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An advanced prediction model for postoperative complications and early implant failure

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Abstract

Objectives: Risk prediction in implant dentistry presents specific challenges including the dependence of observations from patients with multiple implants and rare outcome events. The aim of this study was to use advanced statistical methods based on penalized regression to assess risk factors in implant dentistry.

Material and methods: We conducted a retrospective study from January 2016 to November 2018 recording postoperative complications including bleeding, hematoma, local infection, and nerve damage, as well as early implant failure. We further assessed patient- and implant-related risk factors including smoking and diabetes, as well as treatment parameters including types of gaps and surgical procedures. Univariable and multivariable generalized estimating equation (GEE) models were estimated to assess predictor effects, and a prediction model was fitted using L1 penalized estimation (lasso).

Results: In a total of 1,132 patients (mean age: 50.6 ± 16.5 years, 55.4% female) and 2,413 implants, postoperative complications occurred in 71 patients. Sixteen implants were lost prior to loading. Multivariable GEE models showed a higher risk of any complication for diabetes mellitus ($p = .006$) and bone augmentation ($p = .039$). The models further revealed a higher risk of local infection for bone augmentation ($p = .003$), and a higher risk of hematoma formation for diabetes mellitus ($p = .007$) and edentulous jaws ($p = .024$). The lasso model did not select any risk factors into the prediction model.

Conclusions: Using novel methodology well-suited to tackle the specific challenges of risk prediction in implant dentistry, we were able to reliably estimate associations of risk factors with outcomes.

KEYWORDS

dental implants, dentistry, failure, postoperative complications, prediction model, risk factors

1 | INTRODUCTION

Risk factors such as smoking and diabetes are often associated with postoperative complications ranging from local infection to severe neurological symptoms as well as implant failure (Heitz-Mayfield & Huynh-Ba, 2009; Ramanauskaite, Becker, Sader, & Schwarz, 2019; van Steenberghe, Jacobs, Desnyder, Maffei, & Quirynen, 2002). Hence, risk factors often serve as criteria for patient selection (Alani, Bishop, Renton, & Djemal, 2014). Prediction models are used to evaluate risk factors and assist clinical decision making (Moons, Altman, Vergouwe, & Royston, 2009). Training datasets used to build prediction models usually contain few events compared with the number of possible predictors. This low events-per-variable (EPV) ratio is particularly true in implant dentistry, where the events of interest (e.g., implant failure, peri-implantitis) are rare (Moraschini, Poubel, Ferreira, & Barboza, 2015).

Various statistical methods can be used for risk factor assessment; dental implant research predominantly uses logistic regression models with stepwise selection of risk factors (Brügger et al., 2015; Chrcanovic, Kisch, Albrektsson, & Wennerberg, 2017; Neves, de Araújo Nobre, Oliveira, Martins Dos Santos, & Malo, 2018). However, stepwise methods need to be adapted to dependent outcome data in cohorts where patients have varying numbers of implants. Moreover, stepwise methods often underperform in low-EPV patient cohorts (Steyerberg, Eijkemans, Harrell, & Habbema, 2000). Stepwise methods may not only take the underlying clinical associations between outcomes and predictors into account, but also random variations present in the training dataset (Pavlou et al., 2015). As a consequence, models fitted by stepwise methods may underestimate the probability of an event in low risk patients and overestimate it in high risk patients (Steyerberg et al., 2010). Further, in more complex models accounting for several implants per patients, stepwise procedures may be restricted to a limited number of possible predictors (Groll & Tutz, 2014); if a larger number of possible risk factors is to be assessed, multiple risk factors have to be eliminated a priori from the analysis. Overall, these biases result in compromised models with possible negative consequences for clinical decision making.

