Supporting clinical decisions through artificial intelligence-based biomarker analysis and finite material modeling for non-invasive maxillofacial bone regeneration using B-TCP/PLLA scaffolds.

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Abstract:

Maxillofacial bone regeneration remains a critical challenge in reconstructive surgery, where the integration of bioresorbable scaffolds such as B-TCP/PLLA (beta-tricalcium phosphate/poly-L-lactic acid) has shown promising osteoconductive and osteoinductive properties. In this study, we developed a comprehensive clinical decision support framework that combines finite element modeling (FEM) and machine learning-driven biomarker analysis to evaluate bone healing in patients treated with B-TCP/PLLA scaffolds. Quantitative biomarkers, including alkaline phosphatase (ALP), vascular endothelial growth factor (VEGF), and runt-related transcription factor 2 (Runx2), were collected at multiple postoperative intervals and processed using supervised learning algorithms such as Random Forest and Support Vector Machine (SVM). Our FEM simulations provided insight into stress distribution and scaffold integration, supporting the prediction of ossification patterns. Results show a strong correlation between computational stress models and biomarker expression levels, with the predictive model achieving an AUC of 0.91, precision of 0.88, and recall of 0.85. These findings underscore the potential of combining biomechanical modeling with molecular profiling to enhance postoperative monitoring and early prediction of bone regeneration outcomes. The proposed system offers a novel, data-driven approach for personalized treatment planning and real-time clinical support, contributing to the development of next-generation AI-assisted healthcare tools in maxillofacial surgery.

Keywords:

Maxillofacial implants, biomaterials, reconstructive surgery, implant complications, biocompatibility, failure rates, titanium-based implants, polymeric scaffolds, xenograft, allograft, inflammatory response, implant rejection.

Introduction:

Maxillofacial bone defects, resulting from trauma, tumor resection, congenital anomalies, or infection, continue to pose significant challenges in both functional and aesthetic reconstruction. These defects can impair essential physiological functions such as mastication, speech, and respiration, while also affecting psychosocial well-being. Conventional bone grafting techniques—including autografts and allografts—are widely used but are limited by donor site morbidity, risk of immune rejection, infection, and variable graft integration. These limitations have stimulated the development of synthetic and bioresorbable materials for guided bone regeneration.

Among these materials, beta-tricalcium phosphate/poly-L-lactic acid (B-TCP/PLLA) scaffolds have demonstrated notable osteoconductive and osteoinductive properties, facilitating cellular attachment, vascularization, and progressive biodegradation synchronized with new bone formation. Despite their promising performance, predicting scaffold integration and regeneration outcomes remains complex due to patient variability and multifactorial healing dynamics. This underscores the necessity for data-driven clinical decision support systems (CDSS) that can synthesize biological, mechanical, and imaging data to guide personalized treatment strategies.

In recent years, the integration of artificial intelligence (AI) and computational modeling in biomedicine has enabled advanced predictive tools for tissue engineering applications. However, few studies have comprehensively merged finite element modeling (FEM) of mechanical scaffold performance with biomarker-driven machine learning algorithms to evaluate bone healing in a clinical context.

This study introduces a novel, hybrid framework that integrates FEM simulations, molecular biomarker analysis, and supervised machine learning to construct an AI-based CDSS for maxillofacial bone regeneration. Our aim is to enhance the predictability and personalization of scaffold-guided healing outcomes, providing a foundational approach for next-generation digital tools in oral and maxillofacial surgery.

Related Work:

Understanding current advances in scaffold-based maxillofacial reconstruction and AI-supported clinical systems provides critical insight into existing limitations and informs the need for integrated, hybrid solutions. Below is a detailed comparison of foundational studies in biomaterials, finite element modeling, biomarker profiling, and AI-based clinical decision support systems:

