MRONJ nelle malattie reumatiche

ALESSANDRA BORTOLUZZI

UOC DI REUMATOLOGIA

DIPARTIMENTO DI SCIENZE MEDICHE

UNIVERSITÀ DEGLI STUDI DI FERRARA

MRONJ & rheumatic diseases

non-oncologic patients with osteometabolic pathology treated with oral bisphosphonates (mainly for osteopenia/osteoporosis)

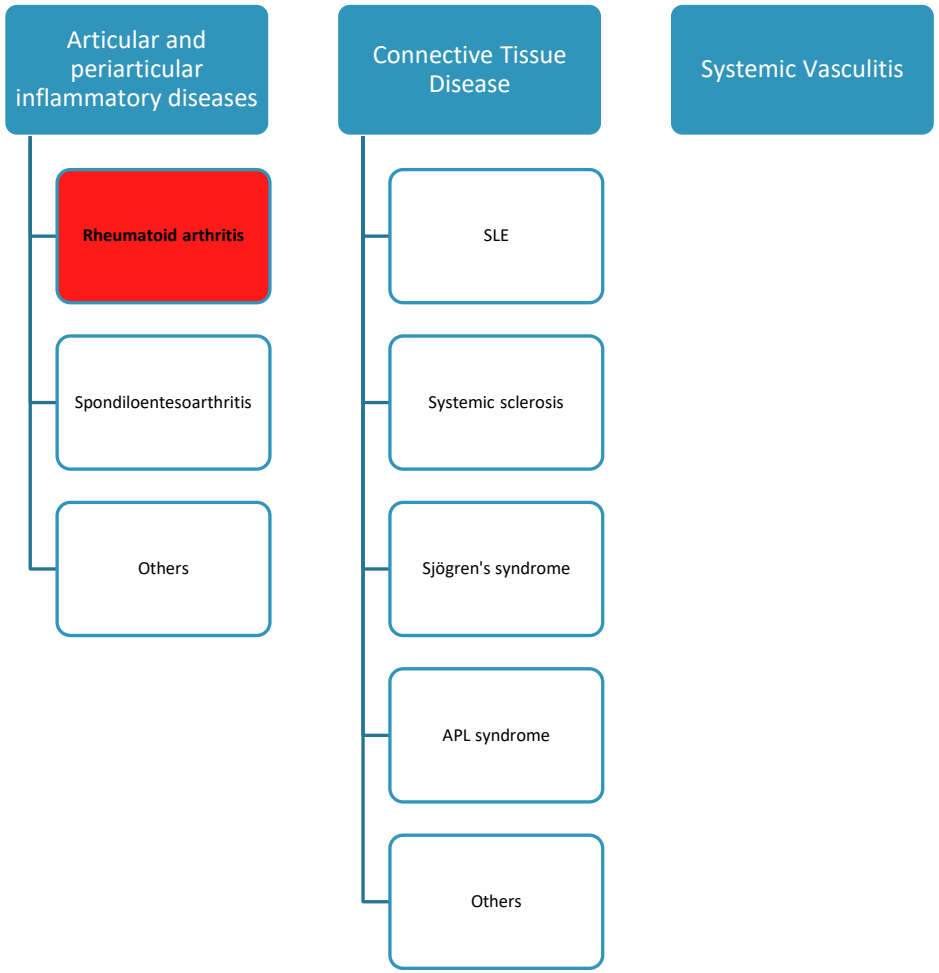
prolonged treatments (typically exceeding 2-3 years)

potential concurrent local and/or systemic risk factors

Classification of rheumatic diseases of the Italian Society of Rheumatology

- Articular and periarticular inflammatory diseases
  - Rheumatoid arthritis
  - Spondiloentesoarthritis
  - Others
- Connective Tissue Disease
  - SLE
  - Systemic sclerosis
  - Sjögren's syndrome
  - APL syndrome
  - Others
- Systemic Vasculitis

Classification of rheumatic diseases of the Italian Society of Rheumatology



Rheumatoid arthritis

- Chronic systemic autoimmune disease characterized by symmetrical polyarthritis disorder in which arthritis, particularly the small joints of the hands and feet, cause significant functional impairment
- The characteristic features of the disease are synovial inflammation and proliferation, accompanied by cartilage erosion and bone loss
- It causes significant morbidity, a reduced life span, and loss of work productivity
- Osteoporosis is a common comorbidity in rheumatoid arthritis and should be considered an extra-articular manifestation

I.B. McInnes, G. Schett, The pathogenesis of rheumatoid arthritis, N. Engl. J. Med. 2011.

Rheumatoid arthritis

Incidence rate in RA are estimated to be 12-16 per 100 000 per year in Europe

Age-standardised **prevalence rate** of 246.6 per 100 000 (95% UI 222.4 to 270.8)

Women are three times more frequently affected than men

…ident cases reached the highest level at **50–54 age group**

Safiri S, et al. Ann Rheum Dis 2019

Osteoporosis in RA

- RA peak incidence in women coincides with a **perimenopausal period**, suggesting a relationship between estrogen deficiency and the development of RA

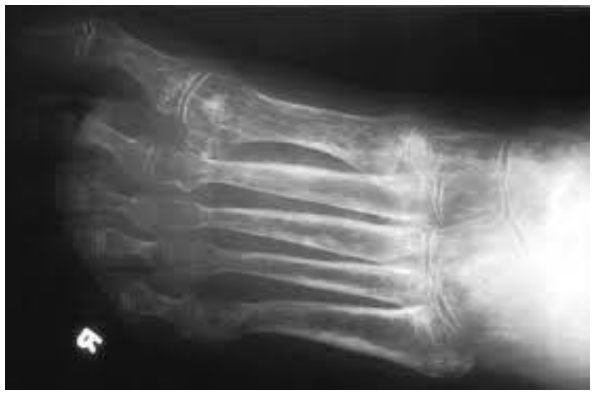
J.A. Kanis et al. Osteoporos. Int. 2008; M. Guler-Yuksel et al. Ann. Rheum. Dis. 2007; A. Deodhar, A.D. Br. J. Rheumatol. 1996; A.K. Gough et al. Lancet 1994

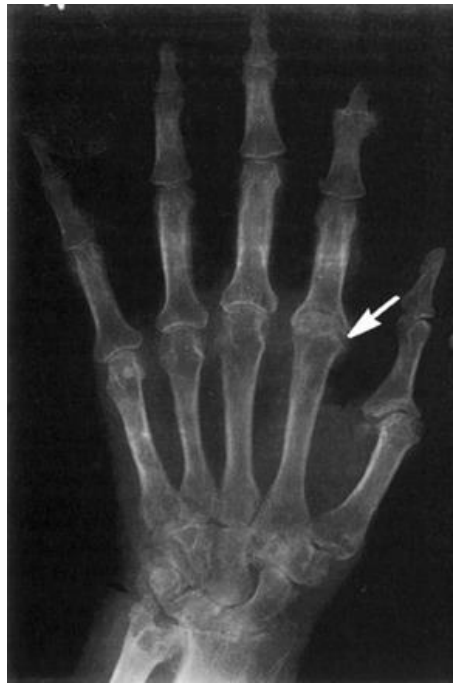
- **early menopause** is a risk factor for developing RA: those women who reached menopause before 45 years of age had a higher risk for RA than did women who reached menopause in a later age

