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REVIEW

Prevalence and characteristics of bronchiectasis in ANCA-associated vasculitis: A systematic review and meta-analysis

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ABSTRACT

Objectives: This systematic review and meta-analysis aimed to investigate the prevalence of bronchiectasis (BR) in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), the association of BR with manifestations of AAV, and the features of BR in AAV.

Materials and methods: PubMed, EMBASE, Web of Science, and Cochrane Library were searched for publications related to AAV and BR in English from January 1, 1994, until December 7, 2022. The prevalence of BR was synthesized using random-effects models, and sources of heterogeneity were assessed by sensitivity and subgroup analyses. Odds ratios (ORs) were calculated using fixed-effects models to evaluate the association of BR with manifestations of AAV. Only qualitative synthesis was performed on the features of BR.

Results: Studies that reported on the prevalence (n=24), the association (n=6), and the features (n=8) of BR were identified. The pooled overall prevalence of BR among AAV was 19% (95% confidence interval [CI] 13-27%). The prevalence of patients with myeloperoxidase (MPO)-ANCA was significantly higher than those with proteinase 3-ANCA (28% *vs.* 13%, p=0.01). The female sex (OR=2.41), peripheral neuropathy (OR=4.58), MPO-ANCA (OR=4.73), and microscopic polyangiitis (OR=2.72) were associated with BR in AAV. Compared to individuals without BR, AAV-BR patients exhibited relatively lower levels of proteinuria. The diagnosis of BR could follow, be concomitant to, or precede that of AAV. However, BR usually did not respond to immunosuppressive therapy.

Conclusion: AAV with BR is a common condition with special manifestations. The association of BR with AAV may not be accidental; however, the underlying pathogenesis remains to be clarified.

Keywords: ANCA-associated vasculitis, systemic review, bronchiectasis, prevalence, association.

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a necrotizing vasculitis, predominantly affecting small vessels, including granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA).[1] Airway involvement is common in AAV. For example, almost all patients with EGPA had asthma in one study.[2] Subglottic stenosis and endobronchial disease were identified in 10% and 6% of GPA patients, respectively.[3] Blood vessels and airways of the respiratory system closely accompany each other. When pulmonary small vessels are involved, the accompanying airways are likely to be involved as well. The chronic inflammatory cells, which are exudated from small vessels and infiltrated around their walls, also invade adjacent bronchioles on histopathology.[4,5] However, the involvement of medium-small airways in AAV is usually underrecognized.

The prevalence of bronchiectasis (BR) ranged from 0.053 to 0.566% according to epidemical data from Europe and America,[6,7] while multiple studies have shown the prevalence of BR in AAV ranged from 2 to 39.6%,[8-11] which is dramatically higher than that in the general population. In BR patients, dysregulation of neutrophil metabolic pathways led to increased neutrophil extracellular trap (NET)-mediated epithelial damage and decreased ability of bacterial clearance.[12] NETs were involved in the pathogenesis and correlated with the severity of BR.[13] In AAV patients, coculture of NETotic neutrophil with myeloid dendritic cells demonstrated induction of ANCA,[14] and ANCA induced NET release

from primed neutrophil.[15] A vicious cycle of NET formation and ANCA production was regarded to be involved in the pathogenesis of AAV.[16] Therefore, it was speculated that BR was likely associated with AAV since the dysfunctional neutrophil played an important role in the pathogenesis of both.

Infection was the leading cause of death in AAV patients.[11,17,18] A previous study of patients with glomerulonephritis showed that patients with AAV and BR (AAV-BR) were four times more likely than AAV patients without BR to have pulmonary infections.[17] In a cohort of patients treated with rituximab, the presence of severe BR was associated with a six-fold increased risk of respiratory tract infections.[19] Infections decreased the quality of life and increased the risk of hospitalization and mortality. Therefore, it is important to gain a better understanding of the prevalence and characteristics of AAV-BR to develop an appropriate management strategy for AAV-BR and provide a theoretical basis for future studies. The current systematic review and meta-analysis aimed to detect the prevalence of BR among patients with AAV, manifestations of AAV associated with the occurrence of BR, and the features of BR in patients with AAV to address these gaps in knowledge.

MATERIALS AND METHODS

In the systemic review and meta-analysis, the primary endpoints were the prevalence of BR in patients with AAV (the prevalence study) and the association of BR with manifestations of AAV (the association study). The secondary endpoint was the features of BR in patients with AAV (the features of BR study). The study was preregistered on PROSPERO (identifier: CRD42022380039) and conducted in accordance with the guidelines of PRISMA 2020 checklist.[20]

Search strategy and selection criteria

Search strategies were built with the keywords of "ANCA-associated vasculitis" or "granulomatosis with polyangiitis" or "microscopic polyangiitis" or "eosinophilic granulomatosis with polyangiitis" and "bronchiectasis." PubMed, EMBASE, Web of Science and Cochrane Library were queried on December 7, 2022 (Supplemental Table 1). Only articles published on January 1, 1994, or later were included since a clear nomenclature of AAV was first proposed at the Chapel Hill Consensus Conference in 1994.[21] Manual searches were performed to identify relevant articles from the reference lists of selected studies as well.

Two reviewers screened titles and abstracts of all potentially eligible publications using the following criteria: *(i)* original studies, *(ii)* cases with >5 patients, *(iii)* published in English, *(iv)* related to AAV-BR. After screening, full texts of relevant articles were assessed for inclusion by the same reviewers. Articles were excluded if they had the following features: *(i)* only abstracts available, *(ii)* focusing on special populations (e.g., the older or children), *(iii)* all participants with traction BR associated with interstitial lung disease (ILD). Only the most comprehensive articles with the highest quality were included if the sources of data overlapped.

Data extraction and quality assessment

Two reviewers independently extracted and cross-checked data for included articles with support from a third reviewer. In addition to the year of publication and the first author, the following data were extracted according to different purposes. For the prevalence study, AAV sample size (denominator), number of AAV-BR cases (numerator), study designs (retrospective or prospective), races (Western or Asian), research periods, screening BR tools, clinical classifications of AAV, ANCA status, and chest involvement or abnormal imaging proportions, median/mean age and female proportions were extracted. In the association study, number of AAV-BR patients (cases), number of AAV patients without BR (controls), manifestations of AAV with significant differences ($p<0.1$) between cases and controls were assessed; dichotomous variables reported in no less than three articles were included in meta-analysis regardless of their differences. The features of BR study included the timeline between BR and AAV diagnoses (BR preceded, was concomitant to, or followed AAV) with interval time, morphology, and severity of BR, and responsiveness to immunosuppressive treatment of BR on imaging.

The Hoy risk of bias tool was used to assess the quality of articles in the prevalence study.[22] This tool contains 10 domains of bias, each given

a score of 0 or 1 for the absence or presence of bias. A summary score of 0 to 2 indicated a low risk of bias, 3 to 4 a medium risk of bias, and ≥5 a high risk of bias. The Agency for Health Care Research and Quality was used to assess the quality of articles in the association study.[23] This assessment tool has 11 criteria. Each criterion was assigned "yes" or "no" based on the information reported in each study. The formal risk of bias tool was not used in the features of BR study since only qualitative analysis was conducted. All studies were independently assessed by two researchers and checked by another researcher to resolve any disagreements.

Data synthesis and statistical analysis

In the prevalence study, we calculated pooled prevalence of AAV-BR using the logit transformation to correct for nonnormally distributed raw proportions. The incidence rate of "0" and "100%" were replaced with "1/(4N)" and "1-1/(4N)" respectively, according to Bartlett's suggestions (N=the number of patients with AAV). A series of sensitivity analyses were conducted to test the robustness of our statistical model. First, a leave-one-out analysis was conducted to assess whether a particular article was one of the sources of heterogeneity. Second, three studies were removed due to all participants with well-defined renal involvement. Third, we limited the analyses to studies that only used chest computed tomography (CT) or high-resolution CT (HRCT) scans as tools for screening BR. In addition, subgroup analyses were also conducted according to different study designs, races, sample sizes, Hoy risk of bias, research periods, median/mean age, sex ratio, ANCA status, and clinical classifications. Chi-square tests were used to evaluate the differences between subgroups.

In the association study, the nonnormally distributed quantitative variables were first summarized with significant differences between AAV patients with and without BR. Second, dichotomous variables reported in no less than three articles were included in the meta-analysis. Odds ratios (ORs) were calculated from odds of events (the number of patients with certain manifestations) in AAV-BR patients (total number of cases) divided by odds of events in AAV patients without BR (total number of controls). In the features of BR study, only qualitative synthesis was conducted due to the small number of studies and substantial variability of findings.

