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Multi-factor early monitoring method based on D-dimer for iliac crest flap loss

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Abstract

Background In recent years, the utilization of autogenous vascularized iliac crest flap for repairing jaw defects has seen a significant rise. However, the visual monitoring of iliac bone flaps present challenges, frequently leading to delayed detection of flap loss. Consequently, there's a urgent need to develop effective indicators for monitoring postoperative complications in iliac crest flaps.

Methods A retrospective analysis was conducted on 160 patients who underwent vascularized iliac crest flap transplantation for jawbone reconstruction from January 2020 to December 2022. We investigated the changes in D-dimer levels among patients with or without postoperative complications. Additionally, multivariable logistic regression analysis was performed to explore potential individual risk factors, including surgical duration, age, pathology type, absolute and relative D-dimer levels, and gender, culminating in the development of a nomogram.

Results On the first day following surgery, patients who experienced thrombosis exhibited a substantial increase in plasma D-dimer levels, reaching 3.75 mg/L, 13.84 times higher than the baseline. This difference was statistically significant ($P < 0.05$) compared to patients without postoperative complications. Furthermore, the nomogram we have developed and validated effectively predicts venous thrombosis, assigning individual risk scores to patients. This predictive tool was assessed in both training and validation cohorts, achieving areas under the curve (AUC) of 0.630 and 0.600, with the 95% confidence intervals of 0.452–0.807 and 0.243–0.957, respectively.

Conclusions Our study illustrates that postoperative plasma D-dimer levels can serve as a sensitive biomarker for monitoring thrombosis-induced flap loss. Moreover, we have developed a novel prediction model that integrates multiple factors, thereby enhancing the accuracy of early identification of patients at risk of thrombosis-associated flap loss. This advancement contributes to improving the overall management and outcomes of such procedures.

Keywords Iliac crest flap, Bone transplantation, Jaw reconstruction, Flap loss, D-dimer, Monitoring method

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Introduction

Jaw defects, result from malignant tumors, large benign lesions, infections like osteomyelitis, or congenital abnormalities, notably disrupt both the aesthetic harmony and functional capacities of those affected. With advancements in microsurgery, the reconstruction of jaw defects frequently involves the use of autogenous vascularized fibula and iliac flaps. Notably, vascularized iliac crest flaps are increasingly utilized in comparison to previous years [1], for several reasons. Firstly, its donor site along the iliac crest is conveniently concealed, thereby minimizing visible scarring. Secondly, its abundant blood supply fortifies the flap with robust anti-infection properties. Thirdly, the iliac flap's intrinsic contour closely mimics the mandible's shape, allowing for a more aesthetically pleasing restoration. Most crucially, the iliac crest flap provides a dependable bone source with enough height, which is essential for the successful reconstruction of jaw defects and the placement of dental implants. These attributes contribute to the widespread preference for vascularized iliac flaps in jaw repair procedures [2–4].

Nonetheless, a recent meta-analysis indicated that about 7% of patients undergoing mandibular reconstruction with vascularized iliac crest flaps experience flap failure [5]. While this percentage might seem small, flap loss can inflict significant consequences, from compromised function and aesthetics to financial strain. It becomes important, therefore, to recognize and reduce the risks associated with the surgical process to maximize patient outcomes. Research pinpoints venous thrombosis as the main cause behind the failure of the vascularized iliac crest flap [6]. In consequence, early and accurate identification of thrombosis within a transplanted iliac crest flap is vital. Such detection can pave the way for prompt surgical intervention to excise the thrombotic blockage or amplify antithrombotic therapy, thereby bolstering the prospects for successful flap survival. Contrary to soft tissue free flaps, such as the anterolateral thigh perforator flap, which can be visually inspected and palpated for signs of compromise, monitoring the vascularized iliac crest flap is uniquely challenging because it is typically enveloped by skin or mucosa at the recipient site. Thus, it is crucial to establish alternative means for the early detection and monitoring of potential complications with the iliac crest flap [7].

Elevated D-dimer levels serve as sensitive indicators of thrombosis, reflecting increased activity in the coagulation and fibrinolytic systems. As fibrin-containing thrombi form in the body, regulatory mechanisms concurrently facilitate the breakdown of cross-linked fibrin, generating fibrin degradation products including D-dimer. Elevated D-dimer levels therefore suggest the presence of thrombosis and are clinically valuable for identifying patients with pathological intravascular clotting [8–10]. Our current research indicates that D-dimer levels, particularly noteworthy changes observed within the first day following surgery, could provide a viable biomarker for ensuing flap loss. Significant elevations in D-dimer were noted in patients who encountered flap failure when benchmarked against patients without complications. Although D-dimer assays are indeed sensitive, their lack of specificity—attributable to diverse influencing variables such as age, malignancy, and trauma—necessitates a more discriminating predictive model [9–11]. We have thus developed a model consolidating multifarious factors based on D-dimer levels, which considerably augments the predictive precision, equipping clinicians with a structured multiparametric scoring system to evaluate flap failure risks in patients exhibiting raised postoperative D-dimer levels.

