

Article

Management of Prediction and Classifying of Wound Healing Results in Plastic and Reconstructive Surgery Based on Machine Learning Models

Larysa Sydorchuk ¹, Ruslan Gumennyi ², Miroslav Škoda ³, Andrii Sydorchuk ⁴, Yana Vyklyuk ⁵, Iryna Batih ⁶, Sai Praveen Daruvuri ¹, Ruslan Sydorchuk ^{7,*} and Maksym Sokolenko ⁸

¹ Department of Family Medicine, Bukovinian State Medical University, 58002 Chernivtsi, Ukraine; lsydorchuk@ukr.net (L.S.); praveenzzz39@gmail.com (S.P.D.)

² Bukovinian Center of Plastic and Aesthetic Surgery, 58000 Chernivtsi, Ukraine; bukestet@gmail.com

³ Department of Management and Accounting, DTI University, 01841 Dubnica nad Váhom, Slovakia; skoda@dti.sk

⁴ Surgery Department, Donauklinik, 89231 Neu Ulm, Germany; andris1595@gmail.com

⁵ Department of Artificial Intelligence, Lviv Polytechnic National University, 79005 Lviv, Ukraine; yasya.vyklyuk@gmail.com

⁶ Department of Surgical Dentistry and Maxillofacial Surgery, Bukovinian State Medical University, 58002 Chernivtsi, Ukraine; batih.iryana@bsmu.edu.ua

⁷ Department of General Surgery and Urology, Bukovinian State Medical University, 58002 Chernivtsi, Ukraine

⁸ Department of Infectious Diseases and Epidemiology, Bukovinian State Medical University, 58002 Chernivtsi, Ukraine; sokolenko_maks@ukr.net

* Correspondence: rsydorchuk@ukr.net

Abstract

Postoperative wound healing complications present a major challenge in plastic and reconstructive surgery, prolonging recovery and impairing outcomes. Early risk identification is difficult due to complex interactions among clinical, laboratory, and molecular factors. This study developed and evaluated machine-learning (ML) models to predict wound healing outcomes and identify key complication predictors. Utilizing a dataset of 95 women and 76 variables (including hematological, biochemical, coagulation, and gene expression profiles), we evaluated several ML approaches, including Decision Tree, Extra Trees, Gaussian/Bernoulli Naive Bayes, Logistic Regression, and Support Vector Machine. Model performance was assessed via k-fold cross-validation, ROC analysis, and SHAP feature importance. Molecular markers (COL1A1, MMP9, MAPK1, MAPK8, IL10, and CCL2) emerged as the strongest predictors, whereas conventional clinical variables showed limited value. The models achieved high discriminative performance, with validation ROC–AUC values ranging from 0.903 to 0.913. Extra Trees and Gaussian Naive Bayes demonstrated the highest sensitivity for detecting complications (Recall = 0.820 ± 0.238 and 0.807 ± 0.246 , respectively). These findings highlight the value of integrating molecular-genetic biomarkers with ML for personalized risk stratification and preventive care in reconstructive surgery.



Academic Editor: Rainer Breitling

Received: 9 June 2026

Revised: 29 June 2026

Accepted: 6 July 2026

Published: 10 July 2026

Copyright: © 2026 by the authors.

Licensee MDPI, Basel, Switzerland.

This article is an open access article distributed under the terms and conditions of the [Creative Commons Attribution \(CC BY\)](https://creativecommons.org/licenses/by/4.0/) license.

Keywords: artificial intelligence; machine learning; models; wound healing; surgery; correlations; management; prediction; classifying; plastic and reconstruction

1. Introduction

Wound healing in healthy individuals represents a complex, multimodal, dynamic, and highly regulated biological process involving coordinated interactions between inflammatory, proliferative, and remodeling phases [1–3]. This process requires precise

orchestration of immune responses, extracellular matrix (ECM) remodeling, angiogenesis, and cellular proliferation. Disruption of these mechanisms may result in delayed healing, chronic wounds, or pathological scar formation, which significantly affects functional and aesthetic outcomes in reconstructive procedures [4].

At the molecular level, wound repair is governed by tightly interconnected signaling networks [5]. Key mediators include pro-inflammatory cytokines such as interleukin-6 (IL-6) and chemokines like C-C motif chemokine ligand 2 (CCL2), which regulate leukocyte recruitment and inflammatory cascades, as well as anti-inflammatory regulators such as interleukin-10 (IL10), which contribute to resolution of inflammation [6–8]. Intracellular signaling pathways, particularly those involving Mitogen-Activated Protein Kinases (MAPK1 and MAPK8), play a central role in transducing stress and inflammatory signals into cellular responses [9]. In addition, ECM remodeling is controlled by metalloproteinases (MMP) such as MMP9, while structural proteins encoded by Collagen alpha 1 chain types 1 and 3 (COL1A1 and COL3A1) determine the quality and mechanical properties of the newly formed tissue [10–12]. The transforming growth factor- β 1 (TGF β 1) pathway is a pivotal regulator of fibroblast activation, collagen synthesis, and fibrogenesis, linking inflammation to scar formation [13].

Recent evidence indicates that dysregulation of these molecular pathways contributes to aberrant healing outcomes, including fibrosis, hypertrophic scarring, and impaired regeneration [12]. For instance, prolonged IL-6-mediated inflammation and imbalance between ECM deposition and degradation may lead to excessive scar formation, while altered expression of MMP9 and collagen genes affects tissue remodeling and tensile strength [5–7]. Furthermore, systemic and local factors such as oxidative stress, microbiome composition, and comorbid conditions modulate gene expression patterns and healing trajectories, highlighting the multifactorial nature of wound repair [14–18].

Despite these advances, conventional approaches to outcome prediction remain limited by the complexity and heterogeneity of biological data. The increasing availability of high-dimensional datasets, including transcriptomic, clinical, and imaging data, necessitates the use of advanced analytical methods capable of capturing nonlinear relationships and interactions among variables. Artificial intelligence (AI) and machine learning (ML) have emerged as powerful tools for addressing these challenges. ML algorithms, such as decision trees, random forests, gradient boosting, and neural networks, enable the integration of multidimensional data and facilitate the development of predictive models with high accuracy. In wound care, ML approaches have already demonstrated potential in predicting healing rates, classifying wound types, and identifying patients at risk of complications, as well as in other diseases [19–27]. Importantly, ML can hypothetically uncover hidden patterns within gene expression data and link them to clinical outcomes, providing insights into the underlying biological mechanisms.

Despite recent advances in ML applications for surgical outcome prediction, most existing models rely predominantly on demographic, clinical, and perioperative variables, whereas the contribution of molecular-genetic biomarkers associated with inflammation, extracellular matrix remodeling, and tissue repair remains insufficiently explored. Furthermore, relatively few studies have combined explainable AI approaches with molecular profiling to identify biologically meaningful predictors of postoperative wound-healing complications [19–22].

Hereupon, the novelty of the present study lies in the integration of clinical, laboratory, and molecular-genetic data within a unified ML framework for postoperative complication prediction. In addition, the study applies SHAP-based explainable AI to quantify the contribution of individual predictors and identify key biological pathways associated with wound-healing outcomes. This approach aims not only to improve predictive performance

but also to enhance the biological interpretability of ML models for personalized risk assessment in reconstructive surgery.

Therefore, the aim of the present study is to develop and validate machine learning models for prediction and classifying of wound healing outcomes and postoperative complications in women in plastic and reconstructive surgery, based on the integration of clinical data and gene expression profiles (IL-6, IL-10, CCL2, MMP9, MAPK1, MAPK8, TGFB1, COL1A1, COL3A1). This approach seeks to advance precision medicine by providing a comprehensive, data-driven framework for improving patient-specific outcomes in plastic and reconstruction practice.

2. Materials and Methods

2.1. Clinical Data Set Collection. Screening. Compliance with Biomedical Ethics

Clinical data was prospectively collected between September 2024 and December 2025 at the “Bukovinian Center of Plastic and Aesthetic Surgery” in Chernivtsi, Ukraine. The investigation was designed as a prospective longitudinal single-cohort study and enrolled 95 women undergoing reconstructive or aesthetic breast surgery. The mean age of participants was 35.48 ± 6.61 years (range: 19–57 years). Prior to inclusion, all participants provided written informed consent and completed a comprehensive baseline evaluation, including demographic and clinical assessment, imaging studies (breast ultrasound and/or mammography), and laboratory testing (complete blood count and biochemical profile).

The study was conducted in accordance with the principles of the Convention on Human Rights and Biomedicine and was approved by the Biomedical Ethics Committee of Bukovinian State Medical University (Protocol No. 1, 19 September 2024). Written informed consent was obtained from all participants prior to enrollment.

All participants were screened for eligibility based on predefined inclusion and exclusion criteria. Inclusion criteria comprised age ≥ 18 years, ability to engage in the study procedures (i.e., absence of severe mental disorders), and provision of written informed consent. Exclusion criteria included age under 18 years; presence of acute inflammatory conditions or exacerbation of chronic inflammatory diseases; active or decompensated autoimmune disorders; connective tissue diseases or other systemic conditions in sub- or decompensated stages; severe metabolic disorders (including type I or II diabetes mellitus in sub- or decompensation stages, and class III obesity or higher); psychiatric disorders; and pregnancy or lactation.

Clinical evaluation encompassed general health status, patient-reported symptoms, findings from physical examination (inspection and mammary glands palpation), ultrasound results, and detailed documentation of the type of mammoplasty performed.

2.2. Stratification of Patients

Participants were categorized according the occurrence of postoperative complications (12.63% with complications vs. 87.67% without), and type of surgical intervention. The distribution of procedures included augmentation mammoplasty (69.47%), mastopexy (6.32%), combined mastopexy with mammoplasty (9.47%), reduction mammoplasty (5.26%), implant replacement (7.37%), and implant removal (2.11%). Reported postoperative complications comprised capsular contracture/fibrosis (6.32%), implant displacement with contour deformity (3.16%), retromammary seroma (2.11%), and implant rupture (1.05%).