Meta-analysis was conducted by random-effects models with the DerSimonian-Laird method ($p<0.05$, $I^2>50\%$) or fixed-effects models with Mantel-Haenszel method ($p\geq0.05$, $I^2\leq50\%$) using Stata version 17.0 (StataCorp, College Station, TX, USA). Heterogeneity between studies was assessed by the Q statistics and the I^2. For all tests, $p<0.05$ was considered statistically significant.

Due to the high heterogeneity shown in the meta-analysis of the prevalence study, funnel plot asymmetry and Egger's regression tests were not used to statistically examine publication bias as conventionally suggested. Moreover, in the association study, the number of included studies was between three and five, which was not enough to make funnel plots.

RESULTS

Study selection

Search strategies identified 420 studies. After the removal of duplicates, we screened titles and abstracts of 345 articles for eligibility, of which 37 full-text articles were reviewed, and finally, 24 unique studies were included for systemic review (Figure 1). In total, all 24 articles were included in the prevalence study,[8-11,17,18,24-41] six articles were included in the association study,[8,11,17,18,31,41] and eight articles were included in the features of BR study.[8,10,11,17,29,31,40,41]

Quality assessment

In the Hoy risk of bias, nine studies presented low risks, 13 studies presented medium risks, and two studies presented high risks (Supplemental Table 2). The majority of included articles were single-center and retrospective studies with small sample sizes. Due to the nature of the studies, the most common domains of risks were "studies not representing the national population," "sampling frame not representing the target population," and "nonresponse bias not minimal."

In the Agency for Health Care Research and Quality, most of the risks were derived from lacking detailed descriptions of data processing

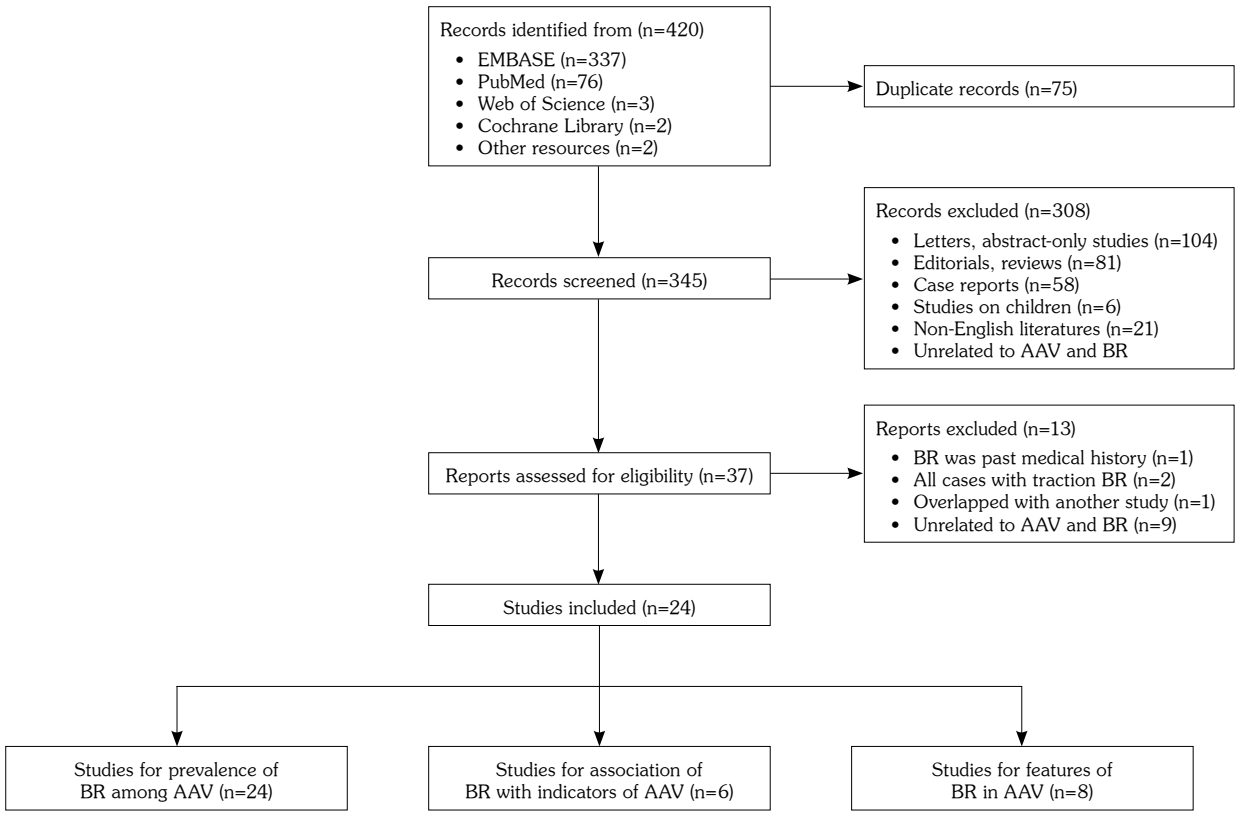

Figure 1. PRISMA flow diagram of studies assessed for AAV with BR.
AAV: Associated vasculitis; BR: Bronchiectasis; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

(Supplemental Table 3). All the included studies failed to describe "how confounding was assessed and/or controlled," "how missing data were handled," or summarize "patient response rates and completeness of data collection."

Prevalence of BR in AAV

The data collected in each study relating to the prevalence of AAV-BR are shown in Table 1. The AAV sample size ranged from 17 to 2,035 patients. The research periods spanned nearly 40 years. The majority of studies were retrospective in design except for three prospective studies. Fourteen studies were conducted in Asian populations, and 10 studies were conducted in Western populations. Most of the studies used CT or HRCT to confirm the BR diagnosis. While some patients of Takahashi et al.,[36] Greenan et al.,[24] and Aydın Tufan et al.[38] studies were diagnosed with BR based on chest X-ray, two cases in Ren et al.'s[8] study were diagnosed with BR by surgical pathology. Seven studies included multiple clinical classifications of AAV. Seven studies focused on MPA, five focused on GPA, and three focused on EGPA. Five studies only included patients with myeloperoxidase (MPO)-ANCA-associated AAV. The proportion of patients with CT or HRCT abnormalities was 38.5 to 100% (data from 11 studies). The proportion of patients with chest or lung involvement was 39.1 to 68.7% (data from nine studies). The mean/median age of the participants was 47 to 76 years old, with 27.1 to 67.7% female participants.

Among the 24 studies, 516 AAV-BR cases were identified from a total of 4,160 patients with AAV. The pooled overall prevalence of AAV-BR in the random-effects meta-analysis with DerSimonian-Laird method was 19% (95% confidence interval [CI]: 13 to 27%). Forest plots of the included studies are shown in Figure 2. In the leave-one-out analysis, the pooled prevalence fluctuated between

Table 1. Studies reporting the prevalence of BR among patients with AAV (n=24)

