Review

The role of tobacco smoking in anti-neutrophil cytoplasmic antibody-associated vasculitis: a systematic review

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ABSTRACT

Objective. *Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are a group of systemic pauci-immune necrotising vasculitides involving small vessels, characterised by the presence of specific ANCA autoantibodies directed to leukocyte proteinase 3 (PR3-ANCA) or myeloperoxidase (MPO-ANCA) and subdivided into three clinical entities: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA). The aetiology of AAV is unknown and many genetic, epigenetic and environmental factors have been reported to be involved in pathogenesis. Smoking is widely recognised as a risk factor for the development of many autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus. This systematic review will analyse known data about the role of smoking in the development, clinical presentation and outcome of AAV.*

Methods. *Articles that examined interactions between tobacco smoking and AAV (GPA, MPA, EGPA) were included. All articles selected were in English. No limitation on publication date was established. Case reports were excluded. The systematic search was performed using PubMed/Medline and Cochrane Library databases.*

Results. *The search provided a total of 131 articles. Three studies were added, obtained from the review of the reference lists of articles. 70 were removed because they were duplicated or written in languages other than English. The title and abstract of 64 articles were screened. Of these, 30 were excluded as the title and/or abstract did not meet the inclusion criteria. Thus, 34 remained for full-text review, of which 8 were excluded. 26 articles were therefore included in this review. The role of smoking in AAV development is unclear. AAV patients current smoking appear appear to be younger and more frequently males, with a lower prevalence of EGPA and MPA than GPA. Ever smokers show higher relapse rate. Smoking seems to be associated with a higher risk of cardiovascular events during follow-up. Smokers incur an increased risk of infections. Finally, many data support smoking as a risk factor for end stage renal disease and mortality in AAV patients.*

Conclusion. *Current data support the hypothesis that smoking influences prevalence, clinical phenotype and prognosis of ANCA-associated vasculitis. However, further studies are required to fully determine its role.*

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are a group of pauci-immune necrotising vasculitides involving small vessels (1), characterised by the presence of specific ANCA autoantibodies directed to leukocyte proteinase 3 (PR3-ANCA) or myeloperoxidase (MPO-ANCA). AAV comprise three clinical entities: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA). AAV commonly show a relapsing-remitting course. Induction and maintenance treatment is based on chronic immunosuppressant therapies (2, 3). Patients undergo severe comorbidities (4, 5), high economic burden (6), poor health related quality of life (7) and high mortality rate (8). Thus, the identification of factors involved in AAV pathogenesis is critical to better un-

derstand physiopathology of AAV and hypothetically prevent onset of AAV.

However, the aetiopathogenesis of AAV is still unknown and polygenic genetic susceptibility, epigenetic modifications and environmental factors have been reported to be involved in pathogenesis (9, 10). Among environmental factors, silica exposure, farming, other pollutants, infections, UV radiation, vitamin D have been associated with AAV (11, 12). Smoking is widely recognised as a risk factors for the development of many autoimmune diseases, such as rheumatoid arthritis (13-15) and systemic lupus erythematosus (16).

Tobacco contains more than 7000 different chemical compounds (17), that mostly interfere with immune system, as enhancers or inhibitors (18). Nicotine shows many immunomodulatory effects. Among immunosuppressive effects, nicotine inhibits toll-like receptor 4 (TLR4), TLR2, tumour necrosis factor alpha (TNF-α) production in monocytes (19, 20), suppresses autophagy in macrophages (21), inhibits proliferation and activation of T lymphocytes, reduces production of T-helper 1 (Th1) (TNF-α and IFN-α) and Th17 associated cytokines (interleukin-17 (IL-17), IL-17F, IL-21, and IL-22) and increases IL-4 production, overall inducing a shift to the Th2 lineage (22). Among pro-inflammatory effects, nicotine induces dose dependent neutrophil extracellular traps (NETs) formation (NETosis) and, in mouse models of rheumatoid arthritis, nicotine exposure is associated with more severe arthritis (23). Acrolein causes cellular DNA damage, induces autophagy and apoptosis of macrophages (24) and, in animal models, reduces NETs formation mediated by respiratory burst (25). In lung tissues benzo[a]pyrene proved to inhibit cytotoxic T cells, dendritic cells, M1 macrophage and neutrophils and immune-stimulatory cytokines, and to induce Treg, tolerogenic dendritic cells, myeloid-derived suppressor cells and M2 macrophage and immunosuppressive cytokines (26). Among heavy metals present in cigarettes, cadmium inhalation causes production of ROS (27) and contributes to NETs formation (28). Mercury leads to TLRs activation (29), also mediated by NETosis (30), proinflammatory cytokine secretion and subsequent specific T-dependent immune response, critical for autoantibody production (31). In mice, aluminium salts induce activation of dendritic cells, release of NETs (32) and production of MPO-ANCA (33). ROS action on lung cells can overload antioxidants systems and cause oxidative stress, leading to lipid peroxidation, DNA and protein oxidative damage. Oxidative stress promotes production of inflammatory mediators, such as prostaglandins and leukotrienes, that are crucial to recruit neutrophils and macrophages. Inflammatory cells subsequently release TNF-α, IL-1 and IL-8, that act as triggers for further recruitment of neutrophils and macrophages, creating a vicious cycle (34).