2.3. Genetic Analysis

Gene expression analysis of IL6, IL10, CCL2, MAPK1, MMP9, MAPK8, COL1A1 and COL3A1 in peripheral blood leukocytes was performed using a pathway-focused PCR primers with iTaq Universal SYBR Green Supermix (SMX500; Thermo Fisher Scientific

Inc., Bio-Rad Laboratories, Waltham, MA, USA). Total RNA was extracted using the GeneAll® Hybrid-R™ Blood RNA Kit (GeneAll Biotechnology, Seoul, Republic of Korea) following the manufacturer's protocol, and subsequently reverse-transcribed into cDNA using the iScript™ gDNA Clear cDNA Synthesis Kit (Bio-Rad Laboratories, Foster City, CA, USA). All genes expression was normalized by the reference gene GAPDH. The methodological approach to transcriptional activity assessment has been described in our previous publications [28–30]. Molecular genetic analysis was carried out in a subset of 50 participants (without missing any relevant data).

2.4. The Study Methodology

Data analysis was conducted in a stepwise manner and comprised the following stages:

- Data acquisition and preprocessing (development of the feature matrix, assessment of duplicates and missing values, transformation of molecular variables);
- Multicollinearity analysis and feature selection;
- Association analysis between predictors and the target variable;
- Correlation analysis (to evaluate relationships among variables and to identify the most informative predictors of postoperative complications in women in plastic and reconstructive surgery);
- Development of ML models and performance assessment (tuning of hyperparameters and quantification of each feature's contribution to model predictions);
- Interpretation of results and identification of consistent predictors (visualization of model performance using SHAP analysis, ROC curves and elucidation of classification mechanisms based on decision tree-derived structures).

The overall methodological framework is presented in Figure 1, illustrating the sequence of analysis stages workflow and interactions between them.

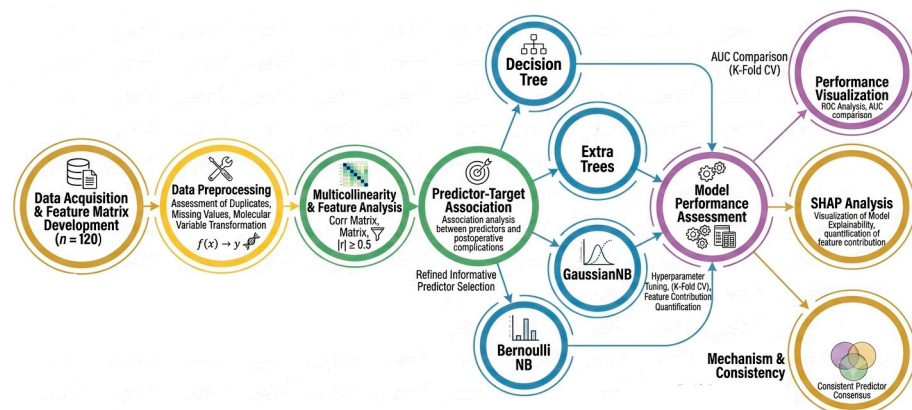


Figure 1. Study methodology framework using Orange flow diagrams.

2.4.1. Data Acquisition and Preprocessing

The initial dataset (76 variables) comprised demographic, clinical, laboratory, and molecular-genetic parameters. Demographic and clinical features included age, place of residence, blood group, Rh factor, body mass index (BMI), systolic and diastolic blood pressure (SBP, DBP), and heart rate (HR). Laboratory parameters encompassed standard hematological indices (erythrocytes (Er-RBC), hemoglobin (Hb), color index (CI), leukocytes (Leu-WBC) and their subpopulations (neutrophils—(NEUT) segmented and band), eosinophils (EO)), lymphocytes (LYMPH), monocytes (Mono), platelet (PTL) and erythrocyte sedimentation rate (ESR)), biochemical markers (glucose, urea, creatinine (Cr), bilirubin (BIL) and its fractions (direct—DBIL and non-direct—N-DBIL), liver enzymes (ALT, AST), total protein, alkaline phosphatase (APh), and estimated glomerular filtration rate (eGFR).

calculated using the CKD-EPI equation), as well as coagulation parameters (prothrombin time (PTt), prothrombin index (PTI), thrombin time (Tt), activated partial thromboplastin time (APTT), fibrinogen (Fib), hematocrit (Ht) and international normalized ratio (INR)).

Based on the Clinical Blood Analysis/Complete Blood Count (RBC, WBC), inflammatory indices were calculated, including the neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), and the systemic immune-inflammation index ($SII = \text{PLT} \times \text{NEUT} / \text{LYMPH}$). Molecular-genetic variables were represented by the relative expression levels of IL6, COL1A1, COL3A1, CCL2, IL10, MAPK1, MAPK8, MMP9 and TGFB1 genes, normalized to the reference gene GAPDH.

The target variable was postoperative complications after plastic and reconstructive surgery, coded as a categorical variable (0/1—NO/YES complication).

Data preprocessing included screening for duplicate records and missing values, none of which were identified, as well as transformation of molecular variables. For molecular markers (IL6, COL1A1, COL3A1, CCL2, IL10, MAPK1, MAPK8, MMP9, TGFB1), a logarithmic transformation (natural logarithm) was applied to stabilize variance and reduce distributional skewness: $x' = \ln(x)$.

2.4.2. Multicollinearity Analysis and Feature Selection

Multicollinearity among predictors was assessed using a generalized association matrix, enabling evaluation of relationships between variables of different types (threshold $|r| \geq 0.7$). Pearson's correlation coefficient was applied to continuous variables, Cramér's V to categorical variables, and the correlation ratio (η^2) to mixed-type variable pairs.

Multicollinearity-based feature filtering (reduction) was performed during the preprocessing stage before model development. Highly correlated predictors ($|r| \geq 0.80$) were identified using pairwise association analysis, and one variable from each strongly correlated pair was excluded to reduce redundancy and improve model stability. This procedure was based solely on predictor–predictor relationships and did not use information from the target outcome. Nevertheless, because feature reduction was performed before cross-validation, a limited degree of information leakage cannot be completely excluded and should be considered when interpreting model performance.

2.4.3. Association Analysis Between Predictors and the Target Variable

The relationship between predictors and the target variable was evaluated using a generalized association matrix. Given that the target variable was binary (0 = NO complication, 1 = YES complication), associations with numerical predictors were assessed using the point-biserial correlation coefficient, whereas appropriate measures of association were applied for categorical variables, including Cramér's V coefficient. The resulting values were used to rank predictors according to the strength of their association with the target variable.

2.4.4. Machine Learning Models Development and Performance Assessment

Considering the binary classification task, machine learning approaches were employed. Due to the relatively small sample size and heterogeneity of features, algorithms with different inductive biases were selected. In particular, tree-based models (Decision Tree Classifier, Extra Trees Classifier) were applied, as they enable modeling of complex nonlinear relationships and inherently account for feature interactions without requiring assumptions about data distribution [31,32].

The evaluated ML algorithms were selected to represent complementary ML principles suitable for a small, heterogeneous biomedical dataset and a binary classification task. The Decision Tree classifier was included as an interpretable baseline model, as it provides threshold-based decision rules that can be clinically examined and translated

into understandable risk-stratification pathways. Extra Trees was selected as an ensemble tree-based method capable of capturing nonlinear relationships and interactions among clinical, laboratory, and molecular predictors while reducing variance through randomized tree aggregation. Gaussian Naive Bayes was included because many predictors, including laboratory and gene-expression variables, are continuous, and this model provides a simple probabilistic classification framework that is often robust in limited-sample settings. Bernoulli Naive Bayes was used to evaluate threshold-like or binarized feature patterns [33,34]. More complex high-capacity models, such as neural networks, were not prioritized because the available sample size was limited and such models would carry a high risk of overfitting.

Model performance was evaluated using Repeated Stratified K-Fold cross-validation (5 folds $\times$ 10 repeats) which reduces variance in performance estimates and improves reliability. At the initial stage, a comparative analysis of models was conducted using key evaluation metrics. To avoid information leakage and ensure unbiased performance estimation, hyperparameter optimization was performed exclusively within the training portion of each cross-validation iteration using RandomizedSearchCV and GridSearchCV, focusing on the most relevant model parameters. The optimal hyperparameter configuration identified from the training data was subsequently applied to the corresponding validation fold. Thus, validation data were not used during model fitting or hyperparameter selection. Due to the limited sample size, a separate hold-out test set was not created, and the reported metrics represent internally cross-validated estimates of predictive performance.

Model performance was assessed using the following metrics: ROC-AUC, Recall, Precision, F1-score, Accuracy, and Balanced Accuracy [35].

For the final models, receiver operating characteristic (ROC) curves were constructed, illustrating the relationship between sensitivity (true positive rate) and the false positive rate. The area under the ROC curve (ROC-AUC) was used as an integral measure of model performance.

In addition, the decision tree model was employed as an interpretative tool to derive classification rules and to visualize the decision-making process.

Given the limited sample size and the molecular-genetic subset of 50 participants, the present analysis was designed as an exploratory predictive modeling study. Repeated stratified cross-validation was used to reduce the variance of performance estimates and to maximize the use of available data. In addition, relatively interpretable and low-to-moderate complexity algorithms were selected to reduce the risk of overfitting compared with high-capacity models.

2.4.5. Interpretation of Results and Identification of Consistent Predictors

Model interpretation was performed using the SHAP (SHapley Additive exPlanations) framework, which enables quantification of the contribution of each feature to the model predictions at both global and individual levels [36]. This method is grounded in cooperative game theory and Shapley values, where the contribution of each feature is defined as its average marginal effect on the model output across all possible feature combinations. This approach provides a consistent and interpretable decomposition of model predictions into contributions from individual predictors.

To identify consistent predictors across different models, a Venn diagram was constructed based on features with the highest absolute SHAP values for each model (Extra Trees, Gaussian Naive Bayes, Bernoulli Naive Bayes).

2.5. Software

All AI analyses were performed in Python (version 3.9.12) using the following libraries: pandas 2.1.3, NumPy 1.26.0, Scikit-learn (version 1.0.2), SHAP 0.44.0, matplotlib 3.8.0, seaborn 0.13.2, and Dython. ChatGPT (OpenAI, model DALL·E 3) was used to generate the graphical abstract.

Continuous variables were evaluated using an independent-samples Welch's *t*-test for normally distributed data ($M \pm SD$), whereas for non-normally distributed variables, identified by the Shapiro–Wilk test, the Wilcoxon–Mann–Whitney U test was applied (presented as median (Me) with interquartile range (Q1–Q3)). Categorical variables/counts (percentage) were analyzed using chi-square test (χ^2) ($df = 1$) and Fisher's exact test when expected frequencies were below 5. Differences were considered statistically significant at $p < 0.05$.

