

ORIGINAL ARTICLE

Can radiomic features extracted from intra-oral radiographs predict physiological bone remodelling around dental implants? A hypothesis-generating study

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Abstract

Aim: The rate of physiological bone remodelling (PBR) occurring after implant placement has been associated with the later onset of progressive bone loss and peri-implantitis, leading to medium- and long-term implant therapy failure. It is still questionable, however, whether PBR is associated with specific bone characteristics. The aim of this study was to assess whether radiomic analysis could reveal not readily appreciable bone features useful for the prediction of PBR.

Materials and Methods: Radiomic features were extracted from the radiographs taken at implant placement (T0) using LifeX software. Because of the multi-centre design of the source study, ComBat harmonization was applied to the cohort. Different machine-learning models were trained on selected radiomic features to develop and internally validate algorithms capable of predicting high PBR. In addition, results of the algorithm were included in a multivariate analysis with other clinical variables (tissue thickness and depth of implant position) to test their independent correlation with PBR.

Results: Specific radiomic features extracted at T0 are associated with higher PBR around tissue-level implants after 3 months of unsubmerged healing (T1). In addition, taking advantage of machine-learning methods, a naive Bayes model was trained using radiomic features selected by fast correlation-based filter (FCBF), which showed the best performance in the prediction of PBR (AUC = 0.751, sensitivity = 66.0%, specificity = 68.4%, positive predictive value = 73.3%, negative predictive value = 60.5%). In addition, results of the whole model were included in a multivariate analysis with tissue thickness and depth of implant position, which were still found to be independently associated with PBR (p -value < .01).

Conclusion: The combination of radiomics and machine-learning methods seems to be a promising approach for the early prediction of PBR. Such an innovative approach could be also used for the study of not readily disclosed bone characteristics, thus helping to explain not fully understood clinical phenomena. Although promising, the performance of the radiomic model should be improved in terms of specificity and sensitivity by further studies in this field.

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KEYWORDS

artificial intelligence, dental implants, early marginal bone loss, physiological bone remodelling, radiomics

Clinical Relevance

Scientific rationale for study: After their insertion, some implants undergo marginal bone resorption, whose severity is supposed to be later associated with a higher rate of progressive bone loss. Although many factors seem to be associated with such an event, it is still unclear whether some bone features could influence its occurrence.

Principal findings: Coupling radiomics and machine-learning methods may help in finding some not readily appreciable bone features, not visible to human eye, associated with higher physiological bone remodelling (PBR).

Practical implications: Once confirmed, this method could help predict PBR and be used to plan maintenance schedule in high-risk patients.

1 | INTRODUCTION

Peri-implant marginal bone stability is regarded as a principal variable influencing the long-term success of implant therapy. Despite this, physiological remodelling of peri-implant crestal bone may occur within the first year of functional loading (Oh, Yoon, Misch, & Wang, 2002). Physiological bone remodelling (PBR), a complex process with multi-factorial aetiology, is determined by numerous surgical and restorative factors including insufficient crestal width (Chen, Darby, & Reynolds, 2007; Grunder, Gracis, & Capelli, 2005; Spray, Black, Morris, & Ochi, 2000), traumatic surgery (Albrektsson, Chrcanovic, Ostman, & Sennerby, 2017; Trisi, Berardini, Falco, Podaliri Vulpiani, & Perfetti, 2014), supracrestal tissue height establishment (Berglundh & Lindhe, 1996; Hermann, Buser, Schenk, Higginbottom, & Cochran, 2000), microbial colonization of the implant-abutment interface (Jansen, Conrads, & Richter, 1997; Piattelli et al., 2003), implant crest module characteristics (Oh et al., 2002), number of abutment connection/disconnections (Tallarico et al., 2018), height of prosthetic abutment (Galindo-Moreno et al., 2014; Spinato et al., 2020), mechanical stability of implant/abutment connection (Caricasulo, Malchiodi, Ghensi, Fantozzi, & Cucchi, 2018) and adaptive bone modifications to early occlusal loading (Oh et al., 2002).

Early exposure of treated implant surface may facilitate adhesion of microbial biofilm from the oral cavity, creating conditions for possible onset of peri-implant pathologies. In two recent prospective studies, Windael and co-workers demonstrated that PBR exceeding 0.5 mm significantly increases the medium-term risk of developing peri-implantitis, especially if a patient presents other associated risk factors such as smoking, history of periodontitis and low oral hygiene compliance (Windael, Collaert, De Buyser, De Bruyn, & Vervaeke, 2021; Windael et al., 2018).

