

## ORIGINAL RESEARCH

## Dental infection is associated with early relapse in patients with ANCA-associated vasculitis

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**ABSTRACT**

**Objectives** Anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) is a systemic autoimmune disease where infections can trigger relapses. Dental infections, being common and associated with systemic inflammation, may play a role in AAV relapse, though their impact remains unclear. We aimed to evaluate the association between severe dental infections and early relapse in patients with AAV.

**Methods** This retrospective cohort study included patients newly diagnosed with AAV between January 2011 and July 2022. Patients with severe dental infections requiring tooth extraction were placed in the dental infection group, while the remaining patients were assigned to the control group. The primary outcome was defined as either vasculitis relapse or all-cause mortality within 1 year of treatment initiation. Adjusted HRs (aHRs) and 95% CIs were estimated using Cox proportional hazards models.

**Results** A total of 93 patients were enrolled with a median age of 74 years. 41 patients (44.1%) had severe dental infections in this cohort. Over the 1-year follow-up period, 13 patients experienced a relapse and two died, resulting in a composite event rate of 20.9 per 100 person-years. Dental infection was independently associated with the composite outcome (aHR, 3.78 (95% CI 1.13 to 12.66);  $p=0.031$ ). Exploratory analysis indicated that composite outcome rates were similar regardless of tooth extraction among patients with dental infections.

**Conclusions** Severe dental infections were associated with increased risk of early relapse or mortality in AAV. These findings highlight the importance of early dental evaluation in AAV management.

**INTRODUCTION**

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a systemic autoimmune disease that primarily affects small-sized and medium-sized blood vessels, leading to damage in multiple organs,

**WHAT IS ALREADY KNOWN ON THIS TOPIC**

⇒ Dental infections have been associated with increased disease activity in autoimmune diseases such as Behçet's disease and systemic lupus erythematosus.

**WHAT THIS STUDY ADDS**

⇒ In a retrospective cohort of newly diagnosed anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) patients, nearly half had dental infections that required tooth extraction.  
⇒ Severe dental infection was independently associated with the relapse or all-cause mortality within 1 year from the treatment initiation in patients with AAV.

**HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY**

⇒ The findings support the importance of routine dental evaluation during the first year of AAV treatment.  
⇒ Further prospective studies including oral microbiome analysis and standardised dental assessments may help clarify these associations.

including the lungs, kidneys and nervous system.<sup>1,2</sup> The major subtypes of AAV include microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA).<sup>3</sup> While remission induction therapy with glucocorticoids (GC) and immunosuppressive agents, such as cyclophosphamide or rituximab (RTX), results in remission for most patients,<sup>4,5</sup> relapse continues to pose a significant clinical challenge during remission maintenance therapy. The reported relapse rate during RTX maintenance therapy (follow-up: 294.5 patient-years) was 24%

(10.2 per 100 patient-years).<sup>6</sup> Another systematic review reported 1-year and 5-year cumulative relapse rates of 12% and 47%, respectively, in patients with AAV receiving cyclophosphamide induction therapy.<sup>7</sup> Identifying the risk factors for relapse is important for improving long-term outcomes in patients with AAV.

Several risk factors for relapse have been identified, including PR3-ANCA positivity, organ involvement and the type of induction regimen.<sup>6 8–10</sup> Infections are also significant contributors, with severe infections associated with a higher relapse rate (HR 4.68).<sup>11</sup> While pneumonia is the most frequently reported infection (81.4%) in this study, dental infections (DIs) have not been sufficiently investigated in this context.

DIs, such as caries and periodontitis, are common. Periodontitis, in particular, is associated with chronic inflammatory and thrombotic conditions, including diabetes, cardiovascular and autoimmune diseases.<sup>12 13</sup> The prevalence of apical periodontitis has been reported to be significantly higher in patients with autoimmune diseases, including rheumatoid arthritis, inflammatory bowel disease and psoriasis, compared with controls.<sup>14</sup> Recent epidemiological studies have demonstrated that patients with periodontitis are more susceptible to systemic inflammatory diseases. For instance, a retrospective cohort study conducted in the UK, which followed over 60 000 patients with periodontitis for approximately 3.4 years, reported an increased risk of developing autoimmune diseases in these patients (HR 1.33).<sup>15</sup> Additionally, several studies have suggested that periodontal inflammation may stimulate the production of ANCA.<sup>16 17</sup> These findings suggest that chronic DIs may contribute to the systemic inflammatory burden and the progression of autoimmune pathology through the periodontitis-induced elevation of ANCA levels. However, the association between DIs and clinical outcomes, such as relapse, has not yet been clarified in patients with AAV.

We hypothesised that patients with DIs would experience an earlier relapse of AAV. Consequently, we conducted a retrospective cohort study to examine the association between severe DIs and relapse of AAV after remission induction therapy.

## METHODS

### Study population and data collection

This single-centre, retrospective cohort study included patients newly diagnosed with AAV who underwent dental evaluation at Okayama University Hospital between January 2011 and July 2022. The diagnosis of AAV, including MPA, GPA, EGPA and unclassifiable vasculitis, was established using the European Medicines Agency algorithm for primary systemic vasculitis.<sup>18 19</sup> We performed sensitivity analyses by reclassifying and reanalysing the data according to the 2022 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria for AAV.<sup>20–22</sup> We excluded patients who failed to achieve

complete remission after induction therapy and those who did not undergo dental evaluation during hospitalisation for induction therapy. Complete remission was defined as the absence of clinical signs and symptoms of active vasculitis, with a Birmingham vasculitis activity score (BVAS) of 0.<sup>23–25</sup> Relapse was defined as a recurrence of clinical symptoms attributable to active vasculitis with a corresponding increase of 1 point or more in BVAS, or as treatment intensification at the discretion of the attending physician.

Two independent reviewers (SN and KM), neither serving as the patient's treating physician, reviewed and extracted data from medical records, including age at dental evaluation, sex, AAV subtype, body mass index (BMI), smoking history, comorbidities (including malignancy, hypertension and dyslipidaemia), and laboratory findings at diagnosis (serum creatinine, C reactive protein and ANCA status). We obtained additional information on organ involvement, vasculitis activity (BVAS at diagnosis), initial daily prednisolone dose and dose per body weight, as well as remission induction therapy regimens (cyclophosphamide or RTX). Renal involvement attributed to active vasculitis was defined by elevated serum creatinine levels, haematuria, proteinuria, the presence of red blood cell casts and/or histopathological evidence of pauci-immune glomerulonephritis on kidney biopsy.<sup>26</sup> Pulmonary involvement was defined by the presence of radiographic abnormalities consistent with alveolar haemorrhage, interstitial lung disease or pulmonary nodules, with or without accompanying respiratory symptoms. Any discrepancies or disagreements were resolved by consensus with a third reviewer (TK) to minimise misclassification between infection and true relapse.