Study	AAV sample size (denominator) (n)	Number of AAV-BR cases (numerator) n (%)	Study designs	Races	Research periods	Screening BR tools	Clinical classifications	ANCA status	Chest involvement/ abnormal imaging proportions	Age	Female proportions (%)
Yang et al.[41]	155	18 (11.6)	Retrospective, single-center	Chinese	2012-2017	HRCT	MPA/GPA: n=100/55	All MPO-ANCA+	Abnormal HRCT: 100%	Median 69 (IQR 63-75)	52.3
Saraya et al.[34]	55	21 (38.2)	Retrospective, single-center	Japanese	2008-2016	CT	all MPA	All MPO-ANCA+	Abnormal CT: 100%	Median 76 (IQR 70-82)	58.2
Ren et al.[8]	212	48 (22.6)	Retrospective, single-center	Chinese	2010-2021	HRCT or lobectomy	MPA/GPA/ EGPA/uAAV: n=151/31/11/19	MPO/PR3/double/ absent-ANCA+: n=162/27/10/13	Chest involvement: 67.0%	Mean±SD 66.5±13.61	51.9
Luo et al.[17]	153	52 (34.0)	Retrospective, single-center	Chinese	2015-2020	CT	MPA/GPA: n=150/3	All MPO-ANCA+	Lung involvement: 59.5%	Median 63 (IQR 54-68)	48.4
Aydın Tufan and Tekkarışmaz[38]	60	8 (13.3)	Retrospective, single-center	Turk	2005-2020	X-ray or CT	All GPA	MPO/PR3-ANCA+: n=18/39	Lung involvement: 86.7%	Median 49 (range: 19-75)	56.7
Trivioli et al.[37]	26	2 (7.7)	Retrospective, multicenter	Italian & British	1999-2018	HRCT	All MPA	NR	Abnormal HRCT: 38.5%	Median 70 (IQR 64-78)	NR
Ono et al.[33]	195	30 (15.4)	Prospective, multicenter	Japanese	2012-2018	CT	MPA/GPA/ EGPA/uAAV: n=89/51/24/31	MPO/PR3/double/ absent-ANCA+: n=143/19/5/28	NR	Mean±SD 69.2±12.2	57.4
Lin et al.[9]	96	38 (39.6)	Retrospective, single-center	Chinese	2011-2017	HRCT	All EGPA	NR	Asthma 100%	Mean±SD 45.9±12.8	49.0
Lhote et al.[10]	2035	43 (2.1)	Retrospective, multicenter	French	1983-2015	CT	NR	NR	NR	NR	NR
Lao et al.[27]	207	30 (14.5)	Retrospective, single-center	Chinese	2012-2017	NR	NR	NR	lung involvement 39.1%	With infection: 55.6±15.7; without infection: 51.7±16.4 (mean±SD)	57.0
Kida et al.[26]	113	37 (32.7)	Retrospective, multicenter	Japanese	2006-2015	CT	All MPA	All MPO-ANCA+	Chest involvement: 48.7% Abnormal CT: 85.8%	Median 72 (IQR 67-78)	46.0
Suzuki et al.[35]	144	19 (13.2)	Prospective, multicenter	Japanese	2011-2014	HRCT	All MPA	MPO/PR3/double/ absent-ANCA+: n=136/1/5/2	Abnormal HRCT: 93.1%	Mean±SD 71.2±11.0	54.2
Néel et al.[11]	58	22 (37.9)	Retrospective, single-center	French	2005-2015	HRCT	MPA/GPA: n=30/28	MPO/PR3-ANCA+: n=39/19	Lung involvement: 46.6%	Median 65.5 (IQR 64.4-76.4)	53.4
Nakamoto et al.[32]	31	4 (12.9)	Retrospective, single-center	Japanese	2001-2015	CT	All EGPA	MPO/absent-ANCA+: n=13/18	Asthma 100%	Median 61 (range: 32-77)	67.7
Greenan et al.[24]	105	12 (11.4%)	Prospective, single-center	British	2000-2013	X-ray or CT	NR	p/c-ANCA+: n=49/56	Abnormal X-ray 56.5%; abnormal CT 92.6%[a]	Mean 67.5	44.8
Tashiro et al.[18]	45	7 (15.6%)	Retrospective, single-center	Japanese	2004-2011	HRCT	All MPA	All MPO-ANCA+	Lung involvement: 68.9%	With BR: 75±6.3; without BR: 72±9.2 (mean±SD)	58.1

Table 1. Continues

Study	AAV sample size (denominator) (n)	Number of AAV-BR cases (numerator) n (%)	Study designs	Races	Research periods	Screening BR tools	Clinical classifications	ANCA status	Chest involvement/ abnormal imaging proportions	Age	Female proportions (%)
Mohammad et al.[31]	140	27 (19.3%)	Retrospective, single-center	British	2000-2012	CT	MPA/GPA: n=61/79	MPO/PR3/ double/absent-ANCA+: n=48/81/1/10	Abnormal CT: 77.1%; chest involvement: 52.9%	mean±SD: 60.1±14.6	53.6
Yamagata et al.[40]	150	59 (39.3%)	Retrospective, multicenter	Japanese	2002-2012	CT	All MPA	MPO/PR3/ double-ANCA+: n=136/3/1	Abnormal CT: 96.7%; chest involvement: 68.7%	median 70 (range: 42-89)	59.3
Guneyli et al.[25]	48	8 (16.7%)	Retrospective, single-center	Turk	2003-2013	CT	All GPA	cANCA+: n=9	Abnormal CT: 68.8%	median 47.3 (range: 28-73)	27.1
Magkanas et al.[30]	21	9 (42.9%)	Retrospective, multicenter	Greek	1999-2009	HRCT	All GPA	cANCA: n=21; PR3-ANCA: n=12	Abnormal HRCT: 90.5%	median 45 (range: 18-72)	60.9
Takahashi et al.[36]	26	9 (34.6%)	Retrospective, single-center	Japanese	1990-2002	X-ray or CT	All MPA	MPO-ANCA+: n=18	NR	mean±SD: 69.5±8.7	53.8
Lohrmann et al.[29]	38	6 (15.8%)	Retrospective, single-center	German	1993-2003	CT	All GPA	ANCA+: n=31	NR	median 55.5 (range: 27-82)	42.1
Lee et al.[28]	30	4 (13.3%)	Retrospective, multicenter	South Korean & Japanese	1993-2001	CT	All GPA	cANCA+: n=24	Abnormal CT: 96.7%	median 54.3 (range: 15-80)	46.7
Worthy et al.[39]	17	3 (17.6%)	Retrospective multicenter	British & Canadian	1988-1998	CT or HRCT	All EGPA	NR	NR	mean±SD: 47±16	41.2

AAV: Associated vasculitis; BR: Bronchiectasis; HRCT: High-resolution computed tomography; CT: Computed tomography; MPA: Microscopic polyangiitis; GPA: Granulomatosis with polyangiitis; EGPA: Eosinophilic granulomatosis with polyangiitis; MPO: Myeloperoxidase; PR3: Proteinase 3; ANCA: Antineutrophil cytoplasmic antibody; IQR: Interquartile range; SD: Standard deviation; NR: Not reported; a: Abnormal X-ray 56.5% (n=85); abnormal CT 92.6% (n=27).

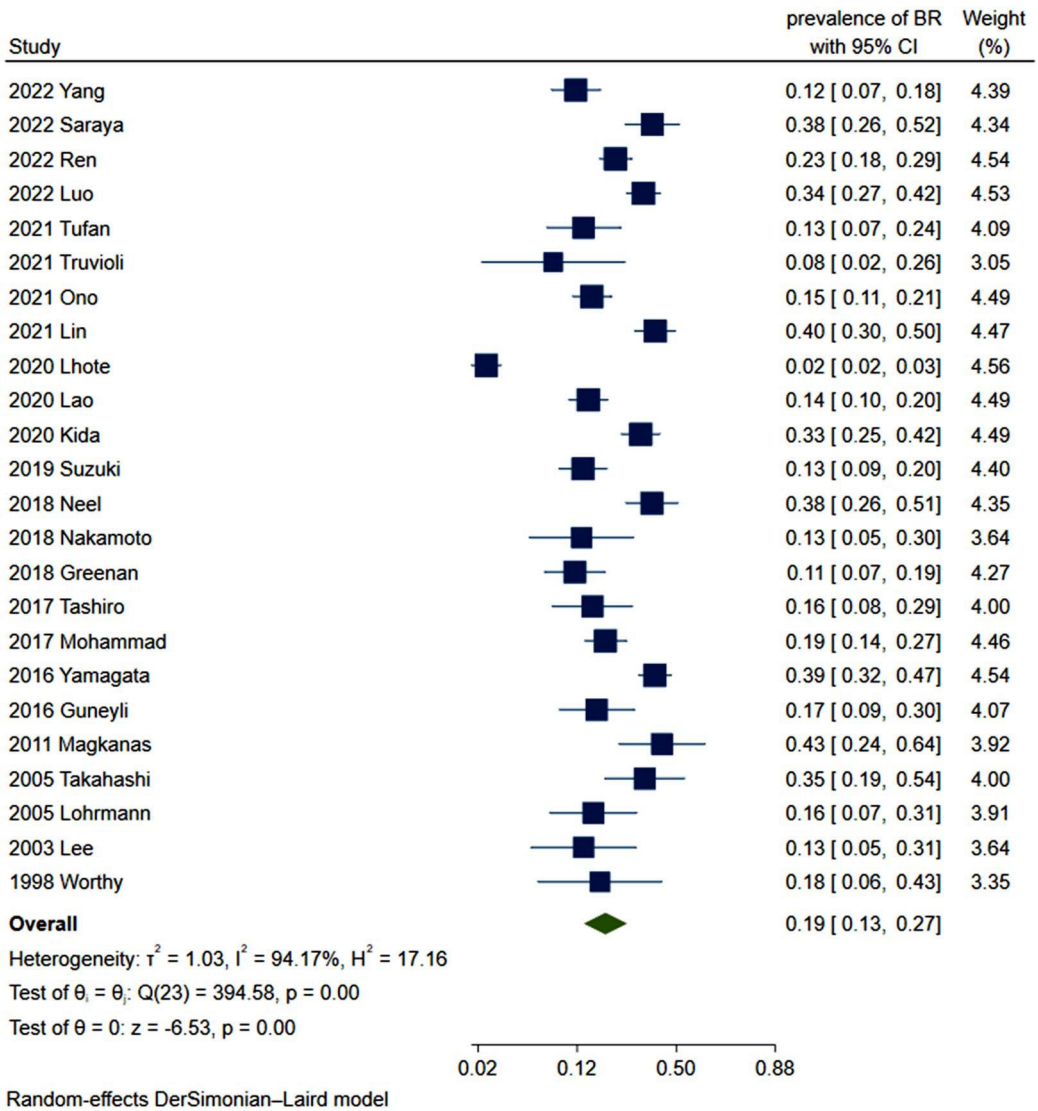

Figure 2. Forest plot and random-effects meta-analysis on the prevalence of BR among patients with AAV (n=24).