In conclusion, this study pioneers the use of postoperative plasma D-dimer levels as a monitoring indicator for transplanted iliac crest flaps. Furthermore, by developing a novel multifactorial model based on D-dimer levels to predict flap loss, the study introduces a new approach to anticipate potential complications with iliac crest flaps, thereby enabling early clinical interventions to potentially salvage compromised flaps.

Patients and methods

This retrospective study was guided by the STROBE initiative [12] (Supplementary Checklist) and was approved by the Review Board of the Ethics Committee of the School and Hospital of Stomatology, Wuhan University (NO. 2023-B42). The need for informed consent was waived due to the retrospective nature of the study. The flow diagram illustrating the case search and selection criteria is depicted in Fig. 1. The medical records of patients who underwent partial jawbone resection surgery at the Department of Oral and Maxillofacial Surgery, Hospital of Stomatology, Wuhan University, China, from January 2020 to December 2022 were reviewed. Patients included in the study met the criteria of primary jawbone reconstruction using vascularized iliac crest flaps. Exclusion criteria encompassed patients who had previously undergone treatment for jawbone lesions such as repair, chemotherapy, or radiotherapy for malignant tumors, those who did not undergo jaw defect repair, and those treated with vascularized fibular flaps or non-vascularized bone flaps. Ultimately, 160 eligible patients were included in the study. The collected data consisted of demographic information, recipient site, pathological diagnosis, baseline plasma D-dimer levels prior to surgery, and plasma D-dimer levels within 5 days after the operation. Additionally, postoperative complications and their corresponding management were recorded and analyzed. Using multivariate logistic regression analysis to identify risk factors associated with elevated D-dimer

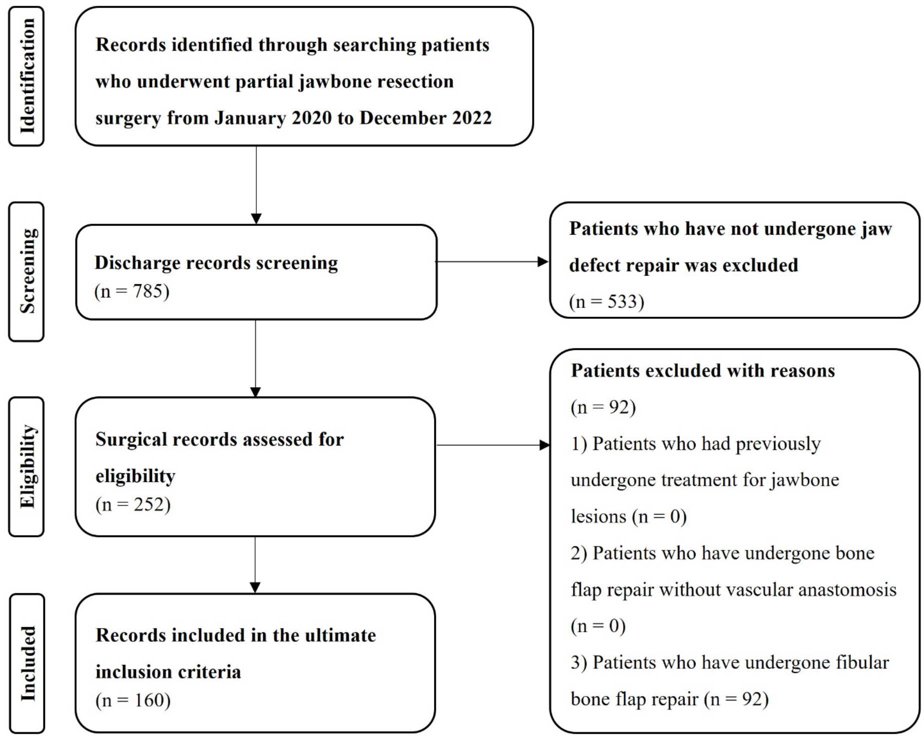

Fig. 1 The flow diagram illustrating the case search and selection criteria

Table 1 Demographics of patients who experienced complications

Variable	FL ($n=7$)	TR ($n=9$)	*p* Value
Age (years)	42.14 ± 10.51	54.33 ± 17.01	0.119
Gender			0.072
Males	2	7	
Females	5	2	
Benign or malignant			0.182
Benign lesions	4	2	
Malignant tumours	3	7	
Pathological diagnosis			
Ameloblastoma	1	1	
Odontogenic cyst (OC)	1	1	
Squamous cell carcinoma	1	6	
Adenoid cystic carcinoma	0	1	
Mucoepidermoid carcinoma	1	0	
Malignant transformation of OC	1	0	
Others	2	0	

Abbreviations FL, flap loss; TR, titanium plate rejection

levels that correlate with flap loss, and constructing a nomogram model. The predictive performance of the nomogram model will be evaluated through receiver operating characteristic (ROC) curve analysis.

Statistical analyses

Statistically significant differences were analyzed using two-sided unpaired Student's *t*-tests, 1-way analysis of variance (ANOVA), using GraphPad Prism 9.3.1 (GraphPad Software). Correlations were determined by Pearson's *r* coefficient. $P<0.05$ was considered statistically significant.

