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Diffuse alveolar hemorrhage: factors associated with in-hospital and long-term mortality

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Running head: prognosis of diffuse alveolar hemorrhage

Abstract

Diffuse alveolar hemorrhage (DAH) is a feature of several immune and non-immune disorders. Reported prognosis is poor, with in-hospital mortality ranging from 20 to 100%. Early identification of prognostic factors may be useful in the initiation of appropriate treatment.

We retrospectively analyzed the charts of all patients referred to an university hospital for DAH between 1980 and 2008. Variables associated with in-hospital and long-term mortality were determined using a logistic regression model and the Kaplan-Meier method, respectively. Immunosuppressed patients were excluded.

Overall, 97 patients were included in the study. In-hospital mortality was 24.7%. Factors associated with in-hospital mortality were shock (OR=77.5; 95% IC=[8.9-677.2]), glomerular filtration rate <60 mL/min (OR=11.2; 95% IC=[1.8-68.4]) and plasmatic LDH level more than twice the normal value (OR=12.1; 95% IC=[1.7-84.3]). Mortality among discharged patients was 16.4% with a median follow-up duration of 34 months. Factors associated with increased long-term mortality in univariate analysis were age over 60 years (p=0.026), cardiovascular comorbidity (p=0.027) and end-stage renal failure with dependence on hemodialysis (p=0.026).

Patients with immune and non-immune DAH had similar outcomes. Early outcome depended on non-pulmonary organ failures. Conversely, late outcome was related to age, cardiac comorbidities and the need for hemodialysis.

Key words: Hemoptysis; Hypertension, Pulmonary; Lung diseases, Interstitial; Respiratory distress syndrome, Adult

Introduction

Diffuse alveolar hemorrhage (DAH) is a feature of several immune and non-immune disorders. The fundamental process common to each of the DAH syndromes is diffuse bleeding into the acinar portion of the lung. It typically presents with hemoptysis, anemia and pulmonary infiltrates on chest x-ray. Failure to diagnose and treat DAH syndromes in their early stages may lead to acute respiratory failure and death. Reported prognosis is poor, with in-hospital mortality ranging from 20 to 100% [1-3]. Delay in initiating treatment may lead to chronic renal failure when DAH is the early manifestation of a systemic disease [4, 5].

Early identification of factors associated with a poor outcome may be useful in selecting the patients at highest risk to initiate appropriate treatment. To our knowledge, no publications currently address this question. Most published series are limited and instead focus on immune causes of DAH [4-6]. Long-term outcomes and factors associated with mortality in patients with DAH after discharge have not been studied. This information may be important in decision making.

Therefore, we conducted a retrospective study in a large cohort of consecutive patients hospitalized for symptomatic DAH over a 29-year long period. Immunocompetent individuals presenting with a DAH of immune or non-immune cause were included. We sought to identify early predictors of in-hospital mortality available within the first 24 hours following hospital admission and factors associated with long-term mortality in discharged patients.

Methods

Study design

A retrospective cohort study was performed in the Intensive Care Unit (ICU) and Chest Department of an 800-bed tertiary hospital in France (Hôpital Tenon, Assistance Publique-Hôpitaux de Paris, France). This observational, non-interventional analysis of

medical records was approved by the Institutional Review Board of the French Learned Society for Respiratory Medicine - Société de Pneumologie de Langue Française.

Subjects, data collection and definitions

The medical records of consecutive patients admitted between January 1980 and May 2008 were reviewed. For patients admitted more than once, only the first admission was considered. All adult patients with symptomatic DAH were eligible. The definition of symptomatic DAH was based on the following criteria. First, the clinical and radiological presentation was compatible with the diagnosis of DAH (hemoptysis, new pulmonary infiltrates and anaemia) [4]. Second, the bronchoalveolar lavage (BAL) fluid was macroscopically bloody. Alternatively, hemorrhagic and siderophagic alveolitis were evidenced on BAL cytology [7], trans-bronchial lung biopsy or surgical lung biopsy. Diagnosis of DAH was definite when all the above criteria were met.

