

Title

Alveolar hemorrhage in ANCA-associated vasculitis: long-term outcome and mortality predictors. A retrospective multicenter study on 106 patients.

Authors

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Key points

1. This is the largest clinical description of alveolar haemorrhage in ANCA-associated vasculitis
2. Unexplained progressive anaemia in AAV should arise the suspicion of AH in AAV
3. Thoracic CT and bronchoalveolar lavage confirm the diagnosis of AH in AAV
4. Clinicians need to carefully consider respiratory failure along with age, comorbidity and risk of infections to manage this severe manifestation

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Figures: 6

Abstract [250 words]

Rationale

Anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (AAV) are a group of systemic vasculitides of small and medium-size vessels. Pulmonary involvement is one of the most frequent manifestations, and alveolar haemorrhage (AH) is considered an important cause of morbidity and one of the strongest predictors of early mortality in AAV.

Objectives

The aim of this study was to identify predictors of outcome, at onset, in AAV patients with AH and to evaluate outcome and causes of death in this subset of patients.

Methods

A multicenter retrospective study was conducted in 28 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 Multivariate analysis were performed to evaluate the predictive role of baseline clinical characteristics and treatments in the AAV-AH outcome.

Measurements and Main 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 renal involvement along with AH. 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 followed by infections.

At Cox regression, age ≥ 65 years at onset, ≥ 2 comorbidities, ≥ 1 cardiovascular comorbidity, infections, respiratory failure and the need for respiratory support were statistically associated with death.

Conclusions

Outcome in AAV-AH is determined by a tricky balance between harms and benefits at the individual patient level both in induction and maintenance treatment strategies.

Introduction [487 words]

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 polyangiitis (GPA), Microscopic polyangiitis (MPA) and Eosinophilic Granulomatosis with polyangiitis (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, 4, 5, 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, 12, 13, 14, 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 [17, 6], 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. In fact, when AH was a life-threatening symptom, it was often part of a pulmonary-renal syndrome, therefore, AH was included

within the poor-prognosis renal factor. It is now known that older age, comorbidities and the extent of alveolar bleeding negatively influence clinical outcome [21, 22]. The degree of hypoxemia, expressed as an SpO₂:FiO₂ ratio <450 at the first point of care, along with the increase of the number of neutrophils in the bronchoalveolar lavage (BAL) fluid and elevated serum C-Reactive Protein levels were recently identified as readily available and significant predictor of impending respiratory failure [10].

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 helpful in formulating early diagnosis (and in starting early treatment) and evaluated usefulness of commonly used diagnostic tools.

Methods [602 words]

We conducted a retrospective multicenter historical cohort study of all consecutive patients with AAV-associated AH evaluated in 28 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 Chapel Hill Consensus definitions for GPA, MPA and EGPA [24, 25, 26]. Mepolizumab trial inclusion criteria for EGPA were also accepted [27].

AH was defined according to the 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 anemia (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 $\geq 20\%$ 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 respiratory support, including all methods of artificial ventilation, with or without the presence of an artificial airway. Respiratory support was taken into account if ≥ 4 liters per minute of oxygen therapy was needed. 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, hypercholesterolemia. 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 hours), rise in serum creatinine $>30\%$ or fall in creatinine clearance of $>25\%$ or need to initiate renal replacement therapy all attributable to active vasculitis. Other organ involvement were evaluated according to Vasculitis Activity Score version 3 (BVAS) [29, 30]. BVAS was used to classify disease activity. Prognosis at diagnosis was evaluated through rFFS. Organ damage was recorded through Vasculitis Damage Index (VDI) [31, 32].

All data are presented as median (interquartile range [IQR]) or percentage (%). Univariate and multivariate 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 \geq 65 years), comorbidities (\leq 1 or \geq 2), cardiovascular comorbidities (0 or \geq 1) and Cyclophosphamide cumulative dose (< 6 grams or \geq 6 grams) were dichotomized. Variables were considered for the multivariate logistic regression models if they occurred before the outcome of interest, had a P value \leq 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 multivariate analysis on the basis of both clinical relevance and stronger association (on a forward selection process). For the Multivariate logistic regression, based on the rules previously outlined, in order to avoid overfitting of the model, we incorporated the need for respiratory support (but not respiratory failure), and infections (but not the cumulative dose of Cyclophosphamide). All analyses were conducted in the statistical package Stata 12 (Stata-Corp, 2011).