Results

Patient summary

A retrospective review of data from 160 patients was carried out, with patient characteristics detailed in Supplementary Table S1. Postoperatively, complications arose in 17 patients, comprising 7 instances of flap loss, and 9 successful flap preservations subsequent to titanium plate removal, with one patient experiencing postoperative bleeding, as noted in Table 1. Those who suffered flap loss exhibited an average age of 42.14±10.51 years, predominantly female (5 out of 7 cases), and primarily diagnosed with benign lesions (4 out of 7 cases). Contrastingly, patients facing titanium plate rejection had an older average age of 54.33±17.01 years, mostly male (7 out of 9 cases), with squamous cell carcinoma (SCC) being the prevalent pathological type (6 out of 9 cases). Such outcomes may be linked to additional radiotherapy typically required for SCC patients' post-surgery, potentially impairing vascular and osseous cells. Occasionally, hypersensitivity to the titanium plate may lead to fistula formation, necessitating plate removal. The demographics of patients who encountered complications are summarized in Table 1.

Discussion

D-dimer, a notable fibrinogen degradation byproduct, becomes elevated in the body's cascade response to venous thrombosis. This condition prompts an enzymatic breakdown of blood clots and fibrinogen degradation, predominantly mediated by plasmin. Enhanced plasmin activity results in the cleavage of fibrinogen, giving rise to a spectrum of fibrin degradation products. As the breakdown persists, these larger molecules yield progressively smaller elements, including D-dimer, formed through the re-polymerization of fibrinogen monomers [8, 13]. The presence of D-dimer, detectable within two hours following thrombus formation [8], is a critical biomarker for timely clinical intervention. The utilization of the D-dimer assay is now common in diagnosing venous thromboembolism, attesting to its high sensitivity in reflecting acute thrombosis and fibrinolytic activation [9, 14, 15]. Our findings revealed that, following surgery, patients who suffered from flap loss demonstrated a rapid and significant elevation in plasma D-dimer levels on the first day. This insight underscores the promising utility of first-day post-surgical plasma D-dimer levels as an early biomarker for the detection of iliac crest flap thrombosis and the consequent flap loss.

However, the assay's sensitivity is countered by its limited specificity due to possible D-dimer elevation from other conditions—such as malignancies, aging, hospitalization, inflammatory states, pregnancy, and surgical trauma [10, 11]. The data strongly supports the notion that surgical trauma can precipitate a rise in D-dimer concentrations. Our investigation centered on 143 individuals with uneventful iliac flap procedures, revealing a range of augmentations in plasma D-dimer levels post-surgery. Notably, by the 5^{th} day post-surgery, these levels had plateaued. This stabilization suggests that the sustained physiological stress prompted by the surgery may engage both the coagulation and fibrinolysis mechanisms [16]. Consequently, we have established a positive correlation between postoperative D-dimer levels and the operation time. Additionally, various independent risk factors previously documented, including age, cancer, and gender exacerbate postoperative D-dimer elevation. With advancing age, there is a discernible escalation of pro-thrombotic factors that engender a hypercoagulable state [11, 17]. This phenomenon is augmented by the greater incidence of comorbid conditions in the elderly demographic, many of which are linked to increased plasma D-dimer concentrations [18]. Consequently, in older patients who experience surgical trauma, idiosyncrasies in microcirculation and clotting functions are likely to yield enhanced D-dimer levels throughout the healing period. The intricate relationship between oncology and coagulation is underscored by the ability of cancer cells to secrete a plethora of coagulation factors, which in turn amplify thrombin generation and precipitate a hypercoagulable milieu in patients with cancer. Such a state is conducive to the onset of venous thromboembolism, as reflected in escalated plasma D-dimer levels [19, 20]. Furthermore, studies suggest that women typically exhibit higher concentrations of both coagulation factors and D-dimer than men, hinting at a potentially heightened susceptibility to hypercoagulability. Consequently, female surgical patients may encounter an augmented risk for venous thrombosis, influenced by elevated coagulation factor levels [21]. Therefore, while the D-dimer assay is an invaluable tool in detecting thrombotic phenomena, its interpretation requires careful consideration of the patient's full clinical picture and corroborative diagnostics to ensure precise diagnosis and appropriate therapeutic strategies.

In light of the myriads of independent risk factors that may elevate post-surgical plasma D-dimer levels, it is imperative to establish a multidimensional analytical model to unravel their respective impacts thoroughly. This incorporates a multivariate logistic regression analysis to scrutinize patient factors correlated with flap loss [16]. Through diligent clinical scrutiny, we selected five pivotal predictors to incorporate into the nomogram, thus enabling intricate risk differentiation. This nomogram, with precise graphical utility, allows for the assessment of individual thrombosis risk in a straightforward manner. Practitioners can establish the score for each variable by drawing a perpendicular line from the respective risk factor value to the score axis, then tallying these to ascertain the total risk score. The risk of flap loss due to venous thrombosis can be easily interpreted by aligning the cumulative score with the total score scale [16, 22]. Our findings reveal that the nomogram affords a commendable accuracy in prognosis, as reflected by the areas under the ROC curves in both training and validation stages. This model serves as a robust instrument for furnishing dependable risk estimates that can significantly inform clinical dialogues, therapeutic choices, and monitoring tactics. Crucially, our model leverages data that are effortlessly accessible within standard clinical procedures, markedly increasing its utility and relevance in real-world settings [22, 23]. This risk-scoring system reveals that individuals undergoing lengthier surgical procedures, those who are older in age, of the female sex, with certain pathological conditions such as SCC, and those registering higher absolute D-dimer figures tend to accumulate a greater risk score. This in turn indicates a higher propensity for a rise in postoperative plasma D-dimer levels, thereby suggesting a correspondingly increased likelihood of thrombotic events. Such a tool is instrumental in identifying patients at greater risk and implementing preventive strategies accordingly.