Exposure to tobacco smoke, thus, can provide immunosuppressive effects but can also promote directly or indirectly production of ROS, generation of proinflammatory cytokines, priming of neutrophils and formation of NETs, all events also involved in AAV pathogenesis (10, 35). However, the role of smoking in ANCA-associated vasculitis is still debated (11) and specific data about interactions between tobacco and AAV pathogenesis are still lacking. Considering that cigarette smoking is a worldwide habit involving approximately a fifth of adults in 2022 (36), the definition of the role of smoking in ANCA-associated vasculitis could prospectively affect AAV epidemiology, clinical characteristics and prognosis. This systematic review, indeed, will collect and analyse known data about the role of smoking in development, clinical presentation and outcome of AAV.

Materials and methods

This systematic review has been composed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol. Studies that examined smoking, tobacco exposure, cigarette use in patients with GPA, EGPA, MPA were included, without restrictions about publication date. Studies wrote in languages other than English and case reports were excluded. The systematic search was performed on 11th December 2023 employing PubMed/Medline and Cochrane Library databases and using the keywords "Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis" as a Mesh term, "smoking", "tobacco", "cigarette" and "smoke". The search strategy was "Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis [Mesh] AND smoking", "Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis [Mesh] AND tobacco", "Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis [Mesh] AND cigarette", "Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis [Mesh] AND smoke". Duplicates were excluded. Additional relevant articles were obtained from the review of the reference lists of articles. Two reviewers, MM and FF, independently screened in a two-step procedure titles and abstracts and, subsequently, full texts of eligible articles. Any disagreement was fixed by a third reviewer, CB. The articles included were analysed for the interaction of smoking with AAV. Data were grouped into three main topics: 1. the role of smoking in AAV development, 2. the role of smoking as a factor influencing disease phenotype (clinical presentation, characteristics of relapse), 3. the role of smoking as a prognostic factor for comorbidities (cardiovascular diseases, infection, end stage renal disease) and overall mortality. Each article was evaluated for: author, year of publication, country of origin, type of study design and methods, sample size and diagnoses included (GPA/MPA/EGPA), topic analysed about smoking, definition of current/previous/ever/never smoker. Results were collected as differences of prevalence/incidence of variables and, where present, as measures of effect size (odds ratio (OR) or hazard ratio (HR)). Extracted data were synthesised in a narrative review without meta-analysis by two reviewers (MM and FF) and summarised in the tables. Statistical analyses were not performed due to the differences of the characteristics of studies, the low number of comparable studies and incomplete reports of effect size.

Results

The search provided a total of 131 articles. Three studies were added, obtained from the review of the reference lists of articles. 70 were removed because they were duplicated or written in languages other than English. The title and abstract of 64 articles were screened. Of these, 30 were excluded as the title and/or abstract did not meet the inclusion criteria. Thus, 34 remained for full-text review, of which 8 were excluded. Flow diagram of process of study selection is available in Figure 1. 26 articles were therefore included in this review.

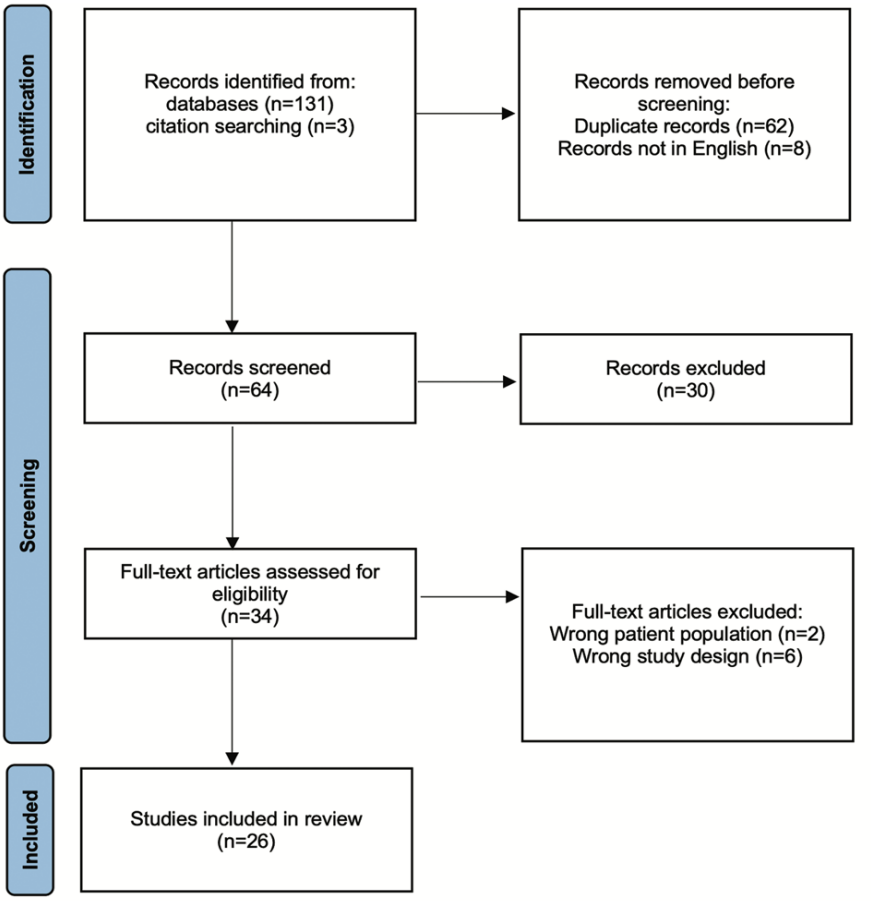

Fig. 1. PRISMA flow diagram describing the process of study selection.

Smoking and AAV development

Many studies focused on the role of tobacco smoking in AAV development, some reporting a protective effect, some reporting a risky effect, others finding no influence. The characteristics of the studies are reported in Table I.