3. Results

3.1. Baseline Characteristics of Patients

The baseline data of enrolled women is given in Table 1. Social employment was significantly less common among patients with complications compared with those without complications (50.0% vs. 79.5%, $p = 0.036$), suggesting a possible association between unemployment and increased complication risk. Type of surgical intervention demonstrated the strongest association with complications ($p < 0.001$ overall). Complications occurred predominantly after implant-related revision procedures: implant replacement (58.3%) and implant removal (16.7%) were observed exclusively in the complication group, whereas primary augmentation mammoplasty was significantly more frequent in patients without complications (77.1% vs. 16.7%). A history of previous surgical interventions was significantly more common in patients with complications (66.7% vs. 18.1%, $p = 0.001$), indicating that prior surgery may represent an important risk factor for adverse postoperative outcomes. Concomitant chronic pathology showed a trend toward higher prevalence in the complication group (33.3% vs. 12.1%), although statistical significance was not reached ($p = 0.074$). Variables that were not significantly associated with complications included: age, place of residence, blood group and Ph-factor ($p > 0.05$ for all comparisons).

Table 1. Baseline characteristics of patients depending on complications' presence.

Clinical and Some Demographic Data		Complications		<i>p</i> Value
		Yes, <i>n</i> = 12 (%)	No, <i>n</i> = 83 (%)	
Age, years, $M \pm SD$		36.33 $\pm$ 9.67	35.21 $\pm$ 5.80	1.0
Social employment, <i>n</i> (%)	Yes	6 (50.0)	66 (79.52)	0.036
	No	6 (50.0)	17 (20.48)	
Place of residence, <i>n</i> (%)	City	9 (75.0)	61 (73.49)	0.610
	Rural area	3 (25.0)	22 (26.51)	
Type of surgical intervention, <i>n</i> (%)	Augmentation Mammoplasty	2 (16.67)	64 (77.11)	<0.001
	Reduction Mammoplasty	1 (8.33)	4 (4.82)	0.499
	Mastopexy	0	6 (7.23)	-
	Mastopexy with Mammoplasty	0	9 (10.84)	-
	Implant Replacement	7 (58.33)	0	-
	Implant Removal	2 (16.67)	0	-

Table 1. Cont.

Clinical and Some Demographic Data		Complications		p Value
		Yes, n = 12 (%)	No, n = 83 (%)	
Blood group, n (%)	0 (I group)	3 (25.0)	32 (38.55)	0.284
	A (II group)	5 (41.67)	22 (26.51)	0.223
	B (III group)	4 (33.33)	22 (26.51)	0.425
	AB (IV group)	0	7 (8.43)	-
Rh factor, n (%)	Rh+	10 (83.33)	72 (86.75)	0.515
	Rh-	2 (16.67)	11 (13.25)	
Surgical interventions in anamnesis, n (%)		8 (66.67)	15 (18.07)	0.001
Concomitant chronic pathology, n (%)		4 (33.33)	10 (12.05)	0.074

3.2. Results of Multicollinearity Analysis and Feature Selection

To identify multicollinearity among predictors, an association matrix was constructed (Figure 2). The color scale represents the strength of relationships between all feature types: light orange indicates the maximum positive association (+1), light blue corresponds to the maximum negative association (−1), whereas darker shades indicate the absence of association (0).

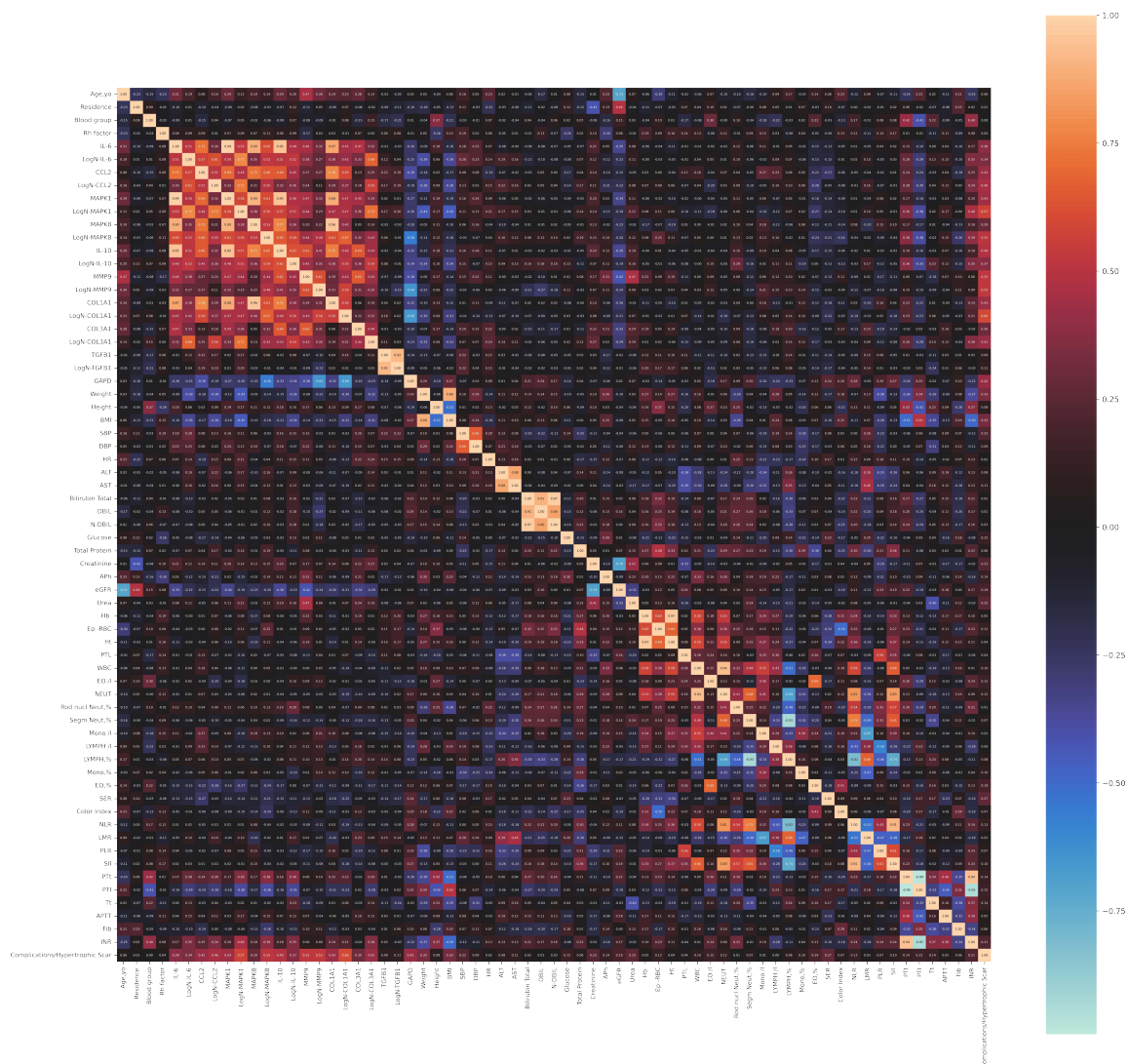


Figure 2. Association matrix.

A substantial number of feature pairs for numerical variables with high correlation coefficients ($|r| \geq 0.8$) were identified, indicating potential information redundancy and a risk of model instability (Figure 3). An almost complete inverse relationship was observed between PTI and PTt ($r = -0.99$). Strong correlations were also detected among molecular markers, including MAPK1 and IL-6 ($r = 0.99$), IL-10 and IL-6 ($r = 0.95$), as well as MAPK8 and MAPK1 ($r = 0.90$). High association values were further identified among biochemical parameters (N-DBIL and total bilirubin, $r = 0.97$; AST and ALT, $r = 0.88$), hematological indices (Ht and Hb, $r = 0.97$; NEUT and WBC, $r = 0.94$), and derived inflammatory indices (SII and NLR, $r = 0.91$).

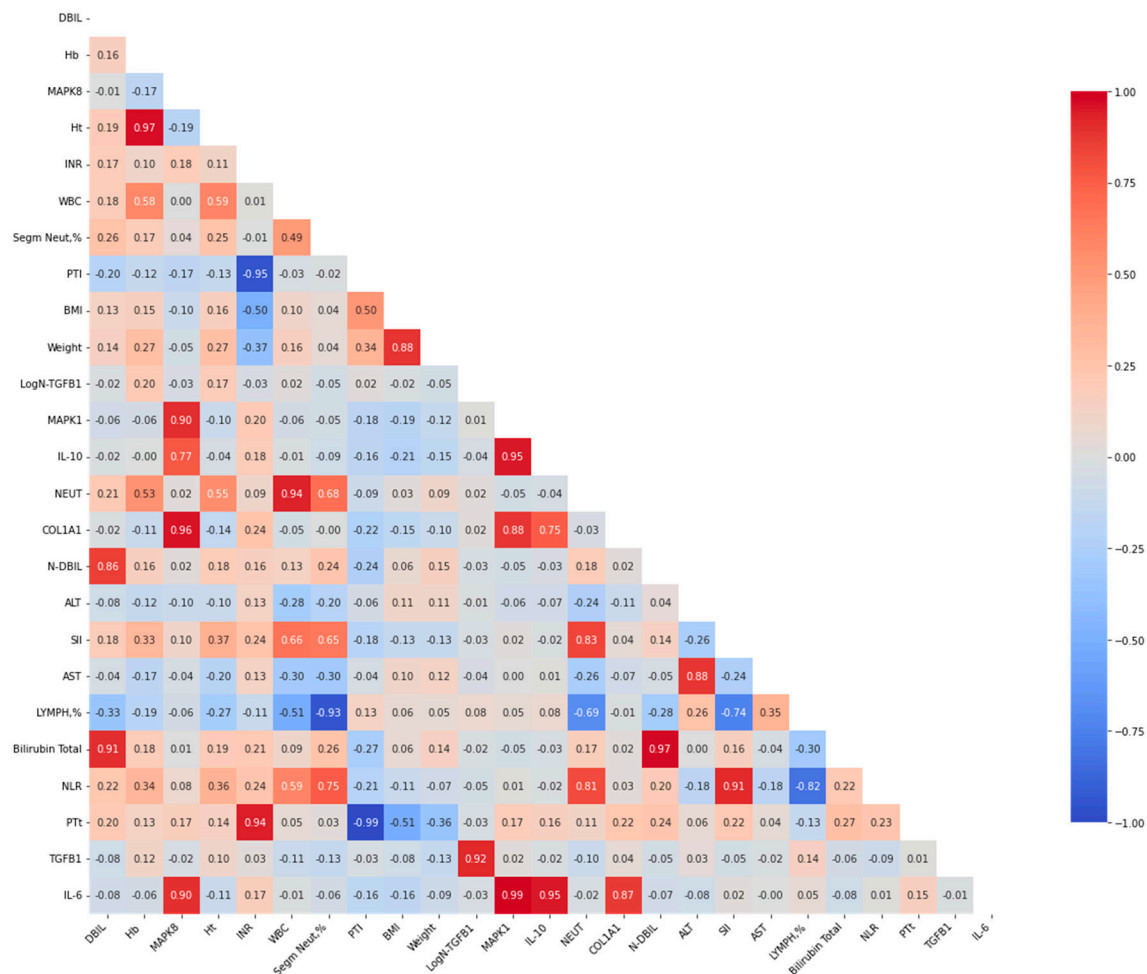


Figure 3. Lower triangular correlation matrix for numerical variables with strong linear relationships. A threshold of 0.80 ($|r| \geq 0.8$) was applied to identify strongly collinear pairs. The color scale ranging from -1 to $+1$ reflects the direction and magnitude of correlations: deep red indicates a strong positive correlation ($+1$), deep blue represents a strong negative correlation (-1), and white denotes the absence of a statistically significant relationship (0).

