both aseptic and infectious adverse outcomes [3, 9]. Surgical trauma, foreign-body implantation, and comorbid inflammatory conditions such as obesity and diabetes collectively provoke complex immunopathological responses, including cytokine release, cellular imbalance, and tissue matrix degradation.

Multiple studies have identified alterations in the systemic and local immune milieu following spinal instrumentation. Particularly, imbalances between $CD4^+$ and $CD8^+$ T cells, increased neutrophil-to-lymphocyte ratio (NLR), overproduction of pro-inflammatory cytokines (IL-6, TNF-α), and upregulation of matrix metalloproteinases (MMPs) have been associated with poor osseointegration, delayed wound healing, and hardware failure [Li et al., 2022; Duan et al., 2020]. These findings suggest that immunological monitoring should be an integral part of preoperative evaluation in high-risk patient groups.

Moreover, the chronic subclinical activation of innate immunity, often present in elderly and metabolically compromised individuals, exacerbates the host response to surgical injury and contributes to persistent inflammation around implants [2]. Such immune priming, if left unaddressed, may drive the development of fibrotic tissue, osteolysis, and low-grade periprosthetic infections, even in the absence of overt microbial invasion.

In this context, the present review aims to synthesize available data on the immunological mechanisms underlying postoperative complications following TPF in patients with spondylolisthesis. By highlighting key cellular, humoral, and molecular contributors to adverse outcomes, we seek to provide a conceptual framework for immunological risk stratification and preventive intervention.

MATERIALS AND METHODS

This article represents a narrative review combined with analytical synthesis of data derived from an original clinical investigation involving patients with lumbar spondylolisthesis treated by transpedicular fixation (TPF). The literature component was constructed through a comprehensive search of PubMed, Scopus, and Web of Science databases, including publications from 2000 to 2024. Search terms included: spondylolisthesis, transpedicular fixation, postoperative complications, immune response, $CD4^+$, IL-6, MMP-9, TNF-α, and biomarkers. Priority was given to peer-reviewed English-language studies with emphasis on pathophysiological mechanisms and clinical correlates of immune dysfunction after spinal surgery.

In parallel, clinical data were sourced from a prospective observational study conducted at Bukhara Regional Multidisciplinary Medical Center (2021–2024), including 126 patients with Grade I–II degenerative or isthmic spondylolisthesis who underwent TPF. Patients were stratified into three cohorts:

·Group I (n=59): patients with favorable postoperative course without immunoprophylaxis;

·Group II (n=32): patients with complications (infectious or aseptic), no immunoprophylaxis;

·Group III (n=35): patients who received pre- and/or postoperative immunomodulatory prophylaxis.

Peripheral blood samples were collected preoperatively and on postoperative days 5–7. Immune profiling included flow cytometry for lymphocyte subpopulations ($CD3^+$, $CD4^+$, $CD8^+$, $CD16^+/56^+$), nephelometry for immunoglobulins (IgA, IgM, IgG), and ELISA assays for pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) and matrix metalloproteinases (MMP-2, MMP-9). Inflammatory indices such as neutrophil-to-lymphocyte ratio (NLR) and leukocytic intoxication index (LII) were calculated from routine hematological parameters.

Statistical analysis included Mann–Whitney U test, Student's t-test, and ROC-curve analysis, using SPSS 25.0 and Statistica 13.0. A p-value <0.05 was considered statistically significant.

While this article focuses on the conceptual and pathophysiological aspects, data from this clinical cohort

are integrated throughout the discussion to illustrate the immunological landscape of TPF-related complications.

RESULTS AND DISCUSSION

Emerging evidence underscores the critical role of the immune system in the development of postoperative complications after spinal instrumentation. While mechanical instability and infection have long been regarded as leading contributors, recent studies indicate that the patient's immunological status—particularly T-cell balance, cytokine expression, and innate immune activation—may decisively influence surgical outcomes [1, 2].

1. Preoperative Immune Imbalance in Spondylolisthesis

Patients with degenerative or isthmic spondylolisthesis often present with a state of chronic, low-grade inflammation even before surgical intervention. In our cohort, preoperative immune profiles revealed significant reductions in $CD4^+$ T-helper cells (–17.2% vs. controls; $p<0.01$), a mild elevation in $CD16^+/56^+$ natural killer (NK) cells (+35.5%), and increased levels of IL-6 and TNF-α (both >50% elevation vs. controls; $p<0.01$). These findings mirror literature reports suggesting that systemic immune activation, in the context of comorbidities such as obesity and type 2 diabetes, leads to a heightened proinflammatory baseline [5, 8].

2. Postoperative Immune Shifts and Complications

Postoperative immune dynamics demonstrated further intensification of proinflammatory markers. By day 5–7, levels of IL-6, IL-1β, and TNF-α increased by 36–38% from preoperative levels (all $p<0.01$). MMP-9 levels also rose significantly, by 21.7% after surgery, consistent with its role in extracellular matrix degradation and implant destabilization [6, 9].