### Exposure and outcomes

In all patients, dentists were consulted to determine whether the DIs required tooth extraction. Patients with severe DIs requiring tooth extraction were classified into the DI group, whereas all other patients, including those with mild DIs not requiring extraction, were included in the control group. The primary outcome was a composite of vasculitis relapse or all-cause mortality occurring first within 1 year of initiating induction therapy. We treated mortality as part of the composite outcome, rather than as a competing risk, as only two deaths were recorded during the 1-year follow-up period. Relapse was defined as a vasculitis flare indicated by an increase in BVAS of more than one point.

The secondary outcome was the incidence of severe adverse events within 1 year, as defined by the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE V.5.0).<sup>27</sup> Serious adverse events included infections requiring hospitalisation or intravenous antibiotics, malignancies, cardiovascular and cerebrovascular events, infusion reaction and other adverse events requiring hospitalisation.

### Statistical analysis

Continuous variables are summarised as medians with IQRs, and categorical variables are presented as frequencies with percentages. Outcomes were reported as proportions and incidence rates (IRs) per 100 person-years (PY). Patients were censored at the earliest of the following events: 1 year after remission induction therapy, the end of the study (31 July 2022), death from another cause, or loss to follow-up during this study period.

We used Kaplan-Meier analysis to estimate the time-to-event outcomes of interest. The log-rank test was used to assess differences between survival curves. A multivariate Cox proportional hazards model was used to evaluate the association between DIs and relapse-free survival. In model 1, adjustments were made for age and sex; model 2 adjusted for age and initial prednisolone dose; model 3 adjusted for age and renal involvement; model 4 adjusted for ANCA subtype (reference: ANCA-negative); model 5 adjusted for ANCA subtype and baseline BVAS; model 6 adjusted for AAV subtype (reference: others) and model 7 adjusted for AAV subtype and baseline BVAS. We assessed the proportional hazards assumption using Schoenfeld residuals in all models applied to the primary outcome, and this assumption was satisfied in all models.

We also performed exploratory subgroup analyses to examine whether the association between DI and relapse varied according to baseline characteristics. Subgroups were defined based on ANCA subtype (proteinase 3: PR3 vs myeloperoxidase: MPO), AAV classification (MPA vs GPA), renal or pulmonary involvement, and whether tooth extraction was performed in patients with a DI. Relapse-free survival was visualised using Kaplan-Meier curves across subgroups.

For sensitivity analysis, we (1) reclassified diagnoses using the 2022 ACR/EULAR criteria for AAV<sup>20-22</sup> and repeated the multivariable Cox proportional hazards models; (2) repeated the primary analyses after excluding

EGPA and (3) performed a relapse-only analysis in which deaths unrelated to vasculitis were excluded from the risk set, while deaths attributable to vasculitis relapse were counted as relapse events.

As an additional analysis to address the limited number of events per variable (EPV), we also performed Lasso Cox with 10-fold cross-validation to select  $\lambda$ , using the covariate set as candidate predictors (age, sex, AAV subtype, ANCA positivity, baseline BVAS, initial prednisolone dose, renal involvement, pulmonary involvement, BMI) and DI. Initially, no covariates were forced; subsequently, DI was forced as an unpenalised term. We report penalised HRs, post-selection unpenalised Cox HRs (95% CIs), non-zero coefficients and EPV. The cross-validation deviance curve (online supplemental figure S1) and coefficient paths (online supplemental figure S2) are shown in the online supplemental materials.

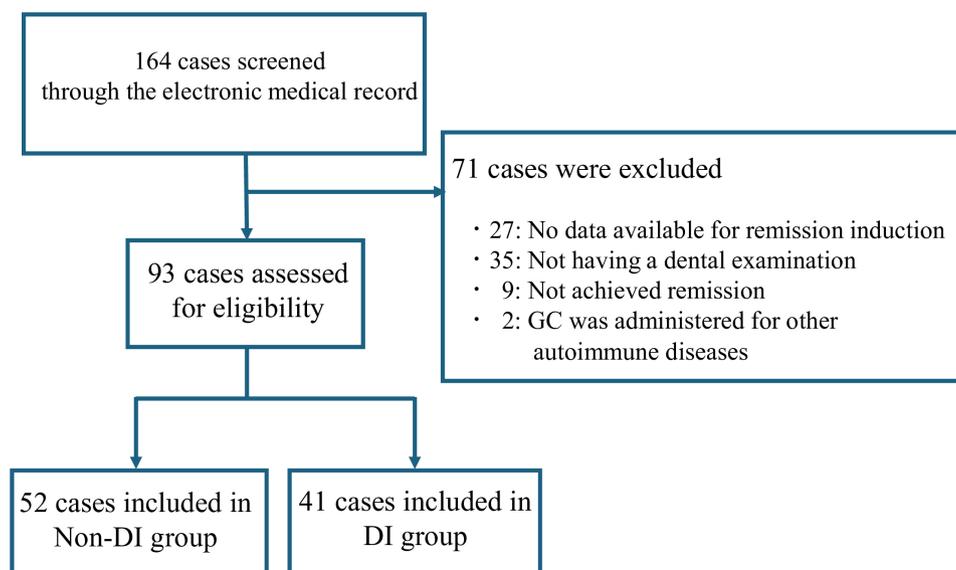
No formal sample size calculations were performed. No variables included in the multivariate models had missing data; therefore, no imputations were required. This study included all patients who were eligible during the study period. All HRs are reported with 95% CIs. Statistical significance was defined as a  $p < 0.05$ . All statistical analyses were performed using Stata software, V.19.5 (StataCorp).

## RESULTS

### Participant characteristics

This study screened 164 patients, of whom 71 were excluded, leaving 93 patients for analysis. The median follow-up duration in this cohort was 12.0 months, with comparable observation periods for patients with and without DIs requiring tooth extraction. Reasons for exclusions are presented in figure 1.