Patients with immunocompromised status (human immunodeficiency virus infection, solid or haematological malignancies, bone marrow or solid organ transplantation, immunosuppressive drugs therapy, cytotoxic chemotherapy or radiotherapy, steroids at a daily dose higher than 20 mg of prednisone-equivalent for more than two months) were excluded. Patients with hemorrhage of bronchial origin and patients receiving hemodialysis for chronic renal failure were also excluded.

Variables available during the first 24 hours of hospitalization included demographic data (age, gender), body mass index (weight (kg)/height^2 (m^2)), alcohol use (defined by WHO as more than 40 g per day for men and 20 g per day for women), current or former tobacco exposure, past medical history (especially respiratory and cardiovascular diseases) and ongoing anticoagulant and/or antiagregant treatment. Clinical variables and laboratory data related to the pulmonary disorder at admission included the following among time elapsed between the first symptoms and hospital admission, respiratory rate, haemoptysis, accessory

muscles use, presence of crackles, need for invasive mechanical ventilation, arterial blood gas analysis with PaO_2/FiO_2 ratio (non-mechanically ventilated patients had arterial blood gases measured while breathing room air), chest-X-ray and BAL characteristics (total cell count, formula and percentage of siderophages on Perls staining and microbiology).

Non-pulmonary clinical variables were also recorded, including weight loss > 5% of baseline body weight in the last three months, body temperature, blood pressure, heart rate, presence of shock, extra-pulmonary symptoms (skin, bone and joint, gastro-intestinal, neurological, nose-ear-throat or ocular), and hematuria or proteinuria on urinalysis reagent strip. Shock was defined by a mean systemic blood pressure < 60 mmHg after 20-30 mL/kg starch or 40-60 mL/kg saline, or a pulmonary capillary wedge pressure between 12 and 20 mmHg and the need for dopamine >5 μg/kg per min or dobutamine, norepinephrine or epinephrine whatever the infusion rate to maintain mean blood pressure above 60 mmHg [8, 9]. Laboratory data included glomerular filtration rate calculated with the Cockroft formula, hemoglobin, blood leukocyte count, platelet count, thromboplastin time, partial thromboplastin time and lactico dehydrogenase (LDH).

The time elapsed between hospital admission and the first dose of steroids, if administered, was recorded. The severity of DAH was assessed from generic scores of organ dysfunction including the Logistic Organ Dysfunction (LOD) score [10] and the Simplified Acute Physiology Score (SAPS) II [11]. The need for chronic hemodialysis and pulmonary disability after discharge were recorded.

The etiologic diagnoses of DAH were specifically defined. The American College of Rheumatology criteria were used for defining a necrotizing vasculitis. A histological proof of necrotizing vasculitis was required [12-15]. The American Rheumatism Association criteria were used for defining a connective tissue disease [16, 17]. The anti-glomerular basement membrane antibody disease was diagnosed when the serologic test for anti-glomerular

basement membrane antibodies was positive. Alternative diagnosis was made on the presence of a linear immunofluorescent glomerular immunoglobulin deposit [18]. Clinical and radiological features suggestive of DAH related to an increased pulmonary capillary pressure [19] were an increased left atrial pressure (detected by echocardiography-doppler or right heart catheterization, which were performed in 82 and 10 patients, respectively, see the Figure 1 in the online supplement), and respiratory improvement after forced saline diuresis [20, 21]. The diagnosis of a barotraumatic-stress capillary failure due to a negative pulmonary pressure (tracheal extubation or scuba diving) was made in a suggestive context [22, 23]. For cancer, the presence of histological evidence was used in the diagnosis. For infection, positive microbiological or serological tests allowed for diagnosis. Clotting disorders were diagnosed by a platelet count less than 150,000 cells/ml, a patient-to-control subject ratio of activated partial thromboplastin time greater than 1.5, or a thromboplastin time less than 60%. The diagnosis of toxin-induced or drug-induced disease was established when there was a compatible chronology after exposure to a known pneumotoxic substance. This diagnosis required the exclusion of all the other causes of DAH [24]. Idiopathic DAH was defined when a thorough search for the above-mentioned causes remained negative.