Smoking as a neutral factor

Hogan *et al*. found a similar prevalence of ever smokers among patients affected by AAV-related glomerulonephritis and controls with other renal diseases (37), and also among healthy controls (38). Rihova *et al*. showed comparable results in a small cohort of AAV patients with pulmonary involvement (39). In a case-control study involving AAV patients and non-vasculitic controls (40), no associations have been reported with ever smoking or smoking in the year before AAV onset. Finally, also in a city-based New Zealand study (41), the proportion of ever smokers did not differ among GPA patients and controls.

Smoking as a protective factor

In a retrospective study involving 197 MPA and GPA German patients (42), 27 (14%) patients were current smokers in the last 2 years before disease onset, in a significantly lower proportion than general German population (24.3% smokers, $p<0.001$) (42). Similar results were reported in a French AAV cohort, where prevalence of current smokers was 9.2% compared to 32.9% in male general population, and 4.2% compared to 29,3% in females (43). Berti *et al*. also found a lower proportion of current smokers in AAV patients than in controls (5% *vs*. 19%; $p=0.04$) (44). Moreover, a cohort of 111 Italian EGPA patients showed a significantly lower proportion of current smokers (smokers in the last six months) than age-, sex- and geographic origin-matched controls (2% *vs*. 29%) [OR 0.04 (95% C.I. 0.01–0.18) $p<0.001$] and a lower pack-year index was observed in ever-smokers cases than in ever-smokers controls [10 (5–20) *vs*. 17 (9–30) $p=0.006$] (45). However, sub-analyses regarding ANCA status showed that protective role of smoking remained significant only in ANCA-MPO negative patients [OR 0.34 (95% C.I. 0.17–0.66) $p=0.002$] (45). The proportion of ever smokers was lower among EGPA patients than among controls also before asthma onset (45). Multivariable logistic regression analysis confirmed that tobacco smoking (former and current smoking) was independently associated with a lower risk of EGPA development [OR 0.39 (95% CI 0.22–0.69), $p=0.001$] (45).

Smoking as a risk factor

In a large US-based study where 473 GPA and MPA were recruited (46), a higher proportion of current and former smokers was observed among AAV patients than among controls (respectively 9% *vs*. 4% [OR 2.70 (95% C.I. 1.76–4.14)] for current smokers and 45% *vs*. 38% [OR 1.58 (95% C.I. 1.25–2.00)] for former smokers). These associations remained strong after stratification by sex, head and neck, renal and pulmonary involvement and ANCA-MPO positivity, while, in ANCA-PR3 positive patients, statistical significance was not achieved (46). Moreover, the odds of having AAV increased with raising pack-years of tobacco exposure [p for trend <0.001] (46). In a case-control study based on medical records from UK primary care and involving 757 GPA patients and age-, sex- and general practice-matched controls (47), former smoking was associated with an increased risk of developing GPA compared with never smokers [odds ratio

Table I. Characteristics of studies on smoking and ANCA-associated vasculitis development.

Smoking and AAV development

Authors	Year	Nation	Study design	Diagnosis (GPA, MPA, EGPA)	n. patients	Smoking status	Main conclusions	Possible role of smoking (risk factor/protective factor/neutral factor)
Hogan *et al.*	2001	US (North Carolina)	Case-control study	ANCA-associated vasculitis with glomerulonephritis	65	48 ever smokers 17 non-smokers	Current and former smoking exposure was similar in patients and control cohorts (48% *vs.* 52%) [OR 0.66 (95% C.I. 0.25-1.78)].	Neutral factor
Hogan *et al.*	2007	US (North Carolina, South Carolina, Georgia, and southern Virginia)	Case-control study	ANCA-associated vasculitis with glomerulonephritis	129	80 ever smokers 49 non-smokers	Smoking history was similar between AAV patients and controls (62% *vs.* 51%, p=0.11).	Neutral factor
Rihova *et al.*	2005	Czech Republic	Case-control study	Wegener's granulomatosis (WG), MPA, Churg-Strauss Syndrome (CSS)	31 (22 WG, 8 MPA, 1 CSS).	13 ever smokers	Exposure to smoking was comparable among AAV and control groups (41.9% *vs.* 43.3%).	Neutral factor
Lane *et al.*	2003	UK	Case-control study	Wegener's granulomatosis (WG), MPA, Churg-Strauss Syndrome (CSS)	75 (47 WG, 12 MPA, 16 CSS)	53 ever smokers 22 non-smokers	No associations have been reported with ever smoking (70.7% *vs.* 70.9%) [OR 0.9 (95% C.I. 0.5-1.6)] or smoking in the year before AAV onset (20% *vs.* 25%) [OR 0.7 (95% C.I. 0.4-1.5)].	Neutral factor
Stamp *et al.*	2015	New Zealand	Case-control study	GPA	49	28 ever smokers 21 non-smokers	Number of ever smokers did not differ among GPA patients and controls (57.1% *vs.* 66.3% - OR 0.59 (95% C.I. 0.28-1.25)).	Neutral factor
Haubitz *et al.*	2005	Germany	Retrospective study	WG, MPA	197 (132 WG, 65 MPA)	27 current smokers 54 former smokers 116 non-smokers	In AAV cohort, current smokers were a lower proportion than in general German population (14% *vs.* 24.3%, p<0.001).	Protective factor
Berti *et al.*	2018	Olmsted County (Minnesota, USA)	Case-control study	GPA, MPA, EGPA	58 (23 GPA, 28 MPA, 7 EGPA)	3 current smokers 24 former smokers 30 non-smokers 1 missing	Proportion of current smokers was lower in AAV patients than in controls (5% *vs.* 19%, p=0.04)	Protective factor
Maritati *et al.*	2021	Italy	Case-control study	EGPA	111	2 current smokers 36 former smokers 73 non-smokers	Tobacco smoking was independently associated with a lower risk of EGPA [OR 0.39 (95% CI 0.22-0.69), p=0.001]. Protective role of smoking remained significant only in ANCA-MPO negative patients [OR 0.34 (95% C.I. 0.17-0.66) p=0.002].	Protective factor
McDermott *et al.*	2020	US	Case-control study	GPA, MPA	473	43 current smokers 211 former smokers 219 non-smokers	A higher proportion of current and former smokers was observed among AAV patients than among controls (respectively 9% *vs.* 4% [OR 2.70 (95% C.I. 1.76-4.14)] for current smokers and 45% *vs.* 38% [OR 1.58 (95% C.I. 1.25-2.00)] for former smokers). The odds of having AAV increased with raising pack-years of tobacco exposure (P for trend <0.001).	Risk factor
Pearce *et al.*	2018	UK	Case-control study	GPA	757	172 current smokers 172 former smokers 349 non-smokers 64 unknown	Former smoking was associated with an increased risk of developing GPA compared with never smokers [odds ratio (OR) 1.5, 95% C.I. 1.2-1.8, p<0.001].	Risk factor