Among the 93 patients, 60 (64.5%) were female, and the median age was 74 years (IQR 68–79). [Table 1](#)



**Figure 1** Flow chart of patient inclusion and exclusion criteria. DI, dental infection; GC, glucocorticoids.

**Table 1** Patients baseline demographics and clinical characteristics

|                              | Total<br>N=93    | Non-DI<br>N=52   | DI<br>N=41       | P value |
|------------------------------|------------------|------------------|------------------|---------|
| Age, years                   | 74.0 (68.0–79.0) | 73.0 (66.5–79.5) | 74.0 (69.0–79.0) | 0.63    |
| Sex, female, n (%)           | 60/93 (65)       | 36/52 (69)       | 24/41 (59)       | 0.28    |
| BMI, kg/m <sup>2</sup>       | 22.1 (19.6–24.5) | 21.4 (19.3–24.4) | 22.4 (20.1–24.8) | 0.56    |
| Smoking, n (%)               |                  |                  |                  | 0.20    |
| Never                        | 56/93 (60)       | 33/52 (63)       | 23/41 (56)       |         |
| Past                         | 25/93 (27)       | 10/52 (19)       | 15/41 (37)       |         |
| Current                      | 7/93 (8)         | 5/52 (10)        | 2/41 (5)         |         |
| Missing                      | 5/93 (5)         | 4/52 (8)         | 1/41 (2)         |         |
| AAV subtype, n (%)           |                  |                  |                  | 0.55    |
| MPA                          | 38/93 (41)       | 21/52 (40)       | 17/41 (41)       |         |
| GPA                          | 36/93 (39)       | 18/52 (35)       | 18/41 (44)       |         |
| EGPA                         | 14/93 (15)       | 9/52 (17)        | 5/41 (12)        |         |
| Others                       | 5/93 (5)         | 4/52 (8)         | 1/41 (2)         |         |
| ANCA positivity, n (%)       |                  |                  |                  | 0.84    |
| Negative                     | 11/93 (12)       | 6/52 (12)        | 5/41 (12)        |         |
| MPO-ANCA                     | 77/93 (83)       | 43/52 (83)       | 34/41 (83)       |         |
| PR3-ANCA                     | 4/93 (4)         | 2/52 (4)         | 2/41 (5)         |         |
| Double positive              | 1/93 (1)         | 1/52 (2)         | 0/41 (0)         |         |
| CRP (mg/dL)                  | 6.2 (1.4–10.7)   | 8.0 (2.1–11.5)   | 5.3 (1.1–9.2)    | 0.16    |
| Creatinine (mg/dL)           | 0.8 (0.6–1.2)    | 0.8 (0.6–1.3)    | 0.9 (0.7–1.1)    | 0.89    |
| Pulmonary involvement, n (%) | 56/93 (60)       | 33/52 (63)       | 23/41 (56)       | 0.47    |
| Renal involvement, n (%)     | 48/93 (52)       | 28/52 (54)       | 20/41 (49)       | 0.63    |
| BVAS                         | 3.0 (2.0–6.0)    | 3.0 (2.0–6.0)    | 4.0 (2.0–5.0)    | 0.82    |
| PSL, mg                      | 45.0 (40.0–50.0) | 42.5 (32.5–50.0) | 50.0 (40.0–50.0) | 0.59    |
| PSL, mg/kg                   | 0.8 (0.7–1.0)    | 0.8 (0.7–1.0)    | 0.8 (0.7–1.0)    | 0.69    |
| Comorbidities, n (%)         |                  |                  |                  |         |
| Current malignancy           | 3/93 (3)         | 2/52 (4)         | 1/41 (2)         | 0.70    |
| Hypertension                 | 39/92 (42)       | 26/51 (51)       | 13/41 (32)       | 0.063   |
| Dyslipidaemia                | 20/93 (22)       | 8/52 (15)        | 12/41 (29)       | 0.11    |
| CHF, n (%)                   | 1/93 (1)         | 0/52 (0)         | 1/41 (2)         | 0.26    |
| Treatment regimen, n (%)     |                  |                  |                  | 0.26    |
| GC only                      | 22/93 (24)       | 11/52 (21)       | 11/41 (27)       |         |
| IV-CY                        | 51/93 (55)       | 26/52 (50)       | 25/41 (61)       |         |
| RTX                          | 14/93 (15)       | 10/52 (19)       | 4/41 (10)        |         |
| Others                       | 6/93 (6)         | 5/52 (10)        | 1/41 (2)         |         |
| Maintain, n (%)              |                  |                  |                  | 0.17    |
| GC only                      | 15/65 (23)       | 6/36 (17)        | 9/29 (31)        |         |
| AZA                          | 19/65 (29)       | 9/36 (25)        | 10/29 (34)       |         |
| MEPO                         | 1/65 (2)         | 1/36 (3)         | 0/29 (0)         |         |
| IVCY≤6 cycles                | 13/65 (20)       | 7/36 (19)        | 6/29 (21)        |         |
| MMF                          | 1/65 (2)         | 0/36 (0)         | 1/29 (3)         |         |
| RTX                          | 12/65 (18)       | 9/36 (25)        | 3/29 (10)        |         |
| Unknown                      | 4/65 (6)         | 4/36 (11)        | 0/29 (0)         |         |

Data are presented as median (IQR) for continuous measures, and No/total (%) for categorical measures.

AAV, ANCA-associated vasculitis; ANCA, anti-neutrophil cytoplasmic antibody; AZA, azathioprine; BMI, body mass index; BVAS, Birmingham Vasculitis Activity Score; CHF, congestive heart failure; CRP, C reactive protein; DI, dental infection; EGPA, eosinophilic granulomatosis with polyangiitis; GC, glucocorticoids; GPA, granulomatosis with polyangiitis; IV-CY, intravenous cyclophosphamide; MEPO, mepolizumab; MMF, mycophenolate mofetil; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PSL, prednisolone; RTX, rituximab.

summarises the demographic and clinical characteristics of the patients. Within the total cohort, 38 patients (40.8%) were diagnosed with MPA, 36 (38.7%) with GPA, 14 (15.1%) with EGPA and 5 (5.4%) with unclassifiable AAV. Lung and/or renal involvement was observed in more than half of the patients. Regarding induction therapy, 51 patients (54.8%) received intravenous cyclophosphamide pulse therapy (intravenous cyclophosphamide), and 14 (15.1%) received RTX. The median initial prednisolone dose was 45 mg (IQR 40–50).