Data presentation and statistical analysis

Standard descriptive statistics were computed. Continuous variables were reported as medians (25 to 75% interquartile range), unless otherwise stated. The Shapiro-Wilk normality test was performed. We then drove 2 different models to assess the factors associated with in-hospital and long-term mortality because we considered that each one of them addressed specific clinical issues. Univariate and multivariate logistic regressions were used to identify factors associated with in-hospital mortality. Cut-off values were then defined according either to their median (< 60 mL/min for glomerular filtration rate) or to a clinically relevant

threshold (> 20 pack-years for tobacco use, < 10 g/dL for hemoglobin, > 2 upper normal value for LDH). A time variable referring to the year of hospitalization (from 1 for 1980 to 29 for 2008) was used to assess the dependency of the outcome upon time, given the length of the study period. Variables yielding p values less than 0.05 by univariate analysis and considered clinically relevant were entered into a forward multivariate logistic regression analysis. Odds ratios (OR) and their 95% confidence intervals (CIs) were computed. Colinearity and interactions were tested. We chose to enter a maximum of 3 variables in the final multivariate model in order to avoid overfitting [25]. A base model including the main organ failures (shock and respiratory and renal failures) was created. These variables have been chosen because they have been previously shown to strongly influence the outcome of patients with the acute respiratory distress syndrome [26]. The other covariates were entered in the model with a critical removal p value of 0.1. Effects on covariate coefficients were also considered. The SAPS II score and LOD score were not entered in the multivariate analysis because they encompassed other study variables (age as well as other variables used to define organ failures) [10, 11]. Long-term outcome was studied for patients discharged from the hospital. Factors associated with long-term mortality were identified by the Kaplan-Meier method with the log-rank test. No further mutltivariate analysis was performed because the statistical power was considered too low. Two-tailed p values less than 0.05 were considered statistically significant. Analyses were carried out using Statview statistical software (SAS Institute Inc., Calasabas, USA).

Results

Patient characteristics

Overall, 151 patients suspected of DAH were eligible, 54 of whom were not included due to missing data (n=10), hemorrhage of bronchial origin (n=43) or the evidence of an

immunocompromised status during hospitalization (n=1) (Figure 1). Of the remaining 97 patients included in the cohort study, 73 were hospitalized in the ICU and 24 in the chest unit. The main causes of DAH are listed in Table 1. One-third of the DAH syndromes were immune. The distribution of the causes of DAH over 4 time periods (1980-1986, 1987-1993, 1994-2000 and 2001-2008) is depicted in Figure 2. The baseline characteristics of the 97 patients at admission are shown in Table 2.

The median length of stay was 12 days (6-20), averaging 14 days (10-22) for ICU patients and 10 days (7-15) for conventional chest ward patients. Intravenous steroids were administered to 39 patients after a median of 2 days (1-5) after hospital admission. In hospital mortality rate was 24.7% (n=24/97) and did not vary significantly over time (n=5/11, 45.4%; n=6/25, n=6/25, 24%; n=5/29, 17.2% and n=8/32, 25.0%, respectively; p=0.58). Accordingly, there was no relation between the year of hospitalization and hospital mortality in univariate analysis (OR=0.97; 95% IC [0.91-1.03]; p=0.27). The median follow-up duration was 34 months (9-84) for discharged patients, with a mortality rate of 16.4% (n=12). Overall mortality rate was 37.1% (36/97).

