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PRECISION BASED CRANIOFACIAL SURGERY: AI ENABLED MOLECULAR PREDICTION OF CRANIOSYNOSTOSIS RELAPSE

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ABSTRACT
Background: Postoperative relapse represents a persistent challenge in the surgical treatment of craniosynostosis and is influenced by a complex interplay of clinical, radiographic, and molecular determinants. Reliable preoperative risk assessment is therefore essential to improve surgical decision-making and long-term outcomes. This study aimed to develop and validate an integrated artificial intelligence (AI)–based model that utilizes multimodal data to predict postoperative relapse in patients with craniosynostosis.
Methods: A retrospective–prospective translational study was performed involving 120 patients with syndromic and nonsyndromic craniosynostosis who underwent primary craniofacial surgery and completed a minimum follow-up period of 24 months. Comprehensive clinical information, radiographic features, and molecular genetic data targeting established craniosynostosis-related genes were collected. Supervised machine learning algorithms were employed to construct predictive models with stepwise integration of clinical, radiographic, and molecular variables. Model performance was evaluated using accuracy, sensitivity, and specificity, positive and negative predictive values, F1 score, and area under the receiver operating characteristic curve (ROC) (AUC).
Results: Postoperative relapse was observed in 27 patients (22.5%), whereas 93 patients (77.5%) remained relapse-free. A significant association was identified between the presence of pathogenic genetic variants and relapse occurrence ($p = 0.008$). The fully integrated clinical, radiographic, molecular AI model demonstrated superior predictive performance, achieving an accuracy of 92.5%, sensitivity of 88.9%, specificity of 94.7%, F1 score of 87.8%, and an AUC of 0.946. The model correctly identified 88.9% of patients who developed relapse and accurately classified 94.6% of patients with favorable postoperative outcomes. Progressive improvements in predictive accuracy were noted with the incremental incorporation of multimodal data.
Conclusion: The integrated AI-based predictive framework exhibited excellent accuracy and discriminative capability for postoperative relapse prediction in craniosynostosis. The inclusion of molecular genetic information alongside clinical and radiographic parameters substantially enhanced risk stratification, supporting the potential role of AI-driven models as clinical decision-support tools for personalized surgical planning and precision-based management of craniosynostosis.

KEYWORDS: Artificial intelligence, Craniosynostosis, Molecular genetics, Postoperative relapse, Precision surgery, Risk stratification

INTRODUCTION
Craniosynostosis is a developmental craniofacial condition caused by the premature closure of one or more cranial sutures, leading to disrupted skull growth. Early fusion of these sutures restricts normal cranial expansion and may result in abnormal head shape, functional deficits, elevated intracranial pressure, and impaired neurodevelopment when not appropriately managed [1, 2]. The estimated incidence is approximately 1 in 2,000–2,500 live births, with wide variation in clinical manifestation, severity, and genetic etiology [3]. Surgical correction remains the primary

mode of treatment, aiming to normalize cranial morphology and intracranial volume; however, long-term outcomes are frequently affected by postoperative relapse and resynostosis [4, 5].

Advances in molecular and genetic research have provided critical insights into the mechanisms underlying craniosynostosis. Mutations in genes regulating cranial suture biology and osteogenic signaling—particularly Fibroblast Growth Factor Receptors (FGFR1, FGFR2, and FGFR3), Twist Family Basic Helix–Loop–Helix Transcription Factor 1 (TWIST1), Ephrin-B1 (EFNB1), and Muscle Segment Homeobox 2 (MSX2)—have been identified in both syndromic and nonsyndromic forms of the condition [6–9]. These genetic disruptions alter cellular signaling pathways involved in osteoblast differentiation and suture maintenance, leading to abnormal bone formation and premature suture fusion [10]. Molecular diversity among patients may also play a role in postoperative healing responses and the propensity for relapse following surgical intervention [11].

Despite refinements in surgical techniques, conventional craniosynostosis treatment planning remains largely dependent on clinical examination, imaging findings, and individual surgeon judgment [12]. Such approaches fail to incorporate the underlying molecular variability that influences disease progression and postoperative behavior. As a result, patients with comparable phenotypic presentations may experience markedly different surgical outcomes [13]. The lack of predictive tools capable of assessing individualized relapse risk restricts the development of tailored surgical strategies [14].

Artificial intelligence (AI) and machine learning have emerged as powerful tools in medical diagnostics, image analysis, and outcome prediction [15]. Within craniofacial surgery, AI-based models have demonstrated promising accuracy in identifying craniosynostosis, evaluating suture fusion patterns, and estimating disease severity using radiographic and facial imaging data [16–18]. Nevertheless, most existing applications rely predominantly on phenotypic features, and incorporation of molecular genetic information into AI-based predictive systems remains limited [19].