Results [582 words]

Patient characteristics and clinical outcomes

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. Fifty-two (49.1%) patients had \geq 1 cardiovascular comorbidity. AH was the onset manifestation of AAV in 76 (71.7%) cases,

while 77 (72.6%) patients had concomitant renal involvement. 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 \geq 3. Upon presentation of AH, anemia 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. 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 steroids (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%) patients received Rituximab alone and 4 (3.8%) Azathioprine. Forty-six (44.7%) patients were also treated with PEX.

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

Fifty-eight (57.4%) patients received antimicrobial prophylaxis during the follow-up. Forty (39.2%) patients experienced \geq 1 infectious complications. First infectious complication was recorded after 3 [IQR 1-8] months. Pneumonia (16 patients) accounted for 40% of cases, while urinary tract infections (8 patients) for 20%.

Statistical analysis

By Cox regression analysis, at onset, neither rFFS ($p > 0.495$) nor BVAS ($p = 0.301$) were found to be predictive of outcome, while age ≥ 65 years (HR 4.27 [95% CI 1.61-11.30], $p=0.003$), presence of 2 or more comorbidities (HR 3.63 [95% CI 1.20-10.96], $p=0.022$), 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], $p=0.005$) were. 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 Figures 3 to 6.

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).

Discussion [1193 words]

Even though rare, AH is a severe manifestation of AAV and has been recognized as the most common vasculitic cause of early death [8]. Given the rarity of this manifestation, Literature provides us little evidence-based guidelines for the management of these patients. Thus, even with clear and known limitations, retrospective analyses of large populations are welcome in the clinical setting in order to increase the body of knowledge and to confirm previous data. To our knowledge, this is the largest cohort of patients with AAV-related AH. Given the severity of AH, we investigated whether the common clinimetric measures used in AAV could be useful in predicting outcome: we found that neither BVAS nor rFFS were

Commento [MG1]: Meglio ricordare quale : presumo "mortality"

Commento [MG2]: Nella presentazione dei risultati seguirei lo schema riportato nella introduzione (pag.8) ovvero :
... 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 helpful in formulating early diagnosis (and in starting early treatment) and evaluated usefulness of commonly used diagnostic tools.

significantly related to mortality, meaning that in this particular subset of patients, dedicated tools are needed.

This study identified age at onset and need for VS 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 expression of intrinsic fragility (general and cardiovascular comorbidities, risk of infections and age at onset). As a consequence, treatment must be individualized and keep into account, alongside AH severity, the patient's baseline characteristics, fragility and risk of infection. This is true ~~of~~ for both induction therapy and maintenance treatment, as justified by the fact that infection is the main cause of death in the follow-up period.

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. 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), 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 was confirmed to be very sensitive (99%), showing 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.

All our patients received glucocorticoids (n=106), together with Cyclophosphamide, in the majority of cases (n=80) and at Univariate analysis, a Cyclophosphamide cumulative dose of ≥ 6 grams was found to be protective suggesting that an aggressive induction treatment, in the absence of severe infections, could lower the risk of death. 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, 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 be protective. The use of PEX may have been biased towards more severe or refractory disease but we did not find any clear distinguishing features. The wide variability in the number of PEX sessions also suggests that there is no agreement on the optimal dose of PEX and emphasizes the importance of the PEXIVAS trial [28], with preliminary data not supporting the use of PEX in AAV-AH patients [16].

Overall, mortality in our population was lower than in earlier studies [5, 18, 33], 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, 34].

In the short term, the main cause of death was AH (7 patients died within 3 months after onset, of whom 4 because of multi-organ failure due to active disease and 2 because of infections). Interestingly, first infectious complication was 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 for active disease. 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.

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 concerns 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.

