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Inflammatory Genetic Biomarkers as Predictors of Clinical Evolution and Postoperative Pain in Patients with Early Medical Care

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ABSTRACT

Background: Postoperative pain and clinical evolution after surgery show substantial interindividual variability, even under standardized early medical care protocols. Genetic inflammatory biomarkers have emerged as potential predictors of postoperative outcomes, supporting the development of personalized medicine approaches in surgical care. **Objective:** To analyze the predictive value of inflammatory genetic biomarkers on postoperative pain and clinical evolution in patients receiving early medical care. **Methods:** A quantitative, observational, longitudinal, and predictive study was conducted in 210 adult surgical patients managed under early medical care protocols. Preoperative genotyping of inflammatory polymorphisms (IL6 rs1800795, IL1B rs16944, TNF rs1800629, IL10 rs1800896, and CRP rs1205) was performed using real-time PCR. Postoperative pain was assessed using the Visual Analog Scale at 24, 48, and 72 hours. Clinical evolution was evaluated through hospital stay duration and postoperative complications. Multivariate linear and logistic regression models were applied. **Results:** Proinflammatory genotypes of IL6 and IL1B were significantly associated with higher postoperative pain intensity ($p < 0.01$). Variants of TNF and CRP were independent predictors of unfavorable clinical evolution, increasing the risk of postoperative complications (OR = 2.31 and OR = 2.67, respectively). Predictive models integrating genetic and clinical variables demonstrated superior explanatory capacity compared to clinical models alone. **Conclusions:** Inflammatory genetic biomarkers are significant predictors of postoperative pain and clinical evolution, even in the context of early medical care. Their integration into preoperative assessment may enhance risk stratification and support personalized perioperative management strategies.

Keywords: *genetic biomarkers; postoperative pain; clinical outcomes; early medical care; personalized medicine.*

INTRODUCTION

Context and relevance of the problem

Postoperative pain and the clinical course after surgery are relevant challenges for contemporary health systems, both because of their impact on patients' quality of life and because of the costs associated with prolonged hospital stays, postoperative complications, and analgesic consumption. Despite advances in surgical techniques, anesthesia, and enhanced recovery protocols, a significant proportion of patients continue to experience severe pain and unfavorable clinical recovery following elective and emergency surgical procedures.

In this context, personalized medicine has acquired a central role, proposing prevention, diagnosis and treatment strategies based on the individual biological characteristics of each patient. Among these, inflammatory genetic biomarkers have emerged as promising tools to predict the response to surgical tissue damage, the intensity of postoperative pain, and the speed of clinical recovery.

Inflammation, genetics, and post-surgical pain

The inflammatory response is an essential physiological process after a surgical attack; however, their magnitude and duration vary widely between individuals. This interindividual variability is explained, in part, by genetic differences that modulate the expression and activity of pro-inflammatory and anti-inflammatory cytokines, as well as other immune mediators involved in nociception and healing. Polymorphisms in genes such as IL6, IL1B, TNF, CRP, and IL10 have been associated with increased susceptibility to pain, persistent inflammation, and postoperative complications. These genetic biomarkers can influence both the intensity of acute pain and the risk of chronic pain, in addition to affecting clinical parameters such as functional recovery, the appearance of infections and the response to analgesic treatment.

Early medical care and its interaction with genetic factors

Early medical care, understood as the timely evaluation, diagnosis, and management of the patient from the initial phases of the surgical process, has been associated with better clinical outcomes. Early intervention protocols allow you to optimize pain control, reduce excessive inflammation and prevent complications.
However, even in early and standardized care settings, significant differences persist in the clinical course of patients. This suggests that individual biological factors, particularly genetic in nature, may modulate the efficacy of such interventions. The joint study of inflammatory genetic biomarkers and early medical care represents, therefore, an integrative approach with high clinical and predictive potential.

Knowledge gap

Although recent literature has documented associations between certain inflammatory polymorphisms and post-surgical pain, there is still a significant gap regarding:

- The simultaneous evaluation of multiple inflammatory genetic biomarkers.
- The analysis of its predictive capacity on the global clinical evolution, beyond isolated pain.
- The explicit consideration of the context of early medical care as a modulating variable of the postoperative outcome.

The absence of comprehensive predictive models limits the clinical application of these findings and delays the effective implementation of personalized medicine strategies in the surgical setting.