AAV: Associated vasculitis; BR: Bronchiectasis.

19% and 22% (Supplemental Figure 1). After removing three studies in which all patients had renal involvement,[17,24,37] the prevalence slightly increased (20%, 95% CI: 13 to 28%). When the analysis was restricted to studies that only conducted CT or HRCT scans, the prevalence was still 19% (95% CI: 13 to 27%).

However, substantial unexplained heterogeneity still remained (I^2=94.17%, p<0.01) after the sensitivity analyses. Subgroup analyses were performed to investigate the sources of heterogeneity (Supplemental Figure 2). The prevalence in retrospective studies was higher than that in prospective studies (20% *vs.* 14%, p=0.10). The prevalence in Asian populations was higher than that in Western populations (23% *vs.* 15%, p=0.29; after the study of Lhote et al.[10] was excluded: 23% *vs.* 19%, p=0.43). No significant difference was found between the studies with different Hoy risk of bias, sample sizes, research periods, median/mean age, and sex ratio.

Patients with different ANCA statuses or classifications of AAV had distinct manifestations. The prevalence in patients with MPO-ANCA was 28% (95% CI: 21 to 36%), which was significantly higher than that in patients with proteinase 3 (PR3)-ANCA (13%, 95% CI: 8 to 21%, p=0.01, Supplemental Figure 3a). The prevalence of BR was 25% (95% CI: 19 to 31%) among MPA patients and 17% (95% CI: 11 to 24%, Supplemental Figure 3b) among GPA patients (p=0.08). And the prevalence was 23% (95% CI: 10 to 47%) in EGPA patients.

Association of BR with Manifestations of AAV

The manifestations with significant differences between AAV patients with and without BR reported in six studies are shown in Table 2. The dichotomous variables reported in no less than three studies were summarized, and ORs were calculated to analyze the association of BR with manifestations of AAV.

No significant difference was found in median/mean age between patients with AAV-BR and controls except for Néel et al.'s[11] study (median age: 72 years in AAV-BR *vs.* 58 years in controls, p=0.002). Compared to males, females exhibited a significantly higher prevalence of BR (OR=2.41, 95% CI: 1.62 to 3.59, Figure 3a). Afterward, the association of BR with different classifications of AAV and ANCA statuses was analyzed. As shown in Figures 3b, c, patients diagnosed with MPA presented a significantly higher prevalence of BR than other clinical classifications (OR=2.72, 95% CI: 1.58 to 4.66), while patients diagnosed with GPA presented a significantly lower prevalence of BR than the others (OR=0.40, 95% CI: 0.22 to 0.72). The pooled analysis revealed a positive association between MPO-ANCA and BR (OR=4.73, 95% CI: 1.70 to 13.18, Figure 3d). Further analysis of the association between PR3-ANCA and BR was omitted because of a lack of data.

The association of BR with organ-specific manifestations of AAV was also analyzed. The meta-analysis revealed that patients with nervous system involvement exhibited a significantly higher prevalence of BR (OR=1.94, 95% CI: 1.25 to 3.01, Supplemental Figure 4a). Moreover, patients with peripheral neuropathy demonstrated a higher prevalence of BR (OR=4.58, 95% CI: 1.68 to 12.48) than those with central nervous system involvement (p=0.06, Supplemental Figure 4b). The results also indicated no significant difference in the pooled analyses of the associations of BR with cutaneous,

Table 2. Studies reporting the association of BR with manifestations of AAV (n=6)

Study	Populations	Cases		Controls		Indicators of AAV with significant differences
			n		n	
Yang et al.[41]	Patients with MPO-ANCA	BR	18	With other pulmonary abnormalities†	137	None
Ren et al.[8]	Patients with AAV	BR	48	Without BR	164	Female, MPA diagnosis, MPO-ANCA, level of proteinuria, smoking, general manifestations, chest involvement
Luo et al.[17]	Patients with MPO-ANCA and GN	BR	52	Without BR	101	Female, nerve system involvement*, level of proteinuria, ILD, PLT, serum C3
Néel et al.[11]	Patients with AAV	BR	22	Without BR	36	Age, female, MPO-ANCA, ENT involvement*, renal involvement*, peripheral nerve involvement, level of proteinuria*
Tashiro et al.[18]	MPA patients with MPO-ANCA	BR	7	Without BR	24	None
Mohammad et al.[31]	Patients with AAV	BR	27	Without BR	113	MPA diagnosis, MPO-ANCA

BR: Bronchiectasis; AAV: Associated vasculitis; MPO: Myeloperoxidase; ANCA: Antineutrophil cytoplasmic antibody; GN: Glomerulonephritis; ILD: Interstitial lung disease; PLT: Platelet; ENT: Ear, nose, throat; † Other pulmonary abnormalities included diffused alveolar hemorrhage, interstitial pneumonia and necrotizing granuloma; * Significance of difference: 0.05< p<0.1.