L.E. Wong et al. Arthritis Care Res. 2015; M. Pikwer et al. Ann. Rheum. Dis. 2012; L.A. Merlino et al. Semin. Arthritis Rheum. 2003

- **bone loss** occurs in the very early course of RA, with the most significant rate of loss appearing early after disease onset
- **~ 25% of patients with early RA show signs of osteopenia at the spine or hip before the beginning of therapy**, and 10% have generalized OP, which is twice as high in comparison with the general population
- the occurrence of **hip and vertebral fractures** is roughly doubled in postmenopausal RA, as compared with age-matched controls

T. Dimitroulas et al. Autoimmun. Rev. 2013; T.P. Van Staa et al. Arthritis Rheum. 2006





RA and bone loss

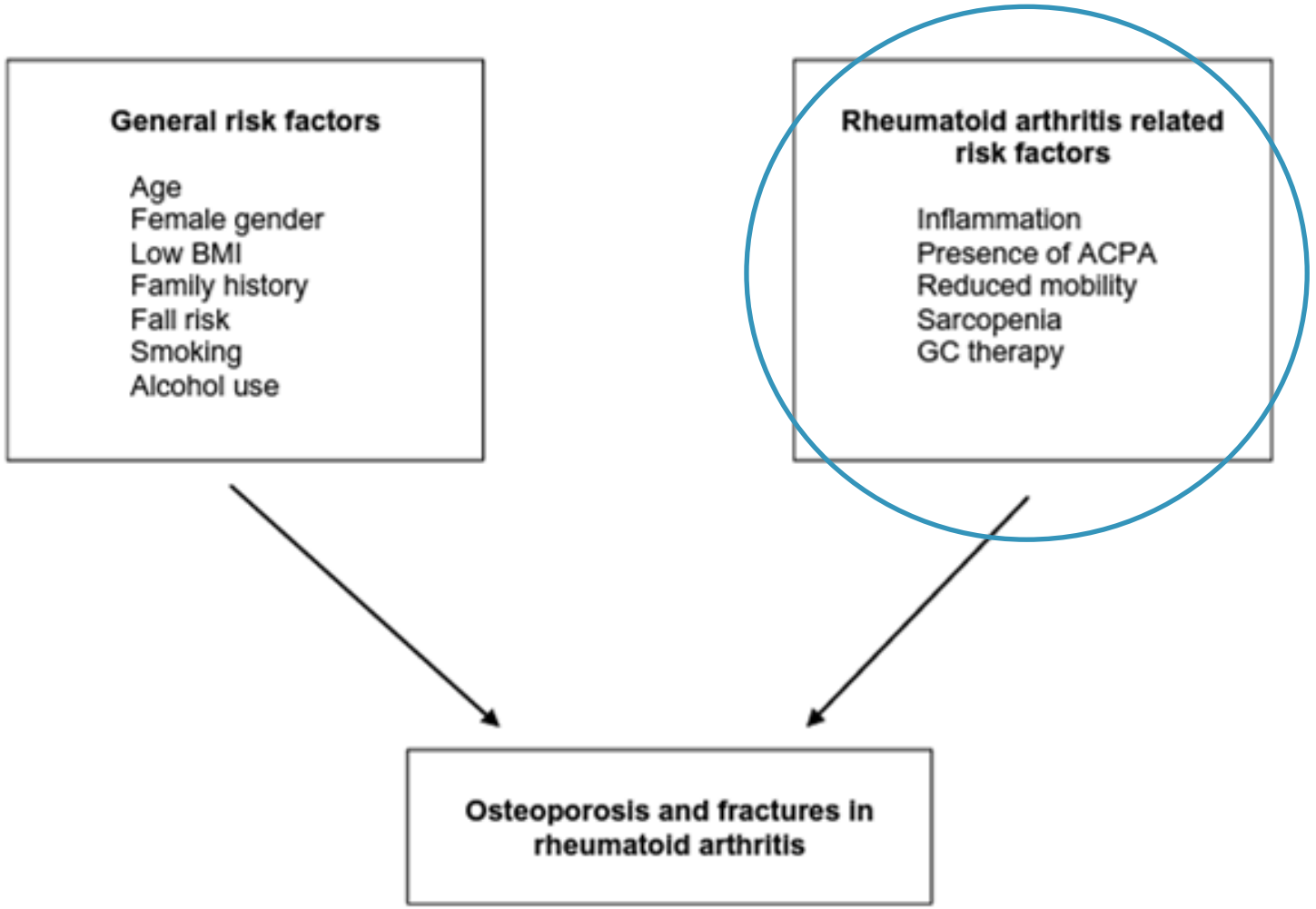
Three radiographically identified forms of altered extra-articular-skeletal remodeling in RA patients

§ **periarticular bone loss**, mainly caused by the proinflammatory cytokines from the inflamed synovium, which is in direct contact with bone. This varies with the disease severity;

§ **erosion of the subchondral bone**, accompanied by mechanisms commonly associated with periarticular osteopenia;

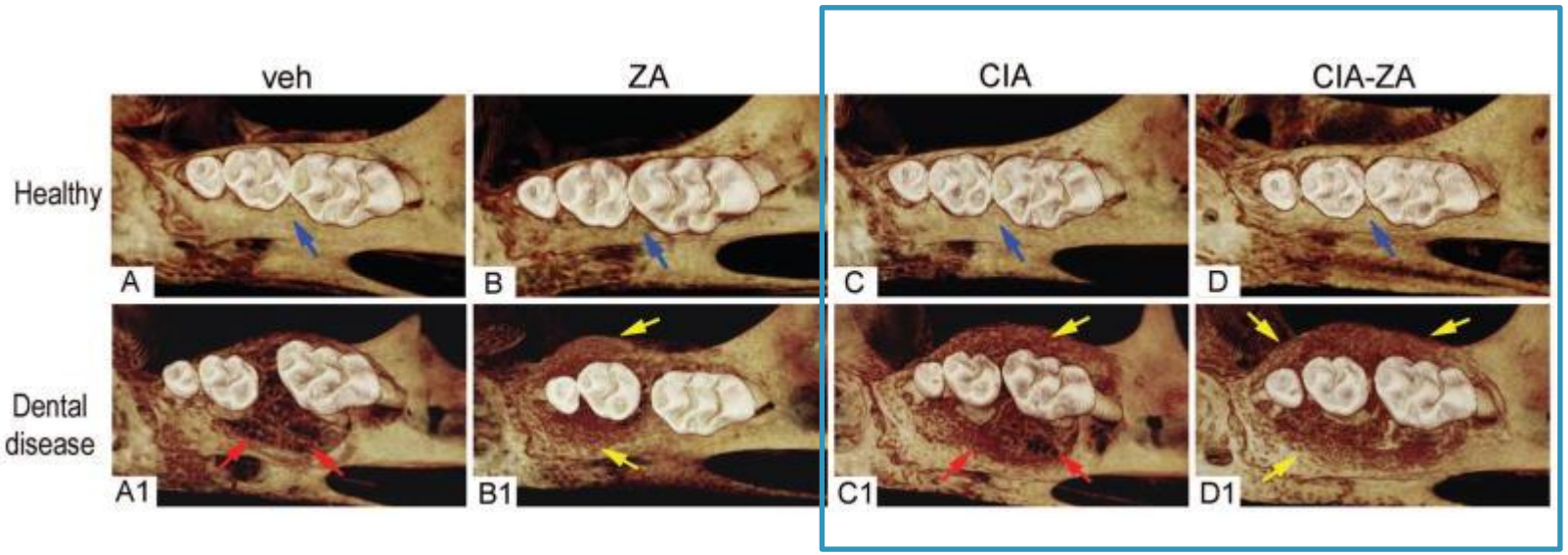
§ systemic/**generalized osteopenia** or osteoporosis involving the axial and appendicular skeleton.

