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Prediction of wound healing status following dental extraction using Adapted-University of Connecticut osteonecrosis numerical scale: A retrospective study

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Abstract

Background and Aims: There is a scarcity of evidence concerning the use of a prognostic instrument for predicting normal healing, delayed healing, and medication-related osteonecrosis of the jaw (MRONJ) occurrence following tooth extraction in medically compromised patients. The present study aimed to predict healing outcomes following tooth extraction in medically compromised patients using an Adapted-University of Connecticut osteonecrosis numerical scale (A-UCONNS).

Methods: The digital medical records of medically compromised patients were reviewed, who underwent tooth extraction. The A-UCONNS parameters included the initial pathological condition, dental procedures, comorbidities (smoking habits, type and duration of medication, and type of intervention), and administered antiresorptive (AR) medications. Each parameter was assigned a different weight, and the scores were then accumulated and classified into three categories: minimal risk (less than 10), moderate risk (10–15), and significant risk (16 or more). The patient's healing status was categorized as normal healing, delayed healing, or MRONJ.

Results: A total of 353 male patients (mean age: 67.4 years) were recruited from a pool of 3977 patients, where 12.46% of patients had delayed wound healing, and 18.69% developed MRONJ. The median A-UCONNS scores for MRONJ were higher based on initial pathology, comorbidity, and AR drugs compared to normal or delayed healing. In addition, a significant relationship existed between A-UCONNS and healing outcomes ($p < 0.05$), with a unit increase in A-UCONNS associated with 1.347 times higher odds of experiencing MRONJ compared to normal healing. In contrast, a low score was linked to an increased likelihood of normal wound healing.

Conclusion: The A-UCONNS could act as a promising tool for predicting wound healing outcomes. It can provide clinicians the ability to pinpoint patients at high risk

and allow tailoring of patient-specific strategies for improving healing outcomes following tooth extraction.

KEYWORDS
delayed healing, osteonecrosis of the jaw, polypharmacy, prognosis, wound healing

1 | INTRODUCTION

Tooth extraction is one of the most common dental procedures performed in clinical practice.[1] Following extraction, the socket undergoes a healing process with four distinct stages that is, hemostasis, inflammation, proliferation, and remodeling. Hemostasis occurs shortly after tooth extraction and involves blood clotting at the wound site.[2] Inflammation begins approximately 24 h after the procedure and lasts up to 72 h. During this stage, the immune system is activated to eliminate potential infections and debris.[3] Proliferation occurs on Days 4–21 and involves the replacement of the provisional fibrin matrix with a new matrix.[4] The final stage, remodeling, can take up to a year and involves the formation of new epithelium and scar tissue.[5]

The post-extraction healing process can be impaired, especially in osteoporotic and oncology patients who are administered polypharmacy and have comorbid conditions.[6,7] One type of non-healing wound following tooth extraction in such patients is medication-related osteonecrosis of the jaw (MRONJ).[8,9] The American Association of Oral and Maxillofacial Surgeons (AAOMS) has established a definition of MRONJ that includes the following criteria: current or previous treatment with antiresorptive (AR) agents alone or in combination with immune modulators or antiangiogenic drugs; exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region persisting for more than 8 weeks; and no history of radiation therapy to the jaw.[10]

Some medications, such as glucocorticoid steroids, non-steroidal anti-inflammatory drugs, and chemotherapeutic drugs, can interfere with clot formation or platelet function.[11] Additionally, AR medications such as bisphosphonates, denosumab, calcitonin, estrogen, and raloxifene may delay repair due to impairment in the remodeling phase.[12] A positive correlation has been observed between the number of medications and the incidence of non-healing wounds.[13] Cancer patients receiving multiple medications and immunosuppression are at an increased risk for developing MRONJ, even in the absence of exposure to AR drugs. A variety of AR medications, including bisphosphonates and denosumab used to treat osteoporosis and malignancies, have a high risk of developing MRONJ. Additionally, non-AR drugs, such as antiangiogenic inhibitors, immunosuppressants, and chemotherapy agents, have recently gained attention for their association with MRONJ as well.[14]