Model overfitting can be reduced by shrinking regression coefficients where usually the estimated amount of overfitting determines the shrinkage factor (Pavlou, Ambler, Seaman, De Iorio, & Omar, 2016). It is preferable to include shrinkage in the model estimation process using penalized regression (Harrell Jr, 2015). Models based on penalized regression include L1 penalized estimation (least absolute shrinkage and selection operator, lasso), L2 penalized estimation (ridge), and the Firth penalization (Firth, 1993), which is often preferred as the amount of penalization does not have to be estimated from sparse data (Van Calster, van Smeden, De Cock, & Steyerberg, 2020). The mathematics behind these methods are similar. Lasso is further capable of variable selection by shrinking coefficients of superfluous variables to exactly zero; this makes the interpretation of results easier. Penalized regression models are more accurate than stepwise models (Kim, Kim, Jeong, Jeong, & Kim, 2018) and perform particularly better in low-EPV cohorts (Ambler, Seaman, & Omar, 2012). Thus, penalized regression models are recommended for EPV < 20 (Steyerberg et al., 2000). Lasso and ridge perform comparably well in low-noise datasets; lasso is recommended over ridge in environments with many noise predictors (Pavlou et al., 2016). Both methods enable the evaluation of an endless number of predictors. The Firth penalization has the additional advantage that it can handle situations of extreme sparsity, where events do not occur in some of the levels of some risk factors (Heinze & Schemper, 2002; Mansournia, Geroldinger, Greenland, & Heinze, 2018; Puhr, Heinze, Nold, Lusa, & Geroldinger, 2017).

Penalized regression is increasingly used in other medical fields, including in prediction models for severe sepsis (Kaukonen, Bailey, & Bellomo, 2015), lung-cancer death (Kovalchik et al., 2013), and the use of functional magnetic resonance imaging to predict physical pain (Wager et al., 2013). These advanced statistical models are not yet routine in dental implant research. Our aim was to develop a prediction model of postoperative complications and early implant failure based on penalized regression to assess risk factors in implant dentistry; we further aimed to concisely describe the association of risk factors with postoperative complications and early implant failures.

2 | MATERIAL AND METHODS

2.1 | Study design

We conducted a retrospective study from January 1, 2016, to November 30, 2018, using data from the electronic patient records of the Medical University of Vienna, University Clinic of Dentistry. The study was approved by the ethics committee of the Medical University of Vienna (No. 2234/2018). Data were extracted by one researcher (FK) and subsequently error-proofed by two researchers (BF, UK) in an independent manner. Only complete data were used in this study.

2.2 | Outcome parameters

Postoperative complications (bleeding/suppuration, swelling, local infection, hematoma, neurosensory disturbance) and early implant failure (i.e., before loading (Esposito, Hirsch, Lekholm, & Thomsen, 1998)) were assessed and designated as primary end points. Patient parameters comprised age, sex, smoking status, systemic conditions (e.g., diabetes mellitus, osteoporosis, osteoarthritis), implant location, and type of gap (single-tooth gap, extended gap, distal extension, edentulous jaw). The following implant parameters were considered: length, diameter, type (bone level, tissue level), material, bone augmentation (guided bone regeneration or sinus floor elevation), timing of implant placement [immediate, early, or late (Hämmerle, Chen, & Wilson, 2004)], use of flapless technique, and use of computer-aided navigation.

2.3 | Statistical analysis

We used a lasso model to develop a prediction model for the combined outcome of any assessed event (early implant failure or postoperative complications) (Groll & Tutz, 2014). We parametrized categorical variables such that the lasso could collapse categories for which similar predictions would result (i.e., fused lasso). The penalty strength was tuned using 10-fold cross-validation. To accommodate dependencies in the data (several implants per patient) when optimizing the penalty strength, we divided the cohort into ten "folds" such that all implants of a patient were assigned to the same fold. The cross-validated deviance criterion was further used to set the penalty parameter. As the lasso model can suffer from problems related to the non-occurrence of events in some levels of a risk factor (Mansournia et al., 2018), we also fitted multivariable logistic regression models with the Firth correction. To accommodate dependent outcomes from patients with multiple implants, we computed *p*-values and confidence intervals (CI) for odds ratios (OR) using generalized estimating equations (GEEs), which took as input the augmented data representation of the Firth-corrected model (Puhr et al., 2017). Moreover, with the GEE and the Firth penalty, we also performed backward elimination of risk factor effects at a *p*-value criterion of .157 (equivalent to selection by Akaike's information criterion) to obtain a more concise description of risk factor-outcome associations (Heinze, Wallisch, & Dunkler, 2018). According to recommendations, these associations were described by *p*-values from the multivariable model with all risk factors included, and OR and associated 95% CI from the model obtained after selection (Heinze et al., 2018). GEE with Firth penalization were also used to estimate the bivariate, unadjusted association of each risk factor with event types. All computations were performed by two researchers (SL, GH) using R version 3.6.1 (R Foundation for Statistical Computing).