Pathophysiology of osteoporosis in RA



JBMR®

Rheumatoid Arthritis Exacerbates the Severity of Osteonecrosis of the Jaws (ONJ) in Mice. A Randomized, Prospective, Controlled Animal Study



- Maxillae and mandibles of control and CIA mice showed bone loss, periodontal ligament (PDL) space widening, lamina dura loss, and cortex thinning.
- Empty osteocytic lacunae and areas of osteonecrosis were present in ZA and CIA-ZA but more extensively in CIA-ZA animals, indicating more severe ONJ.

De Molon et al, Journal of Bone and Mineral Research, Vol. 31, No. 8, August 2016, pp 1596–1607

MRONJ in RA - a systematic review

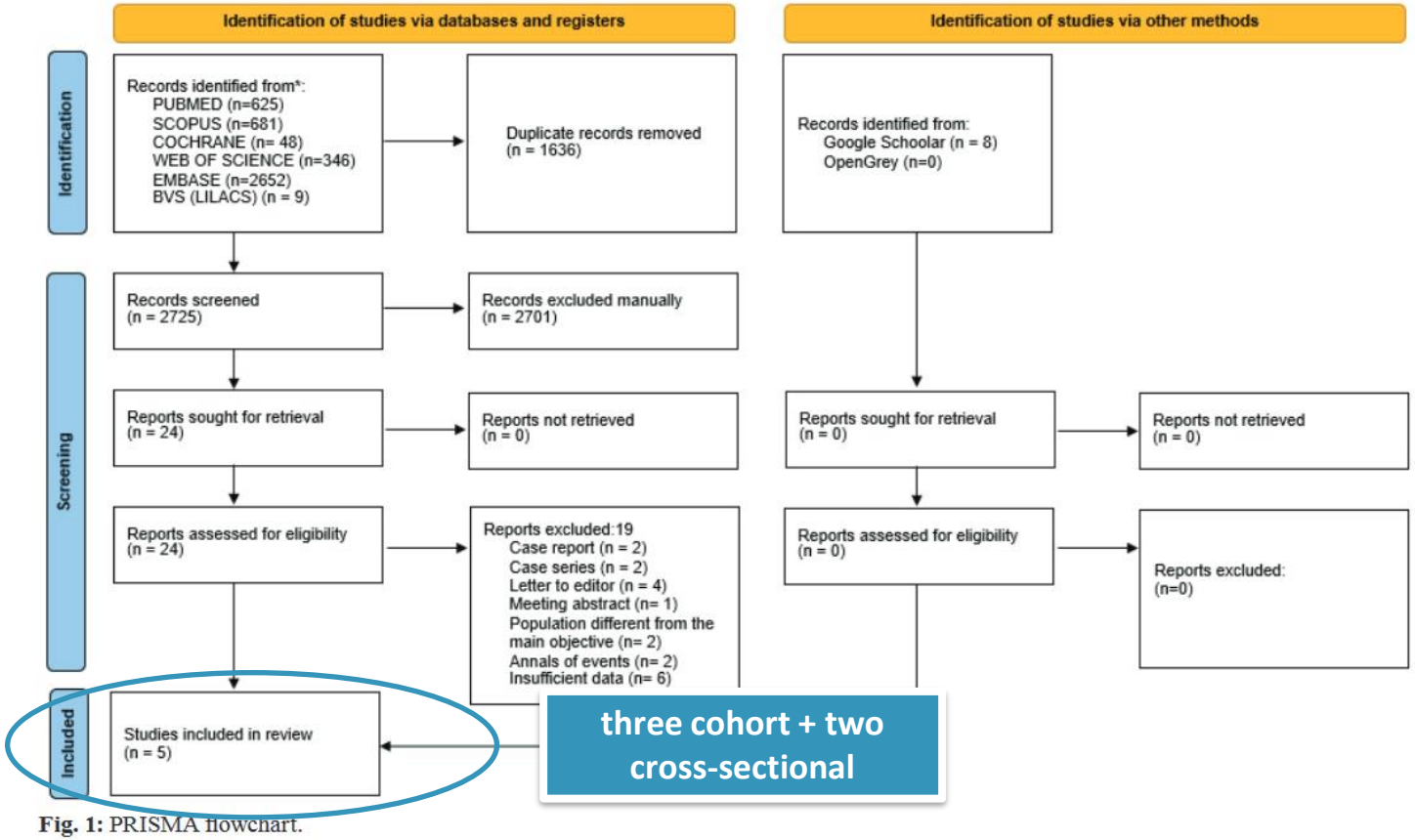


Fig. 1: PRISMA flowchart.