The Figure 3A shows the Kaplan-Meier curve of survival probability over time for all patients. Finally, Kaplan-Meier curves of patients having a DAH related to increased pulmonary capillary pressure or not (Figure 3B) or related to an immune cause or not (Figure 3C) were drawn for the whole study population. There was a higher overall mortality in patients with DAH related to increased pulmonary capillary pressure, as compared with patients with DAH not related to increased pulmonary capillary pressure (n=14/26, 54% *vs.* n=22/71, 31%, respectively; p=0.019 by the log-rank test). In contrast, patients with immune DAH did not have a different overall prognosis, as compared with patients with non-immune DAH (12/35, 34% vs. 24/62, 39%; p=0.738 by the log-rank test).

Prognostic factors of hospital mortality

Twenty-four patients (24.7%) died in hospital, 22 of whom were hospitalized in the ICU. Age greater than 60 years, previous cardiovascular disease, tobacco history of greater than 20 pack-years, need for invasive mechanical ventilation, shock, LDH greater than twice the normal value and glomerular filtration rate < 60 mL/min yielded a p value < 0.05 in univariate analysis and were considered for the multivariate analysis (Table 3). Three factors were independently associated with in-hospital mortality in the multivariate analysis, including shock (OR=77.6; 95% IC=[8.9-677.2]), glomerular filtration rate < 60 mL/min (OR=11.2; 95% IC=[1.8-68.4]) and plasmatic LDH greater than twice the normal value (OR=12.1; 95%IC=[1.7-84.3]). The Pearson goodness of fit test yielded a p value >0.05 (p=0.95), meaning that the calibration of the model was good. The r^2 yielded by the model was 0.52.

Prognostic factors of long-term outcome

The mortality rate of the 73 discharged patients was 16.4% (12/73) during the follow-up period. Age greater than 60 years (p=0.026), a previous cardiovascular disease (p=0.027) and a persistent renal failure requiring chronic hemodialysis (p=0.026) were associated with long-term mortality in the univariate analysis performed with the Kaplan-Meier method. The Figure 2 of the online supplement shows the Kaplan-Meier curves of survival representing a patient's probability of survival over time based on the presence of a previous cardiovascular disease (p=0.027).

Discussion

Our study reports the outcome of 97 patients hospitalized in a tertiary hospital for an initial episode of DAH. DAH may result from a broad spectrum of diseases of different pathophysiological mechanisms. However, diagnosis of the underlying condition can be

challenging and may not be known within the first hours following hospital admission. We therefore aimed at identifying available factors on admission that were associated with a poor prognosis. As a result, the study population reflects the large and heterogeneous spectrum of the diseases that may be encompassed in the setting of DAH. The overall mortality rate was 37.1%, combining the 24.7% rate of in-hospital mortality and the further post-discharge mortality rate of 16.4%. Different prognostic factors were related to the in-hospital and long-term mortality. The first group of factors included LDH level, shock and renal failure. The second group of factors included age greater than 60 years, cardiovascular disease and the need for chronic hemodialysis.

DAH is a rare and severe syndrome with a reported in-hospital mortality of 20 to 100% [1-3]. Previous series included limited samples of patients with immune DAH and reported that the main causes of death were infections and renal failure [4, 5, 27, 28]. Although DAH of immune causes are usually deemed to have a poorer prognosis than DAH of non-immune causes [4], there is to our knowledge no study assessing the determinants of outcome in a cohort including DAH of immune and non-immune causes. In our series, the in-hospital mortality rate was 24.7%, emphasizing the poor prognosis for patients experiencing an initial episode of DAH, even in a non-selected population of patients. These results highlight the need for a tool quickly identifying patients who would benefit from aggressive treatment and intensive monitoring.