Table II. Characteristics of studies on smoking and ANCA-associated vasculitis phenotype.

The role of smoking as a disease-modifier

Authors	Year	Region	Study design	Diagnosis	N. patients	Smoking status	Main conclusions
Haubitz *et al.*	2005	Germany	Retrospective study	WG, MPA	197 (132 WG, 65 MPA)	27 current smokers 54 former smokers 116 non-smokers	Smokers, non-smokers, or ex-smokers did not differ in organ manifestations. Smokers were younger (median age 42 years) than all patients with vasculitis (median age 54 years, $p<0.01$).
Yamaguchi *et al.*	2018	Japan	Retrospective study	MPA, GPA, renal-limited vasculitis (RLV)	122 (96 MPA, 20 RLV, 6 GPA)	21 current smokers 33 former smokers 68 non-smokers	No difference was observed about disease phenotype and organ involvement. Smokers were more frequently male (29.4% *vs.* 88.9%, $p<0.001$). Ever smokers were at a higher risk of relapse at 1, 3 and 5 years than never smokers (log-rank test: $p=0.003$). Current smoking is a predictor of first relapse [univariate HR 3.88 (95% C.I. 1.74-8.58) $p=0.001$, and multivariate HR 7.48 (95% C.I. 2.73-21.0) $p<0.001$]. Risk of relapse is positively associated with cumulative smoke exposure ($p=0.004$).
Patel *et al.*	2023	Poland	Retrospective study	MPA, GPA	223	39 current smokers 68 former smokers 116 non-smokers	Ever smokers need more frequently renal replacement therapy at diagnosis (31% *vs.* 14%; p=0.003) and had a higher mean BVAS (19 *vs.* 17.25, $p=0.04$) and median C -reactive protein level ($p=0.01$). No association between smoking status and relapse rate of AAV was found.
Thayakaran *et al.*	2022	UK	Retrospective study	GPA	649	293 ever smokers 317 non-smokers 39 missing	No difference in smoking exposure was observed among patients with limited disease, extra-renal generalised disease and renal predominant disease.
Benarous *et al.*	2015	France	Retrospective study	GPA, MPA, EGPA	1165 (583 GPA, 326 EGPA, 256 MPA.	76 current smokers 116 former smokers 973 non-smokers	Current smokers had less frequently peripheral neuropathy (28 *vs.* 41%, $p=0.037$), and lower BVAS (15.4±8.1 *vs.* 18.7±9.0, $p=0.037$). In multivariate analysis, current smokers were younger [OR 0.98 (95% C.I. 0.96–0.99), $p=0.01$], more frequently male [2.31 (95% C.I. 1.31-4.08), $p=0.004$], less frequent EGPA [0.44 (95% C.I. 0.23–0.87), $p=0.017$] and MPA [0.36 (95% C.I. 0.14–0.93), $p=0.036$]. In EGPA cohort, current smokers had less frequent constitutional symptoms (29 *vs.* 62%, $p=0.02$), arthralgias (7 *vs.* 35%, $p=0.04$), renal involvement (0 *vs.* 26%, $p=0.025$) and MPO-ANCA–positivity (0 *vs.* 30%, p=0.02) and had lower BVAS (12.5±6.6 *vs.* 18.5±8.1, $p=0.018$) than non-current smokers. In GPA cohort current smokers had more frequent skin involvement (50 *vs.* 32%, $p=0.025$).
Monti *et al.*	2020	Multinational (DCVAS cohort, 32 countries)	Prospective study	GPA, MPA, EGPA	873 (506 GPA, 183 MPA, 184 EGPA)	90 current smokers 251 former smokers 517 non-smokers	Number of current smokers was higher in GPA than EGPA (12.65% *vs.* 2.72%, $p<0.001$) and number of previous smokers was higher in MPA than in EGPA (30.05 *vs.* 28.26, $p=0.024$).
Basu *et al.*	2013	Multinational (EUVAS cohort), UK (VASQoL cohort)	Prospective study	GPA and MPA	EUVAS: 342 (186 GPA, 156 MPA) VASQoL: 360 (265 GPA, 95 MPA)	EUVAS: 36 current smokers 158 ever smokers 148 non-smokers VASQoL: 26 current smokers 191 ever smokers 143 non-smokers	Current smokers were younger (p=0.047 and $p=0.021$, respectively) and showed more frequently gastrointestinal involvement in the EUVAS and in the VASQoL cohorts (17% *vs.* 6% [$p=0.026$] and 12% *vs.* 4% [$p=0.044$], respectively) than non-current smokers. VASQoL current smokers had higher proportion of cutaneous (48% *vs.* 28%, $p=0.035$) and lower proportion of ENT manifestations (44% *vs.* 64%, $p=0.046$).