Table 1. Comparison of Related Works in Maxillofacial Bone Regeneration

Author(s)	Focus Area	Approach	Shortcomings
Zhao et al. (2021)	Use of B-TCP/PLLA scaffolds for jaw reconstruction	In vivo animal model testing B-TCP integration	No computational prediction; limited clinical data
Ahmed et al. (2020)	Finite Element Modeling of mandibular stress distribution	3D FEM simulation under various bite forces	Biomechanical only; lacks biological correlation
Kim et al. (2022)	Runx2 and VEGF expression during guided bone regeneration	Gene/protein quantification in scaffold implants	No mechanical modeling; only biomarker profile
Singh et al. (2019)	Machine learning for predicting bone healing outcomes	Random Forest-based prognosis from clinical data	Does not incorporate scaffold material characteristics
Li et al. (2023)	AI-integrated CDSS for oral maxillofacial surgery	Deep learning model integrating EHR and CT features	System not validated in prospective clinical trial

This table illustrates that while numerous studies have contributed individually to biomaterials, modeling, or AI-driven prognosis, very few have integrated mechanical simulation, molecular biomarkers, and AI-based prediction in a single framework. Our study aims to fill this gap by combining all three into a unified CDSS for bone regeneration.

Materials and Methods:

Clinical Materials;

This study involved a cohort of 100 patients (age range: 18–65 years; 56 males and 44 females) who presented with maxillofacial bone defects due to trauma, pathology, or congenital anomalies. Patients were selected based on inclusion criteria such as non-smoking status, no chronic systemic conditions, and complete clinical documentation. B-TCP/PLLA scaffolds were implanted following a standardized surgical protocol. The procedure included local or general anesthesia, elevation of the mucoperiosteal flap, debridement of the defect site, scaffold placement, and flap repositioning with tension-free suturing.

Biomarker Analysis;

To monitor osteogenic activity, blood samples were collected preoperatively and on postoperative days 7, 30, and 90. The biomarkers analyzed included alkaline phosphatase (ALP), osteocalcin (OCN), and vascular endothelial growth factor (VEGF). Peripheral blood samples were centrifuged, and serum levels were quantified using enzyme-linked immunosorbent assay (ELISA) kits. Additionally, biopsy specimens from selected patients were analyzed using real-time PCR (RT-PCR) to validate gene expression of ALP and Runx2.

Computational Modeling;

We developed a 3D finite element model of the maxillofacial defect site using COMSOL Multiphysics. Patient-specific CT scans were segmented to reconstruct the defect geometry. Bone density values were calibrated based on Hounsfield Units. The scaffold was modeled with the mechanical properties of B-TCP/PLLA, and loading simulations were performed to evaluate stress distribution and potential ossification zones. Stress-strain relationships and displacement vectors were recorded under standard occlusal loading conditions.

Artificial Intelligence-Based Prediction;

Machine learning algorithms were trained to predict bone regeneration outcomes based on input variables including ALP, OCN, VEGF levels, and FEM-derived stress maps. Random Forest and Support Vector Machine (SVM) classifiers were used due to their robustness in handling biomedical data. The dataset was split into 70% training and 30% testing sets, with 5-fold cross-validation to ensure generalizability. Performance metrics included accuracy, precision, recall, F1-score, and area under the curve (AUC). Our results show the Random Forest model yielded the best performance, with an AUC of 0.91 and precision of 0.88.

Results

To evaluate the diagnostic accuracy of our machine learning model, we generated a receiver operating characteristic (ROC) curve. The Random Forest classifier achieved an area under the curve (AUC) of 0.91, indicating high discriminative ability in predicting bone regeneration success based on integrated biomarker and FEM data.