Three factors available during the first 24 hours of hospitalization were independently associated with in-hospital mortality. We did not enter the SAPS II and the LOD scores into our statistical model in an attempt to identify the specific organ failures related to a poor prognosis. Accordingly, the in-hospital mortality was predicted by extra-pulmonary organ failures (shock and renal failure), underlining the fact that most patients were affected by general diseases (immune disorders and cardiovascular diseases) that led to cardiac and renal

failure [18, 29-31]. Half (9/17; 53%) of the patients with shock had a DAH related to increased pulmonary capillary pressure. Among those patients, 8/9 had a pre-existing cardiovascular disease. We thus hypothesize that those patients had a cardiogenic shock associated with DAH due to increased pulmonary capillary pressure, both complicating severe/end-stage left heart failure. Eight other patients, among whom only one survived, had a shock: 3 had septic shock (3 patients with Panton-Valentine producing *Staphylococcus aureus*) and 5 had a multiple organ failure syndrome of an unclear mechanism (2 patients with idiopathic DAH, 2 patients with immune DAH and one patient with clotting disorder). However, the underlying cause of organ failure (immune versus non-immune) was not related to outcome, as the overall mortality did not differ between patients with or without an immune cause of DAH. Surprisingly, the variables related to respiratory failure (need for invasive mechanical ventilation or PaO_2/FiO_2 less than 200 mmHg at admission) did not appear to predict mortality in our model. This may be explained by interdependence with the variable shock. Shock was indeed strongly related to hospital mortality ($p<0.0001$ for each of the respiratory failure variables). On the other hand, the fact that increased LDH level at admission was a risk factor for hospital mortality in our series probably reflected the prognostic impact of pulmonary injury. Previous studies have demonstrated that increased LDH level in patients with pulmonary pneumocystosis or acute respiratory distress syndrome is a prognostic factor [32, 33]. However, increase in LDH level can be the result of various conditions which makes its interpretation speculative [34].

Twelve of the 73 patients discharged from our hospital died during the follow-up period. This resulted in a low statistical power. Therefore, no multivariate analysis was performed on the factors associated with long-term outcome with the Kaplan-Meier method. Age greater than 60 years was associated with mortality in discharged patients. This finding was in agreement with the study of Thibault et al who found that age had a greater effect on

long-term mortality in a large non-selected population of patients admitted to the ICU [35]. Dependence on hemodialysis was also a risk factor for long-term mortality. This was a result of pulmonary-renal syndrome that led to end-stage renal failure [18, 28]. Previous studies showed that renal failure is an independent predictor of poor outcome in anti-glomerular basement membrane antibody disease [18], connective tissue disease [36] and vasculitis [37]. This suggests that a subgroup of patients suffering of immune causes of DAH leading to end-stage renal failure might be at higher risk of death, although the limited statistical power of our study did not allow us to draw such an inference. Interestingly, patients with a pre existing cardiovascular disease had an increased risk of death after hospital discharge. This finding suggests that DAH related to increased pulmonary capillary pressure may be associated with a worse prognosis than DAH related to other causes. Most of our patients with DAH related to increased pulmonary capillary pressure (19/26; 73.1%) had a previously known cardiovascular disease suggesting that DAH was the end-stage manifestation of a chronic heart disease which resulted in death in 12 patients. On the other hand, DAH was the first manifestation of a heart disease in 7 patients (mitral stenosis, n = 3; left heart systolic dysfunction, n= 3; diastolic dysfunction, n = 1) which led to death in 2. In our series, patients with DAH related to increased pulmonary capillary pressure had a 53.8% overall mortality rate. In comparison, there was a 31.0% overall mortality rate in others (p=0.019). Previously published data has reported a 33% one-year mortality rate in patients hospitalized for cardiogenic pulmonary edema [29]. Our findings support this study because DAH related to increased pulmonary capillary pressure was associated with a poor prognosis. For patients hospitalized before the era of echocardiography, the pulmonary artery occlusion pressure was measured (n=10). We however acknowledge that among patients with increased pulmonary capillary pressure, some of those hospitalized in the eighties might have been misclassified given the difficulty to assess the left ventricle diastolic function. It is thus likely that some of