In conclusion, mortality due to AH in AAV is still high, and it should be considered 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 fragility (general and cardiovascular comorbidities, risk of infection and age at

onset), and factors that point to a more severe lung involvement (the presence of respiratory failure and need for respiratory support at onset). Therefore, balancing harms and benefits at the individual patient level is crucial and treatment must keep into account, alongside disease severity, the patient's baseline characteristics, fragility and risk of infection. This is true of both induction therapy and maintenance treatment, as justified by the fact that infection is the main cause of death during the whole follow-up period.

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Tables

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)
<u>Comorbidities</u>	
≥2 comorbidities, no. (%)	57 (53.8)
≥1 CV comorbidities, no. (%)	52 (49.1)
<u>Symptoms and laboratory findings</u>	
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. (%)

Bloody BAL	35 (56.4)
≥ 20% hemosiderin-laden macrophages	7 (11.3)
Both	19 (30.6)

Negative 1 (1.6)

Spirometry, no. (%)

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.

Table 2. **Interventions and Outcome**

<u>Interventions</u>	
Remission induction treatment, no. (%)	
Cyclophosphamide	80 (77.7)
Cyclophosphamide and Rituximab	25 (24)
Rituximab alone	14 (13.5)
Azathioprine	4 (3.8)
Corticosteroids, no. (%)	
IV corticosteroids	94 (90.1)
Oral corticosteroids	106 (100)
PEX, no. (%)	46 (44.7)
Prophylaxis	58 (57.4)
<u>Outcome</u>	
Respiratory failure, no. (%)	68 (66.7)
Respiratory Support no. (%)	48 (46.1)
Intensive Care Unit, no. (%)	31 (29.5)
ECMO, no. (%)	11 (10.5)
Infections, no. (%)	
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

Table 3. **Univariate analysis**

	Haz. Ratio	Std. Err.	P	[95% Conf. Interval]
Age \geq 65 y at onset	4.27	2.12	0.003	1.61-11.30
\geq 2 comorbidities	3.63	2.05	0.022	1.20-10.96
\geq 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 Cyclophosphamide \geq 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
Female sex	0.39	0.20	0.073	0.14-1.09
AH as AAV 1 st manifestation	0.48	0.22	0.115	0.19-1.20
Intensive Care Unit	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 pattem	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 \geq 4	2.63	3.74	0.495	0.16-42.52
Cyclophosphamide	1.71	1.30	0.476	0.38-7.59
Rituximab	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

Y = years, CV = cardiovascular, CD = Cumulative Dose, AH = Alveolar Haemorrhage, 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, PEX = plasmapheresis.

Table 4. **Multivariate analysis**

	Hazard Ratio	Std. Err.	P	[95% Conf. Interval]
Age \geq 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

Figures

Figure 1. Causes of death

CV = Cardiovascular.