The convergence of molecular genetics and AI-driven analytics provides a strong foundation for a precision-based approach to craniosynostosis management [20]. Integrating genetic, radiographic, and clinical data within predictive models may allow early identification of patients at higher risk for postoperative relapse, facilitate optimal surgical timing and technique selection, and enable individualized treatment planning [21,22]. This strategy represents a shift from traditional experience-based decision-making toward a data-driven, patient-specific model of craniofacial surgical care.

MATERIALS AND METHODS

Study Design

A retrospective–prospective translational study design was adopted to evaluate an integrated predictive framework for postoperative relapse in craniosynostosis. The study combined molecular genetic profiling, radiographic assessment, and AI–based analysis to support precision surgical planning. Ethical clearance was obtained from the institutional review board prior to commencement, and informed consent was obtained for genetic testing wherever applicable.

Study Population

The study cohort comprised patients with syndromic and nonsyndromic craniosynostosis who underwent primary craniofacial surgical correction. Eligibility criteria included radiologically confirmed cranial suture fusion, availability of preoperative imaging data, and a minimum postoperative follow-up period of 24 months. Patients were excluded if clinical records were incomplete, follow-up duration was insufficient, or craniofacial abnormalities were secondary to non-craniosynostosis etiologies.

Clinical and Radiographic Data Acquisition

Patient demographic information, clinical characteristics, pattern of suture involvement, age at intervention, surgical technique employed, and postoperative clinical outcomes were systematically documented. Radiographic evaluation was performed using preoperative and follow-up computed tomography or three-dimensional imaging to assess cranial morphology, suture status, and the presence of resynostosis or relapse.

Molecular and Genetic Evaluation

Genetic analysis was conducted using targeted gene panels or next-generation sequencing datasets, focusing on established craniosynostosis-related genes such as FGFR1, FGFR2, FGFR3, TWIST1, EFNB1, and MSX2. Detected variants were interpreted and categorized according to pathogenicity using validated genomic databases and published evidence. Molecular findings were analyzed in relation to phenotypic presentation and postoperative outcomes.

AI and Machine Learning Analysis
Predictive models were developed using machine learning techniques to estimate the risk of postoperative relapse. Integrated datasets incorporating genetic variables, imaging-derived features, and clinical parameters were utilized. Feature extraction from imaging data was performed through automated and semi-automated methods. Supervised learning algorithms, including random forest and support vector machine classifiers, were trained and validated using cross-validation approaches. Model performance was assessed using accuracy, sensitivity, specificity, and area under the receiver operating characteristic curve (ROC) (AUC).

Statistical Methods
The collected data were entered into Microsoft Excel and analyzed using Statistical Package for the Social Sciences (SPSS) version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize the baseline demographic, clinical, radiographic, genetic, surgical, and postoperative outcome variables. Continuous variables, including age at surgery and follow-up duration, were expressed as mean, standard deviation (SD), and standard error (SE), whereas categorical variables such as syndromic status, cranial suture involvement, pathogenic genetic variants, postoperative relapse, and surgical characteristics were presented as frequencies and percentages. The normality of continuous data was assessed using the Shapiro–Wilk test. Comparisons between categorical variables were performed using the Chi-square test or Fisher's exact test, as appropriate. The association between genetic status and postoperative relapse was evaluated using the Chi-square test. The influence of surgical and clinical variables on postoperative relapse was assessed using univariate logistic regression analysis, and the results were expressed as odds ratios (ORs) with 95% confidence intervals (95% CIs). The predictive performance of the AI-based model was evaluated using standard diagnostic accuracy measures, including accuracy, sensitivity, specificity, positive predictive value (precision), negative predictive value, F1 score, and AUC, each reported with 95% CI wherever applicable. ROC curve analysis was used to assess the discriminative ability of the predictive model, with AUC values interpreted according to accepted diagnostic performance criteria. A two-tailed p-value of less than 0.05 was considered statistically significant for all analyses, and the results were interpreted at a 95% CI.

RESULTS
Table 1 and Figure 1 summarize the demographic profile of the study cohort. The study included 120 patients diagnosed with craniosynostosis who met the predefined inclusion criteria. The mean age at the time of surgery was 10.84 ± 4.62 months (SE = 0.42), indicating that surgical correction was predominantly performed during infancy. The mean duration of postoperative follow-up was 31.56 ± 6.84 months (SE = 0.62), which provided sufficient time to evaluate long-term outcomes such as postoperative relapse and resynostosis. The relatively narrow standard errors observed for both parameters indicate limited variability within the sample and support the representativeness of the study population. Overall, these baseline demographic characteristics established a robust foundation for subsequent analyses examining the relationships among molecular, radiographic, clinical, and AI–based parameters and postoperative outcomes.