To improve reproducibility, eliminate multicollinearity and avoid duplication of information, the retained and excluded variables were determined according to the following principles: variables with stronger biological relevance to wound-healing mechanisms, more direct clinical interpretation, and lower redundancy with other predictors were prioritized for retention. Variables excluded due to high correlation included TGFB1, MAPK1, IL-6, MAPK8, PTt, N-DBIL, Ht, INR, WBC, segmented neutrophils (%), SII, DBIL, weight, total bilirubin, ALT, lymphocytes (%), and NEUT. This feature selection procedure reduced predictor-space dimensionality and improved the stability and generalizability of the ML models.

3.3. Analysis of the Relationship Between Predictors and the Target Variable

An association matrix was used to evaluate the relationships between the studied features and the presence of postoperative complications. The strongest positive associations were identified for molecular markers, including LogN-COL1A1 ($r = 0.60$), LogN-MAPK1 ($r = 0.57$), LogN-MMP9 ($r = 0.53$), and LogN-MAPK8 ($r = 0.52$). Moderate positive correlations were also observed for IL-10 ($r = 0.49$) and LogN-CCL2 ($r = 0.46$). Similar findings were obtained for the native expression levels of the corresponding genes, particularly MMP9, COL1A1, and CCL2.

Among the negative associations, the most pronounced inverse correlations were detected for GAPD ($r = -0.42$) and body mass index (BMI; $r = -0.33$). Other clinical and laboratory variables demonstrated weak or no meaningful association with the target variable ($|r| < 0.3$).

3.4. Development of Machine Learning Models and Model Performance Evaluation

Tables 2 and 3 summarize the comparative performance evaluation of the machine learning models. Metric values are presented as mean $\pm$ standard deviation obtained during repeated stratified cross-validation.

Table 2. Performance metrics of machine learning models on the training dataset.

Model	Accuracy	Balanced Accuracy	Precision	Recall	F1-Score	ROC-AUC
GaussianNB	0.951 $\pm$ 0.021	0.961 $\pm$ 0.024	0.844 $\pm$ 0.058	0.982 $\pm$ 0.040	0.906 $\pm$ 0.039	0.992 $\pm$ 0.004
BernoulliNB	0.926 $\pm$ 0.025	0.910 $\pm$ 0.038	0.826 $\pm$ 0.058	0.879 $\pm$ 0.070	0.850 $\pm$ 0.053	0.978 $\pm$ 0.011
ExtraTrees	0.958 $\pm$ 0.020	0.953 $\pm$ 0.030	0.888 $\pm$ 0.053	0.946 $\pm$ 0.058	0.914 $\pm$ 0.040	0.994 $\pm$ 0.005
DecisionTree	0.898 $\pm$ 0.037	0.920 $\pm$ 0.022	0.727 $\pm$ 0.097	0.963 $\pm$ 0.050	0.823 $\pm$ 0.051	0.969 $\pm$ 0.011

Table 3. Performance metrics of machine learning models on the validation dataset.

Model	Accuracy	Balanced Accuracy	Precision	Recall	F1-Score	ROC-AUC
GaussianNB	0.888 $\pm$ 0.090	0.858 $\pm$ 0.125	0.794 $\pm$ 0.222	0.807 $\pm$ 0.246	0.766 $\pm$ 0.184	0.903 $\pm$ 0.129
BernoulliNB	0.876 $\pm$ 0.098	0.847 $\pm$ 0.132	0.757 $\pm$ 0.233	0.793 $\pm$ 0.244	0.747 $\pm$ 0.195	0.913 $\pm$ 0.105
ExtraTrees	0.894 $\pm$ 0.087	0.866 $\pm$ 0.117	0.811 $\pm$ 0.219	0.820 $\pm$ 0.238	0.779 $\pm$ 0.175	0.907 $\pm$ 0.132
DecisionTree	0.778 $\pm$ 0.136	0.754 $\pm$ 0.147	0.576 $\pm$ 0.280	0.707 $\pm$ 0.300	0.591 $\pm$ 0.219	0.791 $\pm$ 0.163

All evaluated models demonstrated high discriminative performance, as evidenced by ROC-AUC values exceeding 0.90. The highest ROC-AUC values were achieved by the Bernoulli Naive Bayes (0.913 $\pm$ 0.105), Extra Trees (0.907 $\pm$ 0.132), and Gaussian Naive Bayes (0.903 $\pm$ 0.129) models.

From a clinical perspective, particular attention was paid to the Recall metric, which reflects the model's ability to correctly identify patients with postoperative complications. The highest Recall values were observed for the Extra Trees (0.820 $\pm$ 0.238) and Gaussian Naive Bayes (0.807 $\pm$ 0.246) models, indicating superior sensitivity toward the positive class. The Bernoulli Naive Bayes model demonstrated a slightly lower Recall value (0.793 $\pm$ 0.244).

In contrast, the Decision Tree model showed the weakest performance, particularly in terms of ROC-AUC (0.791 $\pm$ 0.163) and Recall (0.707 $\pm$ 0.300), suggesting lower stability and a higher susceptibility to overfitting on the present dataset.

Although Extra Trees achieved the highest mean ROC-AUC (0.913 $\pm$ 0.093), the differences in predictive performance among the evaluated algorithms were generally

modest. Most models demonstrated ROC-AUC values above 0.90, indicating consistently high discriminative ability across different machine-learning approaches. Furthermore, the observed standard deviations, particularly for Recall, suggest some variability in performance across cross-validation folds. Therefore, the reported results support the conclusion that several algorithms achieved comparable predictive performance rather than indicating the clear superiority of a single model.

To further assess model robustness and generalizability, 95% confidence intervals (CIs) for ROC-AUC values on the validation dataset were calculated. The Gaussian Naive Bayes (95% CI: 0.867–0.939), Bernoulli Naive Bayes (95% CI: 0.884–0.942), and Extra Trees (95% CI: 0.870–0.944) models demonstrated consistently high and stable performance, characterized by relatively narrow and overlapping confidence intervals, indicating comparable discriminative ability. Conversely, the Decision Tree model exhibited a lower ROC-AUC (95% CI: 0.746–0.836) and a wider confidence interval, reflecting greater variability and reduced model stability.

Receiver operating characteristic (ROC) curves illustrating the discriminative performance of the evaluated models are presented in Figure 4.

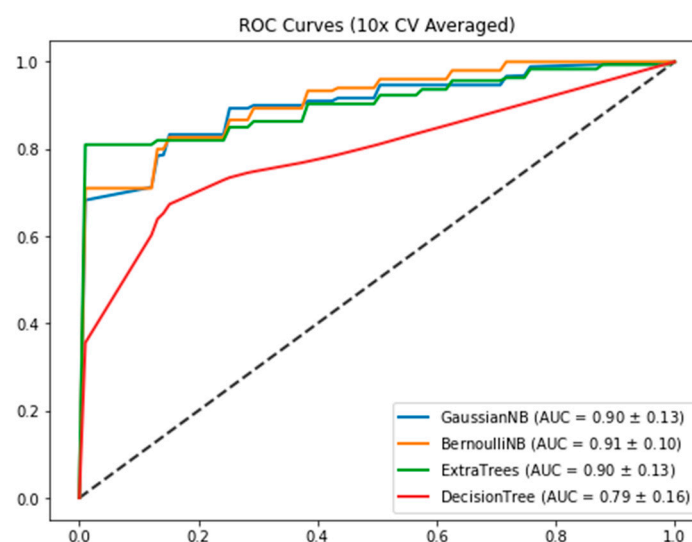


Figure 4. ROC-curves for evaluated models.

The accomplished results are consistent with the previously obtained performance metrics and further support the suitability of the Extra Trees and Naive Bayes classifiers for subsequent predictor interpretation, while confirming the limited generalizability of the Decision Tree model.

To further interpret the relationships between variables and derive logical classification rules, an unconstrained Decision Tree model was constructed. In this model, the target variable was encoded as binary: class 0 corresponded to the absence of postoperative complications, whereas class 1 indicated their presence. Accordingly, the terminal nodes of the tree represent the predicted classification of a patient into one of these categories. The visualization of the Decision Tree is presented in Figure 5.

The developed model enables representation of the decision-making process as a sequence of conditions determining patient assignment to the postoperative complication risk group. Specifically, the tree branches are based on COL1A1, Fib, PTI, creatinine, LogN-MMP9, EO%, and their corresponding threshold (cut-off) values identified during model training. These threshold values may be interpreted as potential clinically relevant limits associated with changes in postoperative complication risk. According to the model, patients with $\text{COL1A1} \leq 4.73$ and $\text{Fib} \leq 2.69$ were classified into the group without

postoperative complications (class 0). In contrast, patients with $\text{COL1A1} \leq 4.73$, $\text{Fib} > 2.69$, and creatinine > 59.74 were assigned to the high-risk complication group (class 1). This sequence of conditional rules illustrates the internal decision logic of the model.