Of the 93 patients, 41 (44.1%) were diagnosed with DIs requiring tooth extraction (figure 1). The prevalence of DIs did not differ significantly according to sex (40.0% in females vs 51.5% in males), AAV subtype (MPA, 44.7%; GPA, 50.0%; EGPA, 35.7%) or ANCA status (negative, 45.5%; MPO-ANCA, 44.2%; PR3-ANCA, 50.0%). The information on baseline markers of systemic inflammation is shown in table 1 and online supplemental table S1. The median timing of dental evaluation was 0 days (IQR –7 to 6 days). Patients with DI had a median of 0 days (IQR –7 to 7), and those without DI had a median of 0.5 days (IQR –6 to 5). Antibiotic use related to DI was common. In the overall cohort with DI, 78% received antibiotics (event-free 80% vs relapse/death 73%,  $p=0.62$ ; online supplemental table S2). Among 23 patients with DI who underwent tooth extraction, 91% received perioperative antibiotics (including 43% on the same day), with similar proportions in event-free (94%) and relapse/death (86%) subgroups ( $p=0.53$ ; online supplemental table S3). Organ involvement, disease activity (BVAS) and initial treatment, such as GC and immunosuppressive therapy, were comparable between the DI and control groups.

### Association between DI and the composite endpoint of relapse or death

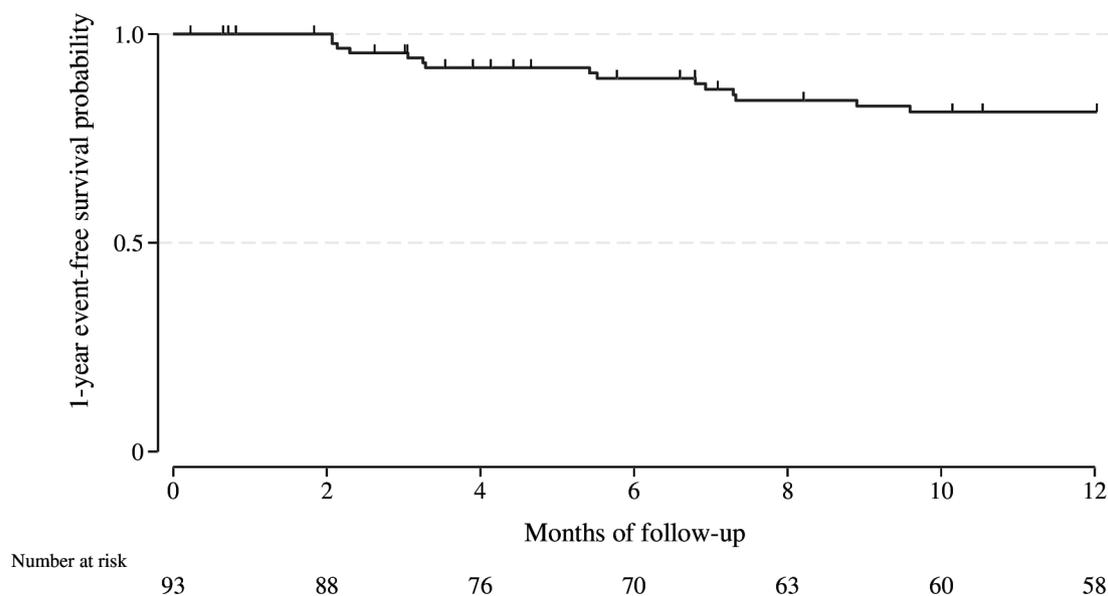
Within 1 year, 15 patients (16.1%) experienced either relapse or all-cause death, including 13 relapses and two deaths (figure 2). The overall IR of this composite outcome was 20.9 per 100 PY. The relapse or death rate was higher in male patients than in female patients (9/33, 27.3% vs 6/60, 10.0%). The 1-year relapse or death proportions according to AAV subtype were as follows: MPA, 3/38 (7.9%), GPA, 9/36 (25.0%) and EGPA, 2/14 (14.3%). We have added the information about the maintenance therapy in online supplemental table S4.

The crude IR of relapse or death was 34.8 per 100 PY (95% CI 19.3 to 63.0) among patients with DIs requiring tooth extraction, and 9.9 per 100 PY (95% CI 3.7 to 26.5) among those without. These correspond to event proportions of 26.8% (11 of 41 patients) and 7.7% (4 of 52 patients), respectively. Kaplan-Meier survival analysis showed significantly lower relapse-free survival in patients with DIs (log-rank  $p=0.025$ ) (figure 3).

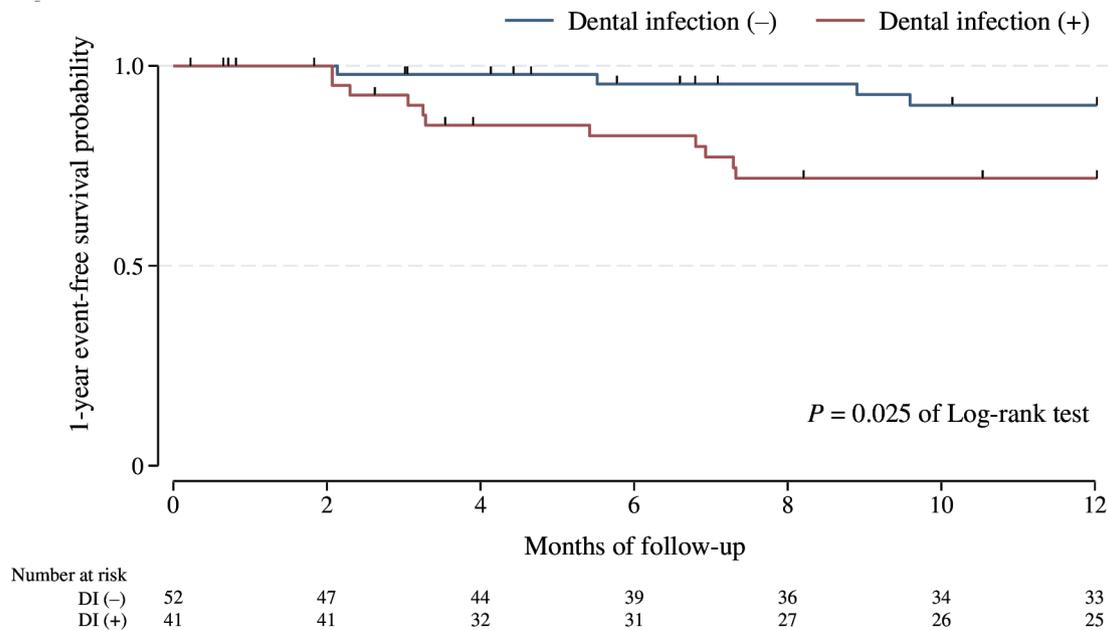
In the main analysis, DIs requiring tooth extraction were significantly associated with composite outcome (relapse and death) in all models (table 2). In the adjusted Cox proportional hazards model (model 7), which included AAV subtype and baseline BVAS, DI remained significantly associated with an increased risk of composite outcome (adjusted HR, 3.78 (95% CI 1.13 to 12.66);  $p=0.031$ ).