So far, numerous risk factors have been recognized as potential contributors to the development of delayed healing or MRONJ.[15–20] Despite this, the pathophysiology of MRONJ remains incompletely understood, and there is a scarcity of evidence regarding the precise prediction of patients who may experience delayed healing or develop MRONJ following tooth extraction. A tool referred to as the University of Connecticut osteonecrosis numerical scale (UCONNS) was previously developed to provide a prognostic score for predicting MRONJ surgical treatment outcomes.[21,22] Nevertheless, there is an existing gap in the evidence concerning the utilization of such a tool for predicting healing outcomes following tooth extraction. This is particularly relevant when attempting to assess and stratify the risk posed by medications and comorbidities in the onset of MRONJ. Therefore, the aim of the present study was to apply an Adapted-UCONNS (A-UCONNS) as a predictor of wound healing outcomes following tooth extraction.

2 | METHODS

2.1 | Study design, setting participants, and outcomes

This retrospective study was conducted in compliance with the World Medical Association Declaration of Helsinki and received ethical approval from the University Hospitals Leuven Ethical Review Board (reference number: S57824). Patient-specific information was anonymized, eliminating the need for informed consent. A review of digital medical records from patients aged 40 years or older was conducted, who underwent tooth extraction at the Department of Oral and Maxillofacial Surgery, UZ Leuven, Belgium, between September 2015 and April 2021. Patients with radiological follow-up and used multiple medications were included, while those with a history of craniofacial radiotherapy or malignant and metastatic diseases of the jaw were excluded. The sample size was determined using G*Power software (Version 3.1.9.2) and was based on previous studies, with a power of 80% and a significance level of 0.05.

The A-UCONNS parameters encompassed initial pathological condition, dental treatment, comorbidities (including smoking habits, medication type and duration, and intervention type), and administered AR medications. Each parameter's score was weighted differently, accumulated, and then categorized as follows: minimal risk (<10), moderate risk (10–15), and significant risk (16 or above) (Table 1).

The healing status of a patient was classified based on the duration and symptoms of the healing process. The three categories were: normal healing, which occurred within 10 days

TABLE 1 Adapted-University of Connecticut osteonecrosis numerical scale reference table.

Parameter	Criteria	Points
Initial pathology condition (max 10)	Healthy	0
	HIV	1
	Diabetes mellitus/rheumatoid arthritis	2
	Other cancer	2
	Breast/prostate cancer	3
	Multiple myeloma	5
Dental therapy (max 5)	Prophylaxis	0
	Restorative procedure	0
	Endodontic treatment	1
	Denture sore	1
	Periodontal surgery	3
	Tooth extraction	4
	Dental implant	5
Comorbid condition (max 10)	Nonsmoker	0
	Former smoker >6 months	1
	Current smoker	2
	Oral steroid	2
	Steroid IV/IM	3
	Immunosuppressants, chemotherapy; 12 months	5
	Immunomodulation (rheumatoid disease, organ transplant; 12 months)	5
Anti-resorptive used	Bisphosphonate <3 years	1
	Bisphosphonate 3–5 years	2
	Bisphosphonate >5 years	3
	Denosumab <3 years	1
	Denosumab 3–5 years	2
	Denosumab >5 years	3
Risk assessment	Minimal risk (<10)	1
	Moderate risk (10–15)	2
	Significant risk (16 or above)	3

Abbreviations: HIV, human immunodeficiency virus; IM, intramuscular; IV, intravenous.
Adapted from Reich et al.[22].

and exhibited no symptoms; delayed healing, which took between 14 days and 8 weeks and was characterized by bleeding, pain, redness, and an open socket that eventually healed; and MRONJ, which persisted for more than 8 weeks and was marked by bone sequestration, pain, and an absence of healing or epithelization. This classification was based on the clinical criteria proposed by the AAOMS and was confirmed radiologically using panoramic radiography.

