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Alveolar haemorrhage in ANCA-associated vasculitis: Long-term outcome and mortality predictors

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ABSTRACT

Introduction: Alveolar haemorrhage (AH) is considered an important cause of morbidity and early mortality in anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (AAV).
Objectives: The aim of this study was to identify predictors of outcome in patients with AH-AAV and to evaluate outcome and causes of death in this subset.
Materials and methods: A multicenter retrospective study was conducted in 29 Italian Centers. Clinicians were asked to recruit all patients diagnosed with AAV-associated AH during the last 10 years, from 2007 to 2016. Univariate and multivariable analysis were performed.
Results: One-hundred and six patients were included (median age at onset of 55 years [IQR 42–67]). The majority were ANCA-positive (PR3 57.1%, MPO 33.7%) and 72.6% had also renal involvement. At presentation, anaemia was shown in 97 (92.4%) patients, hemoptysis in 54 (51.9%), respiratory failure in 68 (66.7%), of whom 48 (70.6%), requiring respiratory support. At the end of the 37 months [IQR 13–77] follow-up, 19/106 (17.9%) patients were dead. The main causes of death were active disease and infections. By stepwise regression analysis, age > 65 years (HR 3.66 [95% CI 1.4–9.51], p = 0.008) and the need for respiratory support (HR 4.58 [95% CI 1.51–13.87], p = 0.007) at AH onset were confirmed to be predictive of mortality.
Conclusions: Predictors of outcome in AAV-AH were determined. Factors related to the patient's performance status and the severity of the lung involvement strongly influenced the outcome. Balancing harms and benefits for the individual patient in induction and maintenance treatment strategies is crucial.

1. Introduction

Anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (AAV) are a group of systemic disorders characterized by inflammation and necrosis of small and medium-size vessels [1]. They include Granulomatosis with polyangioitis (GPA), Microscopic polyangioitis (MPA) and Eosinophilic Granulomatosis with polyangioitis (EGPA). Pulmonary involvement is one of the most frequent manifestations [2]. The derangement of the alveolar basement membrane, resulting from the widespread injury of the pulmonary capillaries promotes the extravasation of red blood cells into the pulmonary alveolar spaces. This condition is known as alveolar haemorrhage (AH) and can occur in 7–45% GPA, and 10–30% MPA patients, while it is considered rare in EGPA [3–6]. Disease severity ranges from life-threatening manifestations to milder forms and concomitant renal impairment is present in up to 97% of cases [7].

Customary therapy for AAV-related AH has consisted of remission induction with high-dose methylprednisolone, in combination with Cyclophosphamide [8]. More recently, Rituximab has been introduced as an alternative to Cyclophosphamide [9] including those needing mechanical ventilation [10]. Plasma exchange (PEX) has been advocated as an adjunct, even though its therapeutic efficacy is not well supported by the Literature [11–15] with preliminary data from the PEXIVAS seeming not to support the use of PEX in these patients [16].

AH is considered an important cause of morbidity and one of the strongest predictors of early mortality in AAV [6,17], with 1-year mortality rate varying between 18 and 50% [7,18]. Nevertheless, AH is included neither in the Five Factor Score [19] nor in the Revisited Five Factor Score (rFFS) [20] as a poor-prognosis factor since the correlation between AH and bad outcome was not statistically significant. It is now known that older age, comorbidities, the extent of alveolar bleeding, the degree of hypoxemia, along with the increase of the number of neutrophils in the bronchoalveolar lavage (BAL) fluid may influence clinical outcome [10,21,22].

Overall, the literature on AH in AAV is complicated by the small size of reported cohorts, variable and unclear definitions of AH, and insufficient description of respiratory failure and its predictors. In addition, patients with severe AH were excluded from the only randomized controlled trial that comprised a sizable number of patients with AH [23].

On this ground, the aim of our study was to identify predictors of mortality at AH onset in AAV. Secondly, we evaluated outcome in order to identify short and long-term causes of death in AH-AAV patients. Thirdly, we identified signs and symptoms that could be helpful in formulating early diagnosis (and in starting early treatment) and evaluated usefulness of commonly used diagnostic tools.

2. Methods

2.1. Study design

We conducted a retrospective multicenter historical cohort study of all consecutive patients with AAV-associated AH evaluated in 29 Italian Centers. Clinicians were asked to recruit all patients diagnosed with AAV-associated AH during the last 10 years from 2007 to 2016.

Patients met inclusion criteria for the study if they had provided authorization for review of their medical records and had well defined AH with a biopsy-proven diagnosis of AAV, or fulfilled the American College of Rheumatology criteria and/or Chapel Hill Consensus definitions for GPA, MPA and EGPA [24–26]. Mepolizumab trial inclusion criteria for EGPA were also accepted [27].

