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Risk Factors Influencing Medication-Related Osteonecrosis of the Jaws (MRONJ) Following Dental Extraction Among Osteoporotic Patients in Taiwan

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ABSTRACT

Aim: Antiresorptive therapy (ART) is commonly used in osteoporotic patients to prevent bone loss. This retrospective cohort study aimed to identify the risk factors associated with medication-related osteonecrosis of the jaw (MRONJ) in osteoporotic patients receiving dental extraction during ART.

Materials and Methods: Data were collected from 937 patients with 1067 dental extractions conducted between January 2003 and May 2022, including 519 patients on oral alendronate, 276 on denosumab, and 172 on zoledronate. Multivariate logistic regression analysis was employed to assess potential risk factors.

Results: Regression model analysis revealed older age (AOR 1.09 per year; 95% CI, 1.06–1.12) and drug treatment exceeding 24 months (AOR 2.07; 95% CI, 1.29–3.30) as significant risk factors. A drug interruption of 3 or more months prior to tooth extraction lowered MRONJ risk (AOR 0.11; 95% CI, 0.07–0.17). Stratified by drug type, denosumab users had significantly lower risk of MRONJ after extraction (AOR 0.14; 95% CI, 0.07–0.27) compared to those on other medications. Factors of drug duration ≥ 24 months, < 3 months of interruption, and posterior mandibular tooth extraction posed the highest synergistic MRONJ risk (AOR 80.29; 95% CI, 33.05–195.09).

Conclusion: Our results suggest an association between a three-month ART interruption prior to tooth extraction and reduced MRONJ risk, especially in long-term ART patients undergoing posterior mandibular extractions. However, these findings require validation through prospective randomized controlled trials.

Clinical Relevance: *Scientific Rationale for Study*: The study fills crucial knowledge gaps regarding MRONJ risks in osteoporotic patients undergoing dental extraction during antiresorptive therapy (ART), providing a foundation for informed clinical decisions.
Principal Findings: Noteworthy findings include elevated MRONJ risk with older age and prolonged ART, the protective effect of a 3-month ART interruption, and denosumab users showing significantly reduced postextraction MRONJ risk.
Practical Implications: Implementing a 3-month ART interruption before dental extraction is recommended to reduce MRONJ occurrences.

1 | Introduction

Osteoporosis is the most common bone disease worldwide and is characterized by compromised bone strength and increased susceptibility to fractures, including the hip, spine, and other skeletal sites [1, 2]. The development of osteoporosis may be attributed to an imbalance between bone resorption and bone formation, caused by a decrease in the lifespan of osteoblasts and an extension of the lifespan of osteoclasts [3]. As a consequence, there is an overall decrease in trabecular bone volume, alteration in microstructure, and subsequent bone loss [4, 5].

Most current therapies for managing osteoporosis and preventing fractures are primarily designed to reduce bone resorption. These antiresorptive therapies (ART) include bisphosphonates (BPs, such as alendronate, risedronate, ibandronate, and zoledronate), denosumab (DMB, a human monoclonal antibody targeting receptor activator of NF-κB ligand (RANKL)), and selective estrogen receptor modulators (SERMs) like raloxifene [6]. However, alteration of bone turnover by antiresorptive agents impairs wound healing of jaw bones [7–9], potentially resulting in an adverse event termed medication-related osteonecrosis of the jaws (MRONJ) by the American Association of Oral and Maxillofacial Surgeons (AAOMS) in 2014 [10]. Even though MRONJ is a relatively rare disease, risk is significantly elevated in patients undergoing dentoalveolar surgery while receiving ART [11, 12]. Evaluation of the use of DMB in osteoporotic patients revealed that the risk of MRONJ is approximately 0.3% after 10 years of use, rising to 1% in patients undergoing tooth extraction. On the other hand, for patients using oral alendronate, the risk of MRONJ was below 0.05% and increased to 0.15% following tooth extraction [10, 13]. According to the AAOMS 2022 position paper on MRONJ [13], it is believed that tooth extraction is a prevalent precipitating event, as evidenced by 62%–82% of patients reporting it as the inciting factor. Other risk factors for MRONJ include local factors (such as infectious dental conditions) and systemic factors (such as diabetes, anemia, or cancer), as well as age, anatomical location, drug duration, drug route, and genetic factors.

To reduce the incidence of MRONJ, the optimization of oral health is considered the most crucial prevention strategy. Thus, prior to initiation of ART, removal of nonrestorable teeth or teeth with a poor prognosis should be considered. Moreover, when it comes to patients undergoing ART, it is advisable to avoid dentoalveolar surgery whenever possible. In cases where extractions are necessary, the approach of interrupting oral BPs or DMB treatment prior to extraction has been controversial. Previously, the AAOMS committee recommended a modified drug holiday strategy of 2 months for osteoporotic patients with an extended exposure period (> 4 years) to oral BPs [10]. In 2022, it was recommended to time planned dentoalveolar surgery at 3–4 months after the last dose of DMB [13], although these recommendations lacked solid evidence to support their validity. On the other hand, an advisory committee from the American Dental Association (ADA) Council on Scientific Affairs and an international consensus paper did not endorse the practice of a drug holiday from oral BPs or DMB prior to invasive dental procedures in patients with osteoporosis [8, 14]. Therefore, our study aimed to explore the multivariate relationships among various risk factors associated with MRONJ, including the implementation of a drug interruption.