2.2 | Statistical methods

Multinomial logistic regression was employed to assess the relationship between the A-UCONNS criterion and healing outcome. In addition, survival regression was used to evaluate differences between different risk groups, with *p*-values adjusted using Tukey's correction. Statistical analysis was performed using S-Plus 8.0 for Linux (Tibco). A p value < 0.05 was considered significant.

3 | RESULTS

The digital medical records of 3977 medically compromised patients were reviewed, who underwent tooth extraction. Of these, 353 male patients, aged between 40 and 90 years (average age: 67.4 years), were chosen based on specific eligibility criteria (Figure 1). The patient characteristics, according to the A-UCONNS parameters, are detailed in Table 2. The majority of the patients were diagnosed with prostate cancer (58 patients). Out of these, 35 patients developed MRONJ, and nine patients experienced delayed healing post-extraction. In terms of healing outcomes, 18.6% of patients developed MRONJ, 12.4% experienced delayed healing, and 65% exhibited normal healing. In the context of comorbid conditions, 22% of patients were former smokers for more than 6 months, and 16.4% had undergone chemotherapy treatment. Notably, 56% of the patients who received chemotherapy developed MRONJ. Regarding the use of AR medication, 23 patients were treated with denosumab, and 17 patients had been using bisphosphonates for less than 3 years.

Figure 2 provides a visual representation of the score distribution for each criterion of A-UCONNS. It is noteworthy that the median scores for MRONJ outcomes were higher for the initial pathology score, comorbidity score, and AR score when compared to the scores of delayed and normal healing outcomes. Moreover, no significant differences were detected in the dental therapy scores. Based on the mean A-UCONNS risk assessment scores and healing outcomes (Figure 3), scores of MRONJ and delayed healing were mainly associated with higher scores, while normal healing outcomes corresponded to lower scores.

The association between each parameter of A-UCONNS and healing outcomes is presented in Table 3. A multinomial logistic regression analysis was conducted to investigate the relationship between pathology score, dental therapy score, AR score, comorbidity score, and healing outcomes. Overall, these variables were highly significant in the development of MRONJ, or delayed healing, compared to normal healing. The dental therapy score ($p = 0.01$, OR = 2.8) and the use of AR medications demonstrated a stronger relationship with MRONJ ($p < 0.001$, OR = 4.6) compared to delayed healing ($p < 0.001$, OR = 3.6).

Figure 4 presented a survival analysis correlating A-UCONNS risk assessment with healing time. The Kaplan–Meier survival analysis was used to compare the duration of healing across three different risk levels. These categorical variables showed statistically significant outcomes ($p < 0.001$), where the comparisons between minimal and moderate risk, minimal and significant risk, as well as moderate and significant risk, all exhibited negative direction. This suggested that individuals with higher risk assessments are more susceptible to experiencing delayed healing or MRONJ. On the other hand, individuals with lower risk assessment scores are more likely to exhibit a faster healing rate.