Table 1: Demographic Characteristics Of The Study Population (N = 120)

Variable	**N**	**Mean**	**SD**	**SE**
Age At Surgery (months)	120	10.84	4.62	0.42
Follow-Up Duration (months)	120	31.56	6.84	0.62

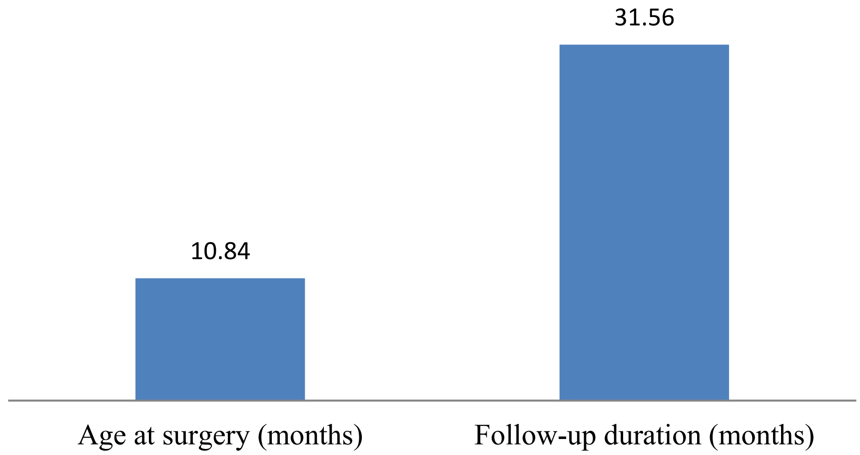

Figure 1: Demographic Characteristics Of The Study Cohort

Table 2 and Figure 2 illustrate the distribution of craniosynostosis based on clinical diagnosis. Among the 120 patients included in the study, 86 (71.7%) were classified as having nonsyndromic craniosynostosis, while 34 patients (28.3%) were diagnosed with syndromic craniosynostosis. The predominance of nonsyndromic cases is consistent with commonly reported epidemiological trends for this condition. Importantly, the inclusion of both syndromic and nonsyndromic cases ensured adequate representation, allowing for a meaningful evaluation of the influence of syndromic status on postoperative relapse and the predictive performance of the integrated AI model.

Table 2: Distribution of Syndromic & Nonsyndromic Craniosynostosis

Diagnosis	**Frequency**	**Percentage (%)**
Nonsyndromic	86	71.7
Syndromic	34	28.3
Total	**120**	**100.0**

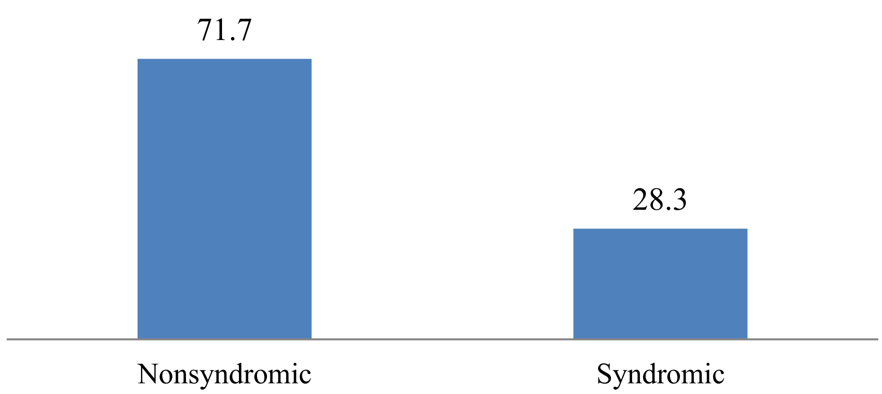

Figure 2: Distribution Of Craniosynostosis According to Clinical Diagnosis

Table 3 and Figure 3 depict the distribution of patients based on the pattern of cranial suture involvement. Of the 120 patients included in the study, sagittal craniosynostosis was the most prevalent subtype, identified in 46 patients (38.3%), and followed by coronal craniosynostosis in 28 patients (23.3%). Metopic suture involvement was noted in 20 patients (16.7%), while involvement of multiple sutures was observed in 18 patients (15.0%). Lambdoid craniosynostosis was the least common subtype, affecting 8 patients (6.7%). The higher frequency of sagittal suture involvement is in accordance with well-documented epidemiological trends in craniosynostosis. Furthermore, the inclusion of both single- and multiple-suture cases resulted in a diverse study population, enabling comprehensive evaluation of the associations among suture involvement patterns, genetic characteristics, AI–based predictions, and the risk of postoperative relapse.