2 | Materials and Methods

2.1 | Patients

To assess risk factors influencing the incidence rate of MRONJ in osteoporotic patients who underwent tooth extraction during ART, a retrospective cohort study was performed. We retrieved and included the patients as these criteria: (1) Osteoporotic patients with a history of dental extraction who followed up at the Division of Oral and Maxillofacial Surgery, Department of Dentistry, National Taiwan University Hospital (NTUH), from January 2003 to May 2022. (2) Patients who received antiresorptive agents including alendronate (Fosamax, oral intake, every 4 weeks), risedronate (Actonel, oral intake, weekly), zoledronate (Aclasta, intravenous form, once a year), ibandronate (Bonviva, intravenous form, every 3 months), romosozumab (Evenity, subcutaneous, monthly), raloxifene (Evista, oral intake, daily), and denosumab (Prolia, subcutaneous, every 6 months). Exclusion criteria were as follows: (1) Patients with sequential use of 2 or more antiresorptive agents prior to dental extraction, as this would prevent a clear comparison of results between different medications. (2) Medications used by fewer than 30 patients were excluded due to insufficient sample size for meaningful statistical analysis. Among these drugs, alendronate, zoledronic acid, and denosumab were the most commonly used and included in statistical analysis.

2.2 | Clinical Evaluation and Data Collection

All included patients underwent extraction of one or more teeth, with procedures performed either at our hospital or at other dental clinics. We reviewed the following information from the medical records of included patients: age, sex, smoking status, medical comorbidities, ART history (including treatment duration and any drug interruptions), and dates of dental extractions. Drug interruption was defined as the time interval between the last dose of ART and the dental extraction. For duration of drug exposure, each medication has its own definition based on its pharmacological effects: (1) Alendronate: the interval between the first prescription and last administration. (2) Zoledronate: from initial dose, lasting for 12 months. (3) DMB: from initial dose, lasting for 6 months. Additionally, we recorded whether patients had discontinued ART prior to tooth extraction, as well as the duration of such interruptions. For patients who underwent tooth extraction at NTUH, we also collected data on pre-extraction bone turnover marker C-terminal telopeptide (CTX), measured using the Serum CrossLaps kit (Roche Diagnostics GmbH, Mannheim, Germany).

2.3 | Detection of MRONJ Lesions

The status of extraction wound healing was also reviewed from medical records. At NTUH, routine follow-up appointments are typically scheduled at 1 and 2 months postextraction. Successful

wound healing was defined as the complete regrowth of overlying mucosa without bone exposure and any signs of inflammation or infection at the 2-month postextraction follow-up. If the doctor's notes did not indicate clinical healing after 2 months, panoramic films and cone-beam computed tomography (CBCT) used for lesion detection were then reviewed. Following a comprehensive evaluation, the presence of MRONJ lesions was confirmed by Lee, an experienced surgeon. All cases fulfilled the diagnostic criteria for MRONJ proposed by AAOMS in 2022, with each of the following characteristics present: current or previous treatment with antiresorptive therapy alone or in combination with immune modulators or antiangiogenic medications, exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for more than 8 weeks, and no history of radiation therapy to the jaws or metastatic disease to the jaws [13]. The endpoint of data retrieval was the end of July 2022, allowing at least 2 months of observation after extraction.

2.4 | Statistical Analysis

The unit of analysis in this study was the individual tooth extraction, rather than the patient. Consequently, multiple data points were generated for patients who underwent extraction of more than one tooth, irrespective of whether these extractions were performed concurrently or at different time points. Quantitative variables were given as mean ± standard deviation (SD). Median and range were also presented for continuous variables. Chi-square tests or Fisher's exact tests (when expected cell frequencies were <5) were used for categorical variables. This allowed us to determine whether there were significant differences in the distribution of the characteristics between the ONJ and non-ONJ groups. Continuous variables were compared using independent *t*-tests or Mann–Whitney *U* tests, based on data normality. The statistical analysis was conducted for all included patients, as well as stratified by three different medications: alendronate, zoledronate, and DMB.

Univariate and multivariate analyses were conducted using logistic regression models to assess the risk factors associated with occurrence of MRONJ. Only factors shown to have statistical significance in the univariate analysis were included in the multivariate analysis. The covariates analyzed were age, extraction site, denture wearing, duration of ART, drug type, duration of ART interruption before extraction, smoking habit, pretreatment CTX levels, and presence of underlying diseases including anemia, diabetes mellitus, rheumatoid arthritis, and systemic lupus erythematosus. Two groups were defined based on pretreatment CTX levels, with a cutoff of 150 pg/mL. This threshold was derived from studies indicating a low risk of MRONJ following dental procedures in patients with serum CTX levels above 150 pg/mL [15, 16].