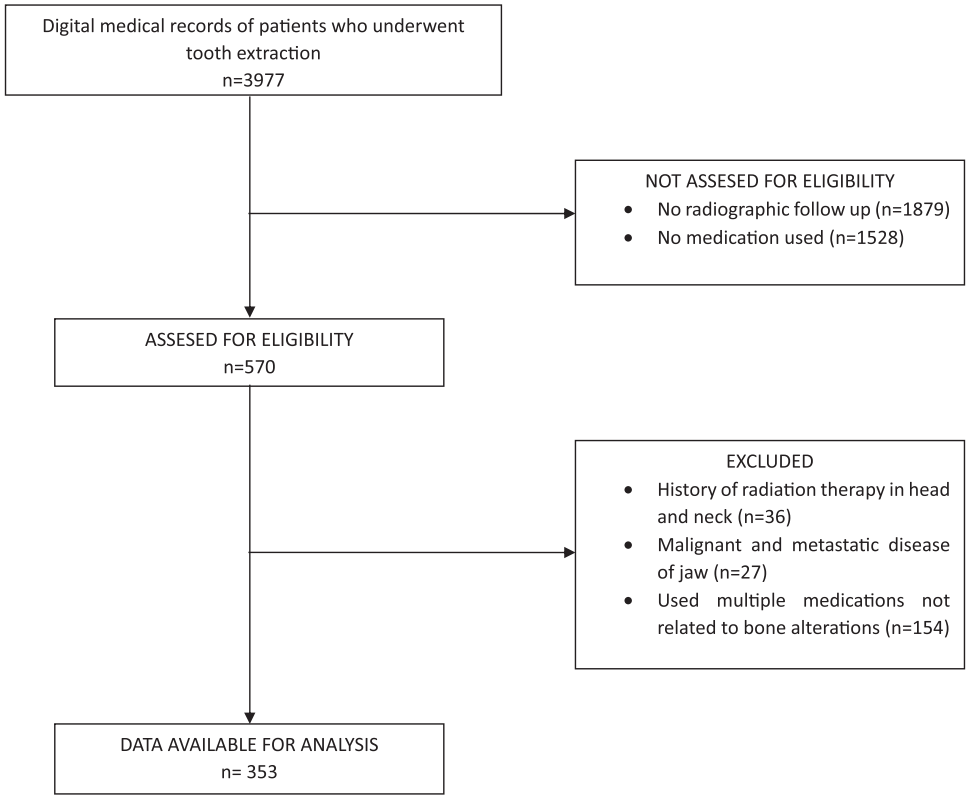


FIGURE 1 Flowchart of the patient selection process.

TABLE 2 Demographic data of included subjects.

Characteristic	Total *N* (%)	MRONJ *n*	Delayed healing	Normal healing
A-UCONN parameter				
Initial pathology condition				
Multiple myeloma	17 (4.8)	13	4	0
Prostate cancer	58 (16.4)	35	9	14
Other cancer	49 (13.9)	24	12	13
Osteoporosis	32 (9.1)	12	10	10
Rheumatoid arthritis	13 (3.6)	9	2	2
Diabetes mellitus	24 (6.8)	12	8	4
HIV	3 (0.8)	2	0	1
Dental therapy				
Restorative procedure	10 (2.8)	0	0	10
Endodontic treatment	12 (3.3)	0	0	12
Tooth extraction	353 (100)	66	44	243
Dental implant	33 (9.3)	4	3	26
Denture sore	27 (7.6)	19	8	0
Periodontal surgery	40 (11.3)	14	8	18
Comorbidities condition				
Former smoker >6 months	78 (22)	14	10	54
Smoker, current or last month	32 (9.1)	4	9	19
Steroid inhale/oral within 12 months	44 (12.5)	26	8	10
Steroid IV/IM within 12 months	36 (10.1)	22	6	8
Immunosuppressants, chemotherapy within 12 months	58 (16.4)	33	13	12
Immunomodulators (rheumatoid arthritis, organ transplant) within 12 months	22 (6.2)	8	5	9
Anti-resorptive used				
Bisphosphonate <3 years	17 (4.8)	11	4	2
Bisphosphonate 3–5 years	10 (2.8)	9	1	0
Bisphosphonate >5 years	14 (3.9)	6	5	3
Denosumab <3 years	23 (6.5)	11	7	5
Denosumab 3–5 years	18 (5)	13	3	2
Denosumab >5 years	5 (1.4)	5	0	0
Risk assessment				
Minimal risk (<10)	261 (74.2)	14	22	225
Moderate risk (10–15)	45 (12.7)	21	12	12
Significant risk (16 or above)	47 (13.3)	31	10	6

Abbreviations: HIV, human immunodeficiency virus; IM, intramuscular; IV, intravenous; MRONJ, medication-related osteonecrosis of the jaw.