### Serious adverse events within 1 year

During the 1-year follow-up period, 10 serious adverse events (SAEs) occurred. The IR was 20.2 per 100 PY among patients with DIs requiring tooth extraction (seven events over 34.6 PY) and 7.8 per 100 PY among those without DIs (three events over 38.6 PY). The unadjusted IR ratio was 2.60 (95% CI 0.59 to 15.6), and the unadjusted IR difference (IRD) was 12.4 per 100 PY



**Figure 2** 1-year survival probability without relapse in all patients.



**Figure 3** 1-year survival probability without relapse in patients with and without DI. DI, dental infection.

(95% CI -4.9 to 29.8), indicating no statistically significant difference between the groups.

Among the 10 SAEs, three were serious infections, yielding an overall IR of 3.8 per 100 PY (over 78.5 PY). These infections occurred in patients with DIs requiring extraction (IR of 8.2 per 100 PY), and none in those without DIs. The unadjusted IRD was 8.2 per 100 PY (95% CI -1.1 to 17.5;  $p=0.10$ ). One case of a serious

infection, lung infection (bacterial pneumonia) in patients with DIs, resulted in death, corresponding to an IR of 1.3 per 100 PY (over 79.0PY).

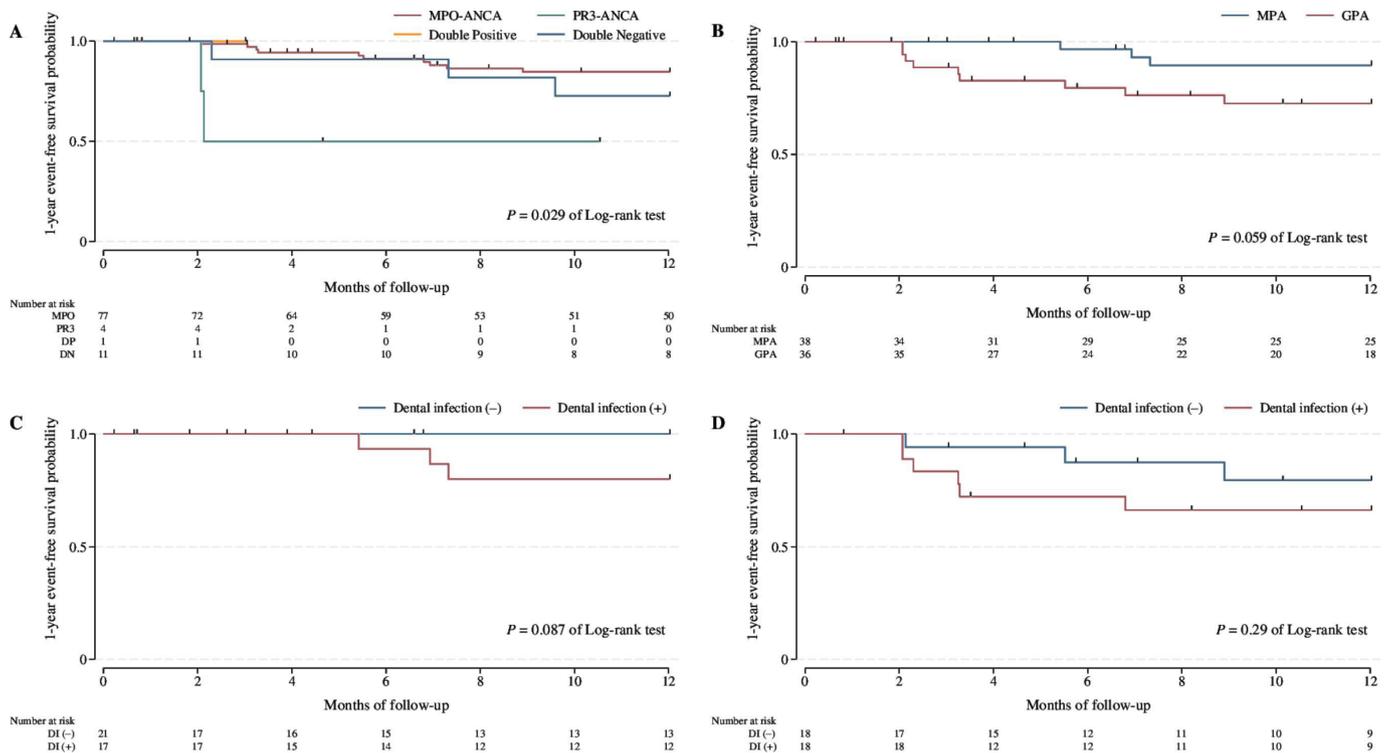
### Subgroup analysis

As part of an exploratory analysis, we examined the differences in relapse rates according to ANCA subtype. Patients who were positive for PR3-ANCA had higher

**Table 2** Univariable and multivariable Cox proportional hazards models for the composite outcome of relapse or death (main and sensitivity analysis 1)

| N=93                                    | Crude                | P value | Model 1              |         | Model 2              |         | Model 3               |         |
|---|----------------------|---------|----------------------|---------|----------------------|---------|-----------------------|---------|
|   | HR (95% CI)          |         | HR (95% CI)          | P value | HR (95% CI)          | P value | HR (95% CI)           | P value |
| Without dental infection                | Ref                  |         |                      |         |                      |         |                       |         |
| (Main analysis) Dental infection        | 3.41 (1.09 to 10.72) | 0.036   | 3.02 (0.95 to 9.59)  | 0.061   | 3.31 (1.04 to 10.48) | 0.042   | 3.14 (0.993 to 9.96)  | 0.051   |
|   | Model 4              |         | Model 5              |         | Model 6              |         | Model 7               |         |
|   | HR (95% CI)          | P value | HR (95% CI)          | P value | HR (95% CI)          | P value | HR (95% CI)           | P value |
| Without dental infection                | Ref                  |         |                      |         |                      |         |                       |         |
| (Main analysis) Dental infection        | 3.20 (1.01 to 10.13) | 0.048   | 3.21 (1.01 to 10.14) | 0.047   | 3.78 (1.13 to 12.67) | 0.031   | 3.78 (1.13 to 12.66)  | 0.031   |
| (Sensitivity analysis) Dental infection |                      |         |                      |         | 3.18 (0.99 to 10.17) | 0.052   | 3.20 (1.001 to 10.24) | 0.050   |