It is still controversial whether bone quality at implant placement affects later onset of peri-implantitis and/or late implant failure (Chrcanovic, Albrektsson, & Wennerberg, 2017; Goiato, dos Santos, Santiago, Moreno, & Pellizzer, 2014). Pre-operative bone quality assessment in implantology has been mainly related to density and topography in radiographic images, with differences among different

sites and jaws (He, Zhao, Deng, Shang, & Zhang, 2015). The Lekholm and Zarb classification, which is essentially qualitative, is the most used tool for such assessment. It takes into consideration the cortical to cancellous bone ratio, ranking bone types into four classes (Oliveira et al., 2021).

Conversely, radiomics is quantitative in its approach to medical imaging, aiming to improve data available to clinicians through advanced mathematical analyses (Mayerhoefer et al., 2020). From extraction and analysis of “features” or “quantitative characteristics” from medical images, radiomics creates prediction models of sufficient accuracy to support clinical decisions (van Timmeren, Cester, Tanadini-Lang, Alkadhi, & Baessler, 2020). To develop a model based on radiomics, five different steps are usually needed:

1. Image acquisition:
Radiomic analysis can be performed on radiographic images of different types [CT, CBCT, positron emission tomography (PET), intra-oral radiographs].
2. Image segmentation:
For any radiomic approach, delineation of the region of interest (ROI) in two-dimensional (2D) or volume of interest (VOI) in three-dimensional (3D) approaches is fundamental.
3. Extraction of features:
Radiomic “features” consist of quantitative information extracted from medical images. Features capture characteristics of tissue and/or lesion (i.e., heterogeneity, shape) and may be used alone or in combination with demographic, histological, genomic or proteomic data, as an accurate predictive support to solve clinical problems.
4. Feature selection (or size reduction):
Depending on the software used for extraction of the features and the number of filters applied during this process, the number of extracted features that must be treated during subsequent phases of statistical analysis and machine learning can be considerable. Reducing the number of features to build statistical and machine-learning models during the feature selection phase (size reduction) is crucial to generate valid and meaningful results.

5. Model development:

The extracted features constitute a large database from which it is possible to derive predictive models of clinical outcomes using machine-learning techniques. Machine-learning algorithms use computational methods to “learn” information directly from data without relying on a predetermined equation. Algorithms adapt to improve their performance based on available data and contribute predictive models that support clinical decisions.

The aim of this study was to extract radiomic features from 2D intra-oral radiographs to develop machine-learning models capable of predicting PBR around dental implants.

2 | MATERIALS AND METHODS

2.1 | Patient selection

The selected patients belonged to a cohort of 49 persons included in a previous multi-centre prospective study investigating whether adaptation of apico-coronal implant positioning in relation to supracrestal tissue height influences PBR around tissue-level implants (Spinato, Bernardello, Lombardi, Soardi, Messina, Zaffe, & Stacchi 2022). Of these, 44 were judged to have radiographs adequate for radiomic analysis and were included in this study. Patients were partially edentulous and required placement of at least one single implant in pristine bone in the posterior mandible. In case of multiple implants, only the most mesial implant was evaluated, so each patient contributed to the study with only one implant.

The general criteria for inclusion were as follows: (1) age >18 years; (2) good general health; (3) absence of systemic diseases affecting bone metabolism and wound healing; (4) no regular medication for at least 3 months prior to treatment; (5) availability and ability to fully comply with the study protocol; (6) willingness to give written informed consent.

Local inclusion criteria were as follows: (1) presence of keratinized mucosa with a minimum bucco-lingual width of 3 mm; (2) bone crest with a minimum width of 6 mm and a height above the mandibular canal of 9 mm, without concomitant or previous augmentation procedures; (3) presence of the opposing dentition.

The exclusion criteria were as follows: (1) history of head or neck radiotherapy; (2) uncontrolled diabetes (HbA1c >7.5%); (3) active infections; (4) immunocompromised patients (HIV infection or chemotherapy within the past 5 years); (5) present or past treatment with intravenous bisphosphonates; (6) women who are pregnant or breastfeeding at any time during the study; (7) poor oral hygiene and patient motivation for home oral hygiene procedures (full-mouth plaque score >25%); (8) untreated periodontal disease; (9) psychological or psychiatric problems; (10) alcohol or drug abuse; (11) participation in other studies such that the present protocol could not be adequately followed; (12) peak insertion torque >60 Ncm.

All patients received oral hygiene instructions and professional de-plaques 1 week before surgery.

2.2 | Surgical and restorative procedures

All patients were treated according to the following protocol:

1. Local anaesthesia using 4% articaine with adrenaline 1:100,000;
2. Mid-crestal longitudinal incision with full-thickness buccal flap raise;
3. Soft tissue probe (SSL, Medesy, Maniago, Italy) used at the centre of future implant site to measure supracrestal tissue height of undetached lingual flap;
4. Full-thickness lingual flap raise exposing the alveolar ridge.