For the univariate analysis, unadjusted odds ratio (OR) with 95% confidence intervals (CI) was calculated to indicate the probability of occurrence of MRONJ. In the multivariate logistic regression model, adjusted odds ratio (AOR) with 95% CI was computed to assess the independent association of each significant factor with MRONJ occurrence, while controlling for potential confounding effects of other variables in the model. *p* Value <0.05 was considered as statistically significant. All

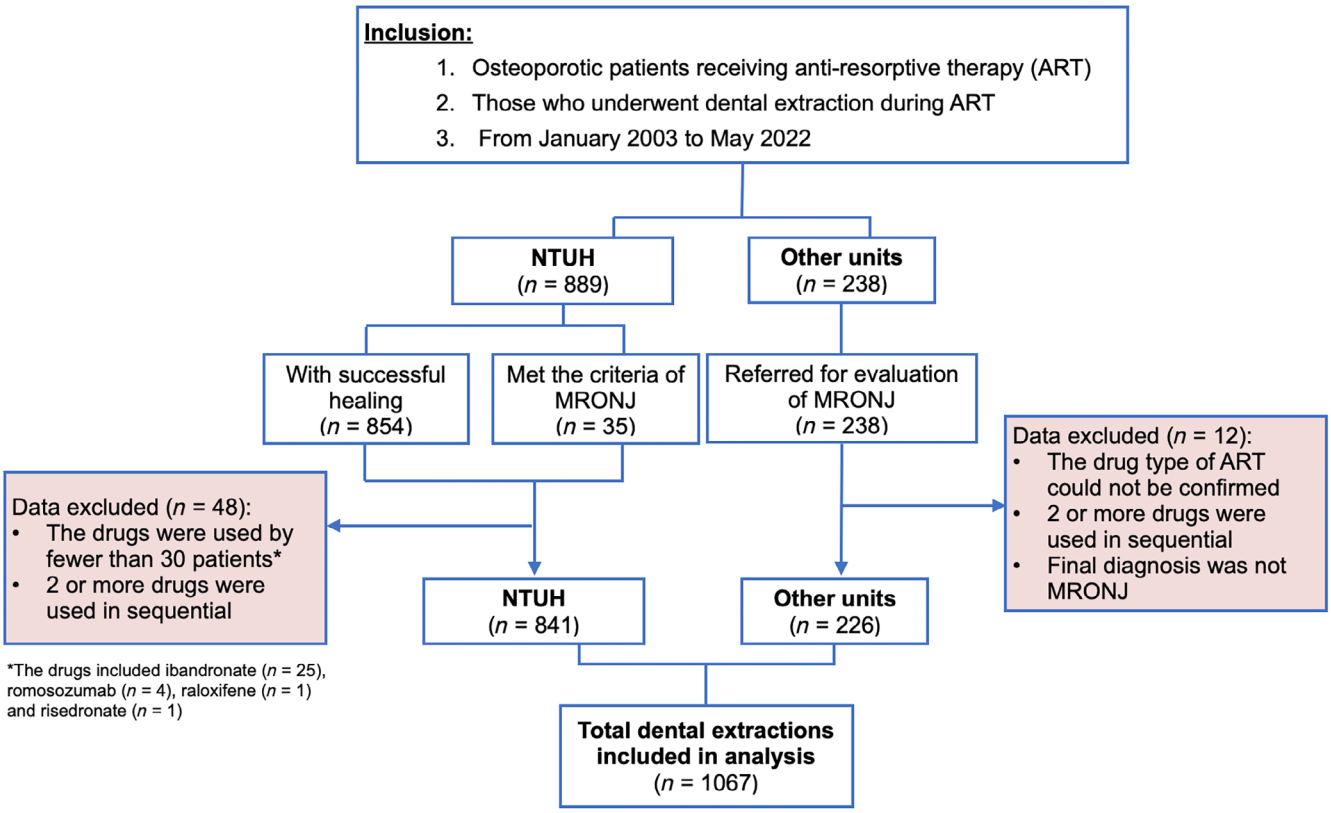

FIGURE 1 | Flow of study design: All MRONJ cases fulfilled the diagnostic criteria for MRONJ proposed by AAOMS in 2022. Exclusion criteria are also presented. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 | Clinical characteristics of included cases and stratified by ART.