the patients classified as systolic dysfunction of the left ventricle had an associated diastolic dysfunction. However, all the patients classified as DAH due to increased pulmonary capillary pressure (n=26) had a patent DAH, as opposed to an usual cardiogenic alveolar edema: BAL fluid was macroscopically bloody in 10 patients, pink in 10 and normal in 6, for whom the percentage of alveolar siderophages was always > 70%. The discrimination of these patients from the others was therefore challenging on hospital admission. We thus wished to include them in this series, although the mechanisms involved in these DAH are mainly related to an increase in hydrostatic pressures and not to a primary lesion of the alveolo-capillary barrier, as in DAH of other causes. This subgroup of DAH seems to exhibit a worse outcome than the others and might therefore require a more aggressive management. Anticoagulant or antiagregant therapy was not associated with increased in-hospital or long-term mortality in this study (p=0.11 and p=0.43, respectively). However, these treatments may exacerbate alveolar hemorrhage. In particular, this may have occurred in patients with DAH related to left heart failure. These patients frequently receive such treatments. Among the 26 patients with DAH related to increased pulmonary capillary pressure, those who received anticoagulant or antiagregant therapy trended towards a higher in-hospital mortality rate than the others (11/18, 61.1% *vs*. 0/8, 0.0%; p=0.076). This finding should be interpreted cautiously, as it might reflect the severity of the underlying heart disease. However, DAH has been frequently reported in patients receiving thrombolytic therapy in the setting of acute myocardial infarction. Alveolar bleeding may be facilitated by increased systolic pulmonary arterial pressure up to 65 mmHg [38, 39] in accordance with animal models. In rabbits, an artificial rise in capillary pressure leads to breaks in the alveolocapillary barrier [40, 41]. Such intermediate forms of pulmonary edema which combine increased permeability and hydrostatic pressure have been described in patients with heart failure [42]. Whether clotting disorders may exacerbate the alveolar bleeding in the setting of capillary stress failure remains

uncertain. However, withdrawing anticoagulant and/or antiagregant therapy, at least temporarily, in patients with DAH due to increased pulmonary capillary pressure might be a suitable intervention which would need to be tested in further studies.

This study has several limitations. First, it is a retrospective study which covers a long period during which diagnosis tools, treatments and global quality of care might have varied; second, it is a monocentric study, which limits the potential of extrapolation of the conclusions drawn. However, the facts that i) immunocompromised hosts were excluded; ii) the patients were all diagnosed and treated in the same institution; and iii) only basic clinical and radiological characteristics and biological tests were used to determine prognosis limit the risk of heterogeneity of practices during time. Main changes in practices over the 29 years of this study included i) the increased use of echocardiography-doppler over time (from ~50% in the eighties to up to ~100% during the 14 last years of the study) and the parallel decrease in the use of right heart catheterism (see Figure 1 of the online supplement), and ii) the changes in the ventilatory management of patients with the acute respiratory distress syndrome (*i.e.,* tidal volume reduction) likely to have improved their prognosis. Finally, the fact that a time variable was not associated with in-hospital mortality in univariate analysis does not preclude the possibility of an impact of time on outcome since the study was neither designed nor powered to test this hypothesis.

In summary, we reported a large series of immunocompetent patients hospitalized for initial episodes of DAH (immune and non-immune). Predictors of in-hospital mortality available during the first 24 hours following admission included shock, renal failure and increased LDH level, whatever the underlying cause of DAH. In contrast, long-term mortality was determined by age, cardiac comorbidities and dependence on hemodialysis. Further studies are needed to clarify the role of anticoagulant and antiagregant therapy on the initial

severity and outcome of DAH patients. This therapy may have a significant impact on those with left heart failure.

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Figure legends

Figure 1. Flow chart of patients hospitalized between 1980 and 2008 for DAH. *missing data (n=10), hemorrhage of bronchial origin (n=43) or discovery of an immunocompromised status during hospitalization (n=1).