Table III. Characteristics of studies on smoking and ANCA-associated vasculitis prognosis.

Smoking status and prognosis: cardiovascular diseases, infection, end stage renal disease and mortality

Authors	Year	Region	Study design	Diagnosis	N. patients	Smoking status	Main conclusions	Role of smoking (risk factor/ protective factor/unclear)
				CARDIOVASCULAR DISEASES				
Berti *et al*.	2018	Olmsted County (Minnesota, USA)	Case-control study	GPA, MPA, EGPA	58 (23 GPA, 28 MPA, 7 EGPA)	3 current smokers 24 former smokers 30 non-smokers 1 missing	No association between smoking status and CVD.	Neutral factor
Vegting *et al*.	2023	Netherlands, Canada	Prospective study	GPA, MPA, EGPA	144 (99 GPA, 25 MPA, 20 EGPA)	74 former smokers	No association between smoking history and CVD.	Neutral factor
Monti *et al*.	2020	Multinational (DCVAS cohort, 32 countries)	Prospective study	GPA, MPA, EGPA	873 (506 GPA, 183 MPA, 184 EGPA)	90 current smokers 251 former smokers 517 non-smokers	Smoking did not influence development of hypertension or diabetes mellitus.	Neutral factor
Moiseev *et al*.	2023	EU, China, Turkey, Russia, UK, US	Retrospective study		2286 (983 GPA, 1165 MPA, 138 EGPA)	729 former smokers	Smoking was a risk factor [HR 1.98, 95% CI 1.48-2.64] for CVD (fatal and nonfatal myocardial infarction, stroke, or both).	Risk factor
Mourguet *et al*.	2019	France	Retrospective study	GPA, MPA	125 (99 GPA, 26 MPA)	37 smokers	Tobacco use was a risk factors for major cardiovascular events [HR 2.7 (95% C.I. 1.07-6.66) p=0.036] and coronary artery disease [HR 8.8 (95% C.I. 2.12-36.56) p=0.003].	Risk factor
Morgan *et al*.	2009	UK	Retrospective study	WG, MPA, CSS	113 (65 WG, 46 MPA, 2 CSS)	64 ever smokers 48 never smokers 1 missing	Ever smoking increased the risk of CV events [HR 3.9 (95% C.I. 1.5-10) p=0,005] in AAV patients overall, and in those without preexisting CVD or who never required dialysis [HR 6 (95% C.I. 1.6-22.8) p=0.005].	Risk factor
Yamaguchi *et al*.	2018	Japan	Retrospective study	MPA, GPA, renal-limited vasculitis (RLV)	122 (96 MPA, 20 RLV, 6 GPA)	21 current smokers 33 former smokers 68 non-smokers	Smokers had a higher number of hospitalisations related to a cardiovascular event (11.1% *vs*. 0%, p=0.006).	Risk factor
				INFECTION				
Lao *et al*.	2019	China	Retrospective study	GPA, MPA, EGPA, RLV	132 (84 RLV, 39 MPA, 5 GPA, 4 EGPA)	25 current smokers 18 former smokers 89 non-smokers	Smoking is independently associated with infections [univariate OR 2.30 (95% C.I. 1.14-4.64), p=0.02, multivariate OR 2.38 (95% C.I. 1.13-5.03), p=0.02]. Smokers suffering from infections had less chance to survive (41.2% *vs*. 31.3%, p p<0.001).	Risk factor