Table 3: Distribution According To Cranial Suture Involvement

Suture Involved	Frequency	Percentage (%)
Sagittal	46	38.3
Coronal	28	23.3
Metopic	20	16.7
Lambdoid	8	6.7
Multiple Sutures	18	15.0
Total	**120**	**100.0**

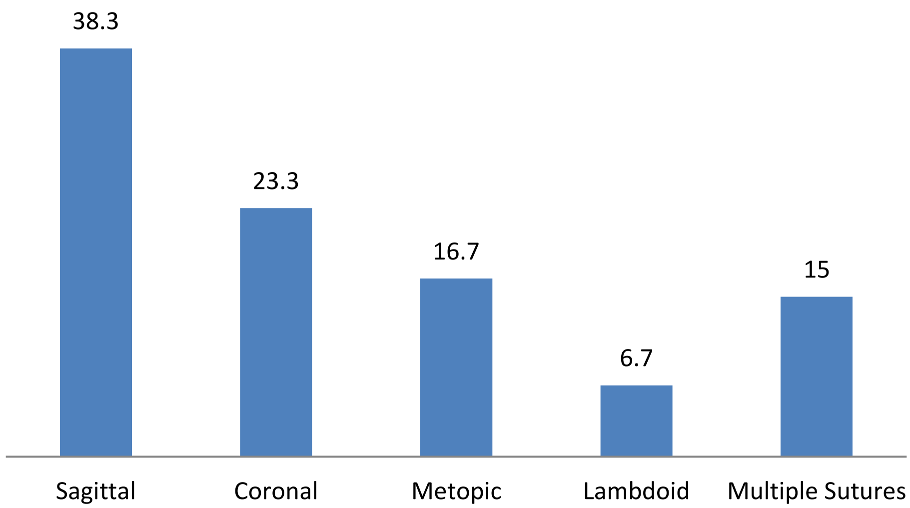

Figure 3: Distribution of Craniosynostosis According to Cranial Suture Involvement

Table 4 & Figure 4 summarize the spectrum of pathogenic genetic variants identified in the study population. Among the 120 patients evaluated, FGFR2 mutations were the most frequently observed, present in 24 patients (20.0%). This was followed by TWIST1 mutations in 18 patients (15.0%) and FGFR3 mutations in 15 patients (12.5%). Alterations in FGFR1 were detected in 11 patients (9.2%), while EFNB1 and MSX2 mutations were identified in 9 (7.5%) and 7 patients (5.8%), respectively. Notably, no pathogenic variants were detected in the analyzed gene panel in 36 patients (30.0%). Overall, pathogenic genetic alterations were identified in 70.0% of the cohort, emphasizing the substantial contribution of molecular factors to the development of craniosynostosis. The higher prevalence of FGFR2 and TWIST1 mutations is consistent with previously reported genetic profiles in syndromic and selected nonsyndromic craniosynostosis, supporting the integration of molecular markers into the AI-based predictive framework for postoperative relapse.

Table 4: Frequency of Pathogenic Genetic Variants

Gene	Positive (n)	Percentage (%)
FGFR2	24	20.0
FGFR3	15	12.5
FGFR1	11	9.2
TWIST1	18	15.0

EFNB1	9	7.5
MSX2	7	5.8
No detectable pathogenic mutation	36	30.0

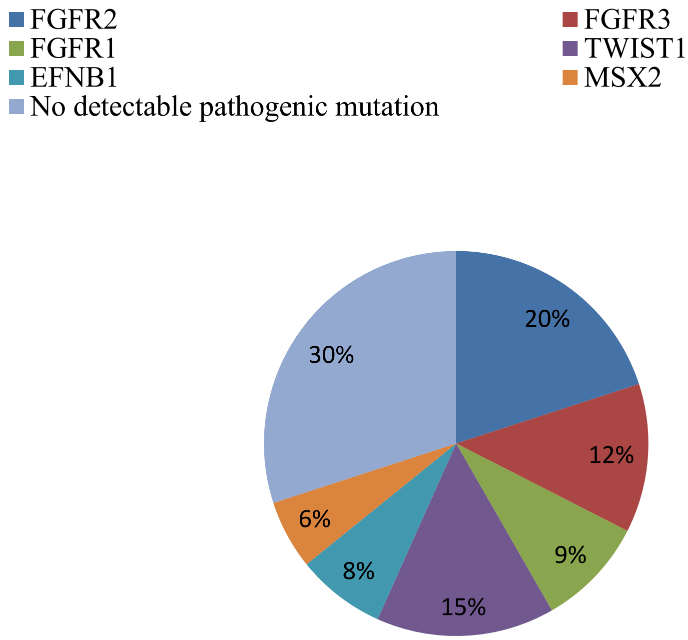

Figure 4: Distribution of Pathogenic Genetic Variants in the Study Cohort

Table 5 & Figure 5 illustrate the relationship between pathogenic genetic variants and the incidence of postoperative relapse. Among the 84 patients who were positive for pathogenic mutations, 24 (28.6%) developed postoperative relapse, while 60 patients (71.4%) showed no evidence of relapse during the follow-up period. In contrast, of the 36 patients in whom no pathogenic mutations were detected, relapse occurred in only 3 patients (8.3%), whereas 33 patients (91.7%) remained relapse-free.