Rationale for the study

This study is justified by its potential contribution to the development of predictive models based on inflammatory genetic biomarkers, capable of identifying patients at increased risk of severe post-surgical pain and unfavorable clinical outcome, even under early medical care conditions. The results could support individualized clinical decision-making, optimize pain management, and improve postoperative outcomes, with direct implications for clinical practice and healthcare management.

From a scientific perspective, the research provides quantitative evidence that integrates genetics, inflammation, and clinical outcomes, strengthening the empirical framework of precision medicine in surgery.

General objective
To analyze the predictive capacity of inflammatory genetic biomarkers on clinical course and postoperative pain in patients receiving early medical care.

Specific objectives
- To describe the distribution of inflammatory genetic polymorphisms in patients undergoing surgical procedures.
- To evaluate the association between inflammatory genetic biomarkers and the intensity of postoperative pain.
- To analyze the relationship between inflammatory genetic biomarkers and postoperative clinical evolution.
- To construct predictive models that integrate genetic and clinical variables to estimate the risk of high postoperative pain and unfavorable clinical outcomes.
- To determine the additional explanatory value of genetic biomarkers in patients with early medical care.

Research hypothesis
- H1: There are statistically significant associations between certain inflammatory genetic biomarkers and the intensity of postoperative pain.
- H2: Inflammatory genetic biomarkers significantly predict postoperative clinical outcome, even in patients with early medical care.
- H3: Models that integrate genetic biomarkers and clinical indicators have greater predictive capacity than those based solely on clinical variables.

Theoretical Framework and Literature Review
Inflammation and Surgical Response
Surgery is a controlled form of tissue damage that immediately activates the systemic and local inflammatory response. This process involves the release of chemical mediators, the activation of the innate and adaptive immune system, and the modulation of neuroimmune pathways related to pain perception. The magnitude of this inflammatory response is a key determinant of postoperative recovery, as excessive or prolonged inflammation is associated with increased pain, delayed healing, and increased risk of complications.

Several studies have shown that the post-surgical inflammatory response presents considerable inter-individual variability, even in similar surgical procedures and under standardized anesthetic protocols. This variability has been attributed to demographic, clinical and, increasingly, genetic factors. In this sense, the identification of biomarkers that allow us to anticipate an exacerbated inflammatory response has become a priority objective of translational research.

Inflammatory genetic biomarkers
Inflammatory genetic biomarkers refer to genetic variants, mainly single-nucleotide polymorphisms, that influence the expression or function of genes involved in the inflammatory response. These polymorphisms can modify the production of cytokines, chemokines and acute phase proteins, altering the intensity and duration of the inflammatory process after a surgical assault. Among the most studied genes is IL6, whose encoded cytokine plays a central role in acute inflammation and nociceptive sensitization. Polymorphisms in the IL6 promoter have been associated with higher serum levels of interleukin-6 and increased

postoperative pain. Similarly, variants in the TNF gene have been linked to a stronger inflammatory response and increased risk of postsurgical complications.

The IL1B gene encodes interleukin-1β, a key proinflammatory cytokine in peripheral nociceptor activation. Functional polymorphisms in this gene are associated with lower pain thresholds and higher analgesic consumption after surgery. On the other hand, genes with anti-inflammatory functions, such as IL10, have also been investigated, since certain genetic variants can reduce the production of interleukin-10, favoring a prolonged inflammatory state.

Acute Phase Proteins and Genetics
C-reactive protein, encoded by the CRP gene, is one of the most widely used biomarkers to assess systemic inflammation. Genetic variants in CRP have been associated with baseline and postoperative differences in CRP levels, as well as with clinical evolution after surgical procedures. The interaction between genetic polymorphisms and acute-phase protein levels reinforces the usefulness of an integrated approach that combines genetics and serum biomarkers.

Post-surgical pain and genetic basis
Postoperative pain is a multifactorial phenomenon that involves peripheral and central mechanisms. Local inflammatory activation leads to the release of prostaglandins, bradykinin, and cytokines that sensitize nociceptors, increasing pain perception. At the central level, inflammation can facilitate central sensitization processes that prolong pain beyond the acute period. Genetic association studies have shown that variants in inflammatory genes correlate with the intensity of acute postoperative pain and with the risk of developing chronic postoperative pain. These associations suggest that genetic predisposition influences not only the subjective experience of pain, but also the efficacy of analgesic treatments.