Yang*et al.*	2018	China	Retrospective study	GPA, MPA, EGPA, RLV	248 (214 MPA, 16 RLV, 10 GPA, 8 EGPA)	59 smokers	Smoking was a risk factor for infections [univariate HR 2.293 (95% C.I. 1.465-3.588) p=0.000, multivariate HR 2.338 (95% C.I. 1.236-4.424) *p*=0.009].	Risk factor
Thayakaran *et al.*	2022	UK	Retrospective study	GPA	649	293 ever smokers 317 non-smokers 39 missing	Smoking was associated with increased risk of antibiotic use (1.13 (1.05-1.22) *p*<0.001).	Unclear
Watanabe-Imai *et al.*	2016	Japan	Prospective study	GPA, MPA, EGPA, RLV, unclassified AAV (U-AAV)	156 (33 GPA, 78 MPA/RLV, 14 EGPA, 31 U-AAV)	50 smokers	Smoking was a risk factors for severe infections within six months of remission induction therapy in AAV patients [HR 2.64 (95% C.I. 1.39-5.01) *p*=0.003].	Risk factor.
				END STAGE RENAL DISEASE AND MORTALITY				
Haubitz *et al.*	2005	Germany	Retrospective study	WG, MPA	197 (132 WG, 65 MPA)	27 current smokers 54 former smokers 116 non-smokers	No difference was observed between smokers, non-smokers, or former smokers about mortality rate and development of end stage renal disease.	Neutral factor
Kotani *et al.*	2023	Japan	Retrospective study	MPA	194	94 smokers	No difference in mortality rate was observed according to smoking history. Brinkman index resulted higher in dead patients (*p*=0.002).	Unclear
Kwon *et al.*	2021	South Korea	Retrospective study	GPA, MPA, EGPA	223 (57 GPA, 122 MPA, 44 EGPA)	6 smokers	Smoking history was associated with all-cause mortality during follow-up [HR 6.052 (95% C.I. 1.787-20.498) *p*=0.004] in univariate but not in multivariate analysis.	Unclear
Yamaguchi *et al.*	2018	Japan	Retrospective study	MPA, GPA, RLV	122 (96 MPA, 20 RLV, 6 GPA)	21 current smokers 33 former smokers 68 non-smokers	Smokers had a higher proportion of death (33.3% *vs.* 13.2%, *p*=0.009) and end-stage renal disease (35.2 *vs.* 14.7%, *p*=0.010) compared to never smokers.	Risk factor
Patel *et al.*	2023	Poland	Retrospective study	MPA, GPA	223	39 current smokers 68 former smokers 116 non-smokers	In the Kaplan-Meier analysis, the ever smokers were found to have a higher mortality hazard [HR 2.89 (95% C.I. 1.47-5.72) *p*=0.002]. In the multivariable Cox regression analysis, ever smoking [HR 2.39 (95% C.I. 1.11-5.54) *p*=0.03] was found to be an independent predictor of mortality.	Risk factor
Caravaca-Fontán *et al.*	2016	Spain	Retrospective study	GPA, MPA	89 (64 MPA, 25 GPA)	27 smokers	Smoking was associated with all-cause mortality [univariate OR 1.683 (95% C.I. 1.021-2.776) *p*=0.041, multivariate OR 1.816 (95% C.I. 1.230-2.682) *p*=0.003] and with renal replacement therapy [HR 1.848 (95% C.I. 1.086-3.145) *p*=0.023].	Risk factor

(OR) 1.5, 95% C.I. 1.2–1.8, $p<0.001$]. However, current smoking tended to be associated with a decreased risk of developing GPA compared with never smokers [OR 0.8, 95% C.I. 0.7, 1.0, $p=0.077$] (47).

The role of smoking as a disease-modifier

Another topic covered in the literature has been whether smoking status could influence disease presentation and phenotype of AAV. The characteristics of the described studies are reported in Table II.

Some studies did not find any association (42, 48). In particular Patel *et al*. described, in their MPA and GPA Polish cohort, that ever smokers and never smokers, and current and past smokers did not differ for clinical presentation, organ involvement or ANCA status (49), but ever smokers showed more frequently the need for renal replacement therapy at diagnosis (31% *vs*. 14% $p=0.003$) and a higher mean BVAS (19 *vs*. 17.25, $p=0.04$) and median C-reactive protein level ($p=0.01$) (49). In a bigger cohort of 649 GPA patients, smoking exposure was not significantly different among patients with limited disease, extra-renal generalised disease and renal predominant disease (50).

However, a retrospective study by Benarous *et al*., based on French Vasculitis Study Group database, which recruited 1165 GPA, MPA and EGPA patients, compared clinical and biological disease phenotype at diagnosis (43). Current smokers (who smoked at least in the last 3 months before evaluation) were significantly younger (45.2±14.4 *vs*. 53.5±16.1, $p<0.0001$), more frequently males (66 *vs*. 45%, $p=0.0008$), as described also by Yamaguchi *et al*. (48) and Patel *et al*. (49), and had more frequently PR3-ANCA (28 *vs*. 41%, $p=0.037$) and less frequently MPO-ANCA (28 *vs*. 41%, $p=0.037$) than former and never smokers (43). The proportion of current smokers in GPA patients was higher than in EGPA and MPA ones ($p=0.0002$) (43), as confirmed also in a study by Monti *et al*. (51), where number of current smokers was higher in GPA than EGPA (12.65% *vs*. 2.72%, $p<0.001$) and number of previous smokers was higher in MPA than in EGPA (30.05 *vs*. 28.26, $p=0.024$). Evaluating overall disease features, current smokers had less frequently peripheral neuropathy (28 *vs*. 41%, $p=0.037$), and lower BVAS (15.4±8.1 *vs*. 18.7±9.0, $p=0.037$) (43). In multivariate analyses, features independently associated with current tobacco use at diagnosis were younger age [OR 0.98 (95% C.I. 0.96–0.99), $p=0.01$], male gender [2.31 (95% C.I. 1.31–4.08), $p=0.004$], less frequent EGPA [0.44 (95% C.I. 0.23–0.87), $p=0.017$] and MPA [0.36 (95% C.I. 0.14–0.93), $p=0.036$] (43). In EGPA cohort, current smokers had less frequent constitutional symptoms (29 *vs*. 62%, $p=0.02$), arthralgias (7 *vs*. 35%, $p=0.04$), renal involvement (0 *vs*. 26%, $p=0.025$) and MPO-ANCA–positivity (0 *vs*. 30%, $p=0.02$) and had lower BVAS (12.5±6.6 *vs*. 18.5±8.1, $p=0.018$) than non-current smokers (43). In GPA cohort current smokers had more frequent skin involvement (50 *vs*. 32%, $p=0.025$) (43). Basu *et al*., in an unpublished work involving two European cohorts (EUVAS and VASQoL) of GPA and MPA patients (52), observed that current smokers were younger ($p=0.047$ and $p=0.021$, respectively) and showed more frequently gastrointestinal involvement in the EUVAS and in the VASQoL cohorts (17% *vs*. 6% [$p=0.026$] and 12% *vs*. 4% [$p=0.044$], respectively) than non-current smokers. VASQoL current smokers had higher proportion of cutaneous (48% *vs*. 28%, $p=0.035$) and lower proportion of ENT manifestations (44% *vs*. 64%, $p=0.046$) (52). Also Haubitz *et al*. observed that, at disease onset, active smokers were younger (median age 42 years) than all patients with vasculitis (median age 54 years, $p<0.01$) (42).