Statistical analysis revealed a significant association between mutation status and postoperative relapse ($\chi^2 = 6.984$, $p = 0.008$). Patients harboring pathogenic genetic variants demonstrated a markedly higher rate of relapse compared with those without detectable mutations. These results indicate that molecular genetic alterations may be important predictors of postoperative outcomes and support the integration of genetic data into AI–based predictive models to enable individualized risk stratification and precision surgical planning in patients with craniosynostosis.

Table 5: Association Between Genetic Variants & Postoperative Relapse

Genetic Status	**Relapse n (%)**	**No Relapse n (%)**	χ^2	**P value**
Mutation Positive (n=84)	24 (28.6)	60 (71.4)	6.984	0.008
Mutation Negative (n=36)	3 (8.3)	33 (91.7)		

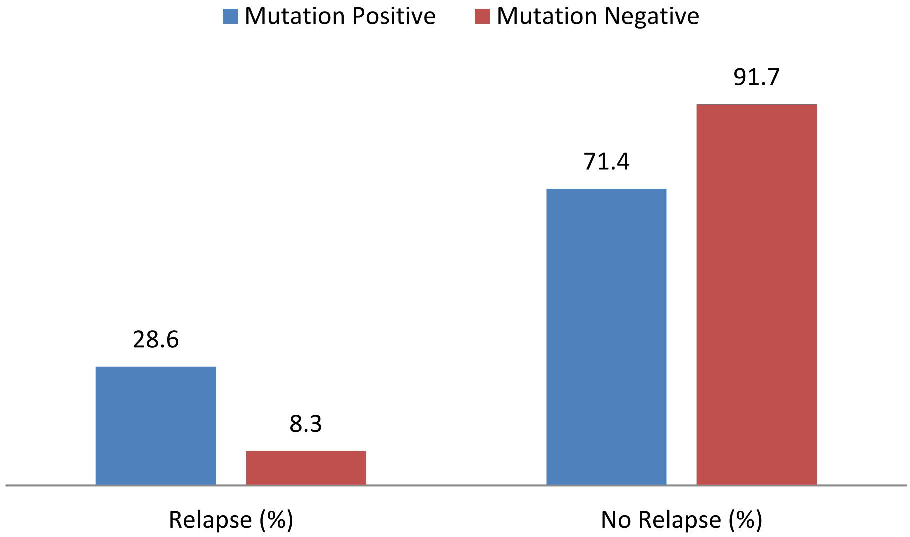

Figure 5: Association Between Pathogenic Genetic Variants & Postoperative Relapse in Craniosynostosis Patients

Table 6 summarizes the association between selected surgical factors & postoperative relapse using OR analysis. Syndromic craniosynostosis demonstrated a statistically significant association with relapse, with affected patients showing more than a threefold increase in relapse risk compared with nonsyndromic cases (OR = 3.18; 95% CI: 1.26–8.04; p = 0.014). In addition, surgical intervention performed after 12 months of age was associated with a significantly higher likelihood of relapse (OR = 2.47; 95% CI: 1.08–5.66; p = 0.031). Open cranial vault reconstruction was also identified as a significant risk factor, conferring a 2.21-fold increase in the odds of postoperative relapse compared with alternative surgical techniques (OR = 2.21; 95% CI: 1.03–4.73; p = 0.041).

In contrast, involvement of multiple cranial sutures did not show a significant association with relapse risk (OR = 1.00; 95% CI: 0.35–2.89; p = 1.000), indicating outcomes comparable to those observed in single-suture cases. Although endoscopic surgery was associated with a lower estimated odds of relapse (OR = 0.58; 95% CI: 0.21–1.61), this association did not reach statistical significance (p = 0.184).

Overall, these findings indicate that syndromic craniosynostosis, delayed surgical intervention beyond 12 months of age, and the use of open cranial vault reconstruction are significant predictors of postoperative relapse. Conversely, multiple suture involvement and endoscopic surgical management were not independently associated with relapse risk in this cohort. Incorporation of these clinically relevant variables may enhance the predictive performance of AI-based models for personalized relapse risk assessment and precision surgical planning.

Table 6: Surgical Variables Associated with Postoperative Relapse

Surgical Variable	**OR**	**95% CI**	**P value**	**Significance**
Syndromic Craniosynostosis	3.18	1.26–8.04	0.014	Significant
Multiple Suture Involvement	1.00	0.35–2.89	1.000	Not Significant
Age At Surgery >12 months	2.47	1.08–5.66	0.031	Significant
Endoscopic Surgery	0.58	0.21–1.61	0.184	Not Significant
Open Cranial Vault Reconstruction	2.21	1.03–4.73	0.041	Significant

Table 7 & Figure 6 present the diagnostic performance metrics of the integrated AI–based model developed to predict postoperative relapse in patients with craniosynostosis. The model achieved an overall classification accuracy of 92.5% (95% CI: 86.5–96.3%), demonstrating strong effectiveness in distinguishing patients who developed postoperative relapse from those who remained relapse-free.