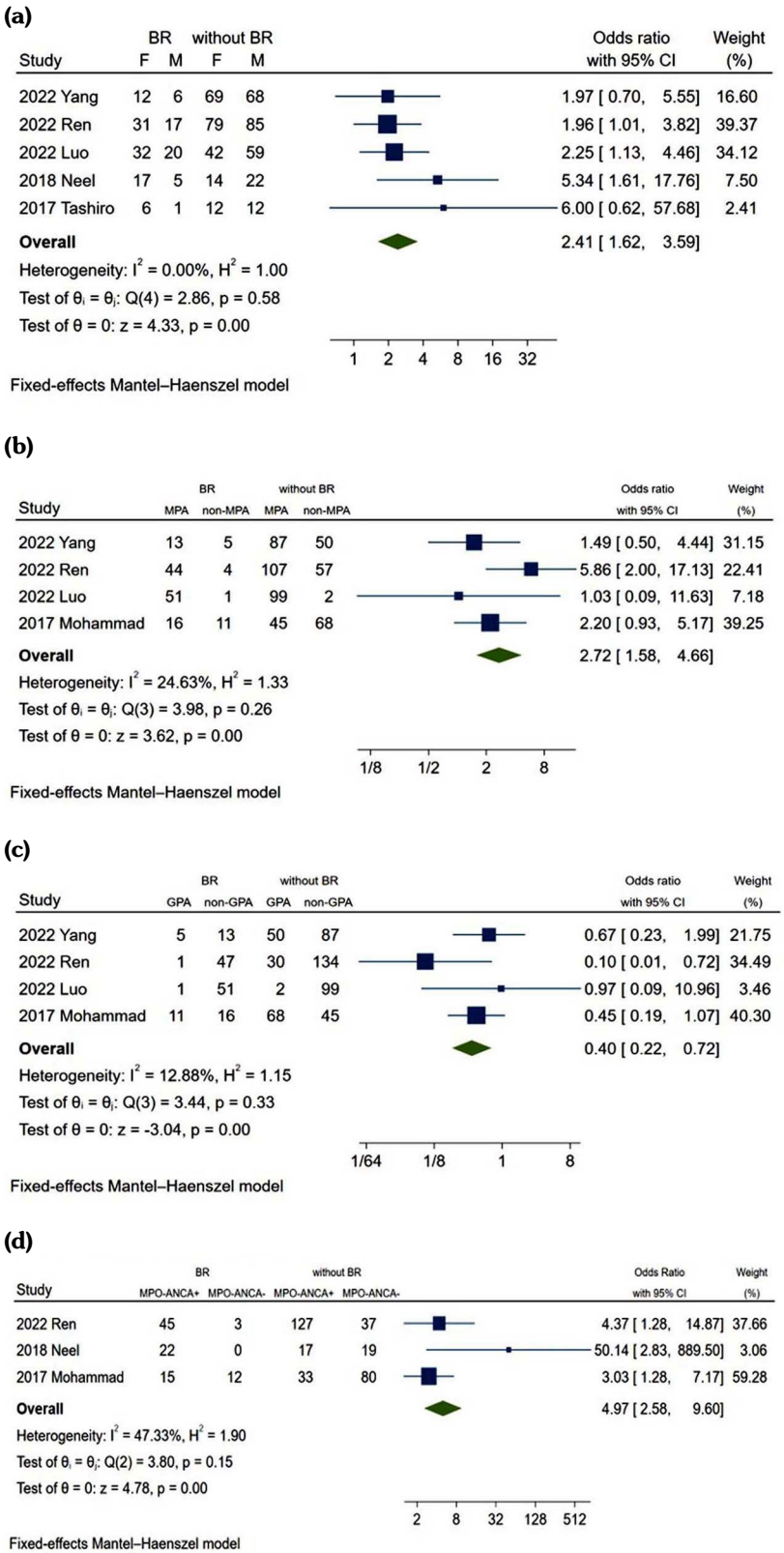

Figure 3. Forest plot and meta-analysis on the association of BR with specific manifestations of AAV.

AAV: Associated vasculitis; BR: Bronchiectasis.

mucous/eye, ear/nose/throat, cardiac, and renal involvement. Although the proportion of renal involvement was not associated with BR, the studies of Ren et al.,[8] Luo et al.,[17] and Néel et al.[11] indicated that AAV-BR patients exhibited relatively lower levels of proteinuria than patients without BR.

Features of BR in AAV

The features of BR in AAV patients reported in eight studies are summarized in Supplemental Table 4. Although the majority of the diagnosis of BR was concomitant to or followed that of AAV (56.3 to 88.5%), 13.6 to 43.8% of the diagnosis of BR still preceded AAV with a median interval time of 8.5 to 16 years. In addition, Ren et al.[8] and Lhote et al.[10] showed that the proportions of patients with nervous system involvement and MPO-ANCA were higher in those diagnosed with BR before the onset of AAV.

The included studies used various tools to assess BR severity on imaging, including FACED, Bhalla, Smith and modified Reiff score. Ren et al.[8] showed that patients diagnosed with BR before AAV presented an increased total Smith score, representing more severe BR. Luo et al.[17] reported that the modified Reiff score was positively correlated with MPO-ANCA titers.

Cylindrical type was the most common pattern of BR in AAV patients (55 to 92.6%), while varicoid and cystic types were rare. Four studies reevaluated CT or HRCT scans after immunosuppressive therapy, showing that most BR lesions remained stable or deteriorated.

DISCUSSION

This systemic review summarized the current evidence on the prevalence and characteristics of AAV-BR in 24 studies. The results showed a pooled overall prevalence of BR among patients with AAV of 19%, indicating that BR was not a rare respiratory complication of AAV. The prevalence of BR was 25% in patients with MPA and 28% in patients with MPO-ANCA. The female sex, peripheral neuropathy, relatively lower levels of proteinuria, positive MPO-ANCA in serum, and diagnosis of MPA were associated with the occurrence of BR in patients with AAV. The diagnosis of BR could follow, be concomitant to, or precede that of AAV. However, BR of AAV patients usually did not respond to immunosuppressive therapy.

The most striking and clinically relevant finding was that BR was highly prevalent in the AAV population, emphasizing that the condition of AAV-BR should be recognized and fully studied. It is well-known that BR is a common extra-articular feature of rheumatoid arthritis. A meta-analysis has shown that the prevalence of BR among rheumatoid arthritis was 18.7%.[42] Our study also obtained the prevalence of BR among AAV (19%), which was similar to that among rheumatoid arthritis, indicating that AAV-BR was not a rare condition. Compared to more fatal complications (e.g., alveolar hemorrhage, ILD, and other vital organ damages) caused by AAV, BR is more likely to be overlooked. However, BR dramatically increased the risk of respiratory tract infection,[17,19] which should be taken into consideration during long-term immunosuppressive treatment. Given that ILD was common in AAV, the coexistence of ILD and BR should be considered. However, ILD-related BR was usually secondary to the surrounding architectural distortion. After excluding fibrosis-related BR, a few included studies showed low incidence rates of BR in AAV patients with ILD.[10,17,35]

The prevalence of AAV-BR ranged from 2.1 to 42.9% across all included studies.[8,10,11,30,31] The incidence rate of 2.1% of AAV-BR was likely to be underestimated in Lhote et al.'s[10] study since HRCT scans were not mandatory at enrollment in the French Vasculitis Study Group database of their study. Although different screening BR tools did not affect the robustness of the statistical model in sensitivity analysis, it is worth noting that the variable response rates (the percentage of AAV patients screened for BR in the real-world cohorts) of included studies were probably the main source of internal bias, as presented by the domain of Hoy risk of bias ("nonresponse bias not minimal").[22] In the retrospective studies included in this study, AAV patients suspected of pulmonary involvement were more likely to be screened with chest imaging, while patients without chest imaging were excluded, resulting in the high prevalence

of BR herein. In the prospective studies, BR was detected in all AAV patients using CT or HRCT scans without any exception. The number of participants with AAV (denominator) represented the real-world sample size. Nevertheless, the pooled prevalence in prospective studies (14%) still deserves to be considered.

Our meta-analysis showed that the female sex, peripheral neuropathy, and relatively lower levels of proteinuria were related to BR in patients with AAV. The female ratio was higher than the male ratio in 63.6% of studies on the prevalence of AAV-BR (Table 1), which was consistent with the epidemiological data of BR in the general populations.[6,7] Peripheral neuropathy and glomerulonephritis are typical organ-specific manifestations of small vessel vasculitis and are closely associated with positive ANCA.[2,43] There was no statistical significance in the proportion of renal involvement between AAV patients with and without BR. However, the severity of renal injury of AAV-BR patients was probably milder than that of AAV patients without BR, which was reflected by the differences in levels of proteinuria rather than serum creatine or glomerular filtration rate.[8,11,17] The underlying mechanism remains to be clarified.

Patients with MPO-ANCA or MPA were more likely to have BR. Previous studies have shown that a few patients initially diagnosed with idiopathic pulmonary fibrosis emerged MPO-ANCA-positive conversion during long-term follow-up, and some of them were even diagnosed with MPA due to ultimately developing multi-organ involvement.[44-46] The duration of the evolution from idiopathic pulmonary fibrosis to positive MPO-ANCA and, finally, MPA could last decades.[44] Similarly, the features of BR study showed a few patients with an initial diagnosis of BR developed typical manifestations of vasculitis during long-term follow-up.[8,10,11,17,41] Therefore, it was speculated that a similar process of BR exhibiting positive MPO-ANCA and resulting in MPA existed in those patients.[8,10,17] The hypothesis was also supported by other results. Patients with MPO-ANCA were more susceptible to BR (Figure 3d), and the positive rate of MPO-ANCA was higher in patients diagnosed with BR preceding AAV.[8,10] Furthermore, a similar process of evolution might exist in patients with GPA. A large case-control study in the UK showed that people with GPA were five times more likely to have a previous diagnosis of BR than controls (mainly composed of nonvasculitis patients),[47] suggesting that preexisting BR was associated with GPA. ANCA was probably associated with the development of AAV in BR patients, while the biomarker associated with BR in AAV was still not identified. In the future, it would be nice to determine a biomarker for the occurrence of BR in AAV.

Bronchiectasis can both precede the onset of AAV or occur during AAV follow-up; each scenario seems to have different underlying pathophysiological processes. More than half of the patients developed BR during AAV follow-up or at the same time, indicating that ANCA was derived from other systems outside the respiratory tracts. In patients whose diagnosis of BR preceded AAV with long interval times, chronic bronchial suppuration might contribute to the development of autoimmunity and ANCA production.[10] Neutrophilic inflammation, which plays an important role in both the pathogenesis of BR and AAV, can be induced by neutrophil dysfunction[12] with degranulation of primary granule components.[13] These granule proteins accrued to an extent that prompted the loss of self-tolerance and production of ANCA,[48] which was regarded as a trigger of AAV onset. Two other findings supported the hypothesis above as well. Patients with BR preceding AAV had more frequent MPO-ANCA,[8,10] and the severity of BR was positively correlated with MPO-ANCA titers.[17] However, since BR has a variety of causes, one should be prudent to attribute BR to AAV in patients whose diagnoses of AAV and BR were not simultaneous. Further longitudinal studies with large sample sizes should be of paramount interest to better decipher the association between the pathogenesis of AAV and BR.