The action of smoking compounds may also influence disease activity and relapse rate. Yamaguchi *et al*., in a Japanese MPA and GPA cohort of almost totally ANCA-MPO positive patients, showed that remission at 2 months was more frequent in non-smokers than in ever smokers (former or current) ($p=0.043$) and that a higher proportion of smokers than non-smokers developed at least 1 relapse during follow-up (39.6% *vs*. 20.9%, $p=0.037$) (48). Analysis of the cumulative probabilities of relapse at 1, 3, and 5 years from disease onset demonstrated that ever smokers were at a higher risk of relapse than never smokers (log-rank test: $p=0.003$). Univariate and multivariate models showed that current smoking, in particular, was a predictor of first relapse [respectively hazard ratio [HR], 3.88 (95% C.I. 1.74–8.58) $p=0.001$, and 7.48 (95% C.I. 2.73–21.0) $p<0.001$] and that risk of relapse was positively associated with cumulative exposure (measured in pack-years) ($p=0.004$) (48). Patel *et al*. did not find any association between smoking status and relapse rate of AAV (49).

Smoking status and prognosis: cardiovascular disease, infection, end stage renal disease and mortality

It is well-known that patients with systemic autoimmune diseases and, specifically, AAV, have an increased risk of cardiovascular disease and infections, due to disease activity, disease damage and immunosuppressive therapies, so implying a higher overall mortality than general population (53). Several studies, thus, focused on defining whether smoking could be an additional and cooperative factor in determining AAV prognosis. The characteristics of the studies are reported in Table III.

Many studies involving AAV patients showed an increased risk of cardiovascular disease (CVD) associated to the disease (44, 54), compared to general population. Thus, considering that tobacco use is an established risk factor for cardiovascular disease including coronary heart disease (55), stroke (56) and sudden cardiac death (57) in the general population, smoking habits were also analysed. Berti *et al*. (44) and Vegting *et al*. (58) found no association between smoking status and CVD in AAV patients. Smoking was also analysed as a possible risk factor for development of hypertension or diabetes mellitus in AAV patients, but results did not show any significant association (51). However, a multinational retrospective study involving 2286 patients with AAV identified smoking as a risk factor [hazard ratio (HR) 1.98,

95% CI 1.48–2.64] for CVD (fatal and non-fatal myocardial infarction, stroke, or both) in univariate and multivariate Cox regression analysis (59). Similar results were published by Mourguet *et al*. (54), who observed that tobacco use was identified as a risk factors for major cardiovascular events [HR 2.7 (95% C.I. 1.07–6.66) p=0.036] and, more specifically, for coronary artery disease [HR 8.8 (95% C.I. 2.12–36.56) p=0.003], in GPA/MPA patients. Morgan *et al*. found that ever smoking was related to CV events [HR 3.9 (95% C.I. 1.5–10) p=0.005] in AAV patients overall, and in those without preexisting CVD or who never required dialysis [HR 6 (95% C.I. 1.6–22.8) p=0.005] (4). According to Yamaguchi *et al*., smokers had a higher number of hospitalisations related to a cardiovascular event (11.1% *vs*. 0%, p=0.006) (48).

Infectious events in AAV patients are related to disease activity, disease damage and, especially, concurrent immunosuppressive therapies. In this context, smoking has been analysed as a possible independent risk factor for infections. A single-centre retrospective study from China displayed that AAV patients with infection were more frequently smokers (32.6% *vs*. 17.3%, p=0.02) and that smoking was a factor associated with infectious diseases in univariate and multivariate analysis [respectively OR 2.30 (95% C.I. 1.14–4.64), p=0.02 and OR 2.38 (95% C.I. 1.13–5.03), p=0.02] (60). Moreover, smokers suffering from infections had less chance to survive (41.2% *vs*. 31.3%, p<0.001) (60). Another Chinese cohort study involving 248 AAV patients evaluated for infectious events showed similar results: the incidence of smoking (36.0% *vs*. 17.3%, p=0.000) was significantly higher among the infected patients and univariate and multivariate Cox regression analysis confirmed smoking as a risk factor for infections [respectively HR 2.293 (95% C.I. 1.465–3.588) p=0.000 and HR 2.338 (95% C.I. 1.236–4.424) p=0.009] (61). Highlighting the role of tobacco use in infection development, in a UK GPA cohort smoking was associated with increased risk of antibiotic use (1.13 (1.05–1.22) p<0.001) (50). Additionally, Watanabe-Imai *et al*. identified smoking as a risk factor for severe infections within six months of introduction of induction therapy in AAV patients [HR 2.64 (95% C.I. 1.39–5.01) p=0.003] (62).