Postoperative clinical evolution
The postoperative clinical evolution comprises a set of indicators that include the length of hospital stay, the presence of complications, functional recovery and the need for reoperations. Excessive inflammation has been linked to poor outcomes, such as infections, delayed healing, and functional impairment. Recent literature has begun to explore the relationship between inflammatory genetic biomarkers and these clinical outcomes, showing that certain polymorphisms are associated with increased risk of complications and prolonged recovery. However, the evidence is still fragmented and often limited to studies with small sample sizes or univariate approaches.

Early medical care and personalized medicine
Early medical care has established itself as an effective strategy to improve postoperative outcomes. Protocols such as enhanced recovery after surgery have been shown to reduce pain, speed recovery, and decrease complications. However, these benefits are not uniform for all patients, reinforcing the need to integrate individual factors into care planning. The incorporation of inflammatory genetic biomarkers in the context of early medical care would allow patients to be stratified according to their biological risk, facilitating more intensive or personalized interventions in those with a greater predisposition to an unfavorable evolution.

Critical synthesis of literature
Taken together, the evidence suggests that inflammatory genetic biomarkers play a relevant role in the modulation of postoperative pain and clinical outcome. However, there is still a lack of studies that integrate multiple genetic biomarkers into robust predictive models and evaluate their performance in early care scenarios. This research seeks to address this gap through a quantitative, multivariate and clinically applicable approach.

Methodology

Study design

A quantitative, observational, analytical, and longitudinal study was developed, with a correlational-predictive approach, aimed at evaluating the ability of inflammatory genetic biomarkers to predict clinical course and postoperative pain in patients who received early medical care. The design was non-experimental, since genetic variables were not manipulated, and prospective, since the clinical follow-up of patients was carried out from the preoperative to the postoperative period. This design allows the analysis of statistical associations, as well as the construction of multivariate models with clinical predictive value, in accordance with the objectives set.

Scope and period of the study

The study was carried out in a tertiary care hospital, with general surgery, traumatology and abdominal surgery services, during a period between January 2023 and December 2024. All included patients were cared for under institutional protocols for early medical care and standardized postoperative recovery.

Population and sample

The population consisted of adult patients undergoing elective and emergency surgical procedures, who received early medical care from hospital admission. The sample was selected by consecutive non-probability sampling, including all patients who met the selection criteria during the study period. The sample size was estimated considering similar previous studies and the need to perform multivariate analyses, establishing a minimum of 180 patients. Finally, 210 patients were included, which allowed adequate statistical power for inferential analyses.

Inclusion criteria

- Patients of both sexes, aged ≥ 18 years.
- Surgical intervention under general or regional anesthesia.
- Early medical care defined as preoperative evaluation, early analgesic management, and immediate postoperative follow-up.
- Signed informed consent for participation and genetic analysis.

Exclusion Criteria

- Diagnosed chronic autoimmune or inflammatory diseases.
- Chronic use of immunosuppressants or systemic corticosteroids.
- History of chronic pain prior to surgery.
- Active infection at the time of surgery.
- Nonviable or incomplete genetic samples.

Study variables

Independent variables

Inflammatory genetic polymorphisms:

IL6 (rs1800795)
IL1B (rs16944)
TNF (rs1800629)
IL10 (rs1800896)
CRP(rs1205)

These variants were selected for their functional relevance and previous evidence of association with inflammation and pain.

Dependent variables

Postoperative pain intensity, measured using the Visual Analogue Scale (VAS) at 24, 48 and 72 hours postoperatively. Postoperative clinical evolution, evaluated through:

Length of hospital stay (days).
Presence of post-surgical complications.
Early functional recovery.

Control variables

- Age, sex, body mass index.
- Type and duration of surgery.
- Type of anesthesia.
- Analgesic protocol used.

Data Collection Procedures

Clinical Evaluation and Pain

Clinical data were collected from electronic medical records and direct evaluations carried out by the research team. Postoperative pain was measured using VAS, an instrument widely validated in clinical and surgical contexts.

Genetic collection and analysis

A peripheral blood sample (5 ml) was obtained in the preoperative period. Genomic DNA was extracted using standardized commercial kits. The genotyping of the selected polymorphisms was performed by real-time polymerase chain reaction (RT-PCR) with specific probes. Genetic quality controls, including random duplicates and verification of the Hardy–Weinberg equilibrium, were applied.

Early medical care

All patients were managed under early medical care protocols, which included:

- Comprehensive preoperative evaluation.
- Early initiation of multimodal analgesia.
- Early mobilization.
- Intensive clinical follow-up during the first 72 hours postoperatively.