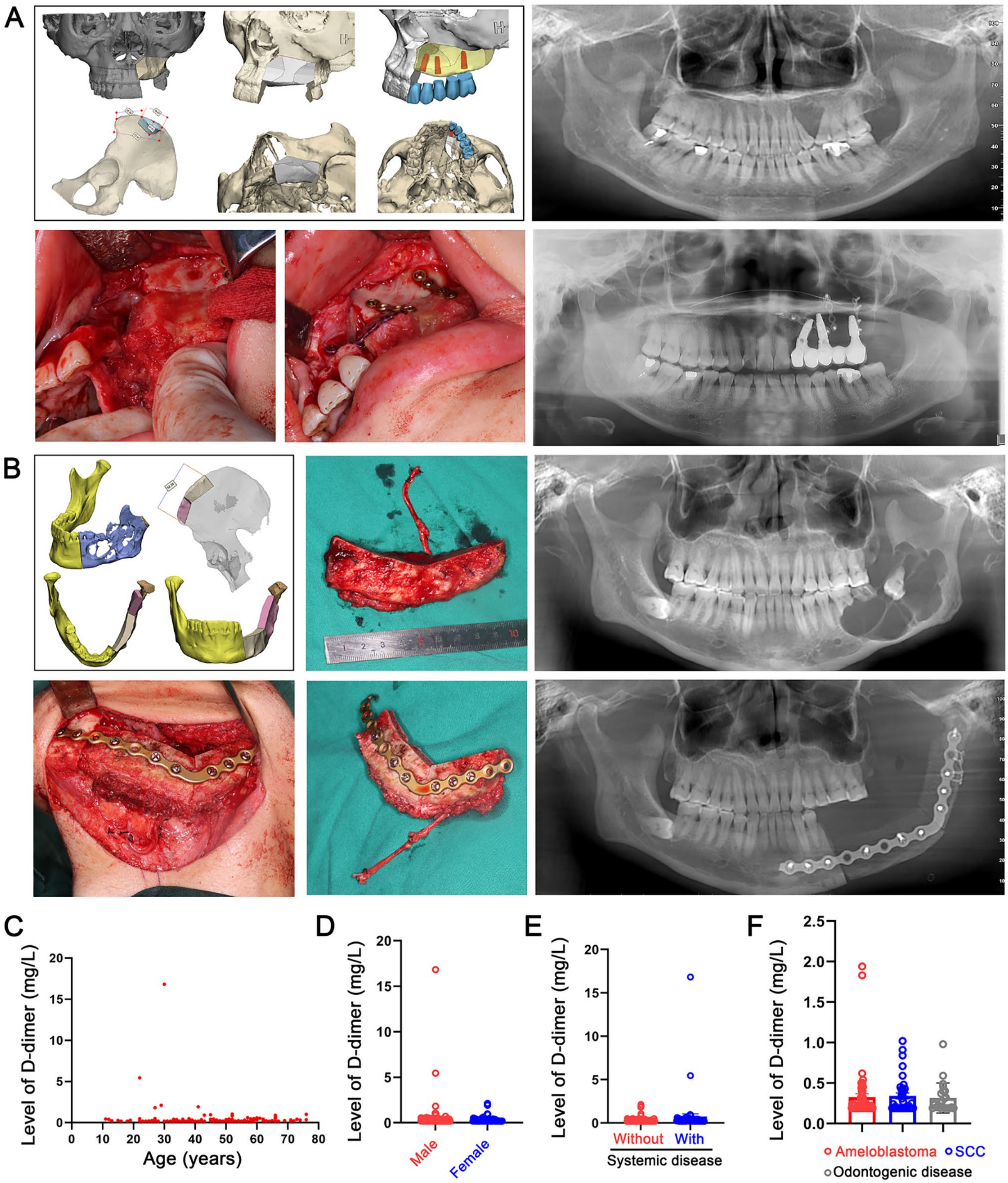

Fig. 2 Multidimensional analysis of preoperative D-dimer levels. Maxillary surgery (**A**) and mandibular surgery (**B**). The baseline levels are categorized by age (**C**), gender (**D**), presence or absence of systemic disease (**E**) and pathological types (**F**)

Several limitations should be acknowledged in this study. Primarily, it relied on retrospective analysis, which inherently introduces potential biases [24]. To minimize confounding bias, we separately analyzed potential influence factors related to changes in D-dimer levels between the non-complication and flap loss groups, such as age,