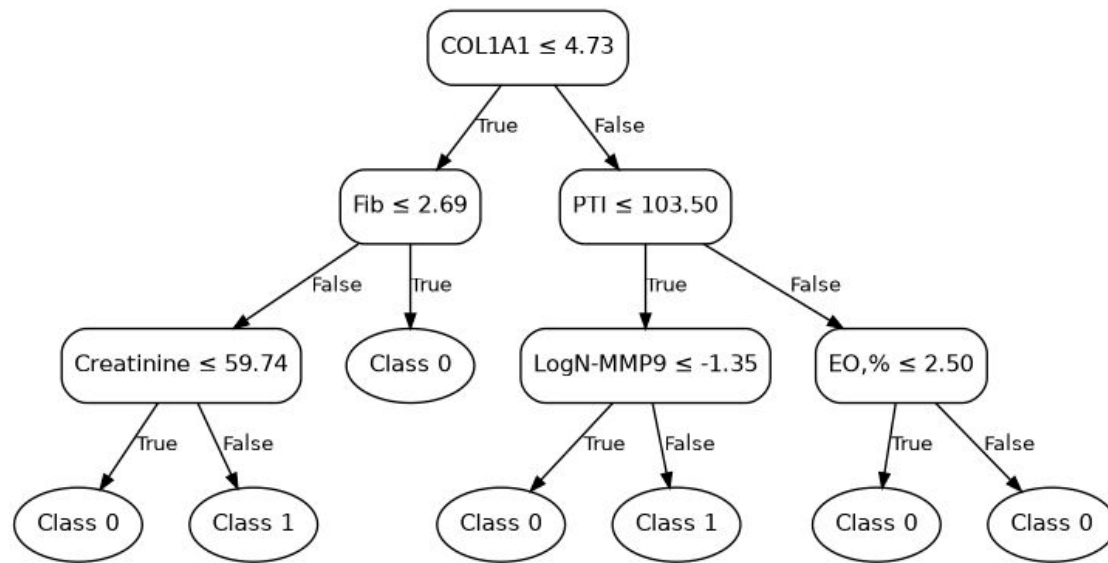


Figure 5. Visualization of the Decision Tree for classification of postoperative complication risk.

3.5. Interpretation of Individual Features Contribution to the Forecast Formation and Identification of Consistent Predictors

To assess the contribution of individual variables to model predictions, SHapley Additive exPlanations (SHAP) analysis was performed. The corresponding SHAP summary plots for the Extra Trees, Gaussian Naive Bayes, and Bernoulli Naive Bayes models are shown in Figure 6a–c.

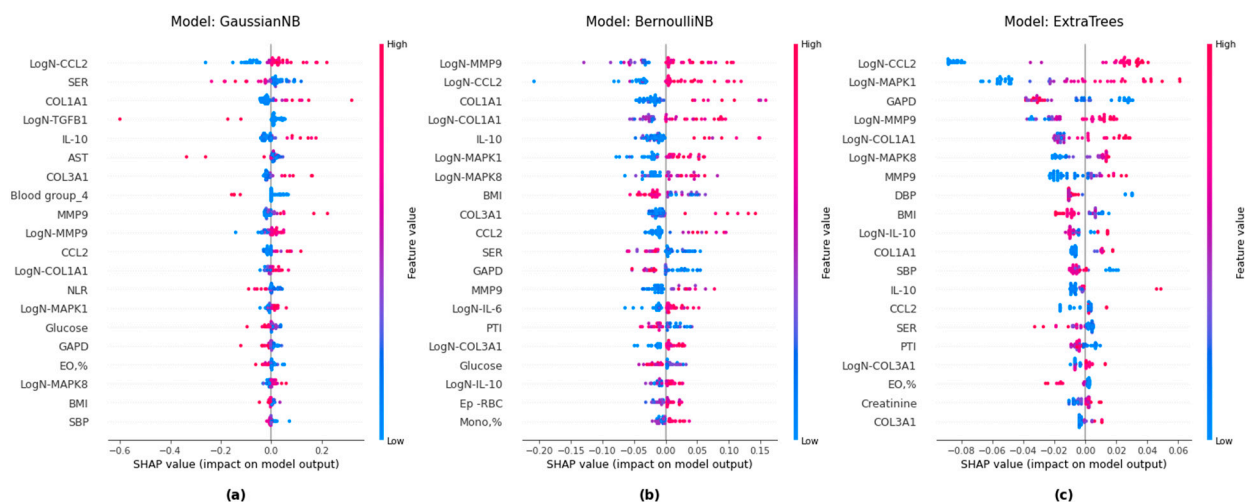


Figure 6. (a–c). SHAP summary plots for the models: (a) Gaussian Naive Bayes, (b) Bernoulli Naive Bayes, (c) Extra Trees.

For the Gaussian Naive Bayes model, the most influential variables according to SHAP values were LogN-CCL2, COL1A1, IL-10, ESR (SER), and LogN-TGFB1. Increased values of LogN-CCL2, COL1A1, and IL-10 were associated with a higher risk of complications, whereas lower values of ESR and LogN-TGFB1 were linked to a reduced probability of favorable outcomes.

In the Bernoulli Naive Bayes model, the most important predictors included LogN-MMP9, LogN-CCL2, COL1A1, LogN-COL1A1, and IL-10. Higher values of all these variables were consistently associated with an increased risk of postoperative complications.

For the Extra Trees model, the leading predictors were LogN-CCL2, LogN-MAPK1, LogN-MMP9, LogN-COL1A1, and GAPD. Elevated levels of LogN-CCL2, LogN-MAPK1, LogN-MMP9, and LogN-COL1A1 were associated with increased complication risk, whereas lower GAPD values were linked to a higher probability of postoperative complications.

To evaluate the consistency of findings across different machine learning models, an overlap analysis of the most important SHAP-derived predictors was performed. The corresponding Venn diagram is presented in Figure 7.

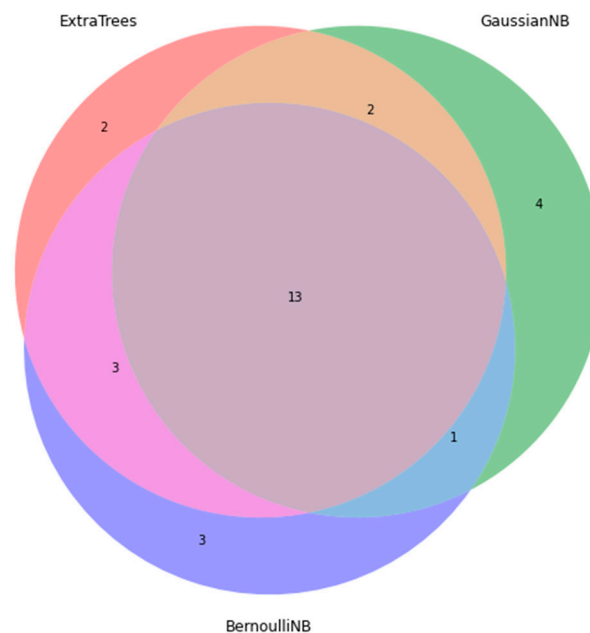


Figure 7. Intersection of the most important features identified using SHAP for Extra Trees, Gaussian Naive Bayes, and Bernoulli Naive Bayes models (Venn diagram).

All three models (Extra Trees, Gaussian Naive Bayes, and Bernoulli Naive Bayes) shared a common set of 13 key predictors, including BMI (1), CCL2 (2), COL1A1 (3), COL3A1 (4), GAPD (5), IL-10 (6), MMP9 (7), as well as their logarithmically transformed representations (LogN-CCL2 (8), LogN-COL1A1 (9), LogN-MAPK1 (10), LogN-MAPK8 (11), and LogN-MMP9 (12)), together with the ESR (13) parameter.

4. Discussion

Wound healing assessment involves both qualitative parameters (e.g., postoperative wound appearance, peri-wound skin condition, and wound margins) and quantitative measurements (e.g., wound size and depth), all of which require standardized monitoring to accurately evaluate healing progression (World Union of Wound Healing Societies, 2025) [37]. Furthermore, the wound healing process is accompanied by changes in systemic blood biochemical parameters and inflammatory markers, depending on severity and concomitant conditions.

AI-driven technologies have demonstrated strong potential for improving digital health and telemedicine applications in wound care by enhancing wound image quality, automating wound characterization, and supporting accurate diagnosis and longitudinal monitoring [38–40]. Despite promising advances, further validation, clinical integration, and multidisciplinary collaboration remain necessary to ensure the reliability and effective implementation of AI systems in routine wound management. Moreover, there are no

studies on predicting wound healing in plastic and reconstructive surgery using AI/ML. However, AI/ML is rapidly expanding in healthcare, with substantial projected market growth and increasing implementation in imaging-based specialties such as radiology and diagnostic imaging [41,42]. The projected 10-year growth of AI use in healthcare is \$11.2 billion in 2023 and \$427.5 billion in 2032 [41].

Our study demonstrates that the integration of molecular biomarkers with ML approaches provides a powerful framework for predicting and classifying wound healing outcomes in plastic and reconstructive surgery. The results extend our previous findings [28] by showing that gene expression signatures associated with inflammation, extracellular matrix remodeling, and fibrogenesis significantly contribute to the predictive performance of ML models.

Wound healing is a multifactorial and dynamic process in which the balance between pro-inflammatory and anti-inflammatory signaling is critical. In this context, elevated expression of IL6 and CCL2 reflects an amplified inflammatory response that may prolong the inflammatory phase and predispose to delayed healing or fibrosis. Conversely, IL10 plays a compensatory anti-inflammatory role, and its insufficient upregulation may contribute to persistent inflammation. These findings are consistent with recent studies demonstrating that dysregulated cytokine signaling is a key determinant of impaired wound repair and pathological scar formation [4–7]. Intracellular signaling pathways mediated by MAPK1 and MAPK8 further modulate cellular responses to stress, including apoptosis, proliferation, and cytokine production. The observed associations between MAPK pathway activity and healing outcomes support the concept that stress-response signaling networks critically influence tissue regeneration. Previous research has highlighted the central role of MAPK signaling in integrating inflammatory and mechanical stimuli during wound repair, particularly in fibroblast activation and keratinocyte migration [8,9].

In our study, altered expression of MMP9 and collagen genes such as COL1A1 and COL3A1 was strongly associated with differences in scar quality and tissue remodeling, participating in ML classification of postoperative complication risk. Excessive collagen deposition, driven in part by TGF β 1, is a well-established mechanism underlying hypertrophic scarring, fibrosis (aberrant fibroblast activity) and excessive extracellular matrix accumulation [10,13,43,44].