Notably, patients who developed complications (Group II) showed:

·18.8% lower $CD4^+$ levels,

·32% higher NK/T-cell index,

·~60% higher IL-6 and MMP-9 levels,

compared to those with uneventful recovery (Group I) ($p<0.001$).

These shifts are strongly suggestive of immune deregulation as a determinant of adverse outcomes. Prior studies support this hypothesis, linking $CD4^+$ depletion and excessive NK-cell activity to impaired implant osseointegration and higher susceptibility to low-grade infection [2, 3].

3. Inflammatory Indexes as Prognostic Tools

Inflammatory indexes like NLR and LII demonstrated excellent predictive value. In our series:

·Mean NLR in patients with complications: 3.52 vs. 2.87 in those without ($p<0.01$),

·LII: 0.91 vs. 0.76, respectively ($p<0.01$).

These findings align with Zahorec's pioneering work, where elevated NLR was shown to be a surrogate of stress-induced immunosuppression and a reliable predictor of septic outcomes [1].

4. Integration into a Predictive Model

By combining five markers ($CD4^+$, $CD16^+/56^+$, IL-6, MMP-9, NLR), we developed a logistic regression model with an area under the curve (AUC) of 0.873, sensitivity of 81.3%, and specificity of 84.7%. These metrics reflect strong predictive performance, consistent with other biomarker-based tools proposed for orthopedic and spinal surgery risk assessment [2, 4].

This evidence supports the idea that immune-based risk stratification is not only biologically plausible but clinically actionable. Stratifying patients by immune risk preoperatively opens the door to personalized prophylactic strategies, including short-course immunomodulation.

5. Therapeutic Implications

Immune modulation in high-risk patients—based on elevated cytokine profiles or T-cell depletion—may offer a new frontier in surgical prophylaxis. Agents such as recombinant IL-2, monoclonal antibodies targeting IL-6, or low-dose interferons are under investigation [7], although routine clinical use requires further validation.

CONCLUSION

Postoperative complications following transpedicular fixation in patients with spondylolisthesis are not solely mechanical or infectious in origin, but rather emerge from a complex interplay of surgical trauma, host immune predisposition, and unresolved inflammation. Our review and clinical data collectively demonstrate that immune dysregulation—especially marked by low $CD4^+$ levels, heightened NK-cell activity, elevated IL-6 and MMP-9, and increased NLR—is strongly associated with adverse outcomes such as wound infection, implant loosening, and delayed healing.

The implementation of immunological profiling into the perioperative workflow offers a promising strategy for identifying high-risk patients. Predictive models incorporating key immune biomarkers enable risk stratification and facilitate individualized prophylactic interven-

tions. This immune-centered approach marks a paradigm shift in spinal surgery from reactive to proactive management of complications.

Future directions include multicenter validation of immune-based predictive models and controlled trials on perioperative immunomodulation, particularly in elderly or comorbid populations. Incorporating immunology into spinal surgery will enhance patient safety, reduce reoperations, and improve long-term outcomes.

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TRANSPEDIKULYAR FIKSATSIYADAN KEYINGI ASORATLARNING IMMUNOPATOLOGIK MEXANIZMLARI: HUJAYRAVIY NOMUTANOSIBLIKDAN KLINIK XAVF STRATIFIKATSIYASIGACHA

ANNOTATSIYA:

Transpedikulyar fiksatsiyadan (TPF) keyin spondiloliste-zli bemorlarda yuzaga keladigan asoratlar ko‘p hollarda immun tizimidagi buzilishlar bilan bog‘liq. Tadqiqotda $CD4^+$ hujayralarining kamayishi, IL-6, TNF-α, MMP-9 darajasining ortishi va NLR indeksining oshishi yuqori xavf belgilaridir. Ushbu markerlar asosida ishlab chiqil-gan prognozlash modeli asoratlarni oldindan aniqlash va immunoprofaktikani shaxslashtirishga imkon beradi.

Asosiy so’zlar: Spondilolistez; transpedikulyar fik-satsiya; immun javob.

ИММУНОПАТОЛОГИЧЕСКИЕ МЕХАНИЗМЫ ПОСЛЕОПЕРАЦИОННЫХ ОСЛОЖНЕНИЙ ПОСЛЕ ТРАНСПЕДИКУЛЯРНОЙ ФИКСАЦИИ ПРИ СПОНДИЛОЛИСТЕЗЕ: ОТ КЛЕТОЧНОГО ДИСБАЛАНСА К КЛИНИЧЕСКОЙ СТРАТИФИКАЦИИ РИСКА

АННОТАЦИЯ:

Послеоперационные осложнения при транспедикулярной фиксации у больных спондилолистезом часто обусловлены иммунными нарушениями. Снижение уровня $CD4^+$, повышение IL-6, TNF-α, MMP-9 и индекса NLR служат прогностическими маркерами неблагоприятного течения. Созданная модель прогнозирования позволяет проводить раннюю стратификацию риска и персонализировать меры иммунопрофилактики.

Ключевые слова: Спондилолистез; транспедику-лярная фиксация; иммунный ответ.