HRs represent the relative hazard for the composite outcome of relapse or death. The proportional hazards assumption was evaluated using Schoenfeld residuals and tested by including time-by-covariate interaction terms (see online supplemental table S5). Crude: Exposure of interest only (dental infection). Model 1: Adjusted for age and sex. Model 2: Adjusted for age, and initial prednisolone dose. Model 3: Adjusted for age, and renal involvement. Model 4: Adjusted for ANCA subtype (reference: ANCA-negative). Model 5: Adjusted for ANCA subtype and baseline BVAS. Model 6: Adjusted for AAV subtype (reference: Others). Model 7: Adjusted for AAV subtype and baseline BVAS. Sensitivity analysis according to the 2022 ACR/EULAR criteria. No events occurred during the first 30 days. Four patients were censored in this interval; therefore, a 30-day landmark analysis (N=89) was performed, yielding estimates consistent with the primary results. AAV, ANCA-associated vasculitis; ACR/EULAR, American College of Rheumatology/European Alliance of Associations for Rheumatology; ANCA, antineutrophil cytoplasmic antibody; BVAS, Birmingham Vasculitis Activity Score; Ref, reference category.



**Figure 4** 1-year survival probability without relapse. (A) Comparison among MPO-ANCA, PR3-ANCA, double-negative and double-positive. (B) Comparison between patients with MPA and GPA. (C) Comparison between patients with and without DI in MPA patients. (D) Comparison between patients with and without DI in GPA patients. ANCA, anti-neutrophil cytoplasmic antibody-associated vasculitis; DI, dental infection; DN, double-negative; DP, double-positive; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; Pr3, proteinase 3.

relapse rates than those positive for MPO-ANCA (figure 4A). The PR3-ANCA positivity rate was 11.1% (4 of 36) in patients with GPA and 2.6% (1 of 38) in patients with MPA. Relapse occurred more frequently in patients with GPA than in those with MPA (figure 4B). Among both MPA and GPA patients, relapse rates were higher in those with DIs requiring tooth extraction than in those without DIs (figure 4C,D).

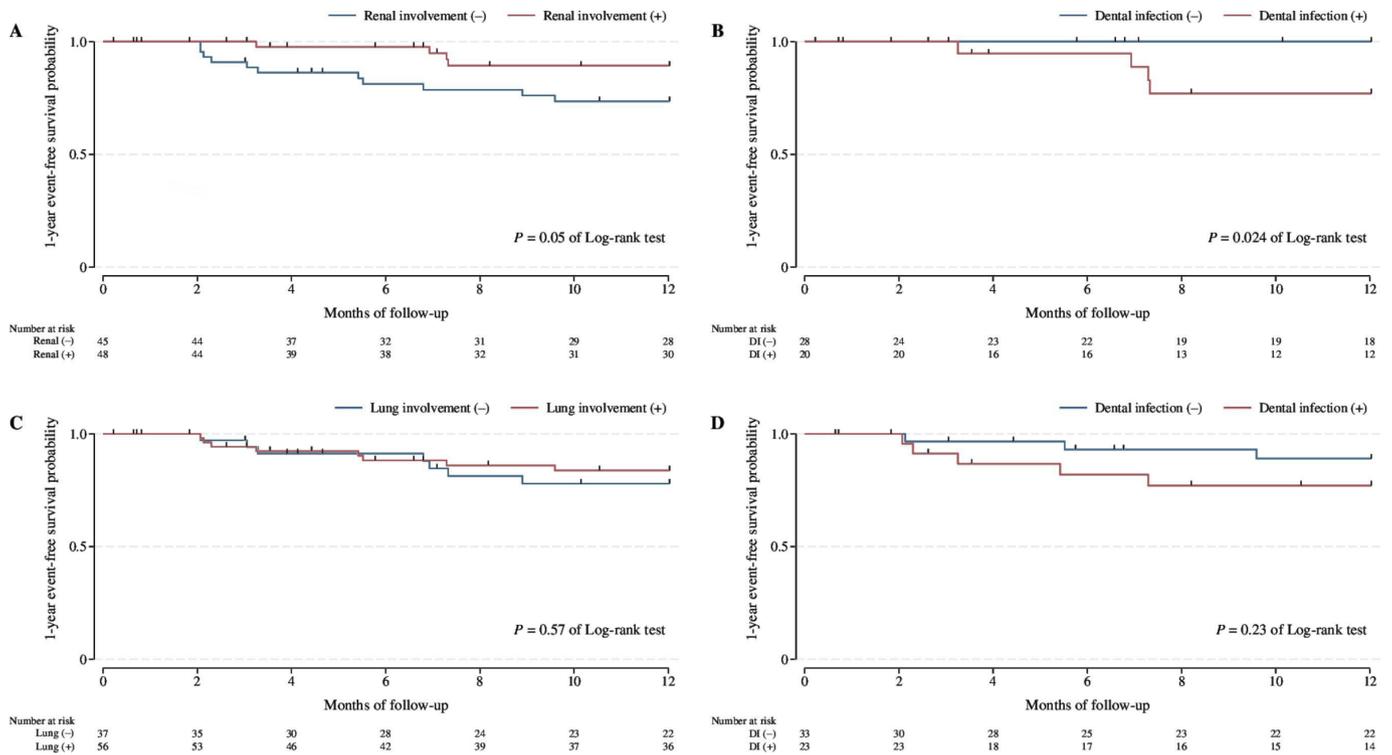
We also conducted exploratory subgroup analyses based on organ involvement. Patients without renal involvement had a tendency to relapse more frequently than those with renal involvement (figure 5A). Among patients with renal involvement, those with DIs had higher relapse rates compared with those without DIs (figure 5B). No significant difference in relapse rates was observed between patients with and without lung involvement (figure 5C); however, relapse was more common in patients with DIs (figure 5D).