AH was defined according to the Plasma Exchange and Glucocorticoids for Treatment of Anti-Neutrophil Cytoplasm Antibody (ANCA) - Associated Vasculitis (PEXIVAS) trial criteria [28], as bilateral alveolar infiltrates on radiological imaging, without alternative explanation, plus at least one of the following: hemoptysis, increased DLCO, bronchoscopic evidence, unexplained drop in hemoglobin (> 2 g/dL), or anaemia (hemoglobin < 10 g/dL). Spirometry was performed in order to evaluate respiratory volumes and DLCO. At bronchoscopy, documentation of progressively bloody BAL fluid and/or ≥20% hemosiderin-laden macrophages in the BAL cell differential count were taken into account. Patients were excluded if AH could be explained by another medical condition (such as other autoimmune or infectious diseases or drugs). Respiratory failure was defined as the need for any type of artificial ventilation, with or without the presence of an artificial airway [10]. Respiratory support was taken into account if oxygen therapy with FiO2 ≥ 40% was needed [29]. Infectious complications were recorded if either intravenous antibiotic therapy or

hospitalization was required. Cardiovascular comorbidities were defined as the presence of one or more of the following conditions at the time of AH diagnosis: ischemic heart disease, congestive heart failure/left ventricular dysfunction, hypertension, diabetes mellitus, stroke, minor stroke, thromboembolism. Smoking history was not taken into account. Vasculitic renal involvement was defined as the presence of hematuria (≥10 red blood cells per high power field with or without red cell casts), proteinuria (≥500 mg/24 h), rise in serum creatinine > 30% or fall in creatinine clearance of > 25% or need to initiate renal replacement therapy all attributable to active vasculitis. Different organ involvement was evaluated according to Vasculits Activity Score version 3 (BVAS) [30,31]. BVAS was used to classify disease activity. Prognosis at diagnosis was evaluated through rFFS. Organ damage was recorded through Vasculitis Damage Index (VDI) [32,33].

2.2. Statistical methods

All data are presented as median (interquartile range [IQR]) or percentage (%). Survival was analyzed by Cox proportional hazard models, after the assumptions were verified. Univariate and multivariable Cox regression analysis were performed to evaluate the predictive role of baseline clinical characteristics and treatments in the AAV-AH outcome. In order to make the model more clinically useful and easy to comprehend, age at onset (< 65 or > 65 years), cardiovascular comorbidities (0 or > 1) and Cyclophosphamide cumulative dose (< 6 g or > 6 g) were dichotomized. Variables were considered for the multivariable Cox regression models if they occurred before the outcome of interest, had a P value < 0.05 in the univariate analysis and were clinically plausible. The final model was determined using both clinical and statistical criteria and taking into consideration collinearity and interaction. In the case of collinearity, variables were used in multivariable analysis on the basis of both clinical relevance and stronger association (on a backward selection process). All analyses were conducted in the statistical package Stata 15.

3. Results

3.1. Patient characteristics

One hundred-six AAV-patients were enrolled. Patients were followed-up for 37 months [IQR 13–77] after AH event. Their characteristics are shown in Table 1. All of them were Caucasian, with a median age at onset of 55 years [IQR 42–67]. The majority were male (54; 50.9%). Fifty-one patients (48.1%) had MPA, 49 (46.2%) had GPA and 6 (5.7%) had EGPA. Most patients (56; 57.1%) were PR3-positive. AH was diagnosed at the onset of the AAV in the majority of the patients (71.7%). Importantly, the most frequent vasculitic involvement other than AH was the renal one (72.6%). Fifty-two (49.1%) patients had ≥1 cardiovascular comorbidity. Upon AAV diagnosis, the median BVAS was 20 [IQR 14–26], while 43 (40.9%) patients had a rFFS of 2, 29 (27.6%) of 1 and 26 (24.7%) a rFFS ≥ 3.

3.2. Predictors of mortality

By univariate Cox regression analysis, at onset, neither rFFS (p = 0.495) nor BVAS (p = 0.301) were found to be predictive of mortality, while age ≥ 65 years (HR 4.27 [95% CI 1.61–11.30], p = 0.003), presence of 1 or more cardiovascular comorbidities (HR 3.95 [95% CI 1.30–12.02], p = 0.015), respiratory failure (HR 11.17 [95% CI 1.49–83.84], p = 0.019) and need for respiratory support (HR 4.84 [95% CI 1.60–14.62], p = 0.005) significantly correlated with mortality due to AH. Infections were also related to mortality (HR 4.24 [95% CI 1.60–11.23], p = 0.004). Only Cyclophosphamide cumulative dose was found to be protective (the higher the dose, the lower the risk (HR 0.11 [95% CI 0.01–0.85], p = 0.035). Full data are shown in Table 3 and in Figs. 3–6.

Variables considered for the multivariable Cox regression models were age ≥65 years, presence of 1 or more cardiovascular comorbidities, infections and need for respiratory support.

By stepwise regression analysis, age ≥65 years (HR 3.66 [95% CI 1.4–9.51], p = 0.008) and the need for respiratory support (HR 4.58 [95% CI 1.51–13.87], p = 0.007) at AH onset were confirmed to be predictive of mortality (Table 4).