The model demonstrated a sensitivity of 88.9% (95% CI: 78.1–95.3%), indicating a high capacity to correctly identify patients at increased risk of relapse. Similarly, the specificity was 94.7% (95% CI: 88.6–98.1%), reflecting excellent accuracy in correctly classifying patients without relapse. The positive predictive value (precision) was 86.7% (95% CI: 75.4–93.6%), suggesting that the majority of patients predicted to experience relapse were correctly identified. In addition, the negative predictive value was 95.8% (95% CI: 90.2–98.5%), highlighting the model's reliability in identifying patients with a low probability of relapse.

An F1 score of 87.8% (95% CI: 81.2–92.4%) indicated an optimal balance between precision and sensitivity, supporting the consistency of the model's performance across outcome categories. Furthermore, AUC was 0.946 (95% CI: 0.902–0.989), demonstrating excellent discriminative ability in differentiating relapse from non-relapse cases.

Overall, these findings indicate that the integrated AI-based model exhibits high predictive accuracy, robust sensitivity and specificity, and outstanding discriminative performance. Collectively, these characteristics support its potential utility as a reliable clinical decision-support tool for individualized risk stratification and precision-guided surgical planning in patients with craniosynostosis.

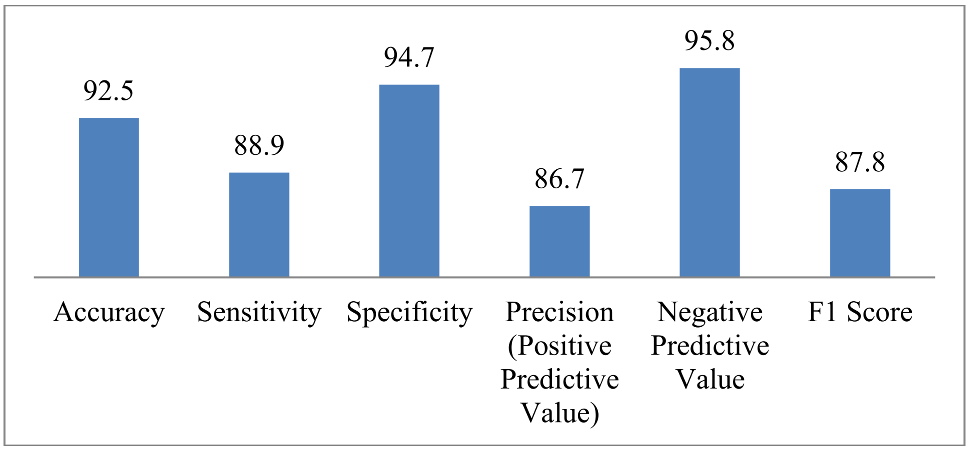

Figure 7: Diagnostic Performance of the Integrated AI-Based Model for Predicting Postoperative Relapse in Craniosynostosis

Table 8 and Figure 7 illustrate the comparative predictive performance of three stepwise models developed to estimate postoperative relapse risk in patients with craniosynostosis.

The clinical-parameter–only model demonstrated a moderate level of predictive capability, achieving an overall accuracy of 76.7%. This model yielded a sensitivity of 70.4%, specificity of 81.2%, and an AUC of 0.781, indicating acceptable but limited discrimination between relapse and non-relapse cases.

Enhancement of the model through the addition of radiographic parameters led to a marked improvement in performance. The combined clinical–radiographic model achieved an accuracy of 84.2%, with sensitivity and specificity values of 80.6% and 86.3%, respectively. The corresponding AUC of 0.872 reflected good discriminative ability and improved identification of patients at elevated risk of postoperative relapse.

The fully integrated clinical, radiographic & molecular AI Model demonstrated the strongest predictive performance. By incorporating molecular genetic markers alongside clinical and imaging features, this comprehensive model achieved an accuracy of 92.5%, sensitivity of 88.9%, specificity of 94.7%, and an AUC of 0.946, indicating excellent discrimination and robust predictive reliability.

Overall, the stepwise enhancement in model performance underscores the substantial value of integrating radiographic and molecular genetic data with clinical parameters. These findings support the role of multimodal, AI-driven approaches in improving risk stratification and enabling precision-guided surgical planning and personalized management in patients with craniosynostosis.