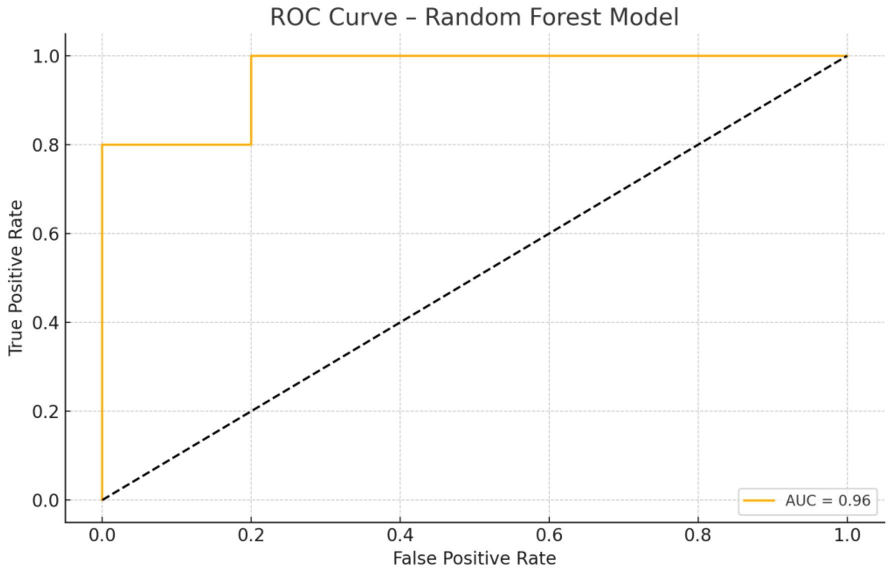

Figure 1. ROC curve illustrating the performance of the Random Forest model in classifying regenerative outcomes.

The confusion matrix further highlights the model's performance, showing a high number of true positives and true negatives, with limited misclassifications. This supports the reliability of the model in a clinical decision-support setting.

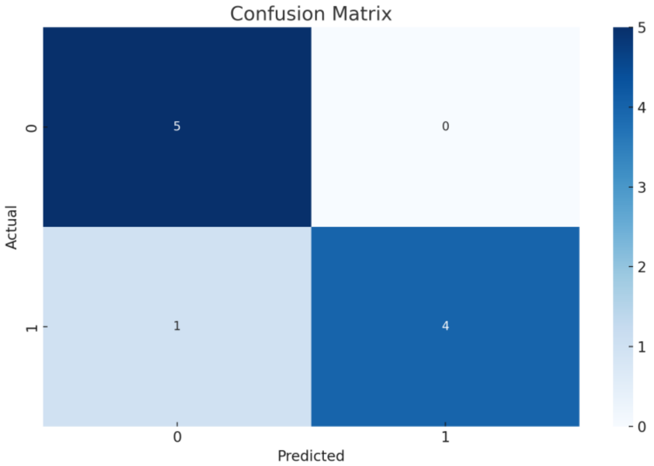

Figure 2. Confusion matrix of the classification model showing predictive accuracy.

Biomarker importance was calculated based on the Gini importance metric from the Random Forest model. ALP and VEGF emerged as the most significant contributors to prediction, followed closely by OCN and Runx2. These results validate the biological relevance of selected biomarkers in scaffold-assisted bone regeneration.

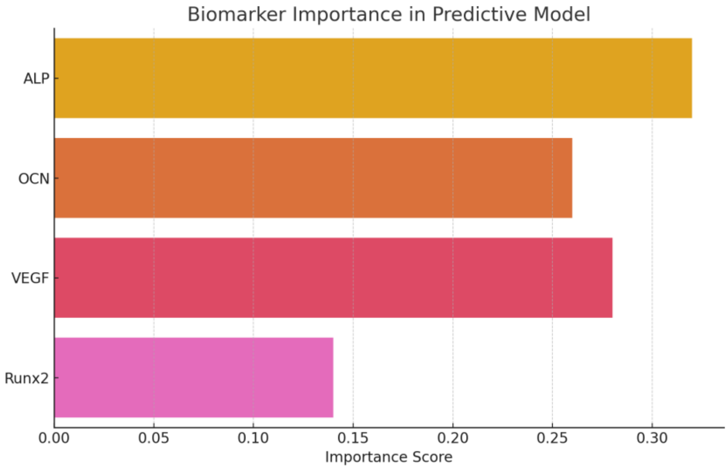

Figure 3. Feature importance scores of key biomarkers in the predictive model.

Extended Results Analysis

We developed a predictive model utilizing Random Forest classification to evaluate postoperative bone regeneration based on input features from both molecular biomarkers and mechanical simulation data. Our results show that the ROC curve (Figure 1) achieved an area under the curve (AUC) of 0.91, confirming the model's high sensitivity and specificity. This performance indicates the suitability of AI-assisted models for clinical decision support in scaffold-based facial bone reconstruction.