Interestingly, when excluding from the multivariable analysis those patients with a follow-up duration equal or less than three months [both patients who died (n = 7) and patients lost from follow-up (n = 4)], age ≥ 65 years was confirmed to be predictive of mortality (HR 4.13 [95% CI 1.09–15.69], p = 0.037), and infections were selected (HR 4.58 [95% CI 1.16–18.16], p = 0.03) instead of the need for respiratory support (HR 1.62 [95% CI 0.45–5.93], p = 0.46).

3.3. Causes of death

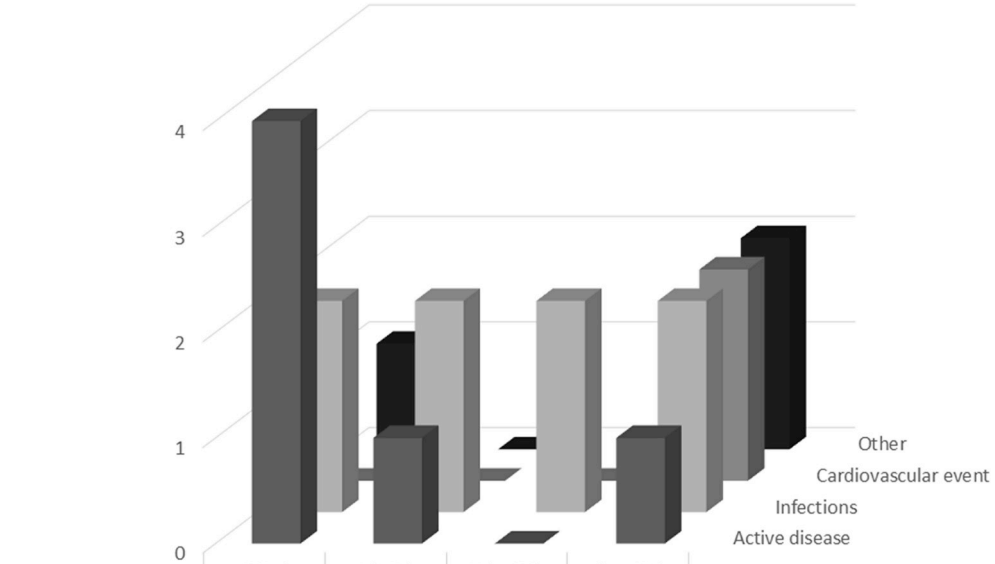
At the end of follow-up, 19 patients (17.9%) were dead. Seven (6.6%) patients died within 3 months of AH onset, of whom, 4 because of multi-organ failure due to active disease, 2 because of infections and one due to both AH and infection. After ≥3 months from AH onset, infections were the main cause of death. Full data are shown in Fig. 1. The estimated overall survival rate was 93% at 3 months, 88% at 1 year and 82% at 5 years (Fig. 2).

Fifty-eight (57.4%) patients received antimicrobial prophylaxis

Table 1
Clinical characteristics.

Sex, no. (%) male	54 (50.9)
Age, median (IQR) years	55 (42–67)
MPA, no. (%)	51 (48.1)
GPA, no. (%)	49 (46.2)
EGPA, no. (%)	6 (5.7)
PR3, no. (%)	56 (57.1)
MPO, no. (%)	33 (33.7)
ANCA negative, no. (%)	9 (9.2)
Comorbidities	
≥1 CV comorbidities, no. (%)	52 (49.1)
Symptoms and laboratory findings	
AH as onset manifestation of AAV, no. (%)	76 (71.7)
Anemia, no. (%)	97 (92.4)
Hemoptysis, no. (%)	54 (51.9)
Other involvement, no. (%)	
Renal	77 (72.6)
ENT	33 (31.1)
PNS	27 (25.7)
Skin	20 (18.9)
Heart	7 (6.6)
Intestine	4 (3.8)
CNS	2 (1.9)
CT findings	
Ground glass opacities	21 (20.8)
Consolidation	25 (24.7)
Both	54 (53.5)
Bronchoscopy, no. (%)	62 (58.5)
Bloody BAL	35 (56.4)
≥ 20% hemosiderin-laden macrophages	7 (11.3)
Both	19 (30.6)
Negative	1 (1.6)
Spirometry, no. (%)	26 (24.5)
Increased DLCO, no. (%)	0 (0)
Clinimetric indexes	
BVAS at onset, median (IQR)	20 (14–26)
rFFS, no. (%)	
0	7 (6.7)
1	29 (27.6)
2	43 (40.9)
≥3	26 (24.7)

No. = number, CV = cardiovascular, ENT = Ear, Nose and Throat, PNS = Peripheral Nervous System, CNS = Central Nervous System, CT = Computed Tomography, BAL = Bronchoalveolar lavage, DLCO = Diffusing capacity of the Lung for Carbon monoxide (CO), rFFS = revisited Five Factor Score.