Finally, 56.1% (23/41) of patients with DIs underwent tooth extraction. The decision to perform tooth extraction was made at the discretion of the attending dentists at the tertiary care centre. Relapse rates did not differ significantly between patients with and without tooth extraction in the DI group (figure 6).

### Sensitivity analysis

Sensitivity analyses were conducted to evaluate the consistency of our findings. First, the diagnosis was reclassified applying the 2022 ACR/EULAR classification

criteria for AAV.<sup>20–22</sup> Four patients initially classified as having GPA and four as having unclassifiable vasculitis according to the EMA algorithm were reclassified as having MPA, resulting in 46 patients (49.5%) with MPA, 32 (34.4%) with GPA, 14 (15.1%) with EGPA and 1 (1.1%) with unclassifiable vasculitis. Multivariable Cox regression analysis showed that DI remained significantly associated with relapse, generally aligned with the main analysis (table 2; online supplemental table S5). Second, excluding patients with EGPA did not meaningfully change the direction or magnitude of the association (online supplemental tables S6 and S7). Finally, in the relapse-only analysis where deaths unrelated to vasculitis were excluded from the risk set and vasculitis-related deaths were counted as relapse events, significant associations were observed only in models adjusted for disease-related variables such as ANCA subtype, AAV subtype and baseline BVAS (models 4–7,  $p < 0.05$ ), whereas models adjusted for demographic or treatment-related variables, whereas models adjusted for demographic and treatment-related variables such as age, sex, initial prednisolone dose or renal involvement (models 1, 2 and 3) did not show statistical significance (online supplemental tables S8 and S9). Clinical manifestations of relapse within 1 year among AAV patients are shown in online supplemental table 10.



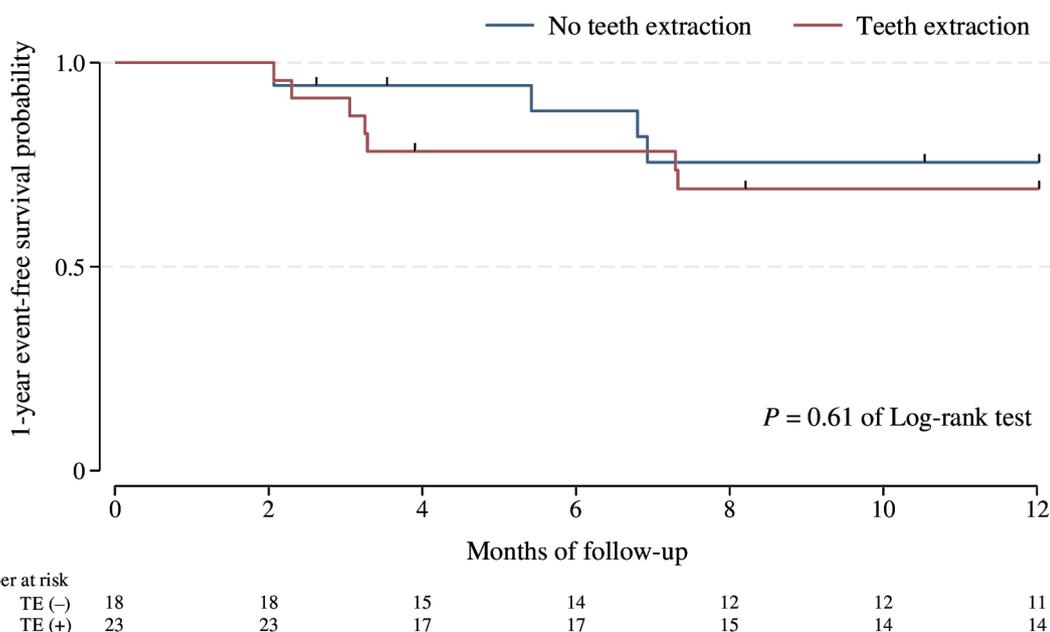
**Figure 5** 1-year survival probability without relapse. (A) Comparison between patients with and without renal involvement. (B) Comparison between patients with and without DI in patients with renal involvement. (C) Comparison between patients with and without lung involvement. (D) Comparison between patients with and without DI in patients with lung involvement. DI, dental infection.

**DISCUSSION**

In the current study, 44.1% of patients with AAV were diagnosed with DIs requiring tooth extraction. During the 1-year follow-up period, 15 patients experienced either relapse or all-cause mortality, with relapse occurring more frequently in patients with DIs compared with those without. Multivariate analysis revealed that DI was

an independent risk factor for AAV relapse. Subgroup analysis showed consistent associations across both MPA and GPA subtypes, as well as in patients with renal or lung involvement. However, tooth extraction did not improve the prognosis of patients with AAV or DIs.

We observed a higher prevalence of DIs requiring tooth extraction in our cohort compared with the



**Figure 6** 1-year survival probability without relapse in patients with and without tooth extraction (TE) among patients with dental infection.

general population. A large cohort study reported mild periodontitis in 21.8% of adults, with moderate or severe disease in 12.6%.<sup>28</sup> Based on a tertiary-care dental assessment, we diagnosed 44.1% of our cohort with DIs requiring tooth extraction. This finding is consistent with previous reports that suggest a role for periodontal inflammation in the pathogenesis of AAV.<sup>17</sup> Although the median age of our cohort exceeded that of the general population, a factor known to increase susceptibility to dental disease, we found no significant age difference between patients with and without DIs. This suggests that factors beyond chronological age contribute to the high prevalence of DIs in AAV. The involvement of infections in the pathogenesis of AAV may further support the association observed in this study. Periodontal diseases and GPA share genetic and immunological mechanisms,<sup>29–31</sup> and ANCA itself may activate neutrophils and monocytes, potentially driving periodontal diseases.<sup>31</sup> Although chronic nasal carriage of *Staphylococcus aureus* has been recognised as an independent risk factor for relapse in patients with GPA,<sup>32</sup> no study has previously linked DIs to AAV relapse.