This study has several limitations. First, the findings were mainly derived from single-center and retrospective studies, which might not represent a true prevalence of the national or international population. The exact prevalence of AAV-BR should be detected by inclusive screening using CT or HRCT scans in an international AAV population. Second, publication bias was not assessed with funnel plots and Egger's regression tests since no more

than five studies were included in the association study. While the heterogeneity among included studies was minimal (I^2 ≤50%), the pooled ORs and ORs calculated by every single study almost directed to the same results (Figure 3). Third, the quantitative analysis was not done in the "features of BR" study due to the small sample size and variable findings. Finally, AAV can be complicated with other airway diseases other than BR, such as bronchiolitis. However, only two of the included studies reported the incidence rate of bronchiolitis (55%[40] and 6.5%[17]). Further studies are needed to confirm the results.

In conclusion, to our knowledge, this is the first systematic review and meta-analysis related to AAV-BR, showing that the prevalence of BR among patients with AAV was nearly 20%. The high prevalence of AAV-BR implies that routine chest CT or HRCT screening should be an integral aspect of clinical management. Female AAV patients and AAV patients with peripheral neuropathy, relatively lower levels of proteinuria, MPO-ANCA, and MPA diagnosis were prone to have BR. The association of BR with AAV appears not accidental, and the underlying pathogenesis needs to be further studied.

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Prevalence and Characteristics of Bronchiectasis in ANCA-Associated Vasculitis: A Systemic Review and Meta-analysis

Supplemental Table 1. Search strategies in four databases to identify studies reporting the prevalence and characteristics of ANCA-associated vasculitis with bronchiectasis

PubMed

Search Strategy:

#1 "Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis"[Mesh] OR "Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis" OR "ANCA-Associated Vasculitis"
#2 "Microscopic Polyangiitis"[Mesh] OR "Microscopic Polyangiitis" OR "Microscopic Polyarteritis"
#3 "Granulomatosis with Polyangiitis"[Mesh] OR "Granulomatosis with Polyangiitis" OR "Wegener Granulomatosis" OR "Wegener's Granulomatosis"
#4 "Churg-Strauss Syndrome"[Mesh] OR "Churg-Strauss Syndrome" OR "Eosinophilic Granulomatosis with Polyangiitis"
#5 #1 OR #2 OR #3 OR #4
#6 Bronchiectasis[Mesh] OR bronchiectasis OR bronchiectasis OR "bronchial dilatation"
#7 #5 AND #6
Published time: from 1994/01/01 to 2022/11/30
Access date: from 30/11/2022 to 07/12/2022

EMBASE

Search Strategy:

#1 'Anca associated vasculitis'/exp OR 'anca associated vasculitis' OR 'anti-neutrophil cytoplasmic antibody-associated vasculitis'
#2 'Microscopic polyangiitis'/exp OR 'microscopic polyangiitis' OR 'microscopic polyarteritis'
#3 'Wegener granulomatosis'/exp OR 'wegener granulomatosis' OR 'granulomatosis with polyangiitis'
#4 'Churg strauss syndrome'/exp OR 'churg strauss syndrome' OR 'eosinophilic granulomatosis with polyangiitis'
#5 #1 OR #2 OR #3 OR #4
#6 'Bronchiectasis'/exp OR 'bronchiectasis' OR 'bronchiectases' OR 'bronchial dilatation'
#7 #5 AND #6
Published time: 01-01-1994 to 30-11-2022
Access date: from 30/11/2022 to 07/12/2022

Web of Science

Search Strategy:

#1 ALL=("Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis" OR "ANCA-Associated Vasculitis")
#2 ALL=("Microscopic Polyangiitis" OR "Microscopic Polyarteritis")
#3 ALL=("Granulomatosis with Polyangiitis" OR "Wegener Granulomatosis" OR "Wegener's Granulomatosis")
#4 ALL=("Churg-Strauss Syndrome" OR "Eosinophilic Granulomatosis with Polyangiitis")
#5 #1 OR #2 OR #3 OR #4
#6 ALL=(bronchiectasis OR bronchiectasis OR "bronchial dilatation")
#7 #5 AND #6
Published time: from 1994-01-01 to 2022-11-30
Access date: from 30/11/2022 to 07/12/2022

The Cochrane Library

Search strategy:

#1 MeSH descriptor: [Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis] explode all trees
#2 'Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis' OR 'ANCA-Associated Vasculitis'
#3 MeSH descriptor: [Microscopic Polyangiitis] explode all trees
#4 'Microscopic Polyangiitis' OR 'Microscopic Polyarteritis'
#5 Mesh descriptor: [Granulomatosis with Polyangiitis] explode all trees
#6 'Granulomatosis with Polyangiitis' OR 'Wegener Granulomatosis' OR 'Wegener's Granulomatosis'
#7 Mesh descriptor: [Churg-Strauss Syndrome] explode all trees
#8 'Churg-Strauss Syndrome' OR 'Eosinophilic Granulomatosis with Polyangiitis'
#9 #1 OR #2 OR #3 OR #4 OR # 5 OR #6 OR #7 OR #8
#10 Mesh descriptor: [bronchiectasis] explode all trees
#11 Bronchiectasis OR bronchiectasis OR 'bronchial dilatation'
#12 #10 OR #11
#13 #9 AND #12
Published time: from 01/01/1994 to 30/11/2022
Access date: from 30/11/2022 to 07/12/2022

Supplemental Table 2. Quality assessment of the articles included in the "prevalence" study (Hoy Risk of Bias)

Study	Target population a close representation of national population	Sampling frame a true or close representation of the target population	Was random selection or census undertaken to select the sample?	Was nonresponse bias minimal?	Data collected directly from subjects	Acceptable case definition	Measurement shown to have reliability	Same mode of data collection for all subjects	Length of shortest prevalence period appropriate	Was numerator(s) and denominator(s) appropriate?	Risk of bias
Yang et al.[41]	0	0	1	0	1	1	1	1	1	1	M
Saraya et al.[34]	0	0	1	1	1	0	1	1	1	1	M
Ren et al.[8]	0	1	1	0	1	1	1	1	1	0	M
Luo et al.[17]	0	0	1	1	1	1	1	1	1	1	L
Aydın Tufan and Tekkarışmaz[38]	0	0	1	0	1	0	0	1	1	1	H
Trivioli et al.[37]	0	0	1	0	1	1	1	1	1	1	M
Ono et al.[33]	0	1	1	1	1	1	1	1	1	1	L
Lin et al.[9]	0	0	1	0	1	1	1	1	1	1	M
Lhote et al.[10]	1	1	1	0	1	1	1	1	1	1	L
Lao et al.[27]	0	0	1	0	1	0	0	0	1	1	H
Kida et al.[26]	0	0	1	1	1	1	1	1	1	1	L
Suzuki et al.[35]	1	0	1	0	1	1	1	1	1	1	L
Néel et al.[11]	0	0	1	1	1	1	1	1	1	1	L
Nakamoto et al.[32]	0	0	1	1	1	0	1	1	1	1	M
Greenan et al.[24]	1	0	1	1	1	0	0	0	1	1	M
Tashiro et al.[18]	0	0	1	0	1	0	1	1	1	1	M
Mohammad et al.[31]	0	1	1	0	1	1	1	1	1	1	L
Yamagata et al.[40]	0	0	1	1	1	1	1	1	1	1	L
Guneyli et al.[25]	0	0	1	1	1	1	1	1	1	1	L
Magkanas et al.[30]	0	0	1	0	1	1	1	1	1	1	M
Takahashi et al.[36]	0	0	1	1	1	1	0	0	1	1	M
Lohrmann et al.[29]	0	0	1	0	1	1	1	1	1	1	M
Lee et al.[28]	0	0	1	0	1	1	1	1	1	1	M
Worthy et al.[39]	0	0	1	0	1	1	1	1	1	1	M

Risk of bias: M: Moderate; L: Low; H: High.