Implant sites were prepared to allow insertion of tissue-level implants with a 3-mm-high, machined, convergent transmucosal portion and external hex connection (i-Smart, i-Res, Lugano, Switzerland) at three different crestal levels. Based on supracrestal tissue height measured after buccal flap detachment, implants were placed: (1) with the moderately rough surface 2 mm below crestal level in presence of thin mucosa (≤ 2.5 mm); (2) with the moderately rough surface 1 mm below the crestal level in the presence of medium mucosa (2.5–3.5 mm); (3) with the moderately rough surface at crestal level in presence of thick mucosa (≥ 3.5 mm). Thanks to adequate ridge width, it was possible to insert all implants with a diameter of 3.75 mm and with variable length (8–10 mm) based on available bone height.

A one-stage protocol was used for all implants, and flaps were sutured around the transmucosal component. Patients were prescribed with antibiotic therapy (amoxicillin 1 g twice a day) for 6 days and non-steroidal anti-inflammatory therapy (ibuprofen 600 mg) if needed. Sutures were removed 12–14 days after surgery. Removable dentures were not used during the healing period, and a final impression was taken 5 months after implant placement. All implants included in the final analysis were clinically examined before proceeding with the prosthetic phase and found healthy according to the 2017 Consensus Report criteria (absence of erythema, bleeding on probing, swelling and suppuration) (Berglundh et al. 2018).

2.3 | Radiographic measurements

Phosphor-plate radiographs (VistaScan Mini, Dürr Dental, Bietigheim-Bissingen, Germany), customized for each patient with a poly(vinyl siloxane) jig, were taken using the long-cone technique with a Rinn-type film holder. Radiographs were taken at implant placement (baseline, T0) and after 3 months of healing (T1). All radiographs were taken using the same X-ray generator (FOCUS, KaVo, Biberach, Germany), set to the same parameters (60 kV, 7 mA).

Calculation of marginal bone loss was performed using a measuring software (Image J, National Institutes of Health, USA) (Schneider, Rasband, & Eliceiri, 2012). Peri-implant bone level was measured on each radiograph as the linear distance between the reference point (implant platform) and the most coronal radiographic bone-implant contact, corrected for the known height and diameter of each implant. The vertical distance between the most coronal point of the implant platform and

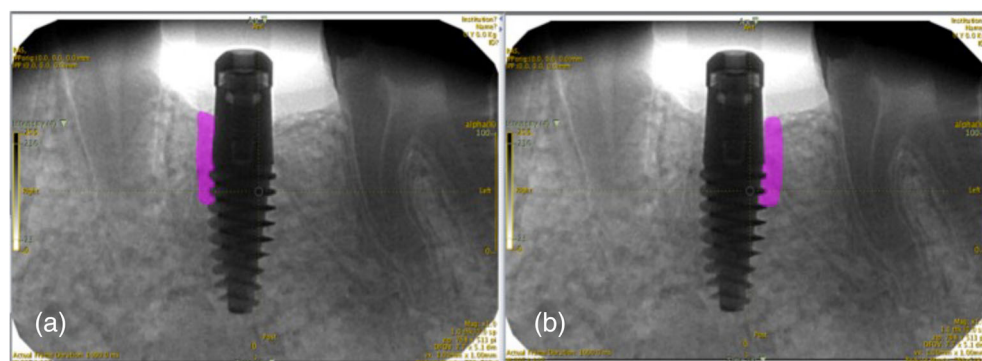


FIGURE 1 (a) Mesial and (b) distal manual delimitation of the region of interest (ROI) for subsequent radiomic analysis. The violet area close to the implant represents the ROI used for the calculation of the radiomic features.

the most coronal point of bone–implant contact was measured on both the mesial and distal aspect of the implant at T0 (implant placement) and T1 (3 months after implant placement).

Mesial and distal bone levels were assessed, and PBR was calculated as changes between T1 and T0, while radiomic analysis was performed on T0 radiographs. Therefore, a greater vertical distance between the implant platform reference point and the crestal bone (the most coronal bone–implant contact) was considered indicative of bone resorption, while a decrease in vertical distance was taken as indicative of bone gain. Two authors (FF and MZ) independently assessed PBR after completing training and calibration in a joint session with an expert author (CS). The rate of intra-class correlation coefficient (ICC) for their assessment was 0.948 (0.886–0.975).