	0-3rd month	4th-6th month	7th-12th month	after 12th month
Active disease	4	1	0	1
Infections	2	2	2	2
Cardiovascular event	0	0	0	2
Other	1	0	0	2

Fig. 1. Causes of death.

during the follow-up. Forty (39.2%) patients experienced ≥1 infectious complication. First infectious complication was recorded after a median of 3 [IQR 1–8] months. Pneumonia (16 patients) accounted for 40% of cases, while urinary tract infections (8 patients) for 20%.

3.4. Clinical presentation, diagnostic tools and treatment

Upon presentation of AH, anaemia was present in 97 (92.4%) patients, hemoptysis in 54 (51.9%), respiratory failure in 68 (66.7%), of whom 48 (70.6%) requiring respiratory support as defined above. Intensive care unit was required for 31 (29.5%) patients at AH onset, and, notably, 11 patients (10.4%) needed ExtraCorporeal Membrane Oxygenation (ECMO). Chest imaging studies were performed in all patients and high-resolution computed tomography of the chest was available for 101 patients, showing both ground glass opacities and consolidation in the majority of cases (54; 53.5%). Bronchoscopy was performed in 62 (58.5%) patients and a progressively bloody BAL fluid was detected in 35 (56.4%). Spirometry was performed in 26 (24.5%) cases, none of them showing an increased in DLCO.

The main interventions and outcomes are summarized in Table 2. All the patients received glucocorticoids (intravenous methylprednisolone in 90.1% of cases) in addition to a remission induction agent. Eighty (77.7%) patients received Cyclophosphamide, of whom 25 (24%) received both Cyclophosphamide and Rituximab; 14 (13.5%)

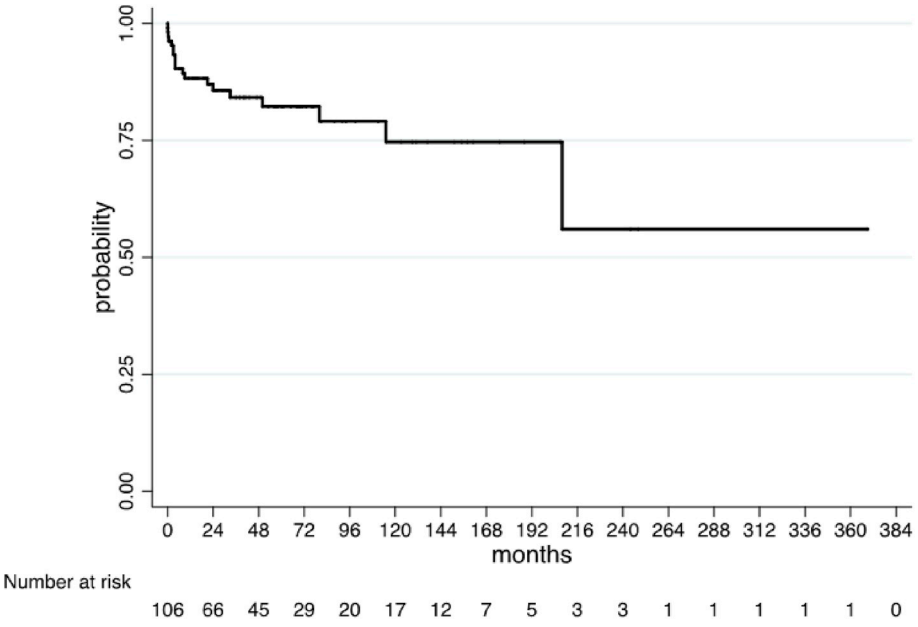


Fig. 2. Overall survival.

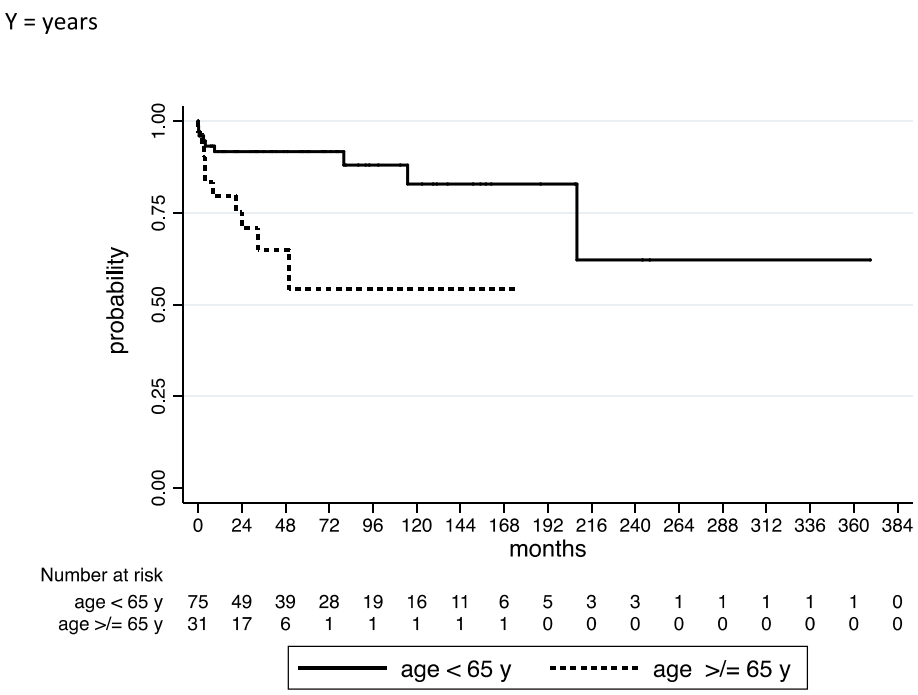


Fig. 3. Overall survival according to age at onset.

patients received Rituximab alone and 4 (3.8%) Azathioprine. Forty-six (44.7%) patients were also treated with PEX.