Our study demonstrates that postoperative complication risk in relatively healthy women can be effectively modeled using a multimodal ML framework integrating molecular, laboratory, and clinical features. We observed a moderate decline in ROC-AUC values for most models when transitioning from the training to the validation datasets. In contrast, the Decision Tree model demonstrated a substantial decrease in performance metrics, indicating pronounced overfitting and limited model stability. The Naive Bayes classifiers exhibited the smallest differences between training and validation metrics, suggesting superior generalizability under conditions of limited sample size.

The proposed ML framework was designed not only to maximize predictive performance but also to preserve interpretability and biological plausibility. The combination of tree-based and probabilistic classifiers allowed the analysis of postoperative complication risk from complementary methodological perspectives. Tree-based models can capture nonlinear interactions and clinically interpretable thresholds, whereas Naive Bayes models provide a probabilistic framework that remains suitable under limited-sample conditions. Therefore, the selected algorithms were considered appropriate for exploratory biomedical prediction where both predictive performance and interpretability are required.

Nevertheless, the proposed approach achieved consistently high discriminative performance, with validation ROC-AUC values ranging from 0.903 to 0.913, corresponding to a large effect size (Δ AUC $\approx$ +0.40–0.45 over random classification). Notably, performance

remained stable under repeated stratified cross-validation, indicating robustness despite the limited sample size ($n = 50$).

An important observation is that the performance differences among the evaluated ML algorithms were relatively small. Validation ROC-AUC values ranged from 0.903 to 0.913, and the associated variability measures showed substantial overlap between models. Consequently, the present findings should not be interpreted as demonstrating the unequivocal superiority of any particular algorithm. Rather, they suggest that multiple ML approaches, including ensemble-based and probabilistic methods, are capable of effectively capturing the predictive information contained within the clinical and molecular dataset. The consistency of predictive performance across diverse modeling strategies further supports the robustness of the identified signal and the biological relevance of the selected predictors.

Moreover, the selected classifiers represent complementary analytical strategies rather than competing implementations of the same modeling principle. This design allowed the evaluation of whether the predictive signal was stable across interpretable tree-based, ensemble-based, and probabilistic learning approaches. The comparable performance of several models suggests that the observed predictive signal is not restricted to a single algorithmic family.

Importantly, the application of ML models allowed the integration of these molecular markers with clinical variables, revealing complex, nonlinear relationships that are not captured by traditional statistical approaches. Algorithms such as random forests and gradient boosting demonstrated superior predictive performance, likely due to their ability to model interactions between multiple biological and clinical features. Similar findings have been reported in recent studies where ML approaches improved prediction accuracy for wound healing outcomes, particularly when incorporating omics data [20,39,45–47]. Some recent studies have reported promising performance of explainable ML models for predicting major postoperative complications in oncological surgery, with AUC-ROC values ranging from approximately 0.73 to 0.77 using clinical and electronic health record data alone [48,49]. Likewise, deep learning and ensemble-based models have shown strong predictive capabilities for postoperative outcomes across large surgical cohorts, highlighting the value of advanced analytical methods for individualized risk assessment [50].

In plastic and reconstructive surgery, ML methods have recently been applied to predict complications following free-flap reconstruction, demonstrating the feasibility of data-driven risk stratification in complex surgical populations [51]. However, most existing studies rely predominantly on demographic, clinical, and perioperative variables [52]. In contrast, our approach integrates molecular-genetic biomarkers involved in inflammation, extracellular matrix remodeling, and wound repair, thereby capturing biological mechanisms directly linked to postoperative healing. The identification of COL1A1, MMP9, MAPK1, MAPK8, IL10, and CCL2 as the most influential predictors is biologically plausible given their established roles in collagen synthesis, tissue remodeling, immune regulation, and wound healing processes.

Our findings are also aligned with recent developments in explainable artificial intelligence, where SHAP-based interpretation has become increasingly important for translating machine-learning predictions into clinically meaningful insights [53]. Rather than functioning as a purely predictive black-box system, the proposed framework provides interpretable information regarding the relative contribution of molecular and clinical variables to postoperative outcomes. Therefore, the present study should be viewed as an exploratory but biologically informed step toward precision medicine in reconstructive surgery, supporting the integration of molecular biomarkers and explainable machine-learning approaches for personalized wound-healing risk assessment. However, SHAP-based feature-importance

rankings should be interpreted cautiously. Although correlation-based filtering was applied to reduce multicollinearity, residual correlations among biologically related molecular biomarkers may still redistribute importance values across related predictors. As a result, the exact rank order of biomarkers may vary depending on the sample composition and model structure. In addition, the relatively small sample size may increase the variability of feature-importance estimates. For this reason, the present study emphasizes predictors that were consistently identified across several models rather than the exact ranking produced by any single SHAP analysis.

An important consideration is the relative contribution of different groups of predictors to model performance. Although formal ablation analyses comparing clinical variables, molecular-genetic biomarkers, and combined feature sets were not performed in the present study, several findings suggest a predominant role of molecular markers in postoperative complication prediction. Both the association analyses and SHAP-based model interpretation consistently identified IL10, CCL2, COL1A1, MAPK1, MAPK8, and MMP9 among the most influential predictors, whereas conventional demographic and clinical variables demonstrated comparatively small effect sizes. These observations are biologically plausible, given the central involvement of extracellular matrix remodeling, collagen synthesis, inflammatory signaling, and immune regulation in wound healing. Nevertheless, future studies should formally evaluate the incremental predictive value of molecular biomarkers by comparing models trained on clinical variables alone, molecular features alone, and integrated multimodal datasets. Such analyses would provide a more rigorous assessment of the individual and combined contributions of each predictor group and further support the development of precision medicine approaches in reconstructive surgery.

The present study contributes to the growing field of precision medicine and explainable artificial intelligence in surgery in several important ways. First, unlike many previous predictive models based primarily on demographic and clinical variables, our framework incorporates molecular-genetic biomarkers directly involved in inflammation, immune regulation, extracellular matrix remodeling, and collagen synthesis. Second, the application of SHAP analysis enabled identification of biologically relevant predictors, including COL1A1, MMP9, MAPK1, MAPK8, IL10, and CCL2, thereby providing mechanistic insights beyond conventional risk prediction. Third, the findings suggest that molecular signatures may contain clinically relevant information that is not fully captured by traditional clinical parameters. Finally, by combining predictive modeling with model interpretability, the proposed approach supports the development of personalized postoperative monitoring strategies and may facilitate future translation of explainable ML methods into reconstructive surgical practice.

Several limitations should be considered when interpreting the present findings. First, although hyperparameter optimization was performed within the training folds of the repeated cross-validation procedure to minimize information leakage, the study relied on internal validation only. Owing to the relatively small cohort size, an independent external test set was not available. Consequently, the reported performance metrics may not fully reflect model generalizability to new patient populations. Second, the molecular-genetic analyses were conducted in a subset of participants, which may limit statistical power. Third, feature reduction was based on predictor redundancy rather than outcome-driven selection; it was performed before cross-validation; therefore, a small degree of information leakage cannot be excluded. Future studies should perform feature reduction within each training fold as part of a fully nested validation pipeline. Fourth, the sample size was limited, particularly for the molecular-genetic subset, which included 50 participants with complete gene-expression data. Therefore, the present findings should be interpreted as exploratory and hypothesis-generating rather than as evidence of a clinically deployable

prediction model. Fifth, SHAP analysis was used as an explainability tool and should not be interpreted as evidence of causal biomarker effects. The stability of biomarker rankings requires confirmation in larger independent cohorts, preferably using repeated external validation and sensitivity analyses. Sixth, formal inferential hypothesis testing (such as Friedman or Wilcoxon signed-rank tests) was deliberately omitted for model comparison. In repeated cross-validation designs, performance metrics across folds are statistically dependent due to overlapping training sets, which violates the independence assumptions of standard tests and artificially inflates Type I error rates. Consequently, robust model ranking remains a limitation of internal validation on small clinical cohorts ($n = 50$). Future multi-center studies with independent, non-overlapping external validation test sets will be required to establish true statistical and clinical superiority among the algorithms. Although repeated stratified cross-validation was used to reduce variance in performance estimates, the limited number of complication cases may affect the stability of model performance, confidence intervals, and feature-importance rankings. Therefore, external validation in larger multicenter cohorts is required to confirm the robustness, reproducibility, and clinical utility of the proposed prediction framework. In addition, formal statistical comparisons between model performance metrics were not performed. Given the overlap of confidence intervals and the relatively small differences in ROC-AUC values, caution is warranted when interpreting ranking differences among algorithms. Larger studies with external validation cohorts will be necessary to determine whether observed performance differences represent true methodological advantages or sampling variability.

Future research should focus on developing multimodal predictive platforms that combine molecular, clinical, and imaging data, as well as on implementing these models in real-time clinical decision support systems. The incorporation of longitudinal data may also improve the ability to monitor healing trajectories and dynamically adjust treatment strategies.

5. Conclusions

Our results revealed a dominant contribution of molecular-genetic markers to predictive performance. Features such as COL1A1, MMP9, MAPK1, MAPK8, IL-10, and CCL2 exhibited the strongest associations with postoperative complications, while traditional clinical variables showed negligible effect sizes.

From a clinical perspective, the ML models demonstrated high sensitivity in detecting complication cases, with Recall values reaching 0.820 ± 0.238 (Extra Trees) and 0.807 ± 0.246 (Gaussian NB). These results correspond to a large positive effect size in true positive detection, which is critical for minimizing clinically unacceptable false negatives.

The interpretable modeling via decision trees enabled extraction of clinically meaningful threshold-based rules, transforming predictive outputs into actionable decision pathways. This provides direct translational utility, bridging statistical learning and clinical reasoning.

SHAP-based explainability analysis quantified feature-level contributions across models and demonstrated consistent directional effects of key predictors. This supports the presence of stable, model-independent feature effects, reinforcing the biological plausibility of identified biomarkers.

Despite the small cohort size, the achieved performance (ROC-AUC > 0.90) and consistency of identified predictors suggest that the proposed framework captures high signal-to-noise structure in the data. This highlights the feasibility of applying machine learning-based risk stratification in data-constrained clinical settings.

Author Contributions: Conceptualization and writing—original draft preparation, L.S., R.G., I.B. and S.P.D.; writing—review and editing, M.Š., A.S., R.S. and Y.V.; supervision, M.S., R.S. and L.S.; project administration L.S., M.S. and R.S.; visualization, A.S., Y.V., M.Š. and S.P.D.; funding acquisition, M.S. and R.G. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The studies involving humans were approved by the Biomedical Ethics Review Committee of Bukovinian State Medical University (Protocol No. 1, 19 September 2024). The studies were conducted in accordance with the international Convention Council on Human Rights, local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. No potentially identifiable images or data are presented in this study.