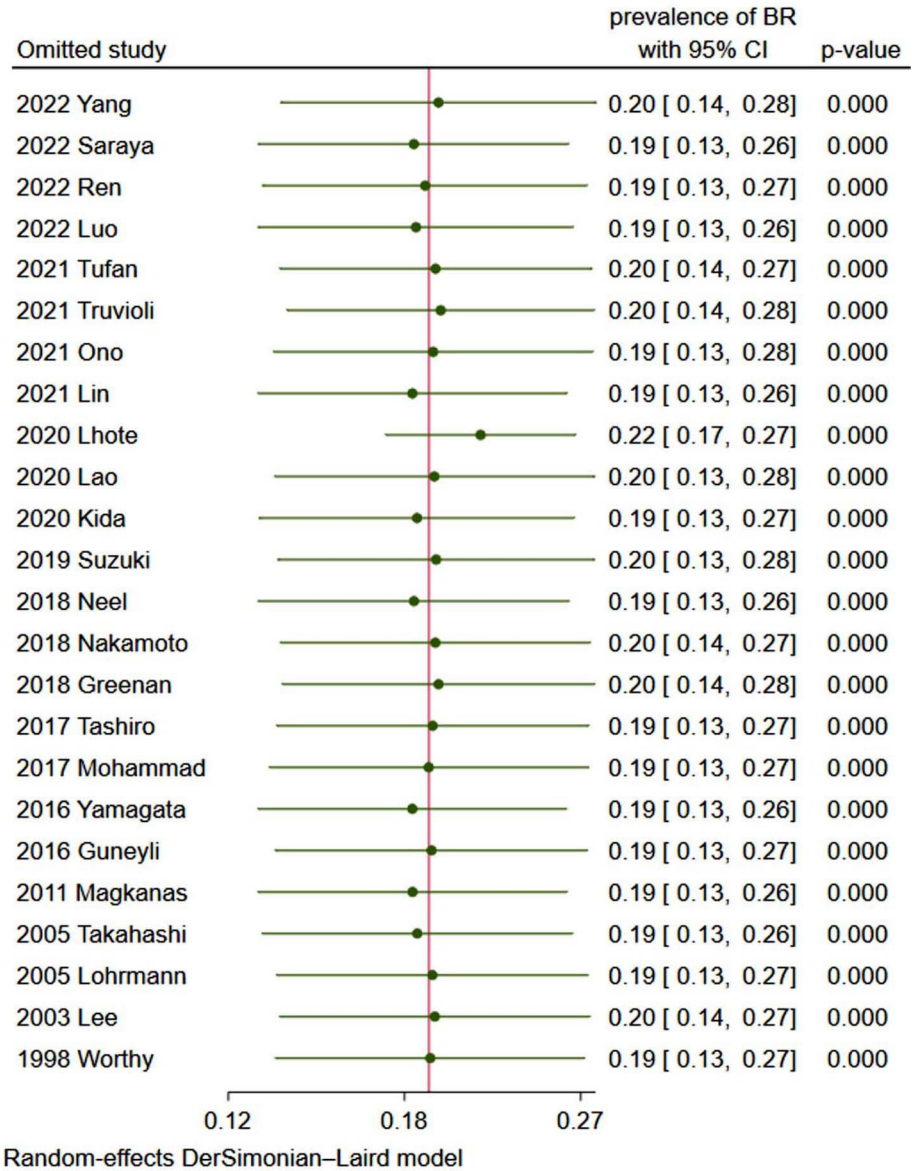
Supplemental Table 3. Quality assessment of the articles included in the "association" study (Agency for Health care Research and Quality)

Study	Define the source of information (survey, record review)	List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications	Indicate time period used for identifying patients	Indicate whether or not subjects were consecutive if not population-based	Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants	Describe any assessments undertaken for quality assurance purposes	Explain any patient exclusions from analysis	Describe how confounding was assessed and/or controlled	If applicable, explain how missing data were handled in the analysis	Summarize patient response rates and completeness of data collection	Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained
Yang et al.[41]	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	Yes
Ren et al.[8]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes
Luo et al.[17]	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	Yes
Néel et al.[11]	Yes	Yes	No	Yes	Yes	Yes	No	No	No	No	Yes
Tashiro et al.[18]	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	Yes
Mohammad et al.[31]	Yes	No	No	Yes	Yes	Yes	No	No	No	No	Yes

Supplemental Table 4. Studies reporting the features of bronchiectasis in patients with ANCA-associated vasculitis (n=8)

Study	BR	Timeline between AAV and BR: number (interval time)	BR morphology (n=cylindrical; varicoid; cystic)	Responsiveness to immunosuppressive treatment
Yang et al.[41]	18	BR preceded: 5 [median 8.5 y (IQR 0.3-33.5)]; Simultaneous & BR followed: 13	NR	NR
Ren et al.[8]	48	BR preceded: 21 [median 180 m (IQR 54-360)]; Simultaneous: 22; BR followed: 5 [median 55 m (IQR 6.5-74)]	29; 10; 3	19 patients reevaluated CT, the BR severity had no significant change
Luo et al.[17]	52	BR preceded: 6; Simultaneous & BR followed: 46	33; 9; 18	NR
Lhote et al.[10]	61	BR preceded: 25 [median 16 y (IQR 4-54)]; Simultaneous: 12; BR followed: 24 [median 1 y (IQR 0-6)]	NR	37 patients reevaluated CT: 6 improved, 9 stable, 22 deteriorated
Néel et al.[11]	22	3 patients with long-lasting symptomatic BR (2 since childhood) before AAV onset	NR	NR
Mohammad et al.[31]	27		25; 1; 1	NR
Yamagata et al.[40]	48		NR	76 BR lesions reevaluated CT: 9 improved, 63 stable, 4 deteriorated
Lohrmann et al.[29]	6		NR	10 BR lesions reevaluated CT: 3 partially improved, 7 stable

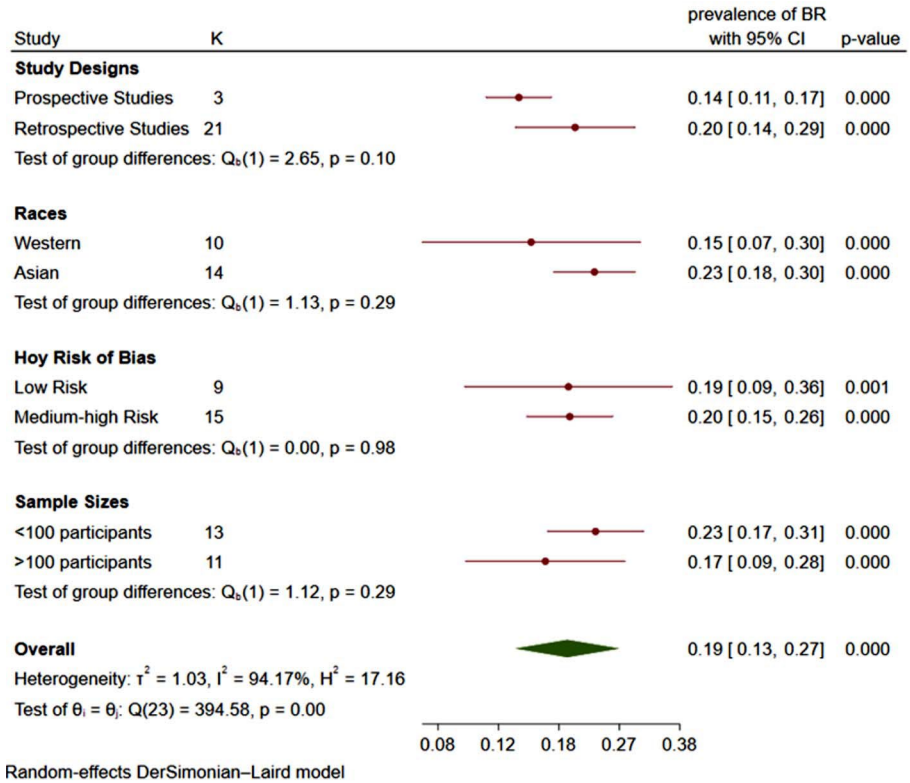
NR: Not reported.