4. Discussion

AH is a severe manifestation of AAV [34] and has been recognized as the most common vasculitic cause of early mortality [8]. To our knowledge, this is the largest cohort of patients with AAV-related AH. Since we reported a long-term follow-up, it was possible to estimate both shortand long-term predictive factors of mortality in this setting. Importantly, as a real-life cohort of AAV, the most severe clinical presentations of AH were herein included: admission into the Intensive care unit was required for almost one third of patients, and about 10% needed ECMO. Notably, in the PEXIVAS trial, which is the largest trial of AAV, enrolling patients with severe AAV, nearly 30% of patients showed a severe form of AH [35].

This study identified age at onset and need for respiratory support as main risk factors for mortality, as previously proved [10,22]. Notably, we demonstrated that the outcome of patients with AH is influenced not only by factors that point to a more severe involvement of the lung parenchyma by the capillaritis (the presence of respiratory failure and need for respiratory support at onset), but also by factors that are

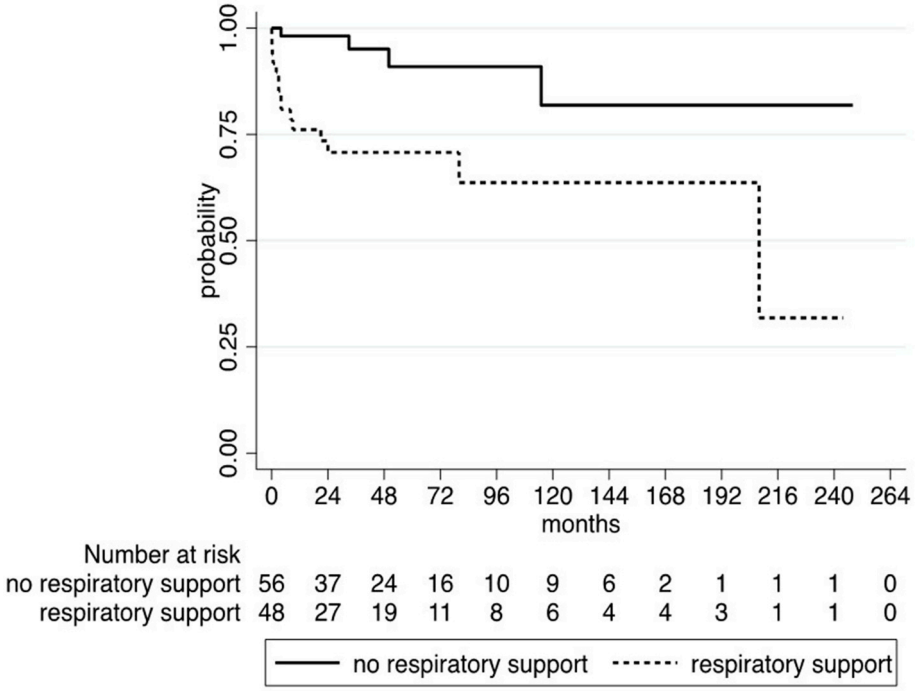


Fig. 4. Overall survival according to the need of respiratory support.

CV = cardiovascular.

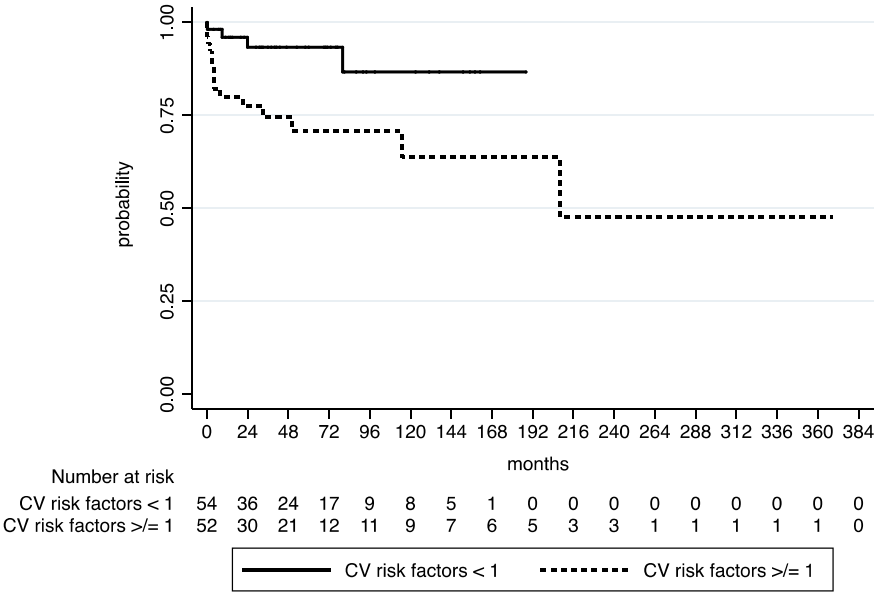


Fig. 5. Overall survival according to cardiovascular comorbidities.