Data Availability Statement: The data presented in this study and the raw data supporting the conclusions of this manuscript will be available on request from the corresponding author.

Acknowledgments: During the preparation of this manuscript/study, the authors used ChatGPT (OpenAI, model DALL-E 3) for generating the graphical abstract. The authors have reviewed and edited the output and take full responsibility for the content of this publication.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ECM	extracellular matrix
IL	interleukin
CCL2	C-C motif chemokine ligand 2
MAPK	mitogen-activated protein kinase
MMP	metalloproteinase
COL1A1, COL3A1	collagen alpha 1 chain types 1 and 3
TGFβ1	transforming growth factor-β1
GAPDH	glyceraldehyde-3-phosphate dehydrogenase
AI	artificial intelligence
ML	machine learning
SHAP	SHapley Additive exPlanations
ROC	receiver operating characteristic
BMI	body mass index
SBP, DBP	systolic and diastolic blood pressure
Er-RBC	erythrocytes—red blood cells
Hb	hemoglobin
CI	color index
Leu-WBC	leukocytes—white blood cells
NEUT	neutrophils
EO	eosinophils
LYMPH	lymphocytes
Mono	monocytes
PTL	platelet
ESR	erythrocyte sedimentation rate
Cr	creatinine
BIL	bilirubin
DBIL, N-DBIL	direct and non-direct bilirubin
ALT, AST	alanine-, aspartate aminotransferase
APh	alkaline phosphatase
eGFR	estimated glomerular filtration rate
PTt	prothrombin time

PTI	prothrombin index
Tt	thrombin time
APTT	activated partial thromboplastin time
Fib	fibrinogen
Ht	hematocrit
INR	international normalized ratio
NLR	neutrophil-to-lymphocyte ratio
LMR	lymphocyte-to-monocyte ratio
PLR	platelet-to-lymphocyte ratio
SII	systemic immune-inflammation index

References

- Almadani, Y.H.; Vorstenbosch, J.; Davison, P.G.; Murphy, A.M. Wound Healing: A Comprehensive Review. *Semin. Plast. Surg.* **2021**, *35*, 141–144. [\[CrossRef\]](#)
- Amjadian, S.; Fatemi, M.J.; Moradi, S.; Hesarak, M.; Mohammadi, P. Mir-182-5p regulates all three phases of inflammation, proliferation, and remodeling during cutaneous wound healing. *Arch. Dermatol. Res.* **2024**, *316*, 274. [\[CrossRef\]](#) [\[PubMed\]](#)
- Atkin, L.; Probst, S. Clinical inertia in chronic wound care. *Wounds Int.* **2025**, *16*, 48–51.
- Krzyszczczyk, P.; Schloss, R.; Palmer, A.; Berthiaume, F. The role of macrophages in acute and chronic wound healing and interventions to promote pro-wound healing phenotypes. *Front. Physiol.* **2018**, *9*, 419. [\[CrossRef\]](#) [\[PubMed\]](#)
- Johnson, B.Z.; Stevenson, A.W.; Prêle, C.M.; Fear, M.W.; Wood, F.M. The Role of IL-6 in Skin Fibrosis and Cutaneous Wound Healing. *Biomedicines* **2020**, *8*, 101. [\[CrossRef\]](#) [\[PubMed\]](#)
- Lin, Z.Q.; Kondo, T.; Ishida, Y.; Takayasu, T.; Mukaida, N. Essential involvement of IL-6 in the skin wound-healing process as evidenced by delayed wound healing in IL-6-deficient mice. *J. Leukoc. Biol.* **2003**, *73*, 713–721. [\[CrossRef\]](#) [\[PubMed\]](#)
- Wong, R.S.Y.; Tan, T.; Pang, A.S.R.; Srinivasan, D.K. The role of cytokines in wound healing: From mechanistic insights to therapeutic applications. *Explor. Immunol.* **2025**, *5*, 1003183. [\[CrossRef\]](#)
- Xiao, Y.; Qian, J.; Deng, X.; Zhang, H.; Wang, J.; Luo, Z.; Zhu, L. Macrophages regulate healing-associated fibroblasts in diabetic wound. *Mol. Biol. Rep.* **2024**, *51*, 203. [\[CrossRef\]](#) [\[PubMed\]](#)
- Ma, Y.-T.; Li, C.; Shen, Y.; You, W.-H.; Han, M.-X.; Mu, Y.-F.; Han, F.-J. Mechanisms of the JNK/p38 MAPK signaling pathway in drug resistance in ovarian cancer. *Front. Oncol.* **2025**, *15*, 1533352. [\[CrossRef\]](#) [\[PubMed\]](#)
- Caley, M.P.; Martins, V.L.; O'Toole, E.A. Metalloproteinases and Wound Healing. *Adv. Wound Care* **2015**, *4*, 225–234. [\[CrossRef\]](#) [\[PubMed\]](#)
- Limandjaja, G.C.; Niessen, F.B.; Scheper, R.J.; Gibbs, S. The Keloid Disorder: Heterogeneity, Histopathology, Mechanisms and Models. *Front. Cell Dev. Biol.* **2020**, *8*, 360. [\[CrossRef\]](#) [\[PubMed\]](#)
- Mayorca-Guiliani, A.E.; Leeming, D.J.; Henriksen, K.; Mortensen, J.H.; Nielsen, S.H.; Anstee, Q.M.; Sanyal, A.J.; Karsdal, M.A.; Schuppan, D. ECM formation and degradation during fibrosis, repair, and regeneration. *npj Metab. Health Dis.* **2025**, *3*, 25. [\[CrossRef\]](#) [\[PubMed\]](#)
- Liu, J.; Wang, Y.; Tang, C.; Zhang, L.; Xiong, S.; Wang, J.; Dong, C. TGF- β in tumor development and progression: Mechanisms and therapeutics. *Mol. Biomed.* **2026**, *7*, 9. [\[CrossRef\]](#) [\[PubMed\]](#)
- Mueller, S.M.; Miller, N.; Gill, J.; Yu, L.C.; Pike, M.D.; Orgill, D.P. Genetic Determinants of Wound Healing: Monogenic Disorders and Polygenic Influence. *Cells* **2026**, *15*, 74. [\[CrossRef\]](#) [\[PubMed\]](#)
- Zielińska, M.; Pawłowska, A.; Orzeł, A.; Sulej, L.; Muzyka-Placzyńska, K.; Baran, A.; Filipiecka-Tyczka, D.; Pawłowska, P.; Nowińska, A.; Bogusławska, J.; et al. Wound Microbiota and Its Impact on Wound Healing. *Int. J. Mol. Sci.* **2023**, *24*, 17318. [\[CrossRef\]](#) [\[PubMed\]](#)
- Patel, B.K.; Patel, K.H.; Huang, R.Y.; Lee, C.N.; Moochhala, S.M. The Gut-Skin Microbiota Axis and Its Role in Diabetic Wound Healing-A Review Based on Current Literature. *Int. J. Mol. Sci.* **2022**, *23*, 2375. [\[CrossRef\]](#) [\[PubMed\]](#)
- Mihai, M.M.; Bălăceanu-Gurău, B.; Ion, A.; Holban, A.M.; Gurău, C.-D.; Popescu, M.N.; Beiu, C.; Popa, L.G.; Popa, M.I.; Dragomirescu, C.C.; et al. Host-Microbiome Crosstalk in Chronic Wound Healing. *Int. J. Mol. Sci.* **2024**, *25*, 4629. [\[CrossRef\]](#) [\[PubMed\]](#)
- Kim, J.H.; Ruegger, P.R.; Lebig, E.G.; VanSchalkwyk, S.; Jeske, D.R.; Hsiao, A.; Borneman, J.; Martins-Green, M. High Levels of Oxidative Stress Create a Microenvironment That Significantly Decreases the Diversity of the Microbiota in Diabetic Chronic Wounds and Promotes Biofilm Formation. *Front. Cell Infect. Microbiol.* **2020**, *10*, 259. [\[CrossRef\]](#) [\[PubMed\]](#)
- Queen, D. Artificial intelligence and machine learning in wound care-The wounded machine! *Int. Wound J.* **2019**, *16*, 311. [\[CrossRef\]](#) [\[PubMed\]](#)
- Nair, H.K.R.; Ousey, K.; Atkin, L.; Inuwa-Dutse, I.; Fletcher, J.; Hong, J.P.; LeBlanc, K.; Probst, A.; Probst, S.; Rippon, M.G.; et al. Understanding artificial intelligence: Barriers and potential in wound care. *Glob. Wound Care J.* **2025**, *1*, S1–S28. [\[CrossRef\]](#)