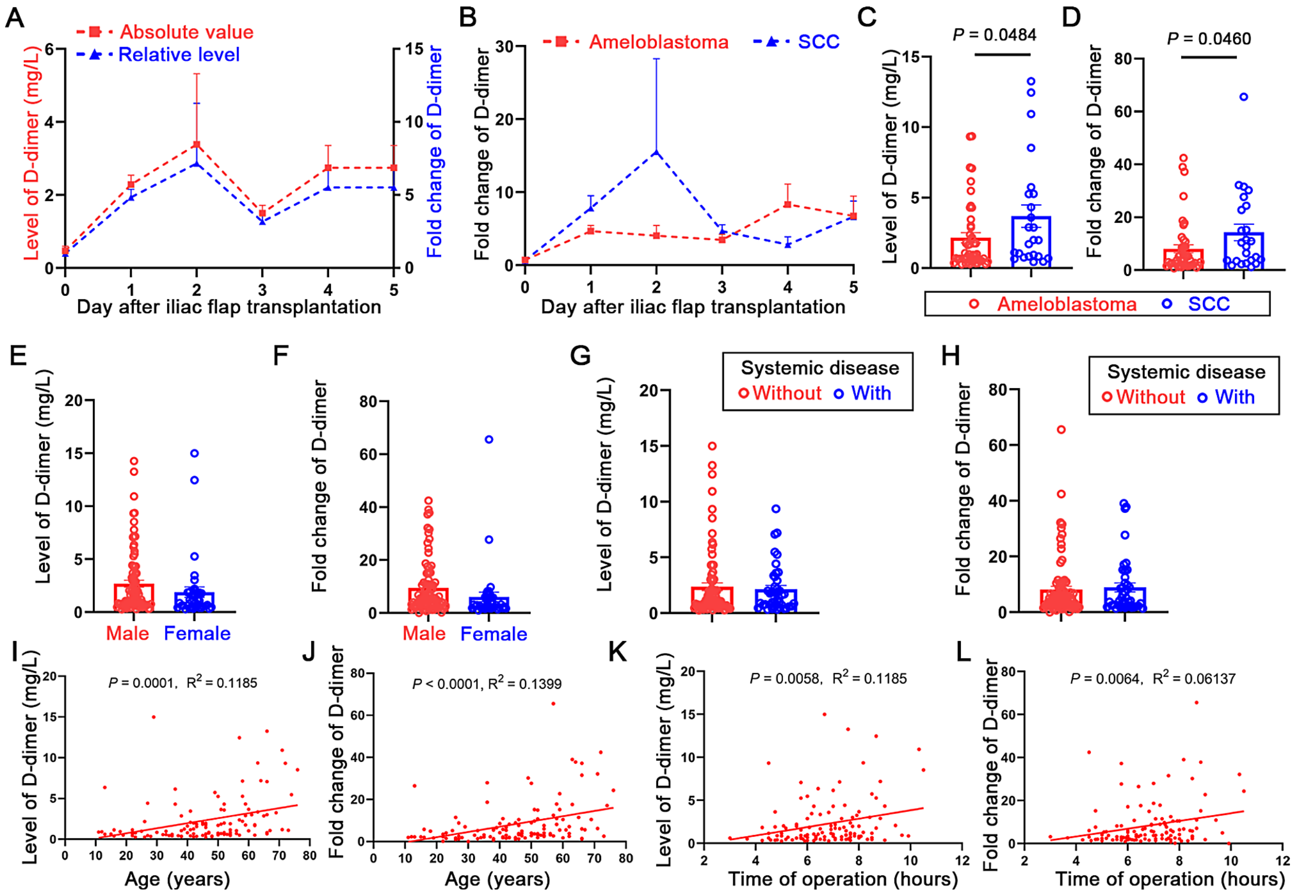

Fig. 3 Post-op D-dimer level changes in uncomplicated patients. Post-op D-dimer levels (**A**) in SCC or ameloblastoma patients (**B**), variations on the first post-op day (**C**-**H**), and correlation with age (**I**, **J**) and operation time (**K**, **L**)

gender, systemic diseases, and preoperative pathological classification. The results showed no statistically significant differences, ensuring that these confounding factors did not impact the exploration of the relationship between D-dimer level changes and flap outcomes. To reduce information bias as much as possible, this study included all patients who underwent vascularized iliac crest flap repair surgery at our hospital within indicated period, thereby avoiding information loss and ensuring an adequate sample size. Secondly, the study's limitations include the modest sample size, limited to individuals from a single country and ethnicity, which may affect the predictive precision and generalizability of our model across diverse populations. Future research should include prospective, multicenter clinical trials to further validate and refine our proposed predictive approach. Despite these limitations, our study provides valuable insights and lays the foundation for future research on assessing flap loss risk in patients undergoing jaw defect reconstruction with iliac crest flaps, focusing on monitoring post-surgical plasma D-dimer concentrations.

In summary, our study stands at the forefront of introducing postoperative plasma D-dimer levels as a novel prognostic indicator for the possibility of iliac flap loss. Furthermore, we have successfully developed a novel prediction model that incorporates multiple factors to refine the prediction of patients prone to iliac crest flap loss. This avant-garde methodology is designed to bolster patient prognosis and finetune the handling of procedures involving iliac crest flaps, ultimately paving the way for enhanced surgical success rates and patient care. Our findings invite further research and validation to substantiate the clinical utility and broaden the application spectrum of our model.