expression of intrinsic frailty (cardiovascular comorbidities, risk of infections and age at onset) As a consequence, treatment must be individualized and keep into account, alongside with AH severity, the patient's baseline characteristics, frailty and risk of infection. In the short term, the main cause of death was AH itself, followed by infections. This feature is clearly highlighted by the role of respiratory support as one of the main variables affecting the mortality. The first infectious complications were recorded 3 months [IQR 1–8] after AH onset and infections were the main cause of death from the 4th month on, with very few patients dying from active disease after the 3rd month. All of this underlies the importance of balancing harms and benefits in choosing immunosuppressive treatment (especially minimizing the dose of glucocorticoids), not only during the induction phase, but also during maintenance therapy. In fact, the occurrence of infections was the most significant variable associated with mortality once passed the acute phase (i.e., after the first three months). Thus, infection control both during the induction phase of treatment and during the maintenance is mandatory to assure a long-term survival in AAV [36]. In addition, clinicians should be aware about surveillance of cardiovascular comorbidity, since it has been demonstrated as an independent predictor of mortality in AAV [37,38].

Notably, we found that neither BVAS nor rFFS were significantly related to mortality, meaning that in this particular subset of patients, dedicated tools are needed.

IC = Infectious complications.

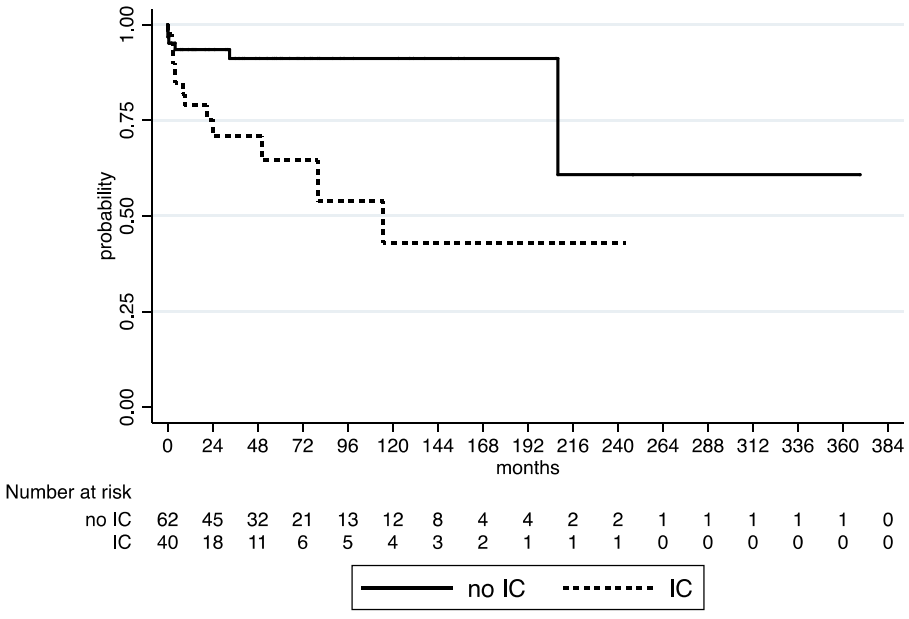


Fig. 6. Overall survival according to infectious complications.

Table 2
Interventions and outcome.

Interventions	
Remission induction treatment, no. (%)	
Cyclophosphamide	80 (77.7)
Cyclophosphamide and Rituximab	25 (24)
Rituximab alone	14 (13.5)
Azathioprine	4 (3.8)
Glucocorticoids, no. (%)	106 (100)
IV glucocorticoids	94 (90.1)
Oral glucocorticoids	106 (100)
PEX, no. (%)	46 (44.7)
Prophylaxis	58 (57.4)
Outcome	
Respiratory failure, no. (%)	68 (66.7)
Respiratory Support no. (%)	48 (46.1)
Intensive Care Unit, no. (%)	31 (29.5)
ECMO, no. (%)	11 (10.4)
Infections, no. (%)	40 (39.2)
Time (months), median (IQR)	3 (1–8)
Death no. (%)	19 (17.9)
Active disease, no.	6 (31.6)
Infection, no.	8 (42.1)
CV events, no.	2 (10.5)

No. = number, IV = intravenous, ECMO = ExtraCorporeal Membrane Oxygenation, CV = cardiovascular.