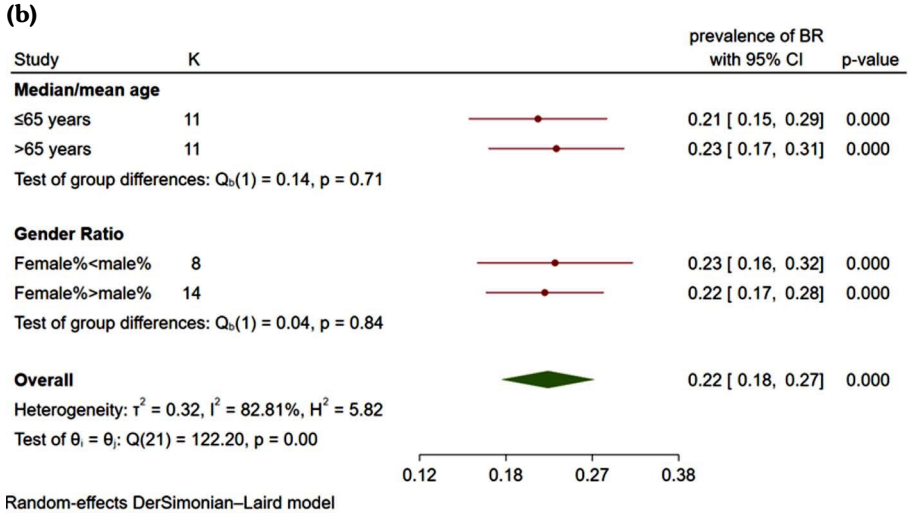
Supplemental Figure 1. Leave-one-out meta-analysis on the prevalence of BR among patients with AAV.

AAV: Associated vasculitis; BR: Bronchiectasis; CI: Confidence interval.

(a)

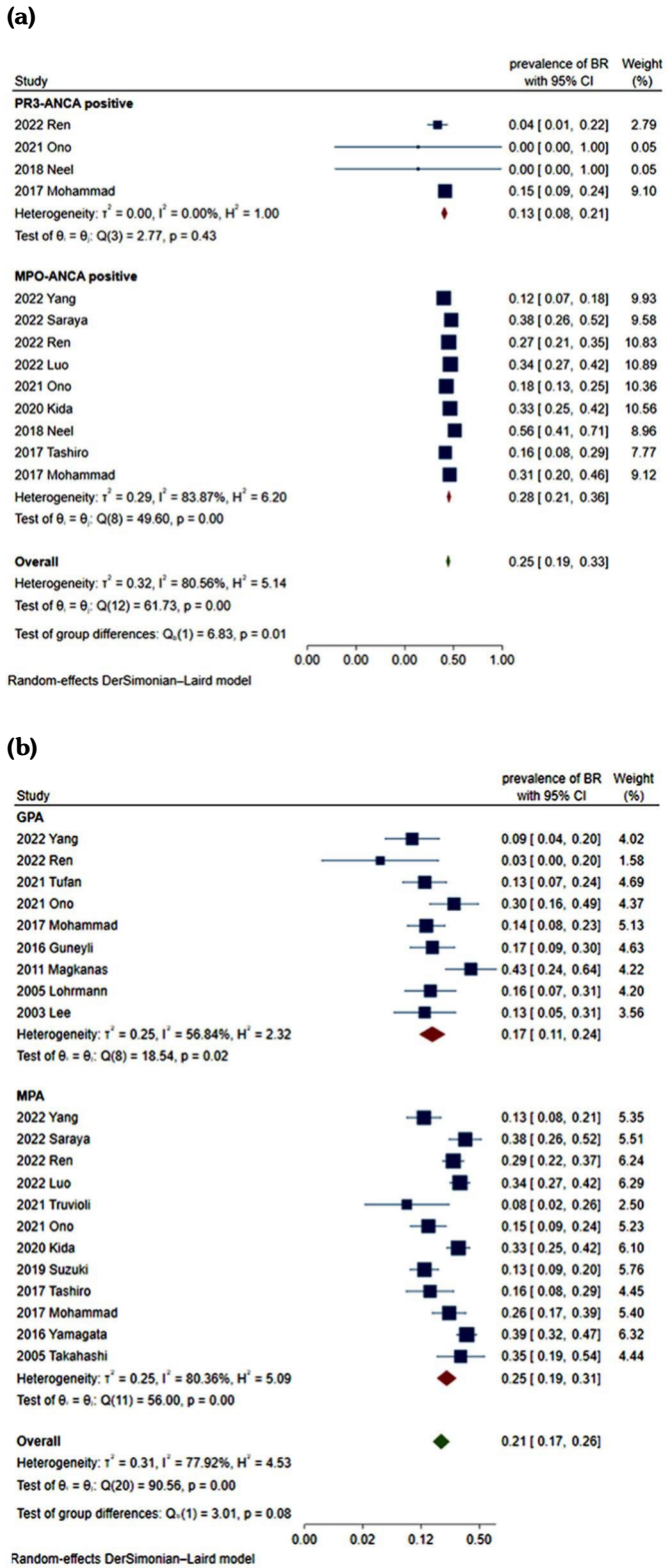


(b)



Supplemental Figure 2. Subgroup analyses on the prevalence of BR among patients with AAV. The analyses were based on different study designs, races, Hoy risk of bias, sample sizes **(a)**, median/mean age, and sex ratio **(b)**. Two studies were excluded in Supplemental Figure 2B due to missing data.

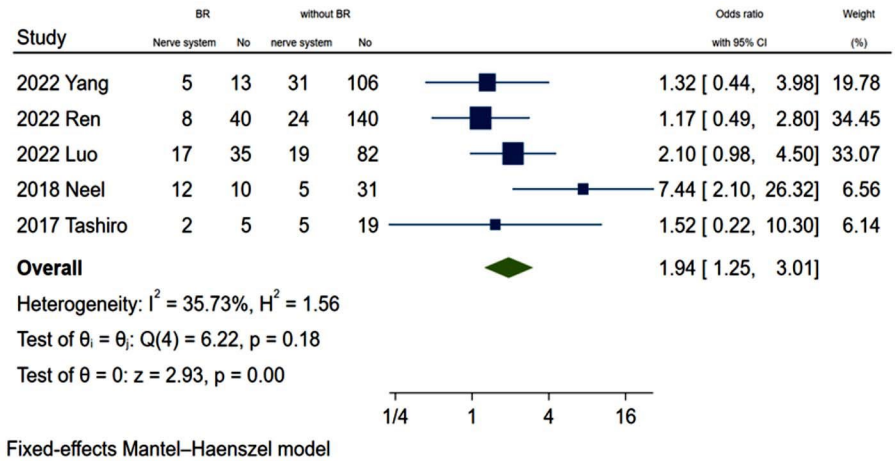
AAV: Associated vasculitis; BR: Bronchiectasis; CI: Confidence interval.



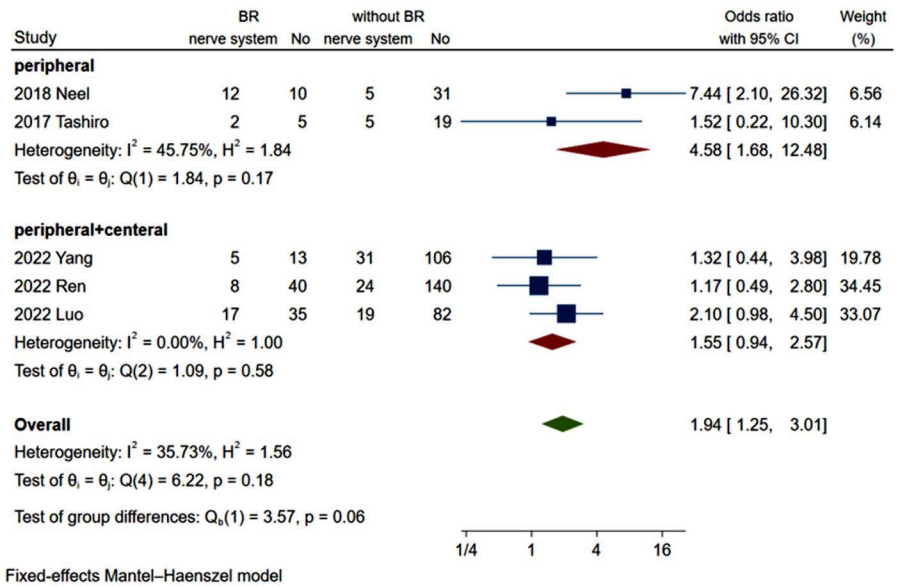
Supplemental Figure 3. Forest plot and random-effects meta-analysis on the prevalence of BR among patients with AAV based on different ANCA statuses **(a)** and clinical classifications **(b)**.

AAV: Associated vasculitis; BR: Bronchiectasis; CI: Confidence interval.

(a)



(b)



Supplemental Figure 4. Forest plot and fixed-effects meta-analysis on nerve system involvement for the association of BR with AAV. **(a)** Includes all nervous system involvement, **(b)** Presents peripheral and central nervous system involvement separately.

AAV: Associated vasculitis; BR: Bronchiectasis; CI: Confidence interval.