TABLE 1 Subject characteristics

	Patients, *n* (%)	Implants, *n* (%)
Patient parameters		
Female	627 (55.4)	1,328 (55.0)
Male	505 (44.6)	1,085 (45.0)
Non-smoker	910 (80.4)	1,912 (79.2)
Light smoker[a]	157 (13.9)	336 (13.9)
Heavy smoker[b]	60 (5.3)	155 (6.4)
DM	33 (2.9)	110 (4.6)
Osteoporosis	31 (2.7)	72 (3.0)
Arthrosis	11 (1.0)	28 (1.2)
Arthritis	9 (0.8)	23 (1.0)
Osteopenia	8 (0.7)	14 (0.6)
Crohn's disease	3 (0.3)	6 (0.2)
COPD	3 (0.3)	11 (0.5)
Implant parameters		
Single implant		1,028 (42.6)
Extended edentulous gap		379 (15.7)
Distal extension		469 (19.4)
Edentulous jaw		537 (22.3)
Immediate placement		105 (4.3)
Early placement		434 (18.0)
Late placement		1,879 (77.7)
Anterior maxilla		314 (13.0)
Posterior maxilla		881 (36.5)
Anterior mandible		256 (10.6)
Posterior mandible		962 (39.9)
Bone augmentation		732 (30.4)

Abbreviations: COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus.

[a] <10 cigarettes/day.

[b] ≥10 cigarettes/day.

3 | RESULTS

3.1 | Subject characteristics

The sample included 1,132 patients (mean age 50.6 ± 16.5 years, 55.4% female, 19.3% smokers) and 2,413 dental implants. The number of implants per patient ranged from one ($n = 525$) to 10 ($n = 5$) with an average of 2.1 implants per patient. Implants 11.5 mm long and 4.3 mm wide were the most common (19.6%). No implants shorter than 8 mm were used, and 86.4% of all implants were between 3.5 and 4.5 mm in diameter. Most of the implants (90.5%) were made of commercially pure titanium. A total of 1,655 implants (68.6%) were placed using a standard surgical procedure without any type of bone augmentation (see Table 1 and Table S1).

3.2 | Postoperative complications and early implant failures

Postoperative complications occurred in 71 patients (6.3%). Local infections were observed in 49 implants (2.0%), making them the most frequent complication. Prolonged swelling was found in 18 patients (1.6%). Neurosensory disturbances were observed in 10 patients (0.9%) that received 13 implants in total, 12 of which were placed in the posterior mandible. All of the observed nerve disturbances were of a temporary nature. Peri-implant bone loss occurred in 10 implants (0.4%). A total of 16 implants (0.7%) were lost before loading (see Table 2 and Table S2).

3.3 | Lasso model

The lasso model did not select any risk factors into the prediction model. Thus, in our patient cohort, the lasso indicated that none of the evaluated risk factors were able to predict an increased or decreased risk for any of the assessed complications or for early

implant failure. Further, at cross-validation, the lasso model did not exhibit sufficient predictive performance (area under the receiver operating characteristic curve = 0.52). The full network graphs of evaluated predictors and complications are shown in Figure 1a–b.

3.4 | Multivariable GEE regression models

Applying Firth's penalization via data augmentation to GEEs, we were able to fit multivariable models to describe the associations of risk factors with any complications (108 events), local infections (49 events), and hematoma formations (37 events). Results are reported as OR with their corresponding 95% CI. Based on the any complications model, bone augmentation (OR = 1.74, 95% CI: 1.04–2.90, $p = .039$) and diabetes mellitus (OR = 4.16, 95% CI: 1.56–11.08, $p = .006$) were associated with a higher risk of a postoperative complication. Bone augmentation was associated with a higher risk of a local infection (OR = 2.67, 95% CI: 1.42–5.04, $p = .003$). Diabetes mellitus (OR = 7.58, 95% CI: 1.61–35.71, $p = .007$) and implants placed in edentulous jaws (OR = 4.92, 95% CI: 1.30 to 18.63, reference: single implant, $p = .024$) were associated with a higher risk of hematoma formation (see Table 3).