Studies focusing on mortality in AAV have also considered the role of tobacco use. Haubitz *et al*. (42) did not describe differences between current smokers, non-smokers, or former smokers in mortality rate and development of end stage renal disease. Data from a Japanese MPA cohort (REVEAL) showed no difference in mortality rate according to smoking history, but Brinkman index resulted higher in dead patients (p=0.002) (63). However, many other studies identified smoking as a risk factor for mortality and end stage renal disease. Yamaguchi *et al*., in a multicentre study involving 122 MPA and GPA subjects, found that smokers had a higher number of deaths (33.3% *vs*. 13.2%, p=0.009) and end stage renal disease (35.2% *vs*. 14.7%, p=0.010) compared to never smokers (48). In a Korean AAV cohort of 223 patients, smoking history was associated with all-cause mortality during follow-up [HR 6.052 (95% C.I. 1.787–20.498) p=0.004] in the univariate but not the multivariate analysis (64). According to Patel *et al*., in their Polish AAV cohort, mortality of ever smokers was higher than never smokers' (23% *vs*. 9%; p<0.001) (49). In the Kaplan-Meier analysis, the ever smokers were found to have a higher mortality hazard [HR 2.89 (95% C.I. 1.47–5.72) p=0.002], with similar distribution of the causes of death (49). In the multivariable Cox regression analysis, ever smoking [HR 2.39 (95% C.I. 1.11–5.54) p=0.03] was found to be an independent predictor of mortality. However, current and past smokers did not display differences according to number of deaths and mortality hazard (49). In a Spanish cohort of 89 GPA and MPA cases with renal involvement (65), smoking exposure was pinpointed in regression analyses as a factor associated with all-cause mortality [univariate OR 1.683 (95% C.I. 1.021–2.776) p=0.041, multivariate OR 1.816 (95% C.I. 1.230–2.682) p=0.003] and with renal replacement therapy [HR 1.848 (95% C.I. 1.086–3.145) p=0.023].

Discussion

Data presented in this systematic review showed that whether smoking promotes, inhibits or is unrelated to development of AAV is unclear. Studies suggesting no role of smoking involve small size groups of patients and are less recently published (37-40). They are all case-control studies whose data on smoke exposure derives from questionnaires. Moreover, they are seldom focused on smoking habits and related data are only briefly reported. Data supporting a protective role of smoking are mostly derived from a few studies. Haubitz *et al*. (42) involves patients recruited in a nephrological setting, so ascertainment and referral bias cannot be excluded. Geographical distribution of patients and socio-economic status could have interfered with analyses. The last considerations could be applied also to other studies (43) (44). In particular, Haubitz *et al*. (42) and Benarous *et al*. (43) did not use a control group for analyses but data from cross-sectional studies. Studies that show smoking as a risk factor for AAV development involve only GPA and MPA patients and are based on large sized samples. Work by McDermott *et al*. (46) is focused specifically on smoking habits with a high prevalence of MPO-ANCA positive patients but cases and controls derived from the same single health care system. Pearce *et al*. include records of GPA patients collected from a longitudinal medical database, limiting recall bias.

However, published data regarding EGPA are more consistent. Ever smoking seems to be a protective factor for EGPA development, especially in ANCA-MPO negative patients and independently from asthma symptoms (45). Current smokers with AAV appear to be younger and more frequently males, as reported in almost all the cited studies. However, the only large sized study focusing on the role of smoking in disease phenotype shows, despite the low frequency of smokers reported, that current smokers have a lower prevalence of EGPA and MPA than

GPA (43). Among EGPA patients, current smokers have less frequent constitutional symptoms, renal involvement and MPO-ANCA positivity, and, among GPA patients, more frequent skin involvement (43, 52). Moreover, ever smokers show higher relapse rate at short and medium term (48). Many consistent data (54, 59) identify smoking as a risk factor for cardiovascular disease during follow-up, despite some evidence that conflicts probably because of small size of samples and geographical and ethnical characteristics of AAV patients involved in those studies (44, 58). Smokers also incur more infections, with a lower survival rate. Finally, almost unanimously tobacco exposure emerges as a risk factor for all-cause mortality and end-stage renal disease in AAV patients.

Similar data have been described in other autoimmune diseases such as rheumatoid arthritis (13, 14), where smoking is directly associated with development and increased disease activity (15), and systemic lupus erythematosus, where smoking affects development (16) and response to treatment (66, 67).

This systematic review has some limitations which should be considered. First, data available from the literature about smoking and AAV are scarce and briefly reported, frequently only in tables. Second, data are derived from heterogeneous studies, with different aims, design, inclusion criteria and outcomes, and many of them are retrospective and case-control studies, with possible ascertainment biases. Third, smoking status has been variably analysed, some studies considering current smoking, some former smoking, others ever smoking, and definitions of smoking exposure (current/former) also vary among studies. Moreover, no data about second-hand smoking are available. Fourth, data on smoking often were self-reported, implying a possible overestimation of non-smokers compared to occasional smokers and so configuring possible recall biases. Fifth, reports of effect size are incomplete or absent in some studies. These limitations did not allow to perform statistical analyses and may have accounted for conflicting results reported in this study.

This systematic literature review highlights a possible relationship between smoking habits and ANCA-associated vasculitis onset, clinical manifestations, comorbidities, and mortality. Thus, additional studies are needed to better understand the interactions between smoking and AAV, in order to definitively clarify its role in pathogenesis, clinical phenotype and prognosis of AAV, and further research should specifically evaluate the impact of smoking cessation on ANCA-associated vasculitis.

Key messages

- The role of smoking in the pathogenesis of ANCA-associated vasculitis remains controversial and further studies are warranted to address this issue.
- Although still debated, smoking habits seem to influence ANCA-associated vasculitis development and clinical manifestations.
- Smoking appears to be a risk factor for cardiovascular comorbidities, severe infections, end stage renal disease and overall mortality in patients with ANCA-associated vasculitis.

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