	Dental extraction, $n = 1067$	Alendronate, $n = 519$ (48.6%)	Zoledronate, $n = 172$ (16.1%)	Denosumab, $n = 376$ (35.2%)	p[a]
Age, years					
Mean ± SD	73.43 ± 10.72	73.76 ± 11.36	76.41 ± 8.82	71.62 ± 10.27	< 0.001
Median (min, max)	74 (20, 95)	75 (20, 95)	78 (48, 90)	72 (20, 92)	
Sex					
Male	73 (6.8%)	28 (5.4%)	15 (8.7%)	30 (8.0%)	0.181
Female	994 (93.2%)	491 (94.6%)	157 (91.3%)	346 (92.0%)	
Extraction site					
UA	147/1046 (14.1%)	67/500 (13.4%)	21/170 (12.4%)	59 (15.7%)	0.015
UP	381/1046 (36.4%)	177/500 (35.4%)	71/170 (41.8%)	133 (35.4%)	
LA	105/1046 (10.0%)	36/500 (7.2%)	22/170 (12.9%)	47 (12.5%)	
LP	413/1046 (39.5%)	220/500 (44.0%)	56/170 (32.9%)	137 (36.4%)	
Extraction jaw					
Upper	528/1046 (50.5%)	244/500 (48.8%)	92/170 (54.1%)	192 (51.1%)	0.469
Lower	518/1046 (49.5%)	256/500 (51.2%)	78/170 (45.9%)	184 (48.9%)	
Denture wearing					
Without	963/1063 (90.6%)	465/516 (90.1%)	158/171 (92.4%)	340 (90.4%)	0.669
With	100/1063 (9.4%)	51/516 (9.9%)	13/171 (7.6%)	36 (9.6%)	
Drug interruption, months					
Mean	10.49 ± 18.61	10.36 ± 21.19	11.07 ± 17.42	14.31 ± 15.00	0.904
Median (min, max)	4.4 (0, 140.9)	3.0 (0, 140.9)	6.0 (0, 71.8)	5.23 (0, 111.6)	
Drug interruption					
< 3 months	278/974 (28.5%)	229/491 (46.6%)	7/114 (6.1%)	42/369 (11.4%)	< 0.001
≧ 3 months	696/974 (71.5%)	262/491 (53.4%)	107/114 (93.9%)	327/369 (88.6%)	
Drug duration, months					
Mean	31.59 ± 27.83	37.89 ± 33.08	27.81 ± 23.22	24.43 ± 17.91	< 0.001
Median (min, max)	24 (0.25, 276)	30 (0.25, 276)	24 (2.5, 120)	24 (2, 120)	
Diabetes					
Without	865/1007 (85.9%)	414/503 (82.3%)	164 (95.3%)	287/332 (86.4%)	< 0.001
With	142/1007 (14.1%)	89/503 (17.7%)	8 (4.7%)	45/332 (13.6%)	
Anemia					
Without	909/919 (98.9%)	431/431 (100%)	172 (100%)	306/316 (96.8%)	< 0.001
With	10/919 (1.1%)	0/431 (0%)	0 (0%)	10/316 (3.2%)	
Smoking					
Without	1058 (99.2%)	513/519 (98.8%)	172 (100%)	373 (99.2%)	0.354
With	9 (0.8%)	6/519 (1.2%)	0 (0%)	3 (0.8%)	

(Continues)

TABLE 1 | (Continued)

	Dental extraction, $n=1067$	Alendronate, $n=519$ (48.6%)	Zoledronate, $n=172$ (16.1%)	Denosumab, $n=376$ (35.2%)	p[a]
RA					
Without	890/920 (96.7%)	423/432 (97.9%)	171 (99.4%)	296/316 (93.7%)	<0.001
With	30/920 (3.3%)	9/432 (2.1%)	1 (0.6%)	20/316 (6.3%)	
SLE					
Without	891/920 (96.8%)	412/432 (95.4%)	172 (100%)	307/316 (97.2%)	0.012
With	29/920 (3.2%)	20/432 (4.6%)	0 (0%)	9/316 (2.8%)	
Thyroid dysfunction					
Without	894/922 (97.0%)	420/434 (96.8%)	166 (96.5%)	308/316 (97.5%)	0.800
With	28/922 (3.0%)	14/434 (3.2%)	6 (3.5%)	8/316 (2.5%)	
CTX level[b], pg/mL					
Mean ± SD	286.73 ± 549.13	260.22 ± 218.28	389.80 ± 1198.12	270.07 ± 285.79	0.179
Median (min, max)	190 (10, 8599)	204 (10, 1410)	178 (102, 8599)	134 (34, 1300)	

Abbreviations: CTX, C-terminal telopeptide of collagen I; LP, lower posterior; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; UA, upper anterior; UP, upper posterior, LA, lower anterior.
[a]Calculated between 3 different drugs.
[b]Only 462 CTX values were available in analysis.

calculations were performed with IBM SPSS Statistics for MAC, version 26.0.0.0 (IBM Corp., Armonk, NY, USA).

3 | Results

3.1 | Patient Demographics

A total of 1067 dental extractions performed in 937 osteoporotic patients during ART were included in the statistical analysis (Figure 1). Demographic and clinical characteristics of the patients are shown in Table 1. Ages of patients ranged from 20 to 95 years (73.43 ± 10.72 years). The majority of patients (93.2%) were female. The tooth extraction sites were distributed as follows: 14.1% in the upper anterior (tooth 13–23, FDI number system), 36.4% in the upper posterior (tooth 14–18 and 24–28), 10.0% in the lower anterior (tooth 33–43), and 39.5% in the lower posterior (tooth 34–38 and 44–48). The mean duration of ART was 31.59 ± 27.83 months (range, 0.25–276 months; median, 24 months). At the time of dental extraction, 71.5% of patients had suspended ART for at least 3 months and the period of drug abstinence ranged from 0 to 140.9 months. Among 1067 dental extractions, 841 were performed in our hospital and 226 were in other medical units. For patients receiving dental extraction in our hospital, 35 out of 841 (4.16%) developed MRONJ lesions, while all cases from other units were diagnosed with MRONJ.