2.4 | Feature extraction procedure

LIFEx (Nioche et al., 2018), the medical software that reads images (DICOM, Nifti, png, tiff, bmp, jpg) locally or over a network using a DICOM browser (for DICOM images only) and includes a powerful 3D reconstruction-based slice viewer, was used for radiomic analysis. LIFEx allows not only segmentation of radiographic images—and therefore has the ability to define ROIs (regions of interest) or VOIs (volumes of interest)—but also extraction of radiomic features from the identified ROIs. The goal of ROI and VOI is to calculate the distribution of image pixel values within the delineated structures of the tissue under examination. ROIs and VOIs can be imported from previously created files or designed and manipulated using LIFEx. Intra-oral radiographs were imported into Lifex by clicking on “Patient” and then “Disk DICOMDIR”. After loading the radiograph, an ROI was drawn, as 2D radiographs were analysed in the present study. Specifically, two ROIs (one mesial and one distal to the implant) were traced at T0 for each radiograph. The ROI was defined between the bone crest and the third thread of the implant extending 2.5 mm into peri-implant bone (Figure 1). A radiograph was considered suitable for the radiomic analysis if the peri-implant bone dimension was sufficient to draw two ROIs of adequate size (mesial/distal), with an additional 2 mm of bone (encircling the ROI) visible in the radiograph. Following the design of the ROI, calculation and extraction of radiomic features were carried out using the LifeX software (more details on the

TABLE 1 Demographics characteristics of patients included in this cohort.

Patient cohort	N = 44	
	n	%
Gender		
Male/Female	19/25	43.18/56.82
Smokers		
No/Yes	33/11	75/25
History of periodontitis		
No/Yes	31/13	70.45/29.55
Age	58.30 ± 12.27	

procedure are reported on Data S1). Radiomic features were extracted as values and saved automatically by the software in CSV format. After this process, 47 valid features were extracted and used for subsequent data analysis. At this stage, the extracted radiomic features are just numerical values that can be used as “biomarkers” for subsequent analysis. More information on what radiomic features are and how they are calculated can be found on focused articles (Avanzo et al., 2020; Mayerhoefer et al., 2020; Scapicchio et al., 2021).

2.5 | Statistical analysis and machine learning

After extracting the features from each mesial and distal ROI of the 44 selected patients, a single Excel file containing a total of 88 measurements was available. PBR values of each patient (T1 – T0) were associated with the extracted features. Two categories of PBR were classified: high (≥ 0.5 mm) or low (< 0.5 mm) (Windael et al. 2021). As the radiographs came from different centres and were taken with different instruments, the ComBat harmonization method was applied. This method harmonizes data coming from different radiographic instruments through machine-learning protocols. Data harmonization is achieved by the application of generative adversarial networks (GANs) (Li et al., 2021). In order to identify and analyse a potential correlation between individual radiomic features and PBR (categorized as high/low), binary logistic regression analysis was performed with

TABLE 2 Results of binary logistic regression analysis using categorized (High/Low) physiological bone remodelling as the dependent variable and single radiomic features as the independent variable.