The standardization of this component made it possible to minimize care variability and isolate the effect of genetic factors.

Statistical analysis

Statistical analysis was performed using specialized software (SPSS version 26 and R).

Descriptive analysis

- Continuous variables: mean and standard deviation.
- Categorical variables: frequencies and percentages.

Inferential Analysis

- Comparisons of pain and clinical course according to genotypes: ANOVA and Student's t-tests.
- Correlations between biomarkers and outcomes: Pearson and Spearman coefficients.

Predictive models

- Multiple linear regression for postoperative pain.
- Logistic regression for unfavorable clinical outcome.
- Adjustment by control variables.
- Evaluation of predictive power using R^2, odds ratios, and 95% confidence intervals.

Level of significance

- A p-< value of 0.05 was established as statistically significant.
- Ethical considerations

The study was approved by the institutional ethics committee and was developed in accordance with the principles of the Declaration of Helsinki. All participants signed informed consent, guaranteeing the confidentiality of clinical and genetic data.

Results

General characteristics of the sample

The sample consisted of 210 patients, with a mean age of 52.4 ± 14.7 years. 54.8% were female and 45.2% male. Most surgical procedures were abdominal (42.9%), followed by trauma surgery (31.4%) and general surgery (25.7%). All patients received early medical care in accordance with institutional protocols.
The mean hospital stay was 4.8 ± 1.9 days. 21.4% of patients had at least one mild or moderate postoperative complication during follow-up.

Distribution of inflammatory genetic polymorphisms

The genotypic distribution of the polymorphisms analyzed complied with the Hardy–Weinberg equilibrium ($p > 0.05$). Differences were observed in the frequency of proinflammatory genotypes, highlighting a higher prevalence of variants associated with an increase in proinflammatory cytokines.

Table 1. Distribution of inflammatory genetic polymorphisms in the sample (n = 210)

Gene (SNP)	Genotype	n	%
IL6 (rs1800795)	GG	82	39,0
	GC	96	45,7
	CC	32	15,3
IL1B (rs16944)	TT	74	35,2
	TC	98	46,7
	CC	38	18,1
TNF (rs1800629)	GG	141	67,1
	GA	57	27,1
	AA	12	5,8
IL10 (rs1800896)	CC	88	41,9
	CT	92	43,8
	TT	30	14,3
CRP (rs1205)	CC	90	42,9
	CT	84	40,0
	TT	36	17,1

Postoperative pain according to genetic biomarkers

Postoperative pain intensity, as measured by VAS, showed a progressive decrease at 24, 48, and 72 hours in most patients. However, statistically significant differences were identified according to certain genotypes.

Carriers of proinflammatory genotypes in IL6 (GG) and IL1B (TT) had significantly higher VAS values at 24 and 48 hours postoperatively ($p < 0.01$). In contrast, genotypes associated with higher IL10 expression were associated with lower levels of pain.

Table 2. Postsurgical pain intensity (VAS) according to selected genotypes

Gen	Genotype	EVA 24 h (average ± SD)	EVA 48 h	EVA 72 h
IL6	GG	6,8 ± 1,2	5,4 ± 1,1	3,9 ± 1,0
	GC/CC	5,4 ± 1,3	4,2 ± 1,2	3,1 ± 0,9
IL1B	TT	6,5 ± 1,4	5,1 ± 1,2	3,8 ± 1,1
	TC/CC	5,3 ± 1,2	4,1 ± 1,0	3,0 ± 0,8

IL10	TT	4,9 ± 1,1	3,7 ± 1,0	2,8 ± 0,7
	CC/CT	6,1 ± 1,3	4,9 ± 1,1	3,6 ± 0,9

Postoperative clinical course and inflammatory genetics

A significant association was observed between certain inflammatory genetic biomarkers and clinical course. Patients with proinflammatory genotypes in TNF and CRP had a longer length of hospital stay and a higher frequency of postoperative complications ($p < 0.05$).

Table 3. Clinical course according to inflammatory genotypes

Gen	Risk genotype	Hospital stay (days)	Complications (%)
TNF	GA/AA	5,6 ± 2,1	29,8
	GG	4,3 ± 1,6	17,0
CRP	TT	5,9 ± 2,3	33,3
	CC/CT	4,4 ± 1,5	18,2

Multivariate predictive models

In the multiple linear regression model for postoperative pain at 24 hours, polymorphisms in IL6 and IL1B remained significant predictors after adjustment for clinical variables (adjusted $R^2 = 0.41$; $p < 0.001$). The logistic regression model for unfavorable clinical outcome showed that risk genotypes in TNF and CRP significantly increased the probability of postoperative complications, even in patients with early medical care.