After stratifying the patients into three groups based on the type of ART (alendronate, zoledronate, and DMB), it was observed that patients using zoledronate were older than those using alendronate or DMB, with median ages of 78, 75, and 72, respectively (one-way ANOVA, $p<0.001$; Table 1). Patients using zoledronate had a shorter average drug duration, and a higher prevalence of diabetes, anemia, rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) compared to patients using alendronate or DMB (all $p<0.05$). There was no significant difference in average duration of drug interruption among different drug types (one-way ANOVA, $p=0.904$). Among all the included samples, approximately 70% of patients had interrupted their ART for more than 3 months. However, only 53.4% of the patients discontinued oral alendronate, which represented the lowest percentage among the three treatment groups (one-way ANOVA, $p<0.001$).

3.2 | Characteristics of MRONJ Cases After Tooth Extraction

Table 2 shows the comparison of clinical characteristics between MRONJ cases and non-MRONJ cases. MRONJ cases were older (median age 79 and 73, respectively, $p<0.001$) and had longer drug duration (median, 34 and 24 months, $p<0.001$) compared to those without lesions. Notably, there was a significant difference in the average duration of drug interruption between these two groups, with 12.79 ± 20.40 months for the non-MRONJ group and 3.37 ± 8.03 months for the MRONJ group ($p<0.001$). Given that the duration of drug interruption and the drug duration exert opposing effects on bone remodeling, we calculated the duration ratio (defined as the ratio of drug interruption duration to drug duration) to assess potential differences between the two groups while considering both factors concurrently. Our analysis revealed that the duration ratio in the non-MRONJ group (1.67 ± 5.00) was significantly higher than that observed in MRONJ (0.11 ± 0.33, $p<0.001$). Among the MRONJ cases, a majority (82.0%) had a history of alendronate use, while 10.0% used zoledronate and 8.0% received DMB treatment ($p<0.001$). Regarding the location of the lesions, the lower posterior region

TABLE 2 | Comparison of clinical characteristics in patients with or without ONJ, all patients.

	Without ONJ ($n=806$)	With ONJ ($n=261$)	p[a]
Age, years	72.14 ± 10.81 (median 73)	77.44 ± 9.38 (median 79)	< 0.001
Sex, female	749 (92.9%)	245 (93.9%)	0.600
Extraction site			
UA	126 (15.6%)	21/240 (8.8%)	< 0.001
UP	303 (37.6%)	78/240 (32.5%)	
LA	96 (11.9%)	9/240 (3.8%)	
LP	281 (34.9%)	132/240 (55.0%)	
Extraction jaw			
Upper	429/806 (53.2%)	99/240 (41.3%)	0.001
Lower	377/806 (46.8%)	141/240 (58.8%)	
Drug type			
Alendronate	305 (37.8%)	214 (82.0%)	< 0.001
Denosumab (DMB)	355 (44.0%)	21 (8.0%)	
Zoledronate	146 (18.1%)	26 (10.0%)	
Denture wearing	67/805 (8.3%)	33/258 (12.8%)	0.032
Drug interruption, months	12.79 ± 20.40 (median 5.4)	3.37 ± 8.03 (median 0)	< 0.001
Drug duration, months	28.17 ± 24.38 (median 24)	42.52 ± 34.60 (median 34)	< 0.001
Duration ratio[b]	1.67 ± 5.00 (median 0.35)	0.11 ± 0.33 (median 0)	< 0.001
Diabetes	94/753 (12.5%)	48/254 (18.9%)	0.011
Anemia	10/672 (1.5%)	0/247 (0.0%)	0.054
Smoking	7 (0.9%)	2 (0.8%)	0.875
RA	28/673 (4.2%)	2/247 (0.8%)	0.011
SLE	26/673 (3.9%)	3/247 (1.2%)	0.042
CTX level[c], pg/mL	288.83 ± 558.58 (median 180)	228.13 ± 85.65 (median 242.5)	0.664

Abbreviations: CTX, C-terminal telopeptide of collagen I; LP, lower posterior; ONJ, osteonecrosis of the jaws; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; UA, upper anterior; UP, upper posterior; LA, lower anterior.
[a]p-Value was obtained from Student's t-test or chi-square test.
[b]Duration ratio was defined as duration of drug interruption (days) divided by drug duration (days).
[c]$n=446$ and 16, respectively.

was the most common site (55.0%) followed by the upper posterior region (32.5%).