Number of sites = 88 Radiomic feature	Univariate analysis		
	OR	95% CI	p-value
CONVENTIONAL_min,	1.06	[0.27–4.19]	.931
CONVENTIONAL_max	0.43	[0.09–2.21]	.316
CONVENTIONAL_Q1	0.41	[0.10–1.71]	.220
CONVENTIONAL_Q2	1.39	[0.51–4.36]	.463
CONVENTIONAL_Q3	0.98	[0.29–3.22]	.969
CONVENTIONAL_Skewness	1.16	[0.38–3.53]	.788
CONVENTIONAL_Kurtosis	0.96	[0.44–2.07]	.914
CONVENTIONAL_ExcessKurtosis	0.59	[0.12–2.88]	.519
DISCRETIZED_mean	0.42	[0.09–1.97]	.270
DISCRETIZED_std	2.06	[0.85–5.03]	.112
DISCRETIZED_Q1	0.89	[0.39–2.04]	.786
DISCRETIZED_Q2	1.24	[0.53–2.91]	.619
DISCRETIZED_Q3	0.96	[0.38–2.42]	.930
DISCRETIZED_Skewness	1.31	[0.43–3.96]	.633
DISCRETIZED_Kurtosis	0.78	[0.33–1.89]	.588
DISCRETIZED_ExcessKurtosis	0.74	[0.28–1.97]	.552
DISCRETIZED_HISTO_Entropy_log2	1.56	[0.76–3.17]	.222
DISCRETIZED_HISTO_EnergyUnifor	0.98	[0.37–2.58]	.971
DISCRETIZED_AUC_CSH	1.35	[0.62–2.94]	.451
PARAMS_BinSize	1.08	[0.49–2.39]	.847
GLCM_HomogeneityInverseDiffere	0.71	[0.28–1.80]	.478
GLCM_EnergyAngularSecondMoment	0.56	[0.28–1.72]	.315
GLCM_ContrastVariance	1.97	[0.84–4.59]	.116
GLCM_Correlation	0.43	[0.15–1.26]	.125
GLCM_Entropy_log10	0.33	[0.16–0.70]	.004*
GLCM_Entropy_log2JointEntropy	1.07	[0.43–2.64]	.880
GLCM_Dissimilarity	1.15	[0.51–2.60]	.725
GLRLM_SRE	1.88	[0.70–5.01]	.207
GLRLM_LRE	1.22	[0.49–3.04]	.667
GLRLM_LGRE	0.88	[0.34–2.25]	.786
GLRLM_HGRE	0.80	[0.36–1.77]	.588
GLRLM_SRLGE	1.30	[0.49–3.45]	.599
GLRLM_SRHGE	0.58	[0.22–1.54]	.273
GLRLM_LRLGE	0.75	[0.24–2.36]	.629
GLRLM_LRHGE	0.80	[0.32–2.00]	.635
GLRLM_GLNU	2.48	[0.88–7.00]	.086
GLRLM_RLNU	1.03	[0.45–2.34]	.945
GLRLM_RP	1.46	[0.55–3.85]	.443
NGLDM_Coarseness	2.94	[0.83–10.4]	.096
NGLDM_Busyness	2.67	[0.75–9.57]	.130
GLZLM_GLNU	5.37	[1.77–16.3]	.003*
GLZLM_SZE	1.99	[0.74–5.37]	.175
GLZLM_LZE	0.87	[0.32–2.34]	.777
GLZLM_LGZE	1.40	[0.64–3.08]	.403
GLZLM_HGZE	0.89	[0.82–1.49]	.512
GLZLM_SZLGE	0.75	[0.28–2.04]	.576
GLZLM_SZHGE	0.67	[0.29–1.54]	.354
GLZLM_LZLGE	1.24	[0.33–4.69]	.746

Note: *p-value < 0.05.

STATA 16.0 software (StataCorp, College Station, USA). Data were then loaded into the Orange software (<https://orangedatamining.com>) and machine-learning analyses were performed. First, data were normalized to a scale between -1 and $+1$. An unsupervised learning method using the whole database of radiomic features was used to find coherent groups of samples (clusters) and compare them with PBR classes (high/low). In particular, different distance metrics, including Euclidean, Manhattan, Pearson, cosine Spearman and Hamming, were applied, and the rate of separation between clusters was assessed using silhouette analysis. Next, ranking of the radiomic features was done by applying different ranking methods, including Infogain, gain ratio, Gini index, ANOVA, X2, ReliefF and fast correlation-based filter (FCBF). Various machine-learning models, including logistic regression, support vector machine, K-nearest neighbours (KNN), decision tree, random forest, artificial neural network, gradient boosting and naive Bayes, were then applied to the radiomic features selected by the FCBF. After applying internal leave-one-out cross-validation, these models made predictions by calculating the area under the receiver operating characteristic (ROC) curve, sensitivity and specificity. In addition, to adjust for possible clinical confounding factors and test for any independent association between radiomic features and PBR, predicted probabilities from the radiomic model were inserted into a multivariate logistic regression model with supracrestal tissue height and depth of implant placement. The performance of different models in AUC terms was further assessed by means of the De Long method (roccomp command on STATA).

3 | RESULTS

3.1 | Clinical cohort and PBR analysis

Intra-oral peri-apical radiographs taken at T0 and T1 in a cohort of 44 patients were used to assess PBR ($T1 - T0$) at both the mesial and distal aspect of 44 implants (one implant per patient) for a total of 88 sites. Radiomic analysis was performed at baseline (on T0 radiographs) at both the mesial and distal aspects independently. The average PBR in the included cohort was $0.48-0.49$ mm, and a threshold of 0.5 mm was fixed to categorize PBR into high PBR (≥ 0.5 mm) and low PBR (< 0.5 mm) for subsequent analysis. After applying this categorization, 50 sites ($50/88$, 56.82%) were considered as low PBR and 38 sites ($38/88$, 43.18%) as high PBR. Demographic data of the patients included in the cohort are reported in Table 1.