- 36 cases of BAONJ-RA
- The incidence ranged from 0.4% to 2.21
- Women between the 6th and 8th decade of life the most affected.
- The duration of bisphosphonates use ranged from 2.7 to 8 years

Tenorio JR et al., Med Oral Patol Oral Cir Bucal 2023

Incidence of and risk for MRONJ: a nationwide cohort-study

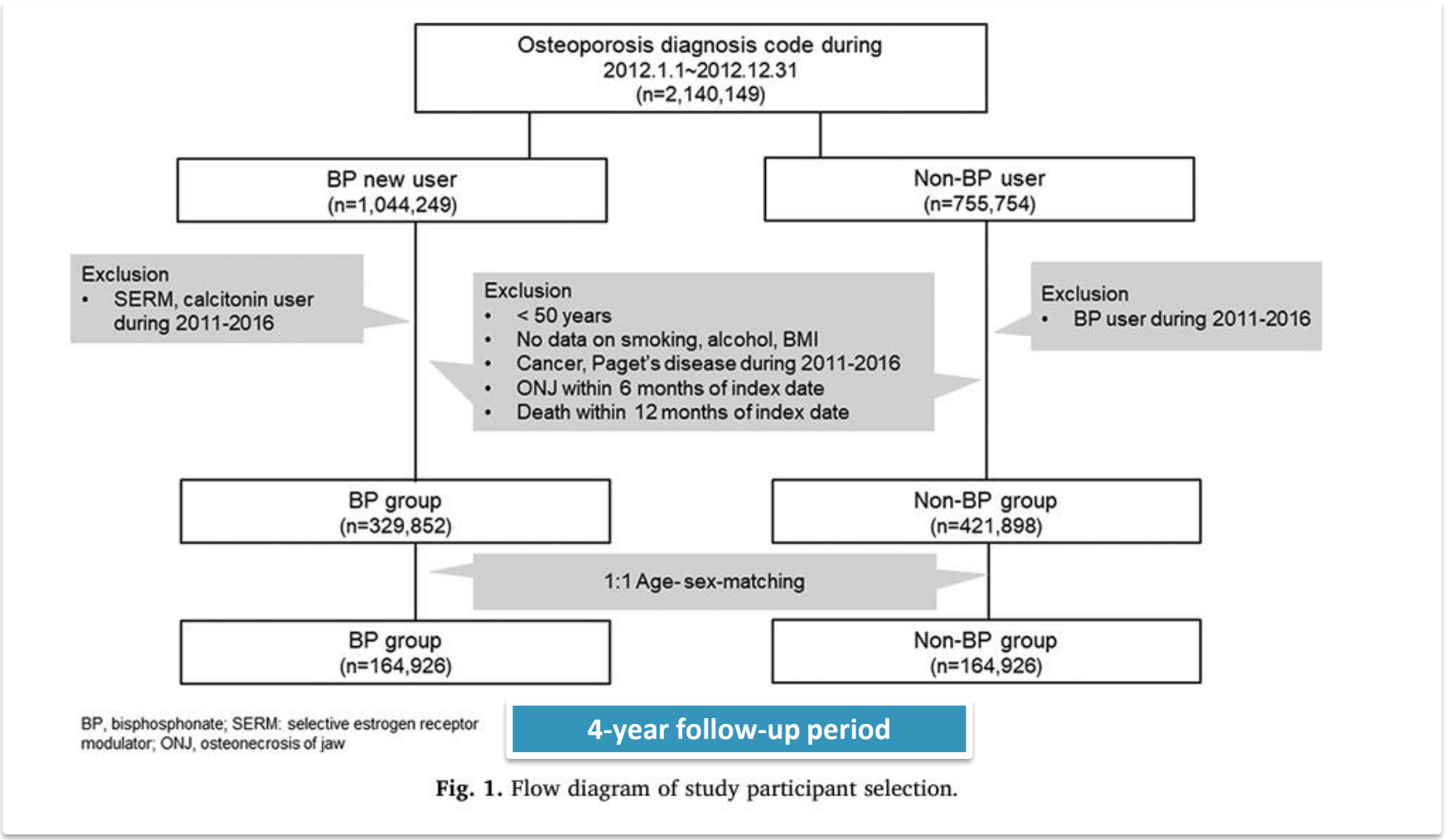


Fig. 1. Flow diagram of study participant selection.

Kim S.H. et al., Bone 143 (2021)

Association between hazard ratio and risk factors based in multivariate Cox model.

Variables	Subgroup	Number of ONJ case/number of subgroup patients	aHR[a]	95% CI	*P*-value
Control/BP group	Control	55/164,871	1.0 (Ref)		
	BP group	166/164,871	3.72	2.70–5.11	< 0.001
Sex	Male	16/28,028	1.0 (Ref)		
	Female	205/301,824	1.48	0.86–2.56	0.156
Age group	50–59 years	23/70,752	1.0 (Ref)		
	60–69 years	65/126,700	1.28	0.79–2.07	0.315
	70–79 years	112/111,882	2.31	1.44–3.69	< 0.001
	≥80 years	21/20,518	2.96	1.59–5.48	< 0.001
BMI	< 18.5 kg/m^2	11/9998	1.0 (Ref)		
	18.5–22.9 kg/m^2	84/118,422	0.67	0.35–1.26	0.221
	23.0–24.9 kg/m^2	59/84,660	0.63	0.33–1.21	0.170
	≥25.0 kg/m^2	67/116,832	0.48	0.25–0.93	0.029
Smoking	Smoking	6/12,069	0.75	0.31–1.76	0.508
Osteoporotic fracture		53/41,548	1.56	1.13–2.14	0.005
Dental disease	Tooth extraction	202/141,358	9.85	6.03–16.08	< 0.001
	Dental implant	16/17,976	0.59	0.35–0.98	0.042
	Gingivitis & periodontal disease	217/255,206	4.78	1.71–13.35	0.002
Co-administered agents	Glucocorticoid	31/31,065	1.01	0.66–1.55	0.946
	Angiogenesis inhibitors	1/234	10.11	1.41–72.40	0.021
Co-morbid disease	Diabetes	51/50,770	1.42	1.02–1.95	0.033
	Hypertension	115/133,091	1.43	1.07–1.88	0.012
	Rheumatoid arthritis	13/3201	7.39	3.90–14.00	< 0.001
	Renal failure	2/1589	1.92	0.47–7.78	0.359
	Heart failure	3/3842	0.87	0.27–2.72	0.809
	Stroke	8/12,861	0.70	0.34–1.43	0.337
	Parkinson's disease	2/2271	0.91	0.22–3.71	0.903

aHR, adjusted hazard ratio; BP, bisphosphonate; CI, confidence interval; BMI, body mass index.
The aHR (95% CI) and *P*-values were obtained using a Cox proportional hazards regression analysis.
[a] Adjusted for age, sex, BMI, smoking, osteoporotic fracture, dental disease, glucocorticoid use, use of angiogenesis inhibitors, and co-morbid diseases.