Table 8: Comparison Between Clinical Model & Integrated AI Model

Model	**Accuracy (%)**	**Sensitivity (%)**	**Specificity (%)**	**AUC**
Clinical Parameters Only	76.7	70.4	81.2	0.781
Clinical + Radiographic	84.2	80.6	86.3	0.872

Clinical + Radiographic + Molecular AI Model	92.5	88.9	94.7	0.946

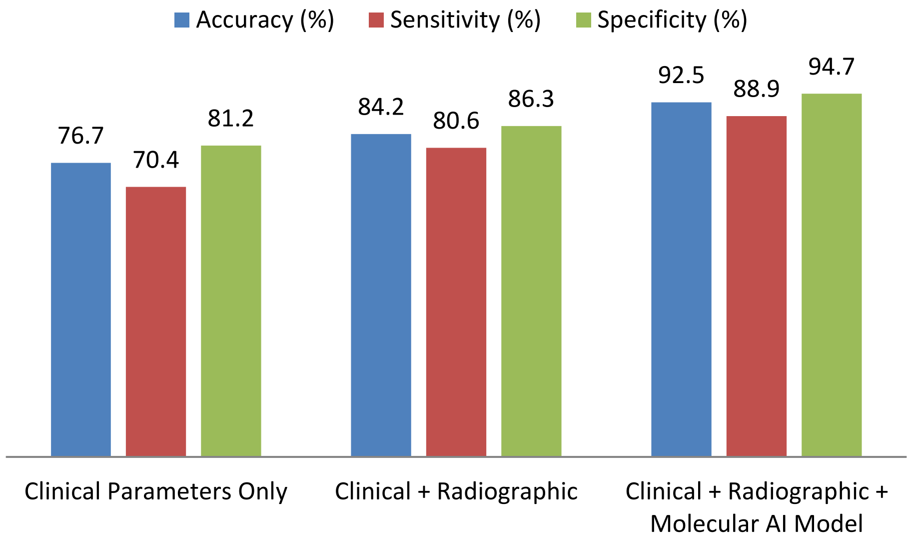

Figure 7: Comparative Performance of Progressive AI-Based Models for Predicting Postoperative Relapse in Craniosynostosis

Table 9 & Figure 8 summarize the predictive performance of the AI based model in relation to postoperative outcomes in the study cohort. Among the 120 patients included, 93 individuals (77.5%) achieved a successful postoperative course without evidence of relapse during the follow-up period, while 27 patients (22.5%) experienced postoperative relapse.

Of the patients who developed relapse, the AI model accurately identified 24 cases (88.9%) as high risk prior to surgery, demonstrating strong predictive capability for relapse occurrence. Likewise, among patients who remained relapse-free, 88 individuals (94.6%) were correctly classified as low risk, reflecting a high level of accuracy in predicting favorable postoperative outcomes.

Overall, the AI-based predictive framework exhibited excellent performance in stratifying patients according to postoperative relapse risk. The high rate of correct classification across both high- and low-risk groups underscores the clinical value of integrating molecular genetic, radiographic, and clinical parameters within AI models to support personalized risk assessment and precision-guided surgical planning in patients with craniosynostosis.

Table 9: Overall Prediction Performance & Postoperative Outcomes

Outcome	**Frequency**	**Percentage (%)**
Successful Outcome Without Relapse	93	77.5
Postoperative Relapse	27	22.5
High-Risk Cases Correctly Predicted By AI	24	88.9
Low-Risk Cases Correctly Classified	88	94.6

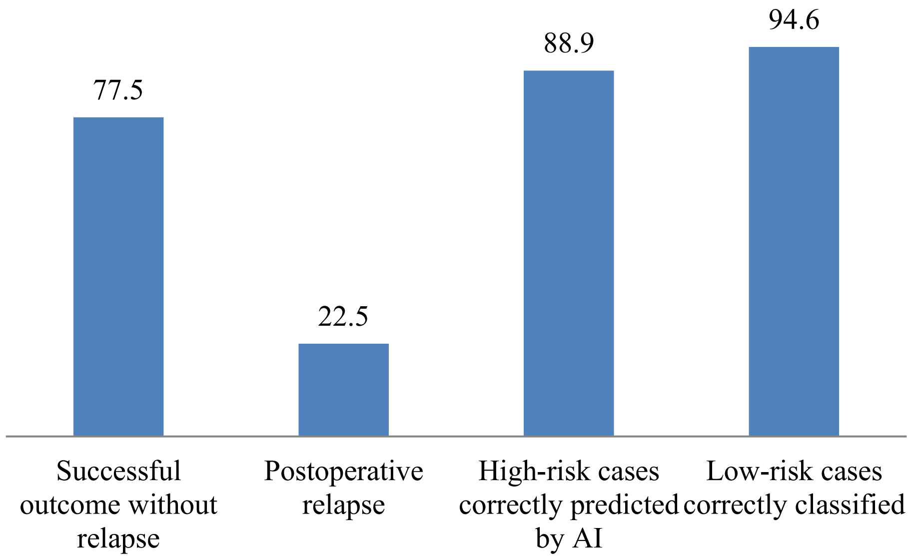

Figure 9: Postoperative Outcome Prediction & Risk Stratification Using the AI-Based Model in Patients with Craniosynostosis