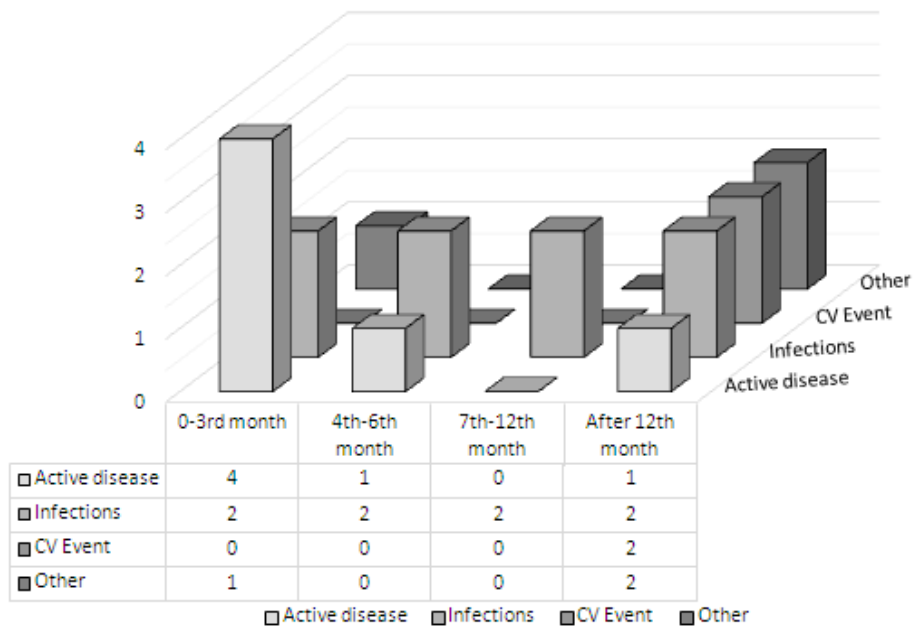


Figure 2. Overall survival

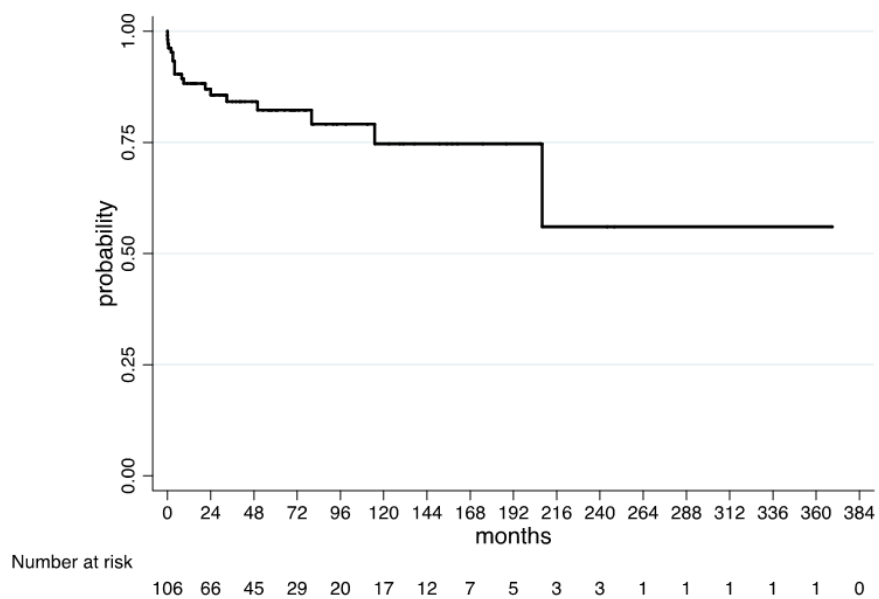
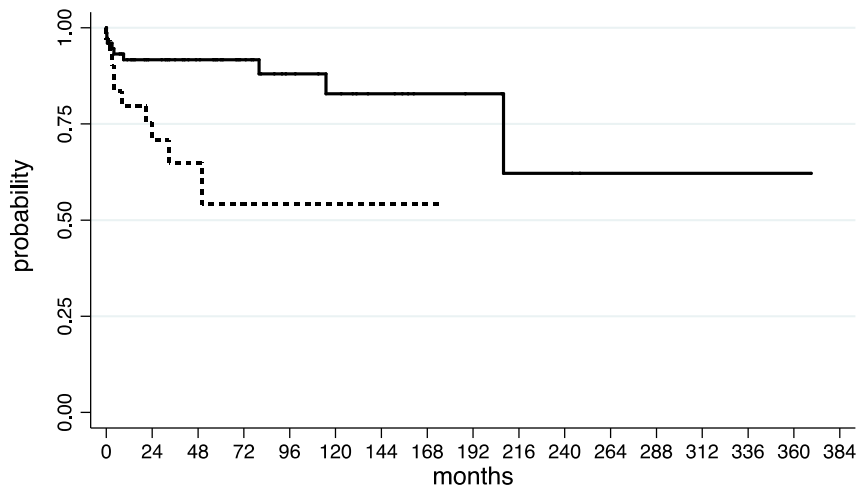


Figure 3. Overall survival according to age at onset

Y = years



Number at risk

age < 65 y	75	49	39	28	19	16	11	6	5	3	3	1	1	1	1	0
age >= 65 y	31	17	6	1	1	1	1	1	0	0	0	0	0	0	0	0