Journal of Bone and Mineral Metabolism (2020) 38:581–588
https://doi.org/10.1007/s00774-020-01089-y

ORIGINAL ARTICLE

Incidence and risk of antiresorptive agent-related osteonecrosis of the jaw (ARONJ) after tooth extraction in patients with autoimmune disease

Yuichiro Fujieda[1] · Mototsugu Doi[1] · Takuya Asaka[2] · Masahiro Ota[3] · Ryo Hisada[1] · Naoki Ohnishi[1] · Michihiro Kono[1] · Hiraku Kameda[1] · Daigo Nakazawa[1] · Masaru Kato[1] · Olga Amengual[1] · Masahiko Takahata[3] · Shinsuke Yasuda[1] · Yoshimasa Kitagawa[2] · Tatsuya Atsumi[1]

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	N (%)
RA	54 (43.2)
SLE	24 (19.2)
SjS	10 (8.0)
Vasculitis	10 (8.0)
PM/DM	9 (7.2)
SSc	3 (2.4)
BD	3 (2.4)
PsA	3 (2.4)
PMR	3 (2.4)
APS	2 (1.6)
Rp	2 (1.6)
Others	5 (4.0)

Variable	Univariate analysis			Multivariate analysis		
	Unadjusted hazard ratio	(95% CI)	*p* value	Adjusted hazard ratio	(95% CI)	*p* value
Age (years)	1.02	(0.98–1.08)	0.32			
BMI (kg/m^2)	1.10	(0.94–1.23)	0.20			
AID	6.94	(1.30–128)	**0.02***	7.16	(1.34–132)	**0.02***
RA	4.77	(1.36–18.7)	**0.02***			
AID without RA	0.89	(0.19–3.19)	0.86			
Glucocorticoid therapy	3.75	(1.11–112)	**0.04***			
Diabetes mellitus	0.77	(0.42–4.11)	0.80			
Previous fractures	2.70	(0.40–10.7)	0.26			
Smoker	3.45	(0.52–13.7)	0.17			
Bisphosphonate	1.63	(0.31–30.1)	0.62			
Administration period of AR	1.03	(1.01–1.04)	**0.0005***	1.03	(1.01–1.04)	**0.0004***

J Stomatol Oral Maxillofac Surg 123 (2022) e458–e463

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Review

Possible association of methotrexate use with osteonecrosis of the jaw: Systematic review

- In total 9 studies with 14 patients were included in the review
- three (21.4%) out of the 14 patients with ONJ were also receiving bisphosphonates concomitantly with the methotrexate, while one (7.2%) patient was also on therapy with prednisone; a further three (21.4%) patients were taking both bisphosphonates and prednisone

Marko Milosavljevi et al. J Stomatol Oral Maxillofac Surg 123 (2022) e458–e463

Vol. 131 No. 4 April 2021

Is medication-related osteonecrosis of the jaw associated with tumor necrosis factor-α inhibition?

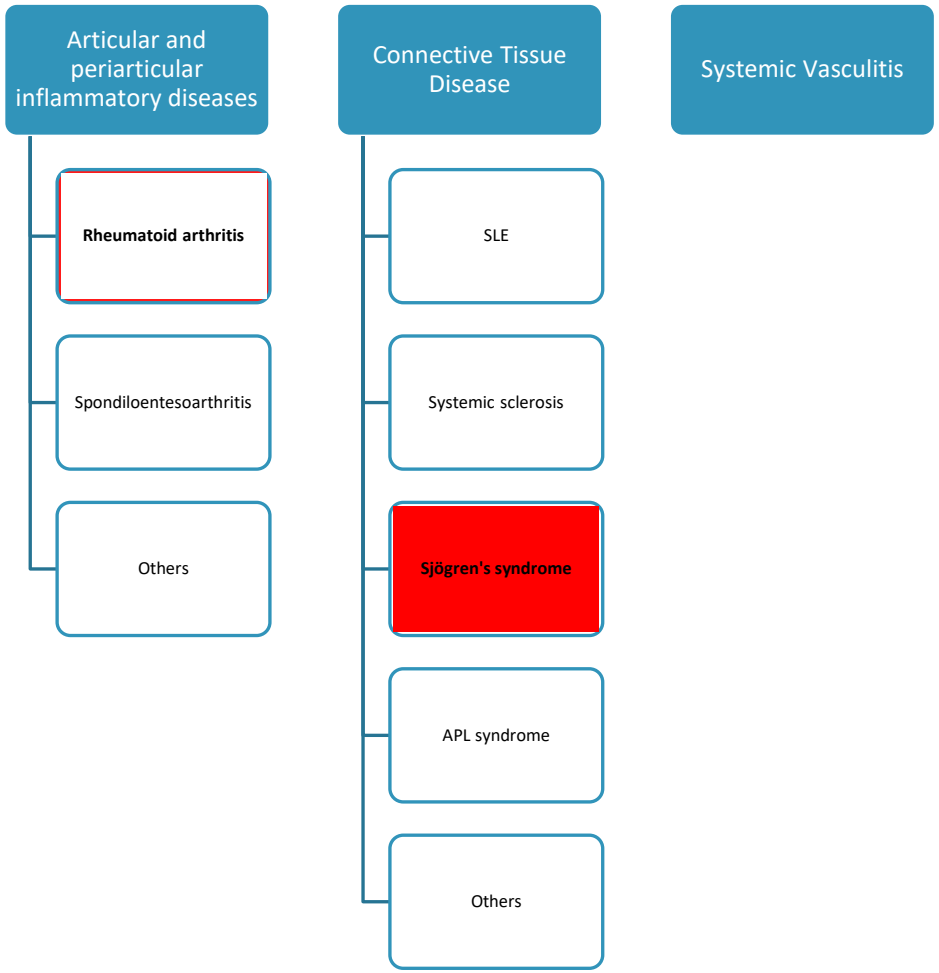
Stacy A. Rosenberg, BS,[a] Cesar Migliorati, DDS, MS, PhD,[b] and Georgios E. Romanos, DDS, PhD[a]

- 5 studies included
- case reports: risk factors included dental extractions or implant placement
- the degree to which TNF-a inhibitors impact bone turnover is not clear

Rosenberg S et al. Oral Surg Oral Med Oral Pathol Oral Radiol 2021;131:422 427

conclusive associations are lacking
disease activity the main driver

Classification of rheumatic diseases of the Italian Society of Rheumatology



Sjögren’s syndrome

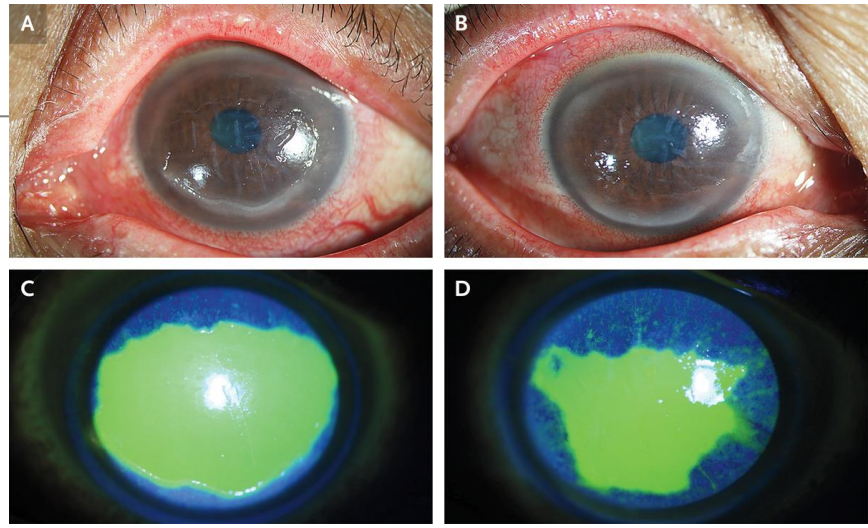
- F: M = 9:1
- There are two peaks of onset, one after menarche (first menstruation) and one after menopause.
- Prevalence is 0.5% - 1% for the primary form; most studies report a prevalence between 0.092% and 3.59%, with the majority of cases below 2%.
- Incidence is 3.9 - 5.3 per 100,000 population per year. Prevalence is higher in the elderly.
- 30% of patients with RA (Rheumatoid Arthritis), SLE (Systemic Lupus Erythematosus), and Scleroderma have secondary Sjogren's syndrome.