DISCUSSION

Craniosynostosis is increasingly recognized as a biologically heterogeneous condition in which genetic, developmental, and biomechanical factors collectively influence disease behavior and surgical outcomes. Earlier molecular studies established that dysregulation of osteogenic signaling pathways plays a pivotal role in premature suture fusion, but more recent work has emphasized the clinical relevance of this molecular variability. Sharma et al. (2013) [23] demonstrated that differences in osteoblast proliferation and differentiation at the suture margins are associated with distinct craniosynostosis subtypes, suggesting that postoperative bone remodeling may be inherently influenced by underlying molecular characteristics rather than surgical technique alone.

Expanding on this concept, Timberlake et al. (2017) [24] showed that rare and common genetic variants contribute to craniosynostosis susceptibility across both syndromic and nonsyndromic cases, reinforcing the notion that genetic risk exists on a spectrum rather than as a binary entity. These findings support the rationale for incorporating molecular data into predictive frameworks, particularly when assessing long-term outcomes such as relapse and resynostosis. Similarly, Justice et al. (2012) [25] highlighted the clinical utility of genotype–phenotype correlations in craniosynostosis, demonstrating that genetic subtype can influence surgical timing, complexity, and recurrence risk.

From a surgical standpoint, postoperative relapse after cranial vault remodeling continues to represent a significant clinical challenge. Seruya et al. (2011) [26] reported considerable interpatient variability in postoperative cranial growth trajectories despite uniform surgical techniques, suggesting that endogenous biological factors influence bone healing and long-term cranial stability rather than operative factors alone. Their findings highlight the inherent limitations of conventional surgical planning paradigms that depend primarily on morphologic and radiographic assessment without accounting for biological variability.

AI has gained increasing attention as a tool capable of addressing this complexity through advanced data integration. Schaufelberger et al. (2022) [27] demonstrated that a radiation-free, machine learning–based classification pipeline using statistical shape modeling can objectively characterize cranial morphology in craniosynostosis. Their approach enabled accurate differentiation of cranial deformity patterns from three-dimensional shape data, providing robust proof-of-concept evidence that computational models can support diagnostic assessment and surgical planning without reliance on ionizing imaging modalities.

Building on this growing body of evidence, Luo et al. (2024) [28], in a comprehensive systematic review, reported that machine learning and deep learning techniques consistently outperformed traditional cephalometric and qualitative methods in craniosynostosis diagnosis and outcome prediction. The authors highlighted the superior ability of AI-driven models to detect subtle craniofacial shape variations linked to disease severity, growth trajectories, and postoperative outcomes, underscoring the expanding role of AI-assisted predictive frameworks in the clinical management of craniosynostosis. Importantly, the transition from phenotype-only AI models to biologically informed predictive systems aligns with broader trends in precision medicine. Collins and Varmus (2015) [29] emphasized that meaningful personalization of care requires integration of genomic data with clinical and imaging information, rather than isolated application of any single modality. In this context, the present study extends existing AI applications in craniosynostosis by incorporating molecular genetic features alongside radiographic and clinical parameters, thereby addressing a critical gap in current literature.

Collectively, these studies support a paradigm shift toward precision-based craniosynostosis management. Integrating molecular profiling with AI-enabled analytics offers the potential to improve relapse risk stratification, optimize surgical planning, and enhance long-term outcomes. Future prospective and multicenter investigations will be essential to validate these integrated models and establish standardized workflows for clinical implementation.

Limitations of the Study

This study has several limitations. The inherent heterogeneity of craniosynostosis phenotypes and genetic backgrounds may reduce the universal applicability of the predictive models. The retrospective component of the analysis carries a risk of selection and documentation bias. Limited sample sizes, particularly among rare syndromic variants, may affect the stability and external validity of model predictions. Additionally, differences in imaging protocols and surgical techniques could introduce variability in outcome assessment. Finally, although the AI models demonstrate strong predictive potential, further prospective validation and real-time clinical integration are necessary before routine clinical implementation.

CONCLUSION

The present study demonstrates the feasibility and potential value of a precision-oriented approach that integrates molecular genetics and AI in the management of craniosynostosis. By leveraging combined genetic, radiographic, and clinical data, AI-based predictive models may facilitate early identification of patients at heightened risk for postoperative relapse and resynostosis. This individualized risk assessment has the potential to improve surgical planning, optimize intervention strategies, and enhance long-term outcomes. The findings support a transition toward data-driven, personalized craniofacial surgery and lay the groundwork for future large-scale, prospective, multicenter investigations.

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