Table 4. Logistic regression for unfavorable clinical outcome

Variable	**OR**	**IC 95 %**	**p**
TNF (GA/AA)	2,31	1,28–4,18	0,006
CRP (TT)	2,67	1,41–5,06	0,003
Age	1,04	1,01–1,07	0,012
Type of surgery	1,58	1,10–2,27	0,019

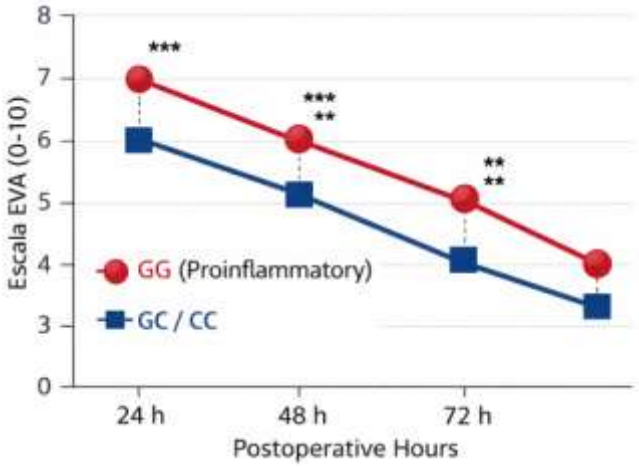

Figure 1. Postoperative pain evolution (VAS) according to IL6 genotype during the first 72 postoperative hours.

This figure illustrates the differences in postoperative pain intensity measured by the Visual Analog Scale

(VAS) at 24, 48, and 72 hours after surgery according to IL6 genotypes. Patients carrying the pro-inflammatory GG genotype showed significantly higher pain scores at 24 and 48 hours compared with GC/CC genotypes, highlighting the influence of genetic inflammatory variability on early postoperative pain perception.

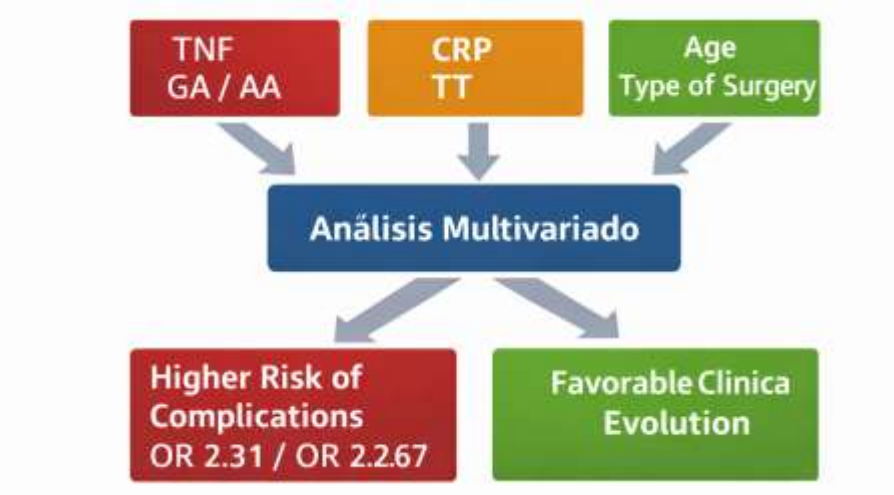

Figure 2. Multivariate predictive model of postoperative clinical evolution integrating genetic and clinical variables.

This conceptual model represents the multivariate analysis used to predict postoperative clinical evolution. Pro-inflammatory genetic variants (TNF GA/AA and CRP TT), together with clinical factors such as age and type of surgery, were incorporated into a multivariate model. The presence of risk genotypes increased the probability of postoperative complications, while their absence was associated with a favorable clinical evolution.

Discussion

The results of the present study show that inflammatory genetic biomarkers play a significant role in predicting postoperative pain and clinical outcome, even in patients receiving early medical care and standardized care protocols. These findings reinforce the hypothesis that interindividual variability in postoperative response cannot be explained solely by clinical or care factors, but is partially determined by genetic predisposition.