AH was more commonly associated with PR3-ANCA (n = 56), vs. MPO-ANCA, (n = 33) in agreement with previous reports [10,12] and we found a high prevalence of renal involvement (n = 77), in keeping with the common pathogenesis of pauci-immune capillaritis.

Saving renal function is one of the most important targets in AAV in order to guarantee long-term survival [39] It is intriguing that renal failure did not appear to be associated with an increased mortality in our cohort. AH was diagnosed at the onset of the AAV in the majority of the patients, including those with renal vasculitis, thus the immediate institution of an intense immunosuppressive regimen, may explain this unexpected result. The wide availability of ANCA testing and improved awareness of the disease, have enabled earlier diagnosis in the past decade but the differential diagnosis of AH, particularly if mild, remains very challenging. In this regard, in our experience, AH was often the onset symptom of AAV (n = 76), but only half of the patients (n = 54) presented with hemoptysis and 9 patients were ANCA negative. The absence of overt clinical symptoms means that AH needs to be actively considered in all vasculitis cases, especially if anaemia is present: in our experience the large majority of patients had a drop-in hemoglobin level (n = 97). According to our findings, chest CT scan showed abnormalities in almost all cases (99%), with both ground glass opacities and consolidation in the majority of cases (n = 54). Bronchoscopy was also helpful in making diagnosis (sensitivity of 98.4%) showing a progressively bloody BAL fluid in 56.4% of cases. Interestingly, spirometry was performed in few patients, none of them showing an increase in DLCO, differently from some observations reported in other series where an increase of DLCO was helpful for supporting the diagnosis of AH in lupus patients [40,41]. Thus, spirometry does not seem to be a useful tool both for diagnosis and follow-up in AAV-AH.

All our patients received glucocorticoids (n = 106), together with Cyclophosphamide in the majority of cases (n = 80). Cyclophosphamide cumulative dose of ≥6 g was found to be protective against the risk of death at univariate analysis, suggesting that an aggressive induction treatment, in the absence of severe infections, may improve survival in these patients. In our study, 39 patients received Rituximab, of whom 14 without Cyclophosphamide. Recently, Rituximab has been introduced as an alternative to Cyclophosphamide [9] in AAV-AH, including in those needing mechanical ventilation [10], but we did not find any statistically significant correlation with outcome. In our cohort only five patients received AZA as induction agent,

Table 3
Univariate analysis.

	Haz. Ratio	Std. Err.	P	[95% Conf. Interval]
Age ≥65 y at onset	***4.27***	***2.12***	***0.003***	***1.61–11.30***
Gender	***0.39***	***0.20***	***0.073***	***0.14–1.09***
≥1 CV comorbidities	***3.95***	***2.24***	***0.015***	***1.30–12.02***
Respiratory failure	***11.17***	***11.49***	***0.019***	***1.49–83.84***
Respiratory support	***4.84***	***2.73***	***0.005***	***1.60–14.62***
CD Cyc ≥6 g	***0.11***	***0.11***	***0.035***	***0.01–0.85***
Infections	***4.24***	***2.11***	***0.004***	***1.60–11.23***
GPA	1.14	0.58	0.796	0.42–3.07
MPA	0.88	0.44	0.796	0.33–2.36
EGPA	2.18	1.72	0.324	0.46–10.26
AH as AAV 1st manifestation	0.48	0.22	0.115	0.19–1.20
ICU	0.87	0.46	0.789	0.31–2.43
ANCA positivity	0.48	0.36	0.333	0.11–2.12
ANCA specificity	1.17	0.40	0.657	0.59–2.30
Renal involvement	1.36	0.77	0.585	0.45–4.14
ENT involvement	0.78	0.39	0.627	0.29–2.10
GI involvement	2.15	2.22	0.459	0.28–16.34
PNS involvement	1.18	0.59	0.740	0.44–3.15
CNS involvement	4.42	4.61	0.154	0.57–34.12
Skin involvement	0.67	0.42	0.526	0.19–2.31
BAL findings	1.10	0.23	0.630	0.73–1.66
CT pattern	0.94	0.12	0.619	0.73–1.21
Anaemia	0.87	0.24	0.615	0.51–1.49
Haemoptysis	0.64	0.30	0.332	0.25–1.59
rFFS = 1	0.52	0.64	0.595	0.047–5.77
rFFS = 2	1.62	1.71	0.648	0.20–12.80
rFFS = 3	1.51	1.66	0.705	0.18–13.07
rFFS ≥4	2.63	3.74	0.495	0.16–42.52
Cyc	1.71	1.30	0.476	0.38–7.59
RTX	0.57	0.30	0.287	0.21–1.59
PEX	1.47	0.72	0.425	0.57–3.83
Antimicrobial prophylaxis	0.90	0.47	0.839	0.33–2.48
BVAS at onset	1.03	0.03	0.301	0.97–1.08
VDI last follow-up	1.10	0.57	0.064	0.99–1.22

By Cox regression analysis, age ≥65 years at onset, presence of 1 or more CV comorbidities, respiratory failure, need for RS and infections were related to mortality. Only Cyc cumulative dose was found to be protective (the higher the dose, the lower the risk).
Legend: Y = years, CV = cardiovascular, CD = Cumulative Dose, AH = Alveolar Haemorrhage, ICU = Intensive Care Unit, ENT = Ear, Nose and Throat, GI = gastrointestinal, PNS = Peripheral Nervous System, CNS = Central Nervous System, BAL = Bronchoalveolar lavage, CT = Computed Tomography, rFFS = revisited Five Factor Score, Cyc = Cyclophosphamide, RTX = Rituximab, PEX = plasmapheresis.