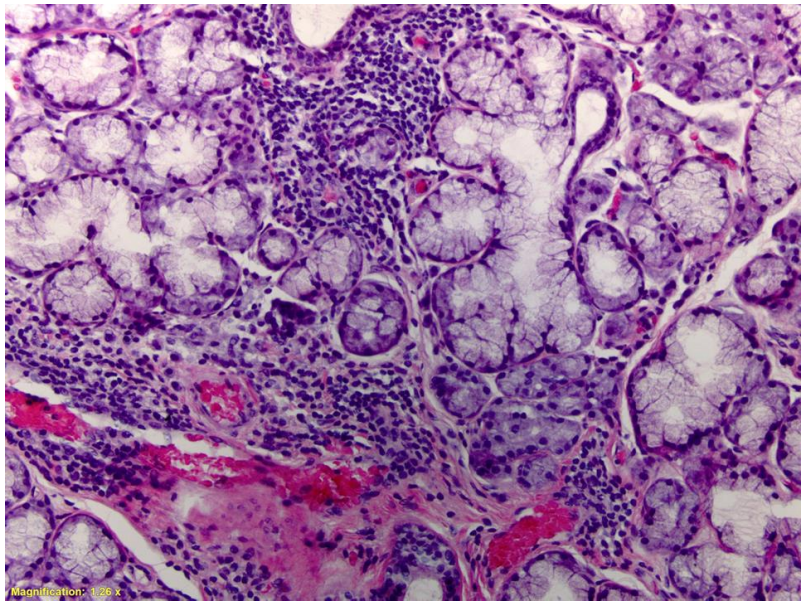
Clinical manifestations

Table 1. 2017 ACR–EULAR Classification Criteria for Primary Sjögren's Syndrome.*

Item	Description	Score
Focus score of ≥1	A score determined by the number of mononuclear-cell infiltrates containing ≥50 inflammatory cells per 4 mm^2 of minor labial salivary gland obtained on biopsy	3
Presence of anti-SSA antibodies†	Measured in serum; only anti-Ro60 antibodies have to be considered; isolated anti-Ro52 antibodies are not specific for Sjögren's syndrome	3
SICCA ocular staining score of ≥5	A score determined by an ophthalmologist on the basis of examination with fluorescein and lissamine green staining; scores range from 0 to 12, with higher scores indicating greater severity	1
Schirmer test of ≤5 mm per 5 min	An assay for measuring tear production by inserting filter paper on conjunctiva in the lower eyelid and assessing the amount of moisture on the paper	1
Unstimulated whole salivary flow of ≤0.1 ml per min	An assay for measuring the rate of salivary flow by collecting saliva in a tube for at least 5 min after the patient has swallowed	1
Total score		**9**

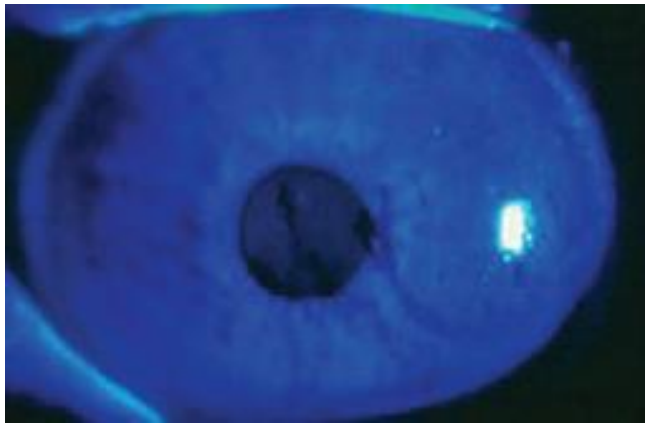
≥4

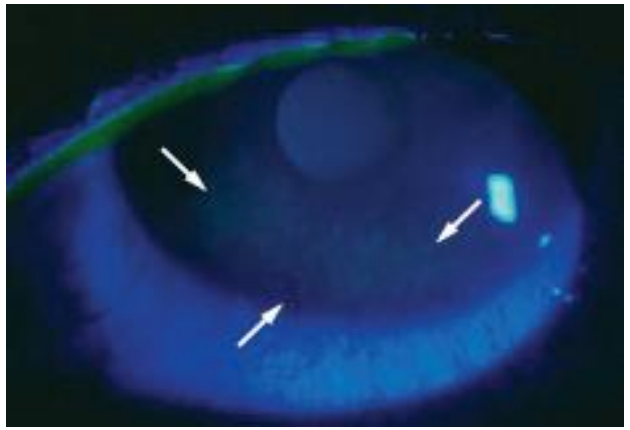




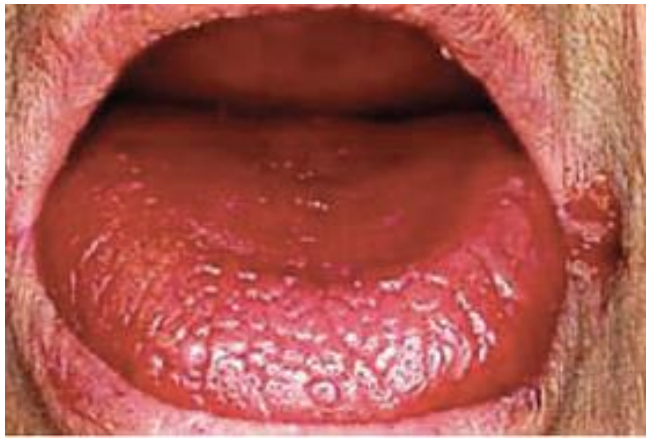
(NEJM)