Baseline level of D-dimer in patients who receive vascularized iliac crest flap transplantation

Upon reviewing the preoperative plasma D-dimer levels in 160 patients undergoing vascularized iliac crest flap procedures for the maxilla (Fig. 2A) and mandible (Fig. 2B), the analysis revealed no substantial correlation with variables such as patient age (Fig. 2C), gender (Fig. 2D), systemic diseases (including hypertension and diabetes) (Fig. 2E), or pathological classifications (Fig. 2F).

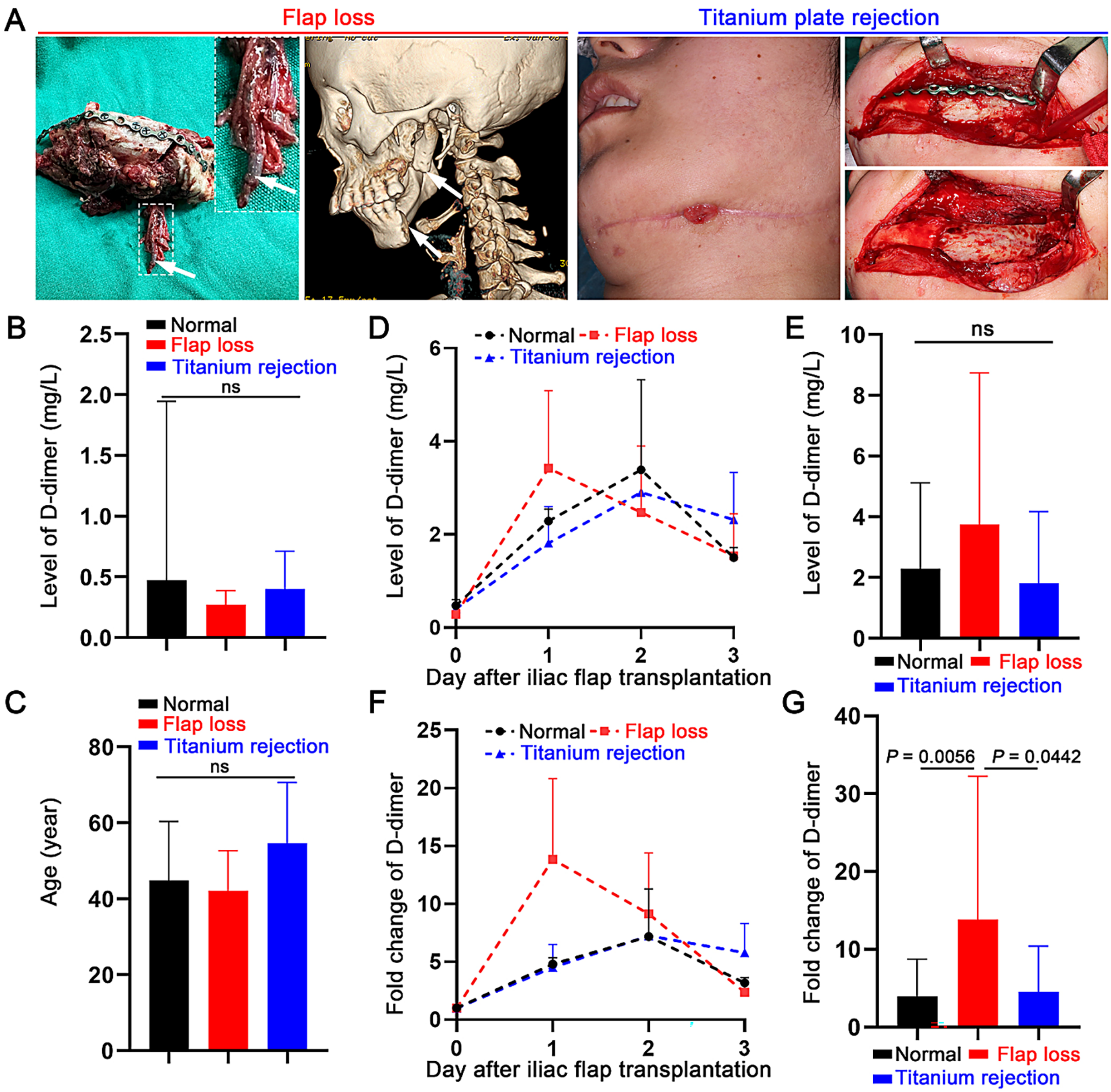

Fig. 4 D-dimer analysis in normal, flap loss and titanium plate rejection patients. (**A**) Imaging and clinical manifestations, (**B**) baseline D-dimer, (**C**) age distribution, (**D**, **F**) absolute and relative post-op D-dimer, (**E**, **G**) absolute and relative day-one post-op D-dimer

Postoperative alterations of D-dimer levels and their influencing factors in patients without complications

An analysis of the plasma D-dimer levels in a cohort of 143 patients, who manifested no post-surgical complications, uncovered a distinct pattern of fluctuation in these levels. It was noted that following the surgery, D-dimer concentrations ascended on the first and second days, peaking on the latter. A marginal decline was then noted on the third day, with levels rebounding on the fourth, stabilizing at a plateau congruent with first-day measurements. The levelling of D-dimer persisted thereafter. Quantitatively, post-surgical D-dimer levels surged to approximately 4.8 times the preoperative baseline on day one, 7.17 times on day two, and settled back to 3.18 times on day three. The highest elevation was recorded on the second day post-operation (Fig. 3A).