— age < 65 y age >= 65 y

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

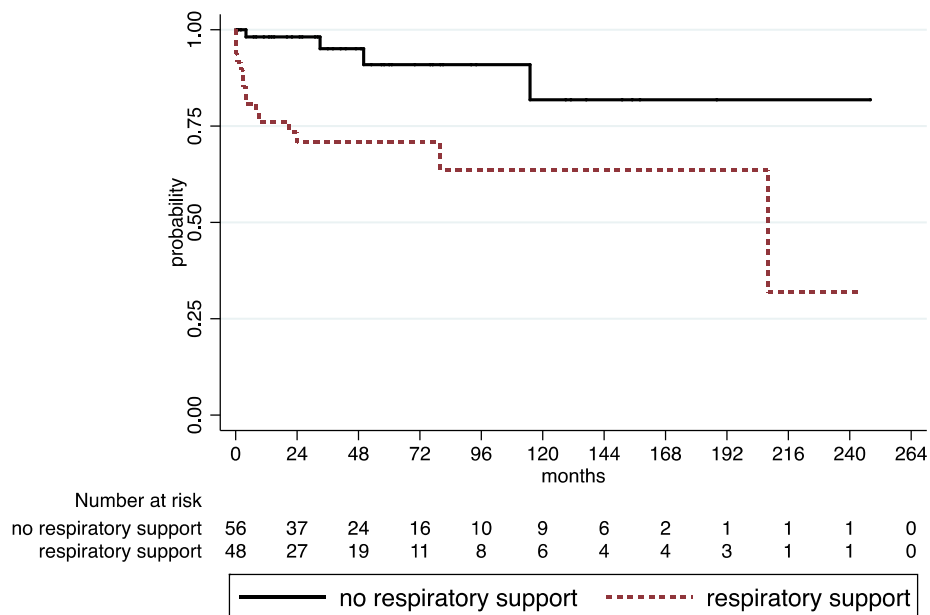


Figure 5. Overall survival according to cardiovascular comorbidities

CV = cardiovascular.

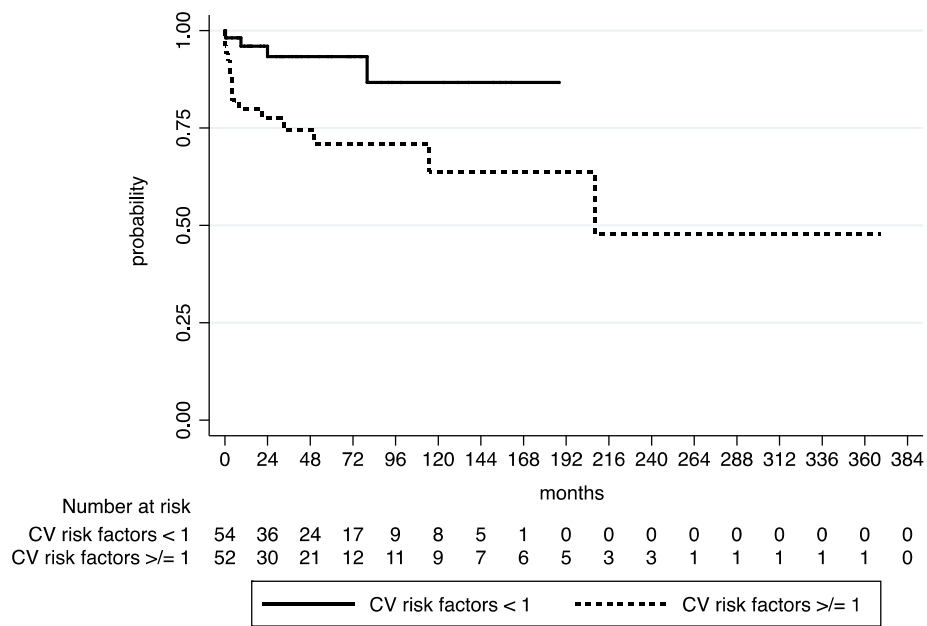


Figure 6. Overall survival according to infectious complications

IC = Infectious complications.