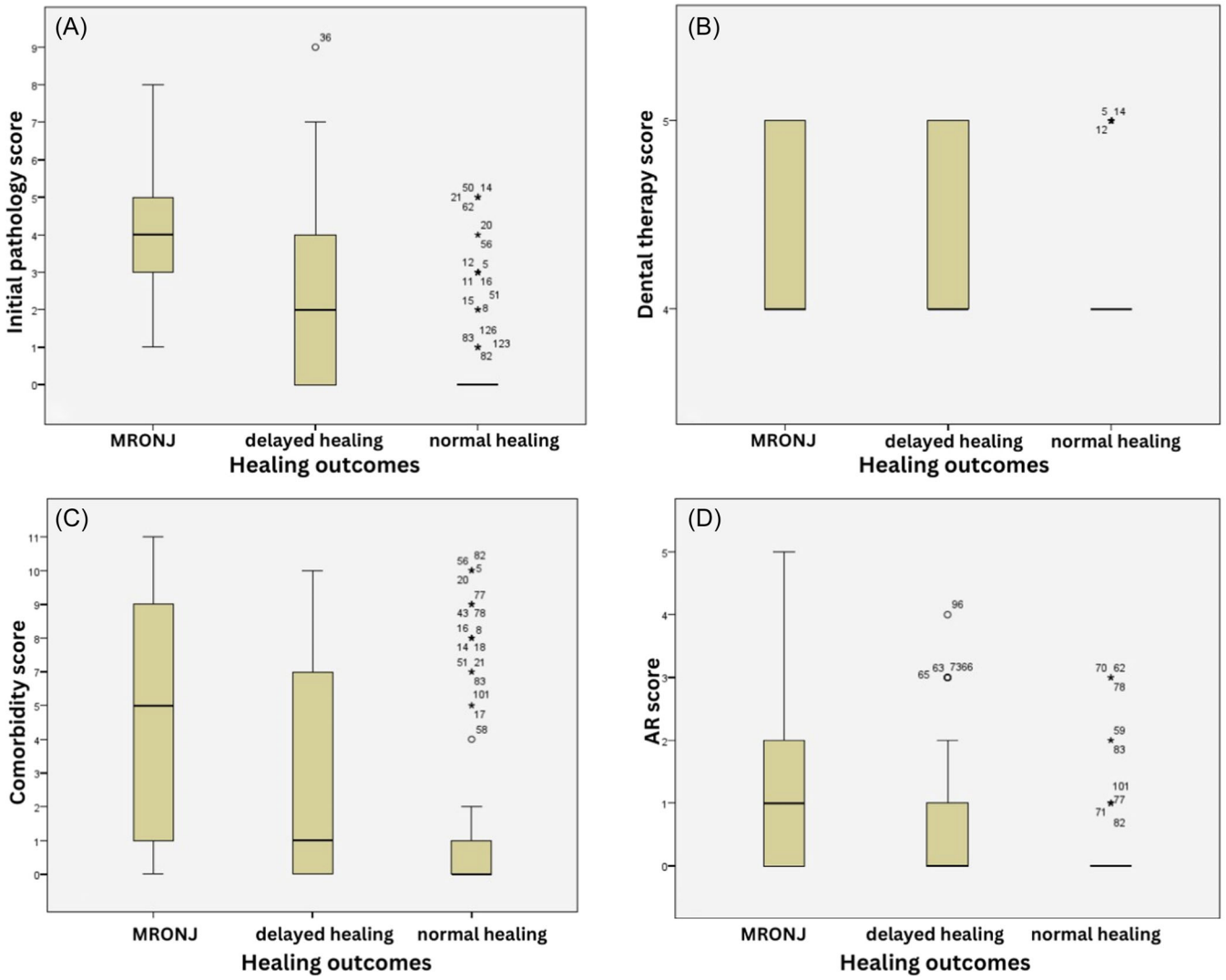


FIGURE 2 Patient distribution based on Adapted-University of Connecticut osteonecrosis numerical scale parameters. (A) Initial pathology score and healing outcomes; (B) dental therapy and healing outcomes; (C) comorbidity score and healing outcomes; and (D) anti-resorptive (AR) score and healing outcomes.