3.3 | Risk Factors of Dental Extraction–Related MRONJ

Univariate analysis by logistic regression model identified eight variables—age, extraction site, denture wearing, drug duration, drug type, duration of drug interruption, diabetes, and RA—significantly correlated with the occurrence of MRONJ after tooth extraction (all $p<0.05$; Table 3). Age, extraction site (lower posterior), drug duration, drug type, and duration of drug interruption were all independent risk factors for MRONJ, as shown by multivariate analysis (Table 3). Compared to patients using alendronate or zoledronate, those treated with DMB had a relatively lower risk of MRONJ with an adjusted odds ratio (AOR) of 0.14 ($p<0.001$; 95% CI, 0.07–0.27). The AOR quantifies the association between each independent variable and MRONJ occurrence while adjusting for other confounding factors, with values below 1 indicating a potential protective effect. Notably, age was found to be associated with a higher risk of MRONJ, with a 9% increase in the expected strength for each 1-year increase in age ($p<0.001$; 95% CI, 1.06–1.12). Patients with an ART duration of more than 24 months exhibited a higher risk of MRONJ, with an AOR of 2.07 ($p=0.002$; 95% CI, 1.29–3.30). Regarding the duration of drug interruption before dental extraction, interrupting ART for 3 months or more was associated with a significantly lower risk of MRONJ, with an AOR of 0.11 ($p<0.001$; 95% CI, 0.07–0.17). Consistently, in each individual drug analysis, multivariate regression revealed that drug interruption of more than 3 months prior to tooth extraction was associated with a lower risk of MRONJ (Tables S1–S3).

TABLE 3 | Univariate and multivariate analyses of ONJ risk factors in all 1067 dental extractions with history of ART.

		Univariate analysis		Multivariate analysis	
	Cases	**OR[a] (95% CI)**	***p***	**Adjusted OR (95% CI)**	***p***
Age					
Per year	1067	1.06 (1.04–1.07)	< 0.001	1.09 (1.06–1.12)	< 0.001
Extraction site					
Maxilla	528	1.00			
Mandible	518	1.62 (1.21–2.17)	0.001	—	—
Extraction site					
UA	147	1.00		1.00	
UP	381	1.55 (0.91–2.61)	0.104	1.72 (0.84–3.52)	0.141
LA	105	0.56 (0.25–1.28)	0.172	0.48 (0.14–1.65)	0.241
LP	413	2.82 (1.70–4.68)	< 0.001	4.36 (2.22–8.58)	< 0.001
Denture wearing					
Without	963	1.00		1.00	
With	100	1.62 (1.04–2.52)	0.034	1.12 (0.58–2.16)	0.743
Drug duration					
< 24 months	405	1.00		1.00	
≧ 24 months	603	2.45 (1.77–3.39)	< 0.001	2.07 (1.29–3.30)	0.002
Drug type					
Alendronate	519	1.00		1.00	
Denosumab (DMB)	376	0.08 (0.05–0.14)	< 0.001	0.14 (0.07–0.27)	< 0.001
Zoledronate	172	0.25 (0.16–0.40)	< 0.001	0.92 (0.49–1.72)	0.797
Drug interruption					
< 3 months	278	1.00		1.00	
≧ 3 months	696	0.09 (0.07–0.13)	< 0.001	0.11 (0.07–0.17)	< 0.001
Diabetes					
Without	865	1.00		1.00	
With	142	1.63 (1.12–2.39)	0.012	1.09 (0.57–2.08)	0.785
Anemia					
Without	909	1.00			
With	10	0.00 (0.00-N/A)	0.999	—	—
RA					
Without	890	1.00		1.00	
With	30	0.19 (0.04–0.80)	0.023	0.51 (0.06–4.47)	0.544
SLE					
Without	148	1.00			
With	2	0.31 (0.09–1.02)	0.054	—	—
Thyroid dysfunction					
Without	673	1.00			

(Continues)

TABLE 3 | (Continued)

		Univariate analysis		Multivariate analysis	
	Cases	OR[a] (95% CI)	*p*	Adjusted OR (95% CI)	*p*
With	249	0.32 (0.10–1.06)	0.061	—	—
Smoking					
Without	1058	1.00			
With	9	0.88 (0.18–4.27)	0.875	—	—
CTX level[b]					
< 150 pg/mL	183	1.00			
≧ 150 pg/mL	279	2.01 (0.64–6.34)	0.233	—	—

Abbreviations: CI, confidence interval; CTX, C-terminal telopeptide of collagen I; LP, lower posterior; OR, odds ratio; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; UA, upper anterior; UP, upper posterior; LA, lower anterior.
[a]OR > 1 indicates a higher probability of occurrence of ONJ.
[b]Only 462 CTX values were available in analysis.

TABLE 4 | Synergistic effects of tooth extraction site, drug duration, and drug interruption for osteoporotic patients.

	Drug duration ≧ 24 months		Drug duration < 24 months	
	Drug interruption ≧ 3 months	Drug interruption < 3 months	Drug interruption ≧ 3 months	Drug interruption < 3 months
Lower posterior extraction	AOR 3.98 (1.67–9.50)	AOR 80.29 (33.05–195.09)	AOR 2.28 (0.95–5.66)	AOR 15.17 (5.55–41.47)
Non–lower posterior extraction	AOR 2.30 (1.01–5.25)	AOR 18.90 (8.36–42.73)	AOR 1.00 (Reference)	AOR 12.87 (5.18–31.99)

Abbreviation: AOR, adjusted odds ratio.