Patients diagnosed with squamous cell carcinoma exhibited a pronounced increment in plasma D-dimer levels, peaking two days post-surgery. Subsequent to a decline that aligned them with the non-complicated cohort on the third day, their levels witnessed further reduction by the fourth day. A resurgence to levels seen

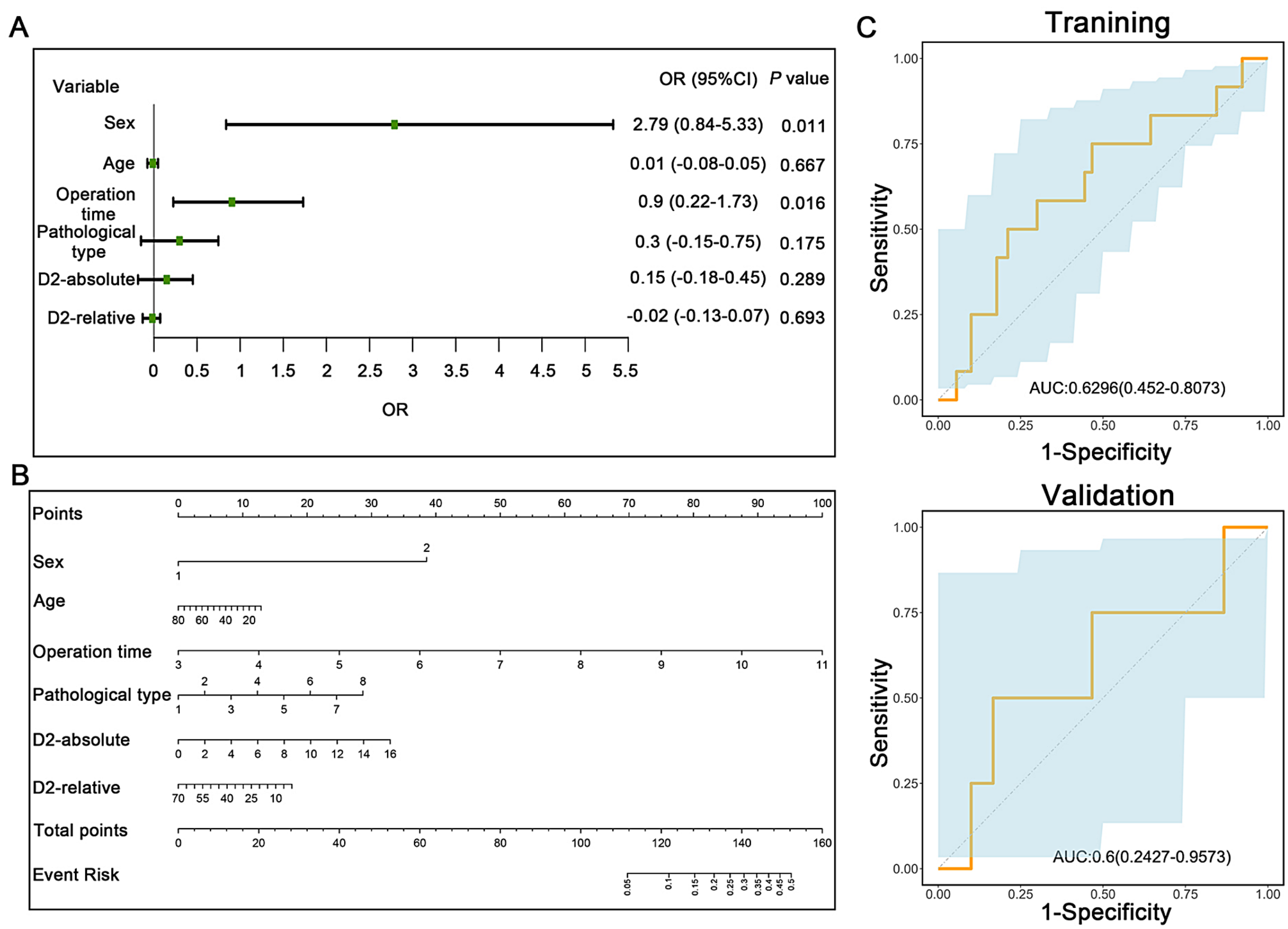

Fig. 5 Multifactor prediction model for post-op D-dimer levels. (**A**) Multivariate regression analysis of risk factors affecting post-op D-dimer levels, (**B**) integrated risk factors for prediction, (**C**) ROC curves for D-dimer prediction in training and validation sets

in the untroubled group characterized the fifth day. Initial escalation in D-dimer for SCC individuals reached about 7.81 times and 15.53 times above baseline on the first and second days, respectively (Fig. 3B). In contrast, those with ameloblastoma presented a moderate rise in D-dimer levels post-surgery, achieving equivalence with the non-complicated group on day one. A gradual downward trajectory ensued through days two and three, with a fourth-day upturn, before a fifth-day fall-off to levels matching those without complications. The D-dimer levels in ameloblastoma patients were about 3.45 to 4.66 baseline multiples from the first to the third day, surging to roughly 8.31 times the baseline on day four (Fig. 3B). Patients of different pathological types exhibit varying changes in postoperative plasma D-dimer levels.