4 | DISCUSSION

In this study, A-UCONNS was utilized to conduct an analysis of potential risk determinants for predicting the wound healing status subsequent to tooth extraction. The findings indicated that a higher A-UCONNS score had an increased likelihood of delayed wound healing and MRONJ. Conversely, lower scores were associated with a higher probability of normal wound healing. The findings were consistent with a previous study that used the "comorbid polypharmacy score" (CPS) to quantify the cumulative severity of disease and medication accumulation.[16] However, it is important to note that the CPS does not account for dental risk factors, which are crucial in determining the likelihood of MRONJ development in a given patient.[17] As such, A-UCONNS was selected to predict wound healing impairment based on relevant risk factors. This research builds upon previous work that employed UCONNS to monitor and prevent MRONJ development,[21] as well as other studies that used this tool to evaluate predisposing factors and prognosis in surgical treatment failure cases following bisphosphonates administration.[22,23] It is noteworthy that comparison with existing evidence was difficult due to a lack of research on the prediction of healing outcomes following dental extraction using UCONNS.

Typically, wounds undergo a healing process that lasts between 4 and 6 weeks.[24,25] Once the wound has closed, the remodeling phase commences. The primary objective of this final stage of wound healing is to restore normal tissue structure and maximize tensile strength through extracellular matrix reorganization, breakdown, and synthesis.[4] The administration of AR drugs might cause the failure of the extraction socket to progress through the normal stages of healing within the expected timeframe, which can either lead to delayed healing or MRONJ occurrence.[26]

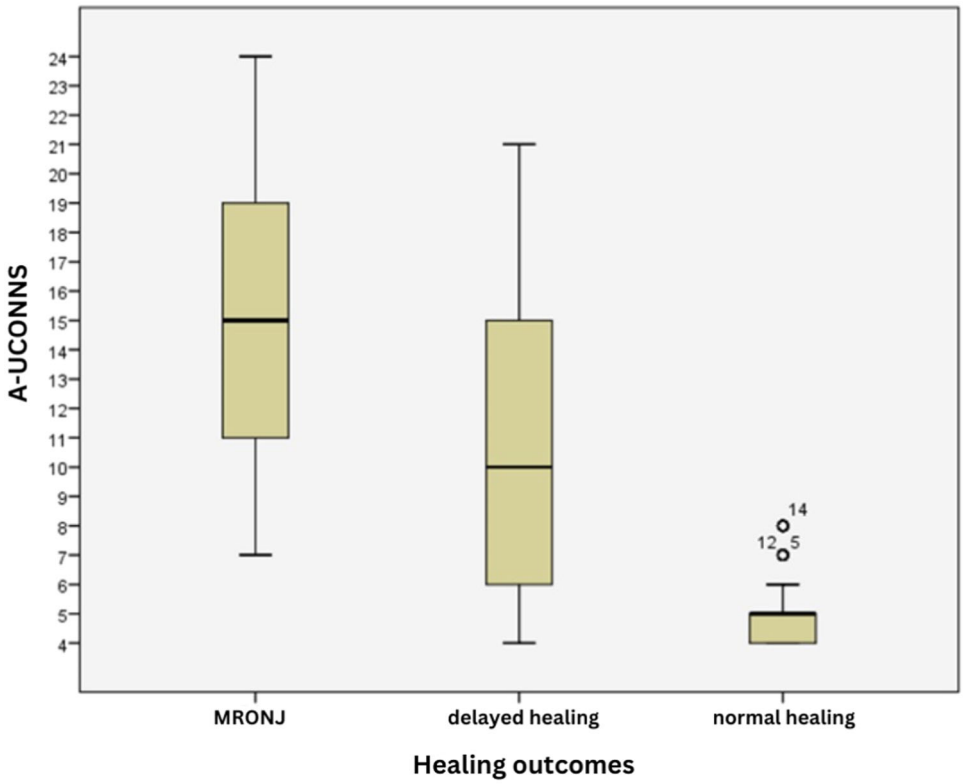


FIGURE 3 Mean and standard deviation of Adapted-University of Connecticut osteonecrosis numerical scale (A-UCONNS) and healing outcomes.