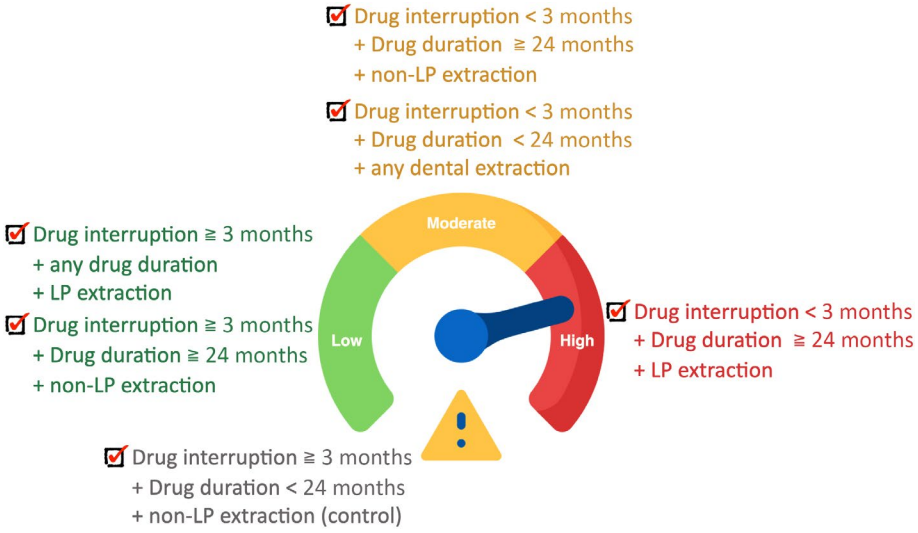

FIGURE 2 | The three-variable synergistic model proposed in this study as a potential tool to evaluate the risk of MRONJ before tooth extraction. [Color figure can be viewed at wileyonlinelibrary.com]

3.4 | Synergistic Effect of Risk Factors for MRONJ After Dental Extraction

Based on the aforementioned regression analysis, the association between the duration of drug interruption and the incidence of MRONJ remained statistically significant, even after adjusting for other covariates. Additionally, a drug duration exceeding 24 months was found to be associated with a higher risk of MRONJ. The lower posterior region, being the most common site of tooth extraction, also showed a higher risk of MRONJ in multivariate analysis. Considering these three factors together, their individual impacts were compared with the combined effect to assess their collective influence on the occurrence of MRONJ. The greatest synergistic effect was observed in patients who had a longer course of ART and did not suspend treatment for a sufficient duration prior to extraction of a lower posterior

tooth, indicating the highest risk. The incidence of MRONJ among individuals who had a drug interruption of less than 3 months, a drug duration exceeding 24 months, and underwent lower posterior tooth extraction was found to be 80-fold higher ($p < 0.001$; AOR 80.29; 95% CI, 33.05–195.09) compared to the incidence among the reference group (Table 4). Notably, the risk of MRONJ decreased among individuals who had suspended ART for 3 or more months, irrespective of drug duration or tooth extraction site. This model suggests that patients undergoing dental extraction during ART can be grouped into low, moderate, and high risk of MRONJ, as shown in Figure 2. The risk stratification is based on AOR values from Table 4, with AOR 1.00 as the reference group, AORs 2.28–3.98 representing low risk, 12.87–18.9 indicating moderate risk, and 80.29 denoting high risk.

4 | Discussion

Regardless of drug type or treatment duration, a drug interruption before tooth extraction was shown to reduce the risk of MRONJ in this study. To the best of our knowledge, this is the first study demonstrating that among osteoporotic patients, those with treatment interruption of 3 or more months prior to tooth extraction had a lower incidence of MRONJ. This finding not only provides robust support for the drug holiday strategy recommended by the AAOMS [10], but also offers practical guideline with a specific time point. In the case of BPs, the potential benefits of drug interruption could arise from the reduction in soft tissue toxicity, which could favor wound healing. This is especially important given that BPs have been associated with the inhibition of oral mucosal healing [17]. Regarding DMB, following a 3-month interval after dosing, there was a significant decrease in serum DMB levels. At the same time, the bone turnover marker CTX began to rise, while improvement was still observed in bone mineral density [18]. Thus, this supports the potential positive effects of drug interruption in our study.

In this study, patients with combined factors of long drug duration ≥ 24 months, drug interruption < 3 months, and extraction of a lower posterior tooth ran the highest risk of MRONJ; the combination of drug duration ≥ 24 months and drug interruption < 3 months came second, followed by extraction of lower posterior tooth and drug interruption < 3 months. The risks were similar to those seen with lower posterior extraction alone, drug duration ≥ 24 months alone, or combination of both. To date, numerous risk factors associated with MRONJ have been reported and several systematic reviews have also been conducted [19–21]. Besides periodontal diseases and peri-implantitis, endodontic failure has also been recently reported as a trigger for MRONJ, and these teeth might be extracted under preclinical or existing osteonecrosis conditions [22, 23]. However, our study is the first to establish a model of synergistic risk factors for MRONJ, specifically highlighting the interactive effects among drug duration, drug interruption, and tooth extraction site. This unique approach not only contributes to our understanding of the combined influence of these factors on the development of MRONJ, but also proposes a risk evaluation tool and treatment guideline for osteoporotic patients who are planning tooth extraction during their ART.