In our cohort, AAV patients with DIs experienced significantly higher relapse rates during the 1-year follow-up than those without infections. Several autoimmune diseases demonstrate a direct association between DIs and disease activity. For example, patients with Behçet's disease have a higher community periodontal index of treatment needs (CPITN) than healthy controls, and CPITN correlates positively with the clinical severity score.<sup>33</sup> Patients with systemic lupus erythematosus show a significant positive correlation between periodontitis score, disease activity index and serum levels of anti-dsDNA antibody and IFN- $\gamma$ .<sup>34</sup> These findings in other autoimmune diseases highlight the potential role of DIs in contributing to disease activity and relapse in AAV. A possible mechanism linking periodontal disease to AAV relapse involves the formation of superantigens derived from periodontal pathogens and the excessive neutrophil extracellular traps (NETs) formation. *Porphyromonas gingivalis*, a key periodontal pathogen, is known to promote TNF- $\alpha$  and IL-17 production.<sup>35–37</sup> The local or systemic presence of superantigens from periodontal pathogens stimulates monocytes and macrophages to secrete proinflammatory cytokines such as TNF- $\alpha$ , which activates neutrophils, resulting in the expression of MPO and PR3 on neutrophils.<sup>1 38</sup> Periodontitis stimulates persistent neutrophil activation,<sup>39 40</sup> prolongs neutrophil survival<sup>41</sup> and induces the release of NETs in gingival tissues.<sup>42</sup> Higher periodontal disease severity is associated with increased NET complexes in the salivary and crevicular fluids.<sup>43 44</sup> Citrullinated histones within periodontal NETs stimulate IL-17 production by local immune cells, thereby enhancing inflammation.<sup>44</sup> These findings suggest that excessive NETs production, which provides autoantigens for MPO-ANCA and PR3-ANCA formation, may represent a mechanism that exacerbates vascular injury and promotes AAV relapse. Although our findings

suggest a potential association between DI and disease relapse, causality cannot be inferred. Prospective studies assessing standardised periodontal care in AAV, such as screen-and-treat programmes and antibiotic stewardship, are warranted to determine its clinical relevance and clarify this relationship. We performed a sensitivity analysis excluding patients with EGPA. This exclusion did not substantially change the main findings (online supplemental tables S6 and S7). Previous reports have indicated that NET formation may also contribute to inflammation in EGPA.<sup>45</sup> We considered that, in the context of DIs, a shared NET-driven mechanism may justify analysing these diseases together.

We found no significant difference in AAV relapse rates between patients who underwent tooth extraction and those who did not. Bacteraemia following invasive dental procedures, including tooth extraction as a treatment for periodontitis, is a common phenomenon,<sup>46</sup> with cases of septic pulmonary embolism and aseptic meningitis having been reported.<sup>47 48</sup> Despite clear indications for tooth extraction, we observed no reduction in relapse risk among patients who underwent the procedure. This suggests that pathogens circulating after periodontitis or dental treatment may sustain vascular inflammation, potentially offsetting the short-term benefits of tooth extraction in patients with vasculitis. Alternatively, the decision to extract teeth may have been influenced by the severity of the DI, with patients who underwent tooth extraction representing a higher-risk group for AAV relapse. The relationship between periodontitis treatment and relapse in patients with AAV remains unclear. Perioperative prophylaxis could biologically attenuate transient bacteraemia and systemic inflammation surrounding extraction; however, in our data, antibiotic use did not differ meaningfully between outcome groups, and associations were not statistically significant. Prospective studies assessing standardised periodontal care in AAV, such as screen-and-treat programmes and antibiotic stewardship, are warranted to determine its clinical relevance and clarify this relationship.

A key limitation of this study is the definition of 'severe DI requiring tooth extraction', which was not based on documented objective criteria due to the retrospective design. Instead, this definition was relied on the clinical judgement of attending dentists rather than standardised, objective criteria. Specific findings such as periapical radiolucency, pocket depth, tooth mobility or presence of fistula were not uniformly documented in our dataset. Therefore, we acknowledge the possibility of diagnostic variability and misclassification. However, especially in an academic medical centre, tooth extraction is typically determined by certified dentists in accordance with an established clinical practice guideline.<sup>49</sup> This recommends extraction when a tooth is non-salvageable due to above-stated structural damage to the periodontal tissues, severity of inflammation or comparable clinical situations, typically corresponding to stage 3 or 4 periodontitis. Although adherence to this guideline was not prospectively verified in this study, all dental evaluations

were performed by dentists affiliated with the same academic medical institution, which may have helped ensure a degree of diagnostic consistency. Such misclassifications, where patients who should have undergone extraction were not classified as having DI, may have attenuated the observed association between DIs and vasculitis relapse, potentially biasing the results towards the null. Additionally, the analysis did not account for potential unmeasured confounders, such as detailed GC tapering schedules, RTX maintenance strategies (fixed-interval vs on-demand), oral-hygiene practices and comorbidities that may influence oral health such as diabetes mellitus and socioeconomic factors. These unmeasured factors may have contributed to residual confounding, and these variables are warranted in future prospective studies. Clinical periodontitis scores were not obtained, which could have provided a more objective assessment of dental disease severity. If a relationship exists between quantified clinical scores of DI or periodontitis and AAV relapse, as observed in a previous study of Behçet's disease,<sup>33</sup> the association could have been stronger and more robust. To address these limitations, further prospective studies using standardised criteria for diagnosing DIs and objective periodontal scoring are required. Additionally, analysis of the oral microbiome may offer valuable insights into the mechanisms by which DIs influence the prognosis of systemic vasculitis. We should also consider the generalisability. This cohort consisted mainly of elderly Japanese patients with MPO-AAV, which differs from the PR3/GPA-dominant epidemiology typically observed in Western populations. Therefore, the present results may mainly reflect the clinical characteristics of the MPO phenotype, and extrapolation to PR3-AAV should be made carefully. Further studies in more heterogeneous populations are warranted. We should also mention the length of the observation period. Because follow-up was limited for some patients, this study mainly reflects early relapse risk within 12 months and may underestimate later relapses, particularly in PR3-ANCA/GPA.

In this study, no significant difference in relapse rates was observed between patients with DIs who underwent tooth extraction and those who did not. Given that a retrospective study revealed that controlling periodontal infection reduces disease activity in rheumatoid arthritis,<sup>50</sup> additional studies are required to determine whether tooth extraction or periodontal treatment can similarly improve the prognosis of patients with AAV. We acknowledge that DI may still act as a marker of early relapse susceptibility, rather than a direct cause, and this possibility cannot be fully excluded.

In conclusion, in this cohort, nearly half of patients with AAV have severe DIs, and DIs requiring tooth extraction are an independent risk factor for AAV relapse. These findings suggest that physicians should consider routine dental examinations for patients with AAV.

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