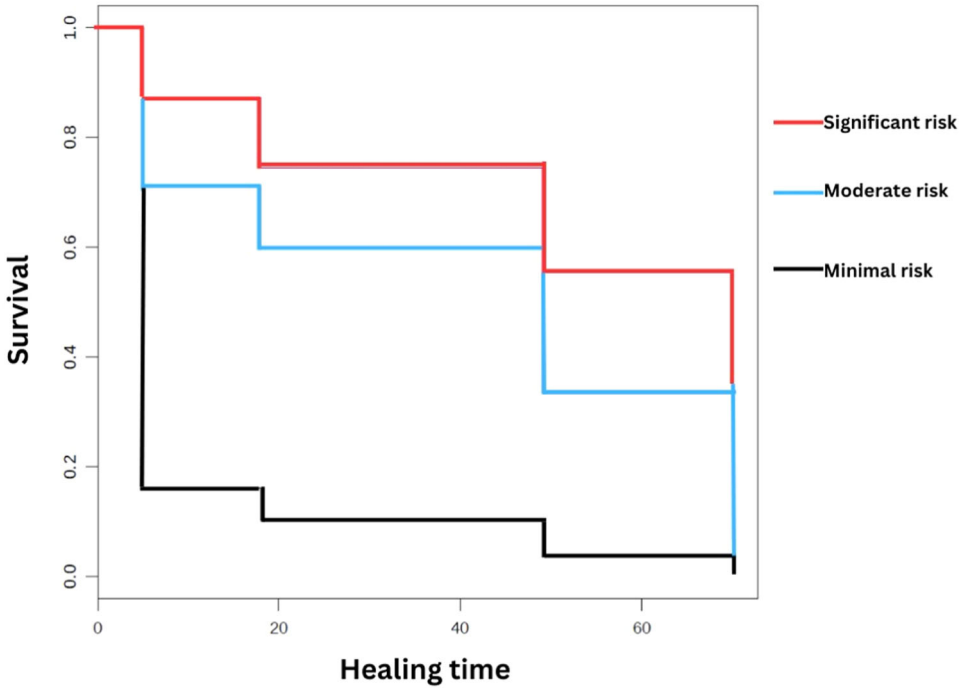
TABLE 3 Relation between each criterion of Adapted-University of Connecticut osteonecrosis numerical scale and healing outcome.

Comparison	MRONJ		Delayed healing		Normal healing
	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value	
A-UCONNS criteria[a]					
Initial pathology condition	2.4 (1.8–3.1)	<0.001	1.6 (1.3–2.1)	<0.001	Reference
Dental therapy	4.6 (1.8–11.7)	<0.001	2.8 (1.3–6.3)	0.01	
Comorbidities condition	1.1 (1.0–1.3)	0.045	1.1 (0.1–1.2)	0.14	
Anti-resorptive used	3.6 (2.2–5.9)	<0.001	2.4 (1.5–3.9)	<0.001	

Abbreviations: MRONJ, medication-related osteonecrosis of the jaw; OR, odds ratio.
[a]Multinomial logistic regression.

Wound healing can be inhibited by multiple variables. These factors can be classified as either local or systemic. Local factors have a direct impact on the characteristics of the wound, while systemic factors pertain to the individual's overall health or disease condition, which can affect their ability to heal.[27] Systemic factors influence wound healing through local effects, and many of these factors are interrelated. Oxygenation, infection, foreign body presence, and venous sufficiency are among the local factors that influence healing time.[28] Systemic risk factors such as immunocompromised conditions and immunosuppression medications, including chemotherapy and steroids, have been reported to contribute toward healing failure.[29,30] Accordingly, the present study also showcased that both corticosteroids and chemotherapy were found to be used by medically compromised patients exhibiting delayed healing or MRONJ.