3.2 | Relationship between radiomic features and PBR

The possible correlation between radiomic features and PBR was analysed using a binary logistic regression model. Analysis results showed that specific radiomic features, extracted at baseline (T0 radiograph), were associated with either high or low PBR at T1. In particular, high $gclm_entropy_log10$ (OR: $0.33-95\%$ CI [$0.16-0.70$], $p = .004$) and $glzlm_glnu$ (OR: $5.37-95\%$ CI [$1.77-16.33$], $p = .003$) were associated

with PBR. Other radiomic features with marginally significant p -values were $ngldm_coarseness$ (OR: $2.94-95\%$ CI [$0.83-10.4$], $p = .096$) and $glrlm_glnu$ (OR: $2.48-95\%$ CI [$0.88-7.00$], $p = .086$). Detailed univariate logistic regression analysis results for all radiomic features are reported in Table 2. It is worth noting that the possible influence of PBR categorization (based on the 0.5 -mm threshold) on the present findings was assessed using univariate linear regression models with uncategorized PBR as the dependent variable. Uncategorized PBR was significantly associated with high $gclm_entropy_log10$ ($p = .002$) and $glzlm_glnu$ ($p = .001$).

3.3 | Unsupervised and supervised machine learning

An unsupervised approach was applied by calculating different distances to assess similarity in radiomic measurements to group-similar data objects. Cluster grouping was then evaluated by calculating a

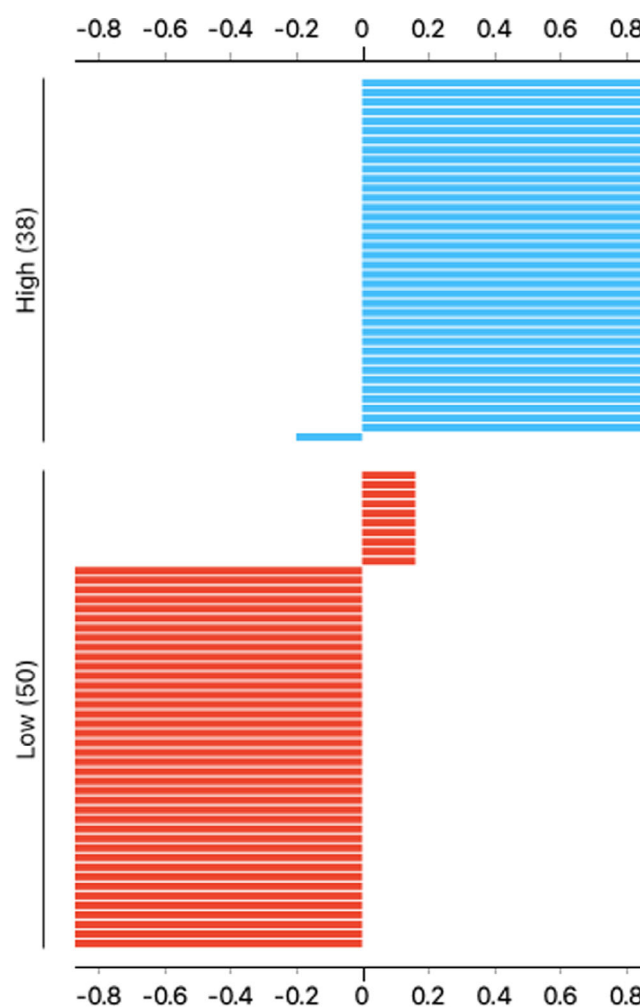


FIGURE 2 Silhouette plot after applying cosine distance as a metric of similarity/dissimilarity based on individual radiomic features to different implants in the cohort. The silhouette plot is a graphical representation of consistency within clusters of data. The silhouette score is a measure of how similar an object is to its own cluster in comparison to other clusters.

TABLE 3 Performance metrics after leave-one-out interval validation for different machine-learning models trained using radiomic features after applying fast correlation-based filter for feature selection.

MODEL	AUC	95% CI	Sensitivity	Specificity	PPV	NPV
Naive Bayes	0.751	0.647–0.854	66.0%	68.4%	73.3%	60.5%
Random forest	0.691	0.578–0.804	70.0%	55.3%	67.3%	58.3%
Gradient boosting	0.646	0.527–0.765	60.0%	57.9%	56.6%	41.7%
Logistic regression	0.646	0.525–0.767	46.1%	71.1%	67.6%	50.0%
K-NN	0.639	0.515–0.763	62.0%	65.8%	70.5%	56.8%
Tree	0.567	0.316–0.550	66.0%	44.7%	61.1%	50.0%
SVM	0.368	0.244–0.491	68.0%	27.3%	54.8%	38.5%
CN2 rule inducer	0.274	0.155–0.393	86.0%	13.3%	56.6%	41.6%

Abbreviations: 95% CI, 95% confidence interval; AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value.

TABLE 4 Multivariate logistic regression analysis with physiological bone remodelling as dependent variable and different clinical variables.

Variables	Multivariate logistic regression analysis		
	OR	95% CI	p-value
Radiomic algorithm	0.15	[0.05–0.40]	.001*
Depth of implant placement	2.00	[0.92–4.34]	.079
Tissue thickness	0.25	[0.62–2.53]	.529

Note: *p-value < 0.05.

Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio.

silhouette score, which measures how similar an object is to its own cluster compared to other clusters. Interesting results appeared with the application of the cosine distance, which revealed high similarity between radiomic features belonging to the high PBR group and, on the contrary, a high dissimilarity between radiomic features belonging to the low PBR group (Figure 2). Cosine similarity is a measure of similarity between two sequences of numbers and can be used to cluster similar data. This result suggests the presence of similar radiomic bone features at baseline in sites that undergo greater marginal bone resorption during the first 3 months of healing (T1). FCBF is a multivariate feature selection method and entropy-based measurement, which also identifies redundancy caused by pair-wise correlations between features where class relevance and dependency between each feature pair are analysed. The algorithm with the best performance was a naive Bayes model followed by either a random forest or a gradient boosting model. The naive Bayes model performed best overall with anAUC = 0.751 (95% CI: [0.647–0.854]), while the random forest model had an AUC = 0.691 (95% CI: [0.578–0.804]). These two models outperformed the logistic regression model, which had an AUC = 0.646 (95% CI: [0.525–0.765]), while gradient boosting showed similar results. In addition, the naive Bayes model had the best specificity value (68.4%), while the gradient random forest was the best in terms of sensitivity (70.0%). Performance details of the trained and internally validated models are reported in Table 3. In addition, although beyond the scope of this study, in 95.45% of patients (42/44) mesial and distal sites of the same implant were

clustered together, supporting the reliability of the results and suggesting that patient-/site-specific bone features could be a reflection of the underlying molecular and genetic characteristics. Finally, to assess whether the association between the radiomic model and PBR was present independently of clinical confounding factors, predicted probabilities of the model were inserted in a multivariate logistic regression model with other clinical variables (supracrestal tissue height and apico-coronal depth of implant positioning). As reported on Table 4, the radiomic model turned out to be independently associated with PBR (OR = 0.15, 95% CI: [0.05–0.40], $p < .001$).

4 | DISCUSSION

The aim of this preliminary study was to develop machine-learning models capable of predicting PBR around dental implants based on radiomic features extracted from 2D intra-oral radiographs. The findings of the present study showed that specific radiomic features are associated with higher PBR around tissue-level implants after 3 months of unsubmerged healing. GLCM_Entropy_log10 and GLZLM_GLNU were significantly associated with a high PBR. The first feature considers the grey level randomness of pairs of voxels, while the second one estimates how much grey values in aggregates of adjacent pixels with the same grey level are present. Interestingly, these features have already been associated with clinical outcomes in the field of oncology (Toyama et al., 2020; Wu, Liu, Liao, Tang, & Wu, 2021). In addition, taking advantage of machine-learning methods, a naive Bayes model was built that is capable of predicting PBR in approximately 75% of cases. A feature-based radiomic pipeline was used in this study; hence, radiomic features were calculated by the Lifex software and machine-learning algorithms were posteriorly applied on the calculated values. This represents a “classical” radiomic pipeline, which differs from the non-feature-engineered radiomic methods, also called “deep radiomics”. Advantages and disadvantages are present in both methods, and future studies should explore also the potential of non-feature-engineered pipelines in the field of implantology (Avanzo et al., 2020; Wang et al., 2021).

Thanks to advances in digitalization in medicine, more and more information is available for clinical and scientific purposes. This information is stored in different ways and provides great analysis possibilities

including the identification of natural patterns previously impossible to demonstrate, leading to the dawn of the current era of “big data”. This great amount of information is multi-dimensional, and the analysis is complex requiring specific analytical skills. Data can also be extracted from medical images by translating specific “colorimetric” characteristics into numbers (van Timmeren et al., 2020). Radiomics assumes that biomedical images contain much more information than the human eye and mind can register, some of which is disease-specific (Lambin et al., 2017). In radiomics, spatial distribution of signal intensities and pixel inter-relationships may be extracted by applying mathematical algorithms generating different radiomic features (Castellano, Bonilha, Li, & Cendes, 2004). Radiomics has been studied mainly in oncology, with positive outcomes in early detection and monitoring of several cancer types (Liu et al., 2019). In the present study, a radiomic approach was applied to the field of implantology to assess whether such techniques, applied to 2D images, is useful to predict the PBR around dental implants. The multi-factorial aetiology of PBR has not yet been fully clarified. In particular, the influence of intrinsic bone characteristics on PBR onset has not been clearly demonstrated (Ibanez et al., 2016), even though previous studies have underlined the importance of bone characteristics in terms of both biological response to surgical trauma and distribution of loading forces (Cehreli, Akkocoglu, Comert, Tekdemir, & Akca, 2007; Ingiam, Suebnukarn, Tharanon, Apatananon, & Sithiseripratip, 2010). Cortical bone has a lower repair response than cancellous bone, which is more vascularized and has greater cellularity with a larger number of undifferentiated repair cells. Simons and co-workers found a correlation between PBR and the quantity of cortical bone at the implant site, and Ibañez and colleagues found significantly lower mean PBR around implants placed in type IV bone than in sites with higher bone density (Ibanez et al., 2016; Simons, De Smit, Duyck, Coucke, & Quirynen, 2015). Radiomics can help the clinician to perform more accurate and in-depth analysis of the radiographic characteristics at programmed implant sites and to provide pre-operative predictions of possible critical issues.