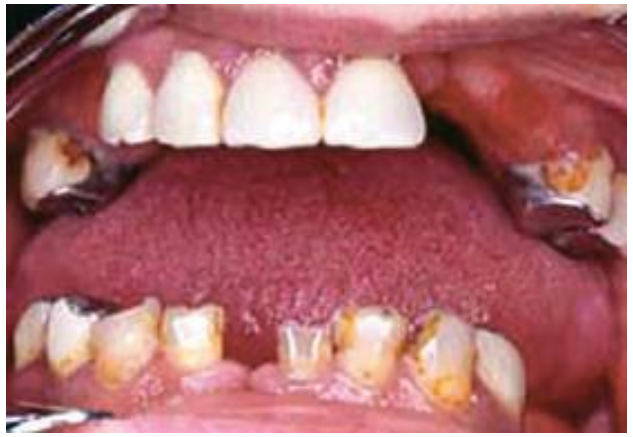
Sicca complex, glandular manifestations





Xeroftalmia





Xerostomia

Association between Sjögren's syndrome and ONJ after tooth extraction

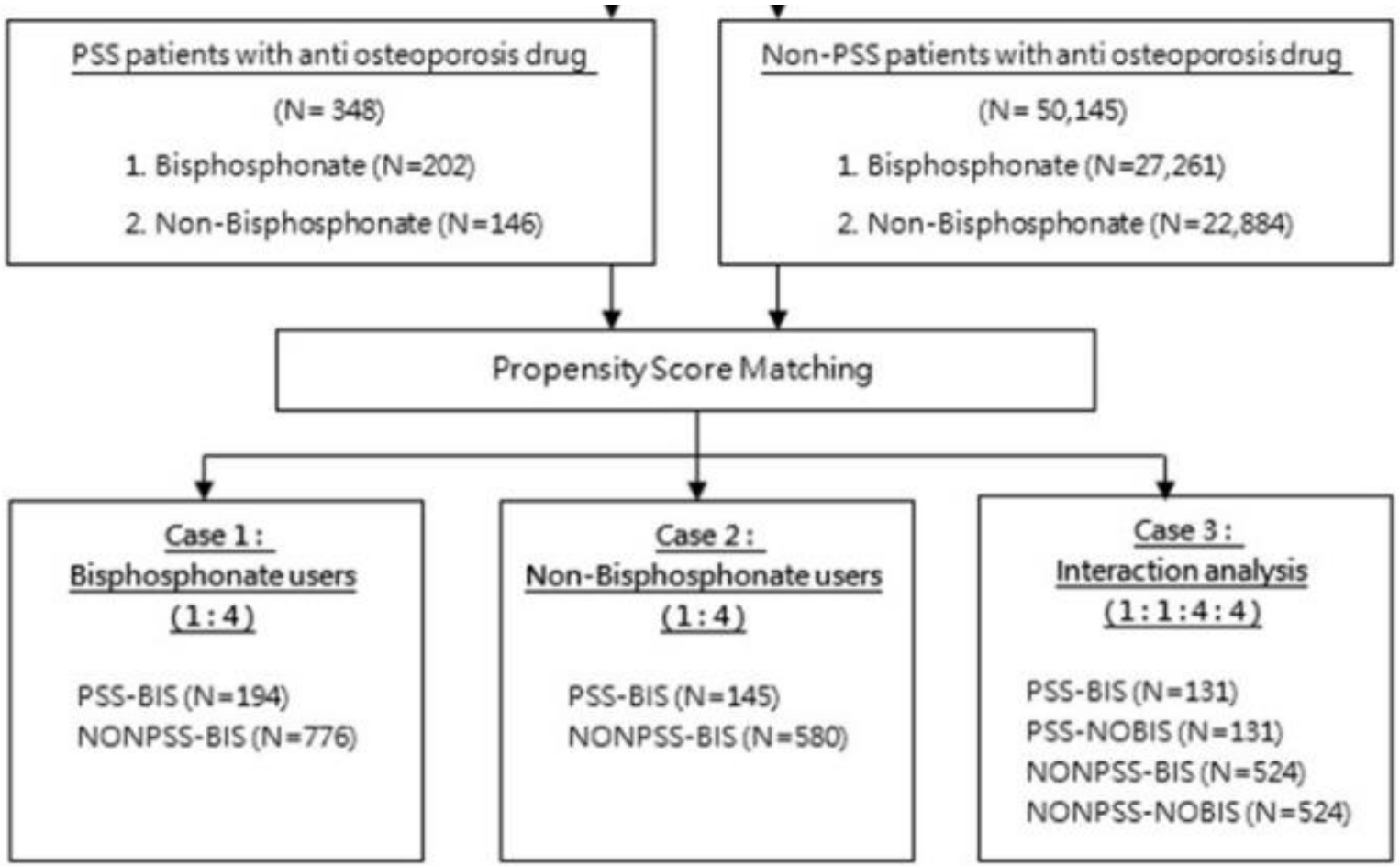
Table 3 Factors associated with osteonecrosis of the jaw according to the Cox regression model

Variables	Crude HR	95% CI	P value	Adjusted HR	95% CI
Sjögren's syndrome	9.047	3.937 to 20.787	<0.001	7.635	3.126 to 18.649
Gender (male)	2.470	1.140 to 5.352	0.022	2.533	1.115 to 5.556
Age (≧60 years vs 20–29 years)	1.035	0.138 to 7.770	0.974	1.024	0.131 to 8.014
Malignancy	1.838	0.781 to 4.326	0.163	1.593	0.659 to 3.848
DM	0.817	0.310 to 2.155	0.683	1.147	0.417 to 3.150
Hypertension	0.624	0.236 to 1.651	0.343	0.643	0.233 to 1.775
Osteoporosis	3.733	0.886 to 15.731	0.073	2.939	0.679 to 12.722
Bisphosphonates	2.538	1.029 to 6.260	0.043	2.488	1.005 to 6.156
Steroids	3.903	0.900 to 16.928	0.069	1.016	0.218 to 4.742
Radiotherapy	1.355	0.973 to 5.034	0.792	1.230	0.783 to 4.526
Chemotherapy	1.421	0.875 to 4.010	0.675	1.211	0.685 to 3.097

P values <0.05 were considered statistically significant HR.
Adjusted HR, adjusted variables listed in the table; DM, diabetes mellitus.