Corticosteroids directly inhibit the production and activity of osteoclasts, osteoblasts, and osteocytes. Specifically, osteonecrosis might have been caused by the induction of apoptosis in osteocytes.[31] Moreover, chemotherapeutic agents delay cell migration into wounds, reduce early wound matrix development, decrease collagen production, impair fibroblast proliferation, and inhibit wound contraction.[32] These medications also weaken the patients' immune system, slowing down the inflammatory phase of the healing process and increasing the likelihood of wound infection. Chemotherapy side



Comparison	Difference	P-value
Minimal risk-Moderate risk	-29.3	0.001
Minimal risk-Significant risk	-41.8	0.001
Moderate risk-Significant risk	-12.5	0.008

FIGURE 4 Survival analysis of Adapted-University of Connecticut osteonecrosis numerical scale (A-UCONNS) risk assessment and healing time.

effects such as neutropenia, anemia, and thrombocytopenia increase the susceptibility of wounds to infection, reduce oxygen delivery to the area, and increase the risk of excessive bleeding at the wound site.[11,28]

The clinical scoring of the A-UCONSS based on administered AR medications showed a strong relationship between the use of AR medications and delayed healing or MRONJ following tooth extraction. However, a study found that the use of alendronate and zoledronic acid did not have a significant association with impaired bone and mucosal wound healing after dental extraction in women with osteoporosis who followed an appropriate surgical protocol and continued bisphosphonate therapy.[33] Hence, it is important to identify and stratify the risk factors and develop patient-specific protocols for improved surgical outcomes.

Within the clinical context, considering risk factors and healing duration, patients classified as low-risk generally demonstrated enhanced healing compared to their counterparts in the moderate and high-risk categories. This data could be instrumental in guiding clinical decision-making processes. It is imperative for healthcare professionals to prioritize patient risk assessment. Patients falling under the moderate risk category may exhibit standard healing patterns, yet these individuals require more consistent monitoring, preventive measures, or targeted treatments. Simultaneously, for those classified as high-risk, healthcare providers should consider personalized treatment strategies, intensive interventions, or more frequent follow-ups to improve their survival prospects, particularly in relation to MRONJ development.

The study had certain limitations, which should be acknowledged when interpreting the results. First, the retrospective approach employed may impede the establishment of a causal link between risk factors and wound healing outcomes. Second, the accessibility of data pertaining to the pharmacological protocol, previous medical history, and drug dosage was limited, thereby complicating the identification of potential confounding factors. Third, the variability in follow-up durations among the patients included in the study could have increased the likelihood of selection bias. Future longitudinal studies with extended follow-up periods could offer valuable insights into the long-term effects of polypharmacy and other risk factors on wound healing. To enhance the reliability of the results, this study implemented multinomial logistic regression to adjust for potential confounding factors. Finally, the sample size was relatively small and lacked diversity, as it only included male patients. Thereby, a larger and more diverse sample could enhance the applicability of the findings to a broader population. Moreover, future research is recommended to consider the aforementioned

limitations in an attempt to improve the prediction capability of the A-UCONNS scale before it can be used in a clinical setting.

5 | CONCLUSION

The A-UCONNS could act as a valuable tool for enhancing care in medically compromised patients, where it can enable a clinician to identify high-risk patients who are more prone to develop MRONJ and allow tailoring of patient-specific treatment planning and postoperative therapy to improve healing outcomes following tooth extraction. To elevate the existing standard of care and improve healing outcomes in medically compromised patients, it is recommended that additional research be conducted to develop risk reduction protocols and clinical practice guidelines based on the stratification of the risk factors.

AUTHOR CONTRIBUTIONS

Isti R. Suryani: Conceptualization; investigation; methodology; writing—original draft; writing—review and editing. **Sohaib Shujaat**: Supervision; visualization; writing—review and editing. **Minh T. That**: Data curation. **Wim Coucke**: Methodology. **Reinhilde Jacobs**: Conceptualization; supervision; validation; writing—review and editing. All authors have read and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. Isti R. Suryani had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

ETHICS STATEMENT

This study was approved by the Ethics Committee of University Hospitals Leuven (reference number: S57824).

TRANSPARENCY STATEMENT

The lead author, Reinhilde Jacobs, affirms that this manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned (and if relevant, registered) have been explained.

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