In this study, we found that the incidence of MRONJ after dental extraction was significantly related to age in our multivariate analysis. While age has been mentioned as a potential risk factor for MRONJ previously [24–30], no statistically significant differences were observed in these studies. There was a discrepancy in mean age between that reported in previous studies (mean age of approximately 65) and our study (mean age of approximately 75). This might be a reflection of the alteration of bone remodeling in aging bone. After reaching the peak of bone mass, there is a gradual decrease in bone turnover indicated by a significant decline in biochemical markers of bone remodeling during the aging process. This decline is associated with a higher prevalence of bone resorption compared to bone formation, suggesting a shift toward a slower rate of bone turnover [31, 32].

Serum C-terminal telopeptide (CTX) has been proposed as an indicator for assessing the efficacy of ART [33]. Marx and colleagues reported that morning fasting CTX is a useful tool to assess risk of MRONJ, where CTX values above 150 pg/mL indicate minimal risk [15]. However, it is important to note that due to the small sample size of 30 participants, these conclusions may be biased. More recently, both supporting [34, 35] and conflicting data [36] have been reported regarding the use of the 150 pg/mL cutoff value. The CTX levels among our patients exhibited significant variation, with 286.73 ± 549.13 pg/mL (mean ± SD). Furthermore, no significant difference was found in CTX levels between the MRONJ and non-MRONJ groups ($p = 0.664$), and the univariate analysis revealed that CTX levels did not act as a risk factor for MRONJ ($p = 0.233$). Several studies have reported significant circannual variation in CTX levels causing within-individual biological variability of CTX [37–39]. This observation may explain the significant variation we found in individual baseline levels of CTX, suggesting that CTX levels may not be a reliable tool for assessing risk and guiding treatment decisions prior to tooth extraction. According to a recent meta-analysis [40], the cutoff of 150 pg/mL in CTX levels was found to have unsatisfactory sensitivity and specificity for predicting the risk of MRONJ. Therefore, these results highlight the need for further studies to explore and develop alternative serum markers that can provide more accurate risk assessment for MRONJ.

Our study has some limitations. First, because some patients received their initial treatment in other medical units, their pretreatment CTX values were not available for analysis. Thus, out of the total 1067 patients, only 536 (51.1%) had CTX values included in the study. A second limitation is the potential underestimation of pre-MRONJ or Stage 0 MRONJ before tooth extraction. For instance, tooth mobility observed at the time of extraction could be attributed to the progression of MRONJ rather than assumed periodontitis. Thus, the actual incidence of MRONJ specifically attributed to tooth extraction may be lower than that in our findings, as pre-existing MRONJ cases could have been mistakenly categorized as postextraction MRONJ. Additionally, it is worth noting that patients seeking dental treatments at our medical center often present with comorbidities and complex inflammatory or infectious dental conditions, which may introduce sampling bias. These factors also contribute to the risk and incidence of spontaneous MRONJ. Similarly, the third limitation is the inability to review preoperative images

for patients who had their teeth extracted at other medical facilities. It is difficult to confirm whether MRONJ lesions were present prior to dental extraction, which results in a high incidence of extraction-related MRONJ. A fourth limitation is the use of a retrospective cohort study design, which limits our ability to accurately assess the effects of drug interruption before tooth extraction. Conducting a prospective study would be preferable, but it raises ethical concerns due to the potential positive effects assumed from drug interruption.

In conclusion, our results suggest that age and prolonged drug use (> 24 months) may increase MRONJ risk in osteoporotic patients undergoing dental extraction. A three-month ART interruption prior to extraction and the use of DMB were associated with lower MRONJ risk. The highest risk was observed in patients simultaneously with prolonged drug use, short drug interruption (< 3 months), and posterior mandibular tooth extraction. While these findings indicate potential benefits of a three-month ART interruption, this study serves as a foundation for future research, highlighting the need for well-designed prospective studies to further elucidate the optimal management strategies for patients on ART requiring dental extractions. While all preventive guidelines offer consensus-based recommendations and cannot ensure complete MRONJ prevention, our findings suggest a more targeted approach, emphasizing cautious management and personalized risk assessment for patients on ART requiring dental procedures.

Author Contributions

Conceptualization: L.Y. Wei and J.J. Lee. Data curation: L.Y. Wei and Y.W. Cheng. Formal analysis: L.Y. Wei. Data interpretation: L.Y. Wei, Y.W. Cheng and J.J. Lee. Writing (drift preparation): L.Y. Wei. Writing (review and editing): W.Y. Chiu, S.H. Kok and J.J. Lee. Project administration: H.H. Chang and S.J. Cheng. Approving final version of manuscript: All authors. All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Ethics Statement

The research ethics committee of NTUH approved this retrospective study (Research Ethics Committee Number 201512177RINA).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data cannot be shared due to ethical restrictions.

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Supporting Information

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