Table 4
Multivariable analysis.

	Haz. Ratio	Std. Err.	P	[95% Conf. Interval]
Age ≥ 65 years at onset	3.66	1.78	**0.008**	1.41–9.51
Respiratory support	4.58	2.60	**0.007**	1.51–13.87

The following variables were introduced in the multivariable model: age at onset, cardiovascular comorbidities the need for respiratory support (but not respiratory failure, because of collinearity), and infections (but not the cumulative dose of Cyc, because of collinearity).

on the basis of severity and clinical judgment. It is nowadays accepted that clinically stable patients who do not need oxygen supplementation can be cared for as outpatients, provided that definitive remission induction therapy is implemented promptly.

PEX is used frequently as adjunctive treatment for severe AH and concurrent renal failure. However, its role in the treatment of severe AH itself is less clear even though PEX has been widely used. In accordance with previous findings [10,12,21], in our population, PEX was not found to reduce mortality. The use of PEX may have been biased towards more severe or refractory disease but we did not find any clear

distinguishing features. The variability in the type of procedure and in the number of PEX sessions makes it difficult to address this issue. Indeed, in the absence of clearcut data in AAV and similarly to other systemic vasculitides, we suggest to apply PEX in AH-AAV in life-threatening conditions, especially in the presence of renal failure [43,44].

Overall, mortality in our population was lower than in earlier studies [5,18,42], with a rate of 6.6% at 3 months (n = 7), 11.3% at 12 months (n = 12) and 17.9% (n = 19) at the end of the 37 months [IQR 13–77] follow-up. Mortality rates are highly variable between different series, this probably reflecting heterogeneity of the disease, patient characteristics, presence of renal involvement [22] and treatments. Possibly, earlier establishment of diagnosis, changes in immunosuppressive agents, use of antimicrobial prophylaxis, improvement in antibiotic therapies and in supportive measures contributed to lower mortality in our study, rather than differences in disease severity, since the BVAS scores in our cohort were similar or even higher than corresponding BVAS reported by others [10,45].

This retrospective multicenter cohort study has inherent limitations. First, we acknowledge possible biases, including open-label therapy, PEX for more severe cases and the fact that not all laboratory data were collected uniformly or in a protocol-driven manner. Second, our cohort consists of an Italian population with predominantly central-Europe backgrounds; therefore, the results are not generalizable. Furthermore, since this analysis concern a specific subpopulation of patients recruited based on the presence of AH, mortality could be underestimated. However, demographics and baseline disease activity at onset appear to be similar to that described in reports from other AH cohorts. Finally, respiratory failure and need of respiratory support are surrogate markers and not direct indices of severity of lung involvement, and they may be influenced by other conditions, such as anaemia or heart involvement. Nevertheless, this study was not designed as an imaging study to capture the real extension of the lung damage in this setting.

5. Conclusion

Mortality due to AH in AAV is still high, and AH should be considered and excluded in all AAV-patients, especially if unexplained anaemia is present. In our experience CT-scan and bronchoscopy with BAL were very useful in confirming a clinical suspicion of AH. We highlighted that outcome is strongly influenced by both factors that are an expression of intrinsic frailty (cardiovascular comorbidities, risk of infection and age at onset), and factors that point to a more severe lung involvement (the need for respiratory support at onset). Therefore, balancing harms and benefits at the individual patient level is crucial and the intensity of the treatment must be carefully tailored at the beginning and during the disease course by taking into account the disease severity, patient's baseline characteristics, frailty and risk of infection.

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CRediT authorship contribution statement

Luca Quartuccio: Conceptualization, Methodology, Software. **Milena Bond:** Methodology, Software, Validation, Formal analysis, Resources, Data curation, Investigation, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Miriam Isola:** Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing. **Sara Monti:** Validation, Investigation, Resources, Data curation, Writing - review & editing. **Mara Felicetti:** Validation, Investigation, Resources, Data curation, Writing - review & editing. **Federica Furini:** Validation, Investigation, Resources, Data curation, Writing - review & editing. **Stefano Murgia:** Validation, Investigation, Resources, Data curation, Writing - review & editing. **Alvise Berti:** Validation, Investigation, Resources, Data curation, Writing - review & editing. **Elena Silvestri:** Validation, Investigation, Resources, Data curation, Writing - 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Declaration of competing interest

None.

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