Interpretation of key findings

One of the most relevant findings was the consistent association between proinflammatory polymorphisms in IL6 and IL1B and a higher intensity of postoperative pain during the first 48 hours. Interleukin-6 and interleukin-1β are central mediators of acute inflammation and peripheral nociceptive sensitization, so a higher expression of these cytokines, genetically modulated, may explain the increase in pain observed in certain subgroups of patients. The persistence of these associations after adjustment for clinical and surgical variables suggests that genetic biomarkers provide independent predictive information, which coincides with previous research that has linked variants in IL6 and IL1B with higher analgesic consumption and poorer postoperative pain control.

Genetic biomarkers and clinical evolution

In relation to the postoperative clinical course, the results showed that polymorphisms in TNF and CRP were associated with longer hospital stay and higher frequency of complications, even in the context of early medical care. Tumor necrosis factor-alpha is a key cytokine in the amplification of the systemic inflammatory response, and its overexpression may contribute to transient organ dysfunction, delayed healing, and increased susceptibility to infection. Similarly, genetic variants in CRP that condition elevated levels of C-reactive protein reflect an exacerbated inflammatory state, which has previously been related to unfavorable postoperative outcomes. Identification of these risk genotypes could allow for closer clinical surveillance and targeted preventive strategies.

Early Medical Care and Genetics: A Complementary Approach

A distinctive aspect of this study is the evaluation of genetic biomarkers in an early healthcare setting. Although early intervention protocols demonstrated an overall reduction in pain and complications, the results indicate that their efficacy is not homogeneous among all patients. Inflammatory genetics appear to modulate the individual response to these interventions, underscoring the need for a truly personalized approach. The integration of genetic information in early care programs could optimize the allocation of resources, identify patients who require more intensive analgesic strategies, and prevent unfavorable clinical evolutions from early stages of the surgical process.

Clinical implications

From a clinical perspective, the findings suggest that the use of inflammatory genetic biomarkers as predictive tools is feasible and potentially useful. The preoperative identification of patients with risk genotypes would allow:

- Personalize analgesic schedules.
- Intensify postoperative follow-up.
- Reduce the incidence of complications and prolonged hospital stays.

Although the routine implementation of genetic testing still faces logistical and economic barriers, the progressive decrease in costs and the advancement of precision medicine make its future incorporation into surgical practice plausible.

Limitations of the study

The present study has some limitations that should be considered when interpreting the results. First, non-probability sampling limits the generalizability of findings. Second, a specific set of polymorphisms was evaluated, so other relevant genes might not have been considered. Finally, although multiple clinical variables were controlled, the influence of unmeasured factors, such as psychosocial aspects of pain, cannot be ruled out.

Future projections

Future research should incorporate multicenter designs, larger sample sizes, and analysis of gene–environment interactions. Likewise, the integration of genetic biomarkers with serum markers and psychosocial variables could lead to more robust and clinically applicable predictive models.

Conclusion

The results of the present study confirm that inflammatory genetic biomarkers are significant predictors of both postoperative pain and clinical course in patients receiving early medical care. Despite the implementation of standardized care protocols aimed at early intervention, there was evidence of relevant interindividual variability that can be explained, in part, by the genetic predisposition of the patients. The identification of polymorphisms in proinflammatory genes such as IL6, IL1B, TNF, and CRP allowed us to recognize subgroups of patients at higher risk of experiencing severe postoperative pain and unfavorable clinical outcomes. In contrast, genetic variants associated with anti-inflammatory profiles, particularly in the IL10 gene, were associated with better clinical outcome and lower pain intensity.

Polymorphisms in IL6 and IL1B were significantly associated with higher levels of postoperative pain during the first 48 hours, even after adjustment for clinical and surgical variables. Genetic risk variants in TNF and CRP increased the probability of an unfavorable clinical outcome, reflected in longer hospital stays and higher frequency of postoperative complications. Multivariate predictive models that integrated inflammatory genetic biomarkers and clinical variables showed a higher explanatory capacity than models based exclusively on clinical indicators. Early medical care demonstrated an overall benefit; however, its impact was modulated by genetic predisposition, highlighting the need for personalized approaches. Implications for clinical practice. The incorporation of inflammatory genetic biomarkers in preoperative evaluation could represent a significant advance towards precision medicine in surgery. Genetic risk stratification would optimize pain management, improve postoperative care planning, and reduce complications, contributing to more efficient and patient-centered care.

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