The clinical value of this new predictive tool is even more important as PBR is associated with late biological complications. In the present study, we categorized high or low PBR using a threshold of 0.5 mm, since two recent studies supported the importance of this value as the threshold of worsening and the onset of complications in the future (Galindo-Moreno et al., 2022; Windael et al., 2021). Authors of these studies have stated that implants with increased PBR rates have a higher probability to undergo a subsequent marginal bone loss, thus compromising their medium- and long-term success. (Galindo-Moreno et al., 2022; Galindo-Moreno et al., 2015; Windael et al., 2021).

To understand the influence of radiographic characteristics on PBR, the radiographs analysed in the present investigation were taken from a cohort of patients included in a prospective study in which other possible confounding factors for PBR were carefully controlled (Spinato et al., 2022). Anatomical and surgical variables with a possible impact on PBR were considered and managed in the study protocol, which dictated a minimum of 6 mm crestal bone width and 3 mm keratinized tissue width at the implant insertion site (Chen et al., 2007; Grunder et al., 2005; Spray et al., 2000). Implant site preparation was performed

under abundant irrigation to avoid bone overheating (Trisi et al., 2014). A maximum peak insertion torque of 60 Ncm was prescribed to prevent excessive compression of the cortical bone (Albrektsson et al., 2017), and tissue-level implants were used to exclude negative effects of the implant-abutment microgap (Jansen et al., 1997; Piattelli et al., 2003). In addition, radiographic evaluation was performed prior to the impression phase to also eliminate the influence of prosthesis-related variables on PBR, including abutment connection/disconnections (Tallarico et al., 2018), prosthetic abutment height (Blanco et al., 2018; Galindo-Moreno et al., 2014; Spinato et al., 2020; Spinato et al., 2019), implant/abutment connection mechanical stability (Caricasulo et al., 2018) and adaptive bone modifications to early occlusal loading (Oh et al., 2002).

However, the present study has some limitations which should be carefully considered before the interpretation and generalization of the results. The choice of 3-month follow-up was done to investigate only the influence of surgery-related factors on PBR around tissue-level implants. At 3 months, bone response to these factors is considered complete (Tomasi et al. 2014). Prosthesis-related factors were deliberately excluded from the present analysis in order to limit the confounding factors, but they will subsequently further affect PBR. Risks of confounding come from the implant positioning at different depths and from the different supracrestal tissue height in the included sample. PBR was measured on 2D radiographs, with no information about possible buccal and/or lingual peri-implant bone changes.

Moreover, the present study has limited external validity, as the data came from patients with specific requisites, expressed in inclusion/exclusion criteria, and from specific sites (posterior mandible). It is known that medical predictive models based on machine learning tend to have the worst performance on new data than on the original cohort, frequently due to covariate shifts or overfitting (Vabalas et al., 2019). Therefore, to draw conclusions about the preliminary findings revealed by this study, external validation on new cohorts is mandatory. Not only should be model validity tested on new cases coming from different clinical settings, but the soundness of external validation should also be assessed with appropriate statistical tools (i.e., meta-validation methods) (Cabitza et al., 2021).

Radiomics, which brings to light not readily appreciable peri-implant bone characteristics, could also help clinicians and researchers with a pre-operative qualitative evaluation of the bone substratum. From a clinical standpoint, it would be interesting to understand whether radiomic features extracted before implant placement can predict future PBR and therefore guide clinical choices. However, the present study correlated, for the first time, specific radiomic features extracted just after implant placement with PBR. In addition, a machine-learning-trained, radiomic-feature-based model was able to predict at baseline an implant site's susceptibility to developing high PBR in approximately 75% of cases. However, before this approach is adopted in clinical practice, external validation on new case cohorts is mandatory.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

This study was approved by the relevant Ethical Committee (Regione Calabria, Sezione Area Centro, Nr. 370/2020).

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SUPPORTING INFORMATION

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