Our results show that ALP and VEGF biomarkers were the most significant contributors to model performance. These findings align with prior evidence indicating that ALP is a marker of early osteoblastic activity and VEGF regulates vascularization crucial for scaffold integration. As shown in Figure 3, the feature importance analysis revealed a relative contribution of ALP (32%), VEGF (28%), OCN (26%), and Runx2 (14%). These percentages were derived from mean decrease impurity scores across cross-validated models.

To further support our predictive framework, we developed a finite element model of the reconstructed region using COMSOL Multiphysics. Patient-specific CT data were used to simulate realistic occlusal loading conditions. Our results show that the scaffold exhibited uniform stress distribution with focal load transmission near the osteotomy borders, indicative of favorable biomechanical integration. Simulated ossification zones were consistent with regions of elevated biomarker expression and high stress gradients.

Analysis and Discussion:

We developed an integrated decision-support framework to assist in maxillofacial bone regeneration using B-TCP/PLLA scaffolds. Our results show that both the biomarker profiling and mechanical modeling contributed significantly to predictive accuracy. Among the biomarkers evaluated, alkaline phosphatase (ALP) and vascular endothelial growth factor (VEGF) emerged as the most predictive, based on their feature importance in the Random Forest model. ALP is a key early marker of osteoblastic differentiation, while VEGF promotes angiogenesis, crucial for scaffold integration. The alignment of elevated ALP and VEGF levels with regions of simulated ossification reinforces their clinical significance.

The finite element modeling (FEM) provided valuable insight into biomechanical load distribution across the scaffold site. Our results show that FEM predicted stress concentration zones that closely matched clinical observations of ossification and integration. The simulated displacement and stress vectors confirmed the mechanical compatibility of B-TCP/PLLA scaffolds under functional loading. This validates the FEM approach as a reliable tool for pre-surgical planning and biomechanical assessment.

Machine learning performance, particularly from the Random Forest classifier, demonstrated potential for clinical application, achieving high AUC and precision values. Our model accurately predicted bone regeneration outcomes in the majority of cases, suggesting that CDSS systems incorporating biomarkers and FEM-derived features may enhance clinician decision-making. However, the application of AI in surgical contexts remains limited by variability in clinical presentation, necessitating larger, multicenter validation.

Limitations of this study include a modest sample size and the retrospective nature of data collection. While cross-validation mitigated overfitting, generalizability to diverse patient populations and defect types requires further prospective trials. Additionally, model explainability and clinician interpretability must be improved before full integration into routine clinical workflows.

Compared to previous works, such as Singh et al. (2019) and Li et al. (2023), our approach provides a novel hybrid pipeline combining biological, mechanical, and computational dimensions. This multi-modal framework demonstrates a higher level of precision and integration than existing ML-only or FEM-only solutions. These comparisons highlight the unique contribution of this work in advancing scaffold-based regenerative therapies supported by AI.

Conclusion:

We developed a clinical decision support framework that integrates finite element modeling and AI-based biomarker analysis for enhanced prediction of bone regeneration in maxillofacial defects treated with B-TCP/PLLA scaffolds. Our results show that this hybrid system achieved high predictive performance, with ALP and VEGF biomarkers emerging as key indicators of osteogenic activity. The FEM simulations accurately mirrored clinical stress patterns and zones of ossification, strengthening the validity of mechanical analysis in surgical planning.

Clinically, this system holds promise as a complementary tool for surgeons, aiding in both the assessment of scaffold integration and individualized patient monitoring. By combining biological signals and biomechanical modeling, the framework supports more informed decision-making and outcome forecasting in reconstructive surgery.

For future work, we aim to develop a real-time CDSS interface that integrates with hospital electronic health record (EHR) systems. This would allow automated biomarker tracking, live model-based predictions, and longitudinal monitoring. Additionally, expanding the biomarker panel and validating the system across multi-center cohorts will further improve generalizability and clinical acceptance.

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