TABLE 2 Postoperative complications and early implant failures

Complication	Implants, *n* (%)
Any complication	108 (4.5)
Local infection	49 (2.0)
Hematoma	37 (1.5)
Early implant failure	16 (0.7)
Nerve damage	13 (0.5)
Peri-implant bone loss	10 (0.4)
Bleeding	6 (0.2)

3.5 | Bivariate associations

We were able to fit bivariate models for early implant failure, local infections, and hematoma formation. Results are reported as percentages of affected implants. Associations with early implant failure were identified for the timing of implant placement (immediate: 1.0%, early: 1.8%, late: 0.4%, $p = .006$). Associations for local infection were identified for bone augmentation (yes: 3.1%, no: 1.6%, $p = .043$). Associations for hematoma formation were identified for the indication for implant placement (single implant: 0.4%, extended edentulous gap: 1.1%, distal extension: 0.2%, edentulous jaw: 5.2%,, $p < .001$), for the region of implant placement (anterior maxilla: 1.3%, posterior maxilla: 0.7%, anterior mandible: 5.9%, posterior mandible: 1.3%, $p < .0001$), for bone augmentation (yes: 0.6%, no: 2.0%, $p = .048$), and for diabetes mellitus (yes: 10.9%, no: 1.1%, $p = .001$; see Table S3).

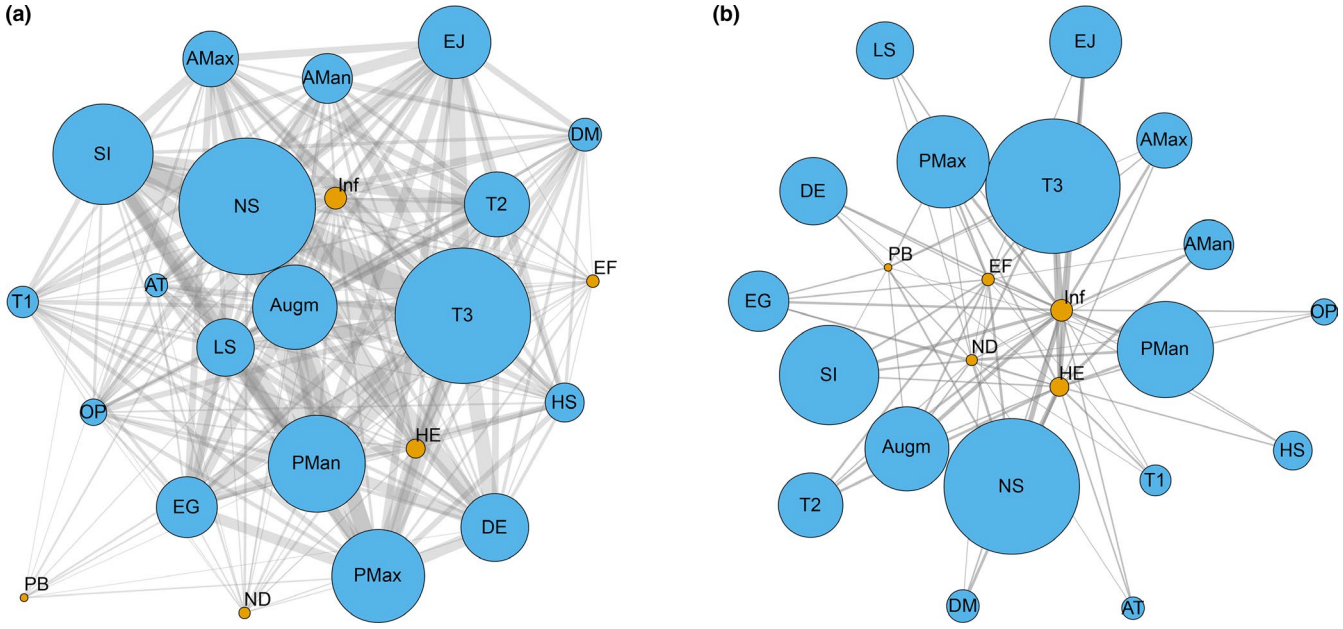

FIGURE 1 (a–b) Network graphs. (a) The complete network graph shows all interconnections (gray edges) between the evaluated risk factors (blue nodes) and postoperative complications (yellow nodes). (b) A reduced version of the network graph shows interconnections only to and from complications, but not interconnections between risk factors. In both graphs, the thickness of the edges indicates the number of interconnections between nodes. AMan, anterior mandible; AMax, anterior maxilla; AT, antiresorptive therapy; Augm, bone augmentation; DE, distal extension; DM, diabetes mellitus; EF, early implant failure; EG, extended gap; EJ, empty jaw; HE, hematoma; HS, heavy smoker (≥ 10/d); IN, local infection; LS, light smoker (< 10/day); ND, nerve damage; NS, non-smoker; OP, osteoporosis; PB, postoperative bleeding; PMan, posterior mandible; PMax, posterior maxilla; SI, single implant; T1, immediate implant placement; T2, early implant placement; T3, late implant placement.