21. Chen, M.Y.; Cao, M.Q.; Xu, T.Y. Progress in the application of artificial intelligence in skin wound assessment and prediction of healing time. *Am. J. Transl. Res.* **2024**, *16*, 2765–2776. [[CrossRef](#)] [[PubMed](#)]
22. Griffo, D.; Natale, A.; Merli, Y.; Starace, M.; Curti, N.; Mussi, M.; Castellani, G.; Melandri, D.; Piraccini, B.M.; Zengarini, C. Artificial Intelligence in Wound Care: A Narrative Review of the Currently Available Mobile Apps for Automatic Ulcer Segmentation. *BioMedInformatics* **2024**, *4*, 2321–2337. [[CrossRef](#)]
23. Sydorchuk, L.; Sokolenko, M.; Škoda, M.; Lajcin, D.; Vyklyuk, Y.; Sydorchuk, R.; Sokolenko, A.; Martjanov, D. Management of Severe COVID-19 Diagnosis Using Machine Learning. *Computation* **2025**, *13*, 238. [[CrossRef](#)]
24. Fleuren, L.M.; Klausch, T.L.T.; Zwager, C.L.; Schoonmade, L.J.; Guo, T.; Roggeveen, L.F.; Swart, E.L.; Girbes, A.R.J.; Thorat, P.; Ercole, A.; et al. Machine learning for the prediction of sepsis: A systematic review and meta-analysis of diagnostic test accuracy. *Intensive Care Med.* **2020**, *46*, 383–400. [[CrossRef](#)] [[PubMed](#)]
25. Cobiachi, L.; Piccolo, D.; Mas, F.D.; Agnoletti, V.; Ansaloni, L.; Balch, J.; Biffl, W.; Butturini, G.; Catena, F.; Coccolini, F.; et al. Surgeons' perspectives on artificial intelligence to support clinical decision-making in trauma and emergency contexts: Results from an international survey. *World J. Emerg. Surg.* **2023**, *18*, 1. [[CrossRef](#)] [[PubMed](#)]
26. Cobiachi, L.; Dal Mas, F.; Agnoletti, V.; Ansaloni, L.; Biffl, W.; Butturini, G.; Campostrini, S.; Catena, F.; Denicolai, S.; Fugazzola, P.; et al. Time for a paradigm shift in shared decision-making in trauma and emergency surgery? Results from an international survey. *World J. Emerg. Surg.* **2023**, *18*, 14. [[CrossRef](#)] [[PubMed](#)]
27. De Simone, B.; Abu-Zidan, F.M.; Saeidi, S.; Deeken, G.; Biffl, W.L.; Moore, E.E.; Sartelli, M.; Coccolini, F.; Ansaloni, L.; Di Saverio, S.; et al. Knowledge, attitudes and practices of using Indocyanine Green (ICG) fluorescence in emergency surgery: An international web-based survey in the ARTificial Intelligence in Emergency and trauma Surgery (ARIES)-WSES project. *Updates Surg.* **2024**, *76*, 1969–1981. [[CrossRef](#)] [[PubMed](#)]
28. Sydorchuk, L.; Gumennyi, R.; Sydorchuk, A.; Batih, I.; Vasiuk, V.; Sydorchuk, R.; Kamyshna, I.; Petakh, P.; Halabitska, I.; Kamyshnyi, O. Genetic Modulation of Wound Healing Pathways and Postoperative Risk in Plastic and Reconstructive Surgery: A Cohort Study. *J. Clin. Med.* **2026**, *15*, 2794. [[CrossRef](#)] [[PubMed](#)]
29. Sydorchuk, A.R.; Sydorchuk, L.P.; Gutnitska, A.F.; Dzhuryak, V.S.; Kryvetska, I.I.; Sydorchuk, R.I.; Ursuliak, Y.V.; Iftoda, O.M. Endothelium function regulation markers and carotid intima-media thickness in arterial hypertension depending on NOS3 (rs2070744) and GNB3 (rs5443) genes polymorphism: A prospective case-control study. *Endocr. Regul.* **2022**, *56*, 104–114. [[CrossRef](#)] [[PubMed](#)]
30. Sydorchuk, A.; Sydorchuk, L.; Gutnitska, A.; Vasyuk, V.; Tkachuk, O.; Dzhuryak, V.; Myshkovskii, Y.; Kyfiak, P.; Sydorchuk, R.; Iftoda, O. The role of NOS3 (rs2070744) and GNB3 (rs5443) genes' polymorphisms in endothelial dysfunction pathway and carotid intima-media thickness in hypertensive patients. *Gen. Physiol. Biophys.* **2023**, *42*, 179–190. [[CrossRef](#)] [[PubMed](#)]
31. Aria, M.; Gnasso, A.; Iorio, C.; Pandolfo, G. Explainable Ensemble Trees. *Comput. Stat.* **2024**, *39*, 3–19. [[CrossRef](#)]
32. Geurts, P.; Ernst, D.; Wehenkel, L. Extremely randomized trees. *Mach. Learn.* **2006**, *63*, 3–42. [[CrossRef](#)]
33. Manzali, Y.; Akhiat, Y.; Chahhou, M.; Elmohajir, M.; Zinedine, A. Reducing the number of trees in a forest using noisy features. *Evol. Syst.* **2023**, *14*, 157–174. [[CrossRef](#)]
34. Khan, Z.; Gul, A.; Perperoglou, A.; Miftahuddin, M.; Mahmoud, O.; Adler, W.; Lausen, B. Ensemble of optimal trees, random forest and random projection ensemble classification. *Adv. Data Anal. Classif.* **2020**, *14*, 97–116. [[CrossRef](#)]
35. Bradley, A.P. The use of the area under the ROC curve in the evaluation of machine learning algorithms. *Pattern Recognit.* **1997**, *30*, 1145–1159. [[CrossRef](#)]
36. Lundberg, S.M.; Lee, S.I. A unified approach to interpreting model predictions. In *Proceedings of the 31st Conference on Advances in Neural Information Processing Systems (NIPS 2017)*; Curran Associates, Inc.: Long Beach, CA, USA, 2017; pp. 4765–4774. Available online: <https://proceedings.neurips.cc/paper/2017/file/8a20a8621978632d76c43d4d28b67767-Paper.pdf> (accessed on 7 May 2026).
37. World Union of Wound Healing Societies. *Implementing Wound Balance: Outcomes and Future Recommendations*; Wounds International: London, UK, 2025. Available online: www.woundsinternational.com (accessed on 21 May 2026).
38. Bai, X.; Zhang, H.; Jiao, Y.; Yuan, C.; Ma, Y.; Han, L. Digital Health Interventions for Chronic Wound Management: A Systematic Review and Meta-Analysis. *J. Med. Internet Res.* **2024**, *26*, e47904. [[CrossRef](#)] [[PubMed](#)]
39. Rippon, M.G.; Fleming, L.; Chen, T.; Rogers, A.A.; Ousey, K. Artificial intelligence in wound care: Diagnosis, assessment and treatment of hard-to-heal wounds: A narrative review. *J. Wound Care* **2024**, *33*, 229–242. [[CrossRef](#)] [[PubMed](#)]
40. Zhu, G.; Fu, Z.; Guo, G. Applications and prospects of artificial intelligence in wound healing. *Regeneration Repair. Rehabil.* **2025**, *1*, 12–19. [[CrossRef](#)]
41. Faiyazuddin, M.; Rahman, S.J.Q.; Anand, G.; Siddiqui, R.K.; Mehta, R.; Khatib, M.N.; Gaidhane, S.; Zahiruddin, Q.S.; Hussain, A.; Sah, R. The Impact of Artificial Intelligence on Healthcare: A Comprehensive Review of Advancements in Diagnostics, Treatment, and Operational Efficiency. *Health Sci. Rep.* **2025**, *8*, e70312. [[CrossRef](#)] [[PubMed](#)]
42. Tanno, R.; Barrett, D.G.T.; Sellergren, A.; Ghaisas, S.; Dathathri, S.; See, A.; Welbl, J.; Lau, C.; Tu, T.; Azizi, S.; et al. Collaboration between clinicians and vision-language models in radiology report generation. *Nat. Med.* **2025**, *31*, 599–608. [[CrossRef](#)] [[PubMed](#)]

43. Sun, Y.; Liu, W.Z.; Liu, T.; Feng, X.; Yang, N.; Zhou, H.F. Signaling pathway of MAPK/ERK in cell proliferation, differentiation, migration, senescence and apoptosis. *J. Recept. Signal Transduct. Res.* **2015**, *35*, 600–604. [[CrossRef](#)] [[PubMed](#)]
44. Frangogiannis, N. Transforming growth factor- β in tissue fibrosis. *J. Exp. Med.* **2020**, *217*, e20190103. [[CrossRef](#)] [[PubMed](#)]
45. Liu, H.; Sun, W.; Cai, W.; Luo, K.; Lu, C.; Jin, A.; Zhang, J.; Liu, Y. Current status, challenges, and prospects of artificial intelligence applications in wound repair theranostics. *Theranostics* **2025**, *15*, 1662–1688. [[CrossRef](#)] [[PubMed](#)]
46. Verdú Soriano, J. Artificial Intelligence in Wound Care: From Experimental Promise to Clinical Reality. *Intern. J. Wound Res.* **2025**, *1*, 64–66. [[CrossRef](#)]
47. Khorsandi, J.; Kahen, J.; Blank, L.; MacDavid, J. 833. Artificial Intelligence in Burn and Wound Care: Image Analysis, Prediction, and Clinical Integration. *J. Burn. Care Res.* **2026**, *47*, S239. [[CrossRef](#)]
48. Hernandez, M.C.; Chen, C.; Nguyen, A.; Choong, K.; Carlin, C.; Nelson, R.A.; Rossi, L.A.; Seth, N.; McNeese, K.; Yuh, B.; et al. Explainable Machine Learning Model to Preoperatively Predict Postoperative Complications in Inpatients With Cancer Undergoing Major Operations. *JCO Clin. Cancer Inform.* **2024**, *8*, e2300247. [[CrossRef](#)] [[PubMed](#)]
49. Shickel, B.; Loftus, T.J.; Ruppert, M.; Upchurch, G.R.; Ozrazgat-Baslanti, T.; Rashidi, P.; Bihorac, A. Dynamic predictions of postoperative complications from explainable, uncertainty-aware, and multi-task deep neural networks. *Sci. Rep.* **2023**, *13*, 1224. [[CrossRef](#)] [[PubMed](#)]
50. Lopez-Lopez, V.; Morise, Z.; Albaladejo-González, M.; Gavara, C.G.; Goh, B.K.P.; Koh, Y.X.; Paul, S.J.; Abu Hilal, M.; Mishima, K.; Krüger, J.A.P.; et al. Explainable artificial intelligence prediction-based model in laparoscopic liver surgery for segments 7 and 8: An international multicenter study. *Surg. Endosc.* **2024**, *38*, 2411–2422. [[CrossRef](#)] [[PubMed](#)]
51. Asaad, M.; Lu, S.-C.; Hassan, A.M.; Kambhampati, P.; Mitchell, D.; Chang, E.I.; Yu, P.; Hanasono, M.M.; Sidey-Gibbons, C. The Use of Machine Learning for Predicting Complications of Free-Flap Head and Neck Reconstruction. *Ann. Surg. Oncol.* **2023**, *30*, 2343–2352. [[CrossRef](#)] [[PubMed](#)]
52. Dallmann, A.C.; Sheridan, M.; Mattke, S.; Ennis, W. Prediction of Healing Trajectory of Chronic Wounds Using a Machine Learning Approach. *Adv. Wound Care* **2025**, *14*, 645–654. [[CrossRef](#)] [[PubMed](#)]
53. Song, Y.; Zhang, D.; Wang, Q.; Liu, Y.; Chen, K.; Sun, J.; Shi, L.; Li, B.; Yang, X.; Mi, W.; et al. Prediction models for postoperative delirium in elderly patients with machine-learning algorithms and SHapley Additive exPlanations. *Transl. Psychiatry* **2024**, *14*, 57. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.