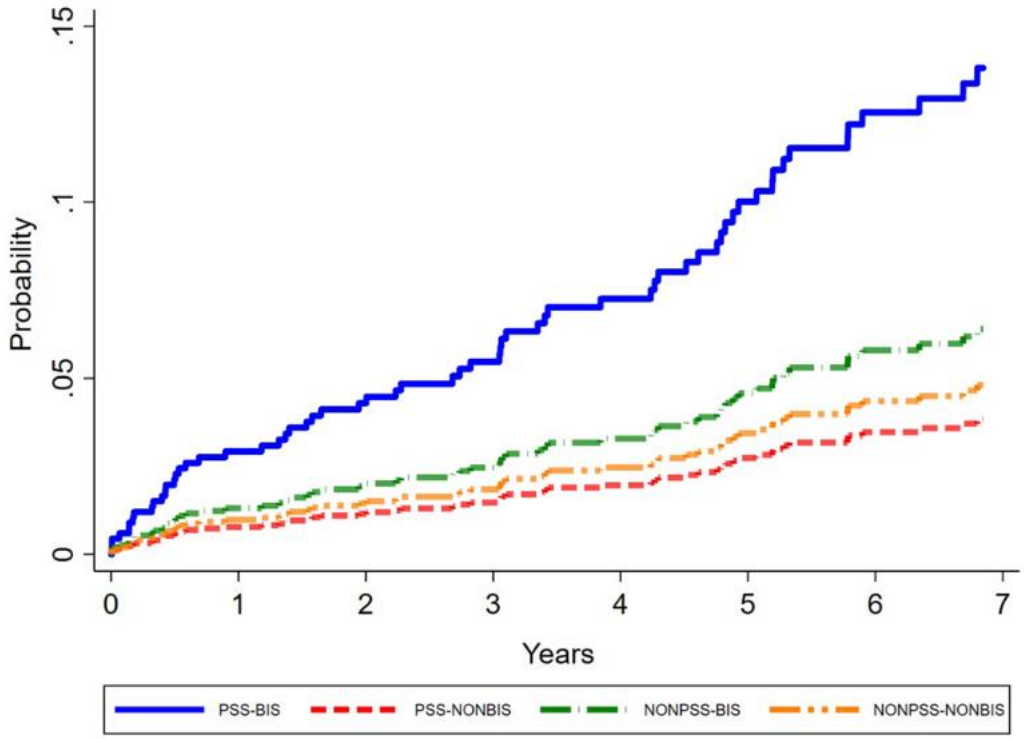
Liao M-t, et al. BMJ Open 2019;9:e024655. doi:10.1136/bmjopen-2018-024655

Population-based propensity-score-matched cohort study



Kuo P et al., Scientific Reports, (2021) 11:1612

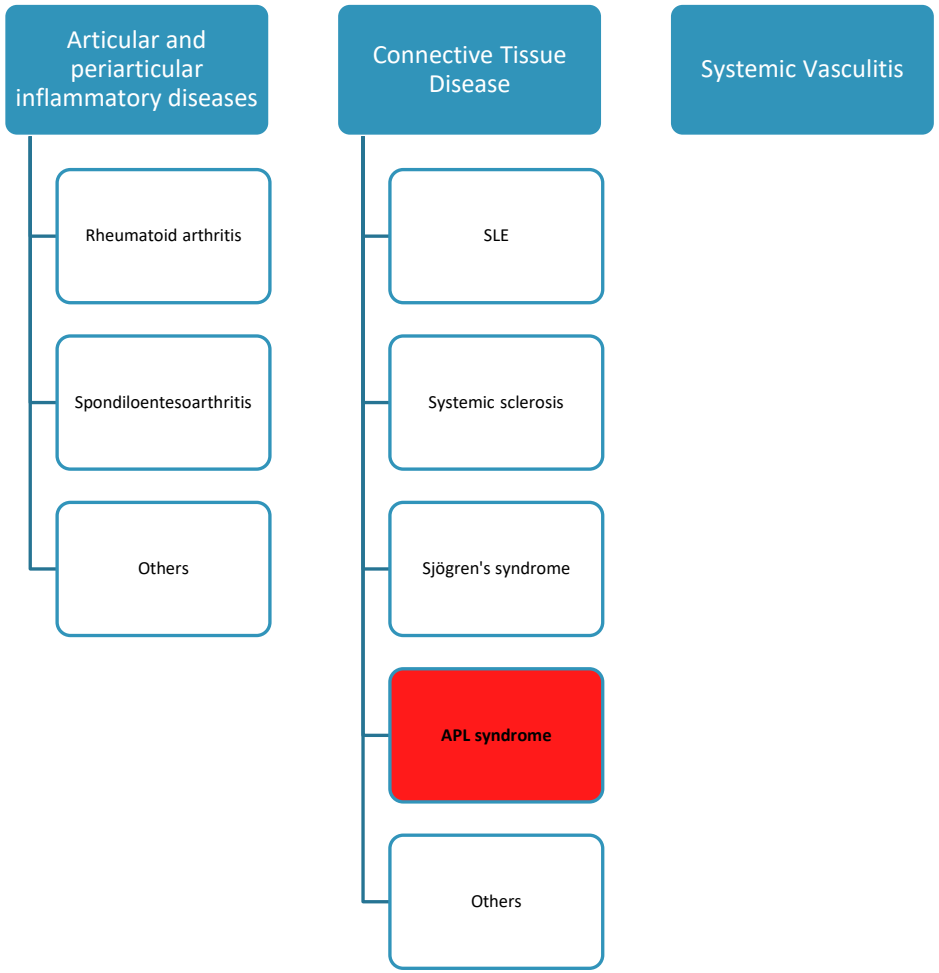
Cumulative risk of ONJ



Group	Adj. HR	95 CI for Adj. HR
pSS-BIS	3.01**	(1.50–6.06)
pSS-NONBIS	0.79	(0.29–2.20)
NONpSS-BIS	1.34	(0.77–2.34)
NONpSS-NONBIS	Ref.	

Kuo P et al., Scientific Reports, (2021) 11:1612

Classification of rheumatic diseases of the Italian Society of Rheumatology



Antiphospholipid syndrome

Is a systemic autoimmune disorder with a wide range of vascular and obstetric manifestations associated with thrombotic and inflammatory mechanisms orchestrated by antiphospholipid (aPL) antibodies.

Clinical criteria

1. Vascular thrombosis

One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ

2. Pregnancy morbidity

(a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology (b) One or more premature births of a morphologically normal neonate **before the 34th week** of gestation because of: (a) eclampsia or severe preeclampsia or (b) recognized features of placental insufficiency (c) three or more unexplained consecutive spontaneous abortions before the 10th week of gestation

Laboratory criteria

1. Anticardiolipin antibody of IgG and/or IgM isotype in serum or plasma
2. Lupus anticoagulant present in plasma
3. Anti-b2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma

Persistent positivity at least 12 weeks apart

Risk stratification (single, double, triple positivity)

primary APS or associated with other diseases mainly SLE

International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). **Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, Derksen RH, DE Groot PG, Koike T, Meroni PL, Reber G, Shoenfeld Y, Tincani A, Vlachoyiannopoulos PG, Krilis SA.** 2006, Journal of Thrombosis and Haemostasis, p. 4 : 295-306.

APL and Osteonecrosis

The presence of aPL has been described in several cases with idiopathic osteonecrosis of the jaw and femoral head

In a study by Glueck et al, 43 of the 55 patients with idiopathic osteonecrosis had one or more tests positive for thrombophilia and/or hypofibrinolysis; 8 out of those patients (33%) were aCL positive

Gruppo et al found abnormal serum aCL titers in 18 (33%) of 55 patients with idiopathic alveolar osteonecrosis of the jaw

The high frequency of aPL in all the above studies with idiopathic osteonecrosis suggests an important role for these antibodies in the pathogenesis of the osteonecrotic lesions

Conclusions

Patients with AID who undergo dental extraction are at high risk of MRONJ

Patient's profile: RA, Sjogren, dental extraction, age, duration of AR treatment

Role of inflammation in MRONJ disease prevalence, severity and resolution >> therapy (GCs, IS)