TABLE 3 Results from multivariable GEE logistic regression models

	Local infection		Hematoma formation		Any complication	
Predictor	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**
Indication for implant placement	.8144		.0240		.2695	
Single implant		1 (ref.)		1 (ref.)		1 (ref.)
Extended edentulous gap		1 (n.s.)		1 (n.s.)		1 (n.s.)
Distal extension		1 (n.s.)		1 (n.s.)		1 (n.s.)
Edentulous jaw		1 (n.s.)		4.92 (1.3, 18.63)		1 (n.s.)
Region of implant placement	.1427		.4240			
Anterior maxilla		1 (ref.)		1 (ref.)	.3035	1 (ref.)
Posterior maxilla		0.53 (0.25, 1.11)		1 (n.s.)		0.58 (0.35, 0.97)
Anterior mandible		2.03 (0.87, 4.74)		1 (n.s.)		1 (n.s.)
Posterior mandible		1 (n.s.)		1 (n.s.)		1 (n.s.)
Timing of implant placement	.8446		.0705		.1300	
Immediate		1 (n.s.)		11.82 (2.1, 66.51)		2.41 (0.78, 7.5)
Early		1 (n.s.)		3.09 (0.78, 12.26)		1 (n.s.)
Late (reference)		1 (ref.)		1 (ref.)		1 (ref.)
Smoking	.3325		.4269		.3952	
Non-smoker (reference)		1 (ref.)		1 (ref.)		1 (ref.)
Light or heavy smoker		1 (n.s.)		1 (n.s.)		1 (n.s.)
Bone augmentation	.0026		.6720		.0387	
No		1 (ref.)		1 (ref.)		1 (ref.)
Yes		2.67 (1.42, 5.04)		1 (n.s.)		1.74 (1.04, 2.9)
Diabetes mellitus	.4801		.0072		.0064	
No		1 (ref.)				1 (ref.)
Yes		1 (n.s.)		7.58 (1.61, 35.71)		4.16 (1.56, 11.08)
Antiresorptive therapy	.0614		.1529		.4392	
No		1 (ref.)				1 (ref.)
Yes		1 (n.s.)		5.72 (0.6, 54.62)		1 (n.s.)
Osteoporosis	.6175		.3078		.8390	
No		1 (ref.)		1 (ref.)		1 (ref.)
Yes		1 (n.s.)		1 (n.s.)		1 (n.s.)
Age	.3157		.0554		.1617	
Per year		1 (n.s.)		1.06 (1, 1.12)		1.02 (1, 1.04)

Abbreviations: CI, confidence interval, n.s., not selected in backward elimination; OR, odds ratio; ref., reference level.

4 | DISCUSSION

We studied risk factors for postoperative complications and early implant loss and found that using GEEs with penalized estimation using Firth's correction, several predictors were associated with local infections, hematoma formation, or any complication. This demonstrated the need for advanced methods to deal with problems typical for studies in implant dentistry: rare outcome events and dependent outcomes from patients with multiple implants. Conventional multivariable logistic regression cannot deal satisfactorily with either of the problems, and even less if they collide as in our study. We also adapted lasso regression to the situation of dependent outcomes by randomly grouping patients, not implants, into ten folds when performing cross-validation to determine the lasso tuning parameter and testing the model. However, lasso regression could not identify a prediction model that would be of any use to prognosticate outcome events. Traditionally, researchers have often used univariable regression models to identify correlations between possible predictors and complications and have used the such identified risk factors as independent variables in a multivariable model, which has then been undergone further forward or backward selection. Such conventional stepwise regression methods present multiple issues that are particularly relevant in implant dentistry. Applying simple stepwise regression in a mechanical way

on univariate models ignores if multiple implants are placed in the same patient. This is important since patient-related factors such as smoking can affect every implant in a single patient, while implant-related factors such as implant position possibly only affect a single implant. Moreover, the problem of separation, which is common when studying rare outcomes or risk factors with some infrequent levels, leads to invalid inference of predictor effects and can thus severely affect the results of stepwise regression.