Individual analysis of factors potentially linked to the escalated post-surgical plasma D-dimer levels revealed a significant correspondence with lesion pathology, with SCC showing notably greater increases compared to ameloblastoma, a difference proven statistically momentous ($P<0.05$, Fig. 3 C, D). However, distinctions in D-dimer surges were not significantly related to either gender or systemic disease presence (Fig. 3E-H). A substantial association was established between the rise in D-dimer concentrations and both patient age ($P\leq0.001$, Fig. 3I, J) and the duration of the operation ($P<0.01$, Fig. 3K, L).

Postoperative alterations in D-dimer levels and their influencing factors in patients with complications

The study examined plasma D-dimer level changes within the first three days following surgery among different patient cohorts: those with an good recovery, those who suffered thrombosis culminating in flap loss (Fig. 4A, left side), and those who experienced a rejection of the titanium plate (Fig. 4A, right side). Preoperative baseline D-dimer readings were relatively consistent across the groups and indicated minor variations, with the good postoperative group (normal) showing levels at 0.47 mg/L, the thrombosis group (flap loss) at 0.27 mg/L, and the titanium plate rejection group at 0.40 mg/L (Fig. 4B). Additionally, there were no statistically relevant age differences among the patient cohorts (Fig. 4C). The data revealed that on the first postoperative day, patients afflicted with thrombosis that led to flap loss experienced a pronounced elevation in plasma D-dimer levels, markedly higher than those seen in patients who had a smooth postoperative course. These heightened levels subsided on the second and third days, eventually aligning with the levels observed in the complication-free group by the third day. Conversely, patients who rejected titanium plates demonstrated D-dimer levels and trajectories over the three-day post-surgery period that mirrored those observed in patients who had uneventful recoveries (Fig. 4D, F).

A meticulous analysis was conducted focusing on the first postoperative day's plasma D-dimer levels among the three patient categories. The measurements from those patients who suffered titanium plate rejection (1.81 mg/L, 4.52 times above baseline) were found to be comparable to those of the patients with an uneventful postoperative trajectory (2.29 mg/L, 3.96 times above baseline). However, the thrombosis group, which faced complications resulting in flap loss, displayed significantly elevated D-dimer values (3.75 mg/L, 13.84 times above baseline). These differences reached a level of statistical significance ($P<0.05$, Fig. 4E, G).

Predicting complications of vascularized iliac crest flap transplantation through a multifactor prediction model

While elevated plasma D-dimer levels show correlation with flap loss, it is essential to recognize that this association is influenced by various factors. Therefore, we conducted further multivariate logistic regression analysis to assess multiple independent risk factors, including surgical time, age, pathological type, absolute and relative D-dimer levels, and gender. The surgical time corresponds with a 0.90-fold rise in thrombosis risk (OR=0.90, 95% CI: 0.22–1. 37, $p=0.016$); age associates with a 0.01-fold increase in risk of thrombosis (OR=0.01, 95% CI: -0.08–0.05, $p=0.667$); the pathological type contributes a 0.30-fold increase (OR=0.30, 95% CI: -0.15–0.75 $p=0.175$); gender has a 2.79-fold increased risk of thrombosis (OR=2.79, 95% CI: 0.84–5.33, $p=0.011$); the absolute D-dimer value predicts a 0.15-fold increase in thrombosis risk (OR=0.15, 95% CI: -0.18–0.45, $p=0.289$); and the relative D-dimer value shows a -0.02-fold increased risk of thrombosis (OR = -0.02, 95% CI: -0.13–0.07, $p=0.693$, Fig. 5A). A comprehensive model encapsulating these independent risk factors was formulated, yielding a nomogram for clinical use (Fig. 5B). The performance of the nomogram was rigorously evaluated with two distinct sets of patient data—the training and the validation cohorts—reaching a diagnostic reliability represented by areas under the ROC curve (AUC=0.630, 0.600, 95% confidence interval: 0.452–0.807, 0.243–0.957), respectively (Fig. 5C).

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12903-024-04712-w.

Supplementary Material 1

Supplementary Material 2; Supplementary Checklist

Acknowledgements
Not applicable.

Author contributions
Z.-L. Yu and J. Jia contributed to conception and design, analysis, critically revised the manuscript; Y. Zhou contributed to data acquisition; Z.-Y. Wu drafted the manuscript. S.-R Ma revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of the work.

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Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This retrospective study was approved by the Review Board of the Ethics Committee of the School and Hospital of Stomatology, Wuhan University (NO. 2023-B42). Written informed consent was not required for this study as it relied on retrospective data collection. All patients included in our investigation had previously received treatment at our department and had already consented to the use of their image data for research purposes by signing informed consent forms prior to treatment. This study was granted exemption from requiring additional informed consent by the Review Board of the Ethics Committee of the School and Hospital of Stomatology, Wuhan University, based on these grounds. The exemption from informed consent does not compromise the rights or health of the patients included in this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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