To avoid these biases, we used logistic models based on GEE, as these models are suitable for our dataset where patients have up to 10 implants. These models are further able to build a model without eliminating any risk factors prior to the analysis. To deal with sparse data, we implemented the Firth penalization into GEE, which unlike conventional approaches is robust to the problem of separation. Despite these advances, a multivariable model including all risk factors that were considered a priori may be not well suited for a concise description which predictors are relevant to predict a particular outcome. On the other hand, it has been repeatedly argued that any inference from stepwise selection is hampered by overestimation bias in the predictor-outcome associations and associated *p*-values that are biased low. To also solve these latter problems, we followed recent recommendations on conducting analyses with variable selection. We first evaluated these associations in the multivariable model without any selection and reported the *p*-values appropriately estimated by GEE with Firth's penalization. Further, we performed backward elimination of predictors that do not meet a *p*-value criterion of .157 and reported the resulting OR with the associated 95% CI. In this backward elimination scheme, we always applied the Firth penalty which was computed for the starting model such that overestimation bias by focusing on the apparently "significant" effects was avoided. In order to increase model stability, the Firth penalization provides a fair amount of shrinkage of OR toward parity (i.e., shrinkage of predicted probabilities toward 0.5) such that some of the corresponding effects were not selected after backward elimination. This explains why many OR are estimated as 1. According to recently published recommendations, we obtained *p*-values for all effects from the global (starting) models to avoid problems of invalid inference after model selection. The *p*-value criterion of .157 corresponds to selection by the Akaike information criterion and hence selects a model that is suitable for predictions. However, the rareness of outcome events did not allow to put aside a test cohort in which the models could be evaluated, and we must leave this task to future work.

We also ran conventional univariable GEE models for comparison. In our patient cohort, the lasso did not identify any correlations between possible risk factors and complications. In contrast, conventional models showed several correlations, most notably between the timing of implant placement and early implant failure. We consider these correlations identified by univariable regression models unreliable based on (i) the biases we mentioned before, (ii) the exceedingly large confidence intervals for some of the identified predictors, as well as (iii) the fact that none of the identified correlations could be confirmed using lasso. These stringent caveats prevent any meaningful prediction based on univariable regression models. The results from univariable models are also dissimilar to results from a comparable dataset of 1,568 patients (Brügger et al., 2015). Individual patient-specific characteristics might have played a role in the development of postoperative complications and early implant failure in our cohort. At this point, the occurrence of these events cannot be distinguished from bad luck for the individual patients. Risk factors thus did not predispose patients in our cohort to postoperative complications or early implant failure, suggesting that with the right clinical protocol, patients that are considered high risk can be successfully treated with implants.

An alternative approach to ours would have been ridge regression. Both lasso and ridge shrink regression coefficients toward zero to reduce model overfitting; a distinctive feature of lasso is variable selection which shrinks some coefficients to exactly zero. Lasso thus eliminates superfluous predictors completely which makes for an easier interpretation of the results. Ridge and lasso perform comparably well in low-noise settings but lasso has an advantage in datasets with more noise (Pavlou et al., 2016). Variable selection is not available when using ridge. Considering the importance of easily interpretable results, we deemed variable selection important and thus chose lasso, but also applied variable selection in the Firth-penalized GEE models. Models that include all covariates (e.g., GEE) or a large subset of covariates do not converge due to quasi-separation. Occasionally, this may even happen in univariate models. We fixed this issue by accommodating GEEs with penalized regression using the Firth penalty (Mansournia et al., 2018).

Our study is inherently limited by its retrospective nature as well as the relatively low prevalences of postoperative complications and implant failures in the patient cohort. We further did not include any multiplicative effects in our model. To do so, a larger sample size would have been needed. Future research should consider applying our models in different patient cohorts to evaluate the replicability of these results, particularly in different populations. Long-term evaluation of risk factors for implant failure as opposed to only early failure, as well as the assessment of possible risk factors not evaluated in our study (e.g., periodontal disease, prosthetics), should also be taken under consideration for future research.

5 | CONCLUSION

Using novel methodology well-suited to tackle the challenges in implant dentistry, such as dependence of observations from patients with multiple implants and rare outcome events, we were able to reliably estimate associations of risk factors with outcomes.

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CONFLICT OF INTEREST

The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

AUTHOR CONTRIBUTIONS

BF, RG, and UK conceived the ideas; FK collected the data; BF, SL, and GH analyzed the data; BF, SL, and GH drafted the manuscript; RG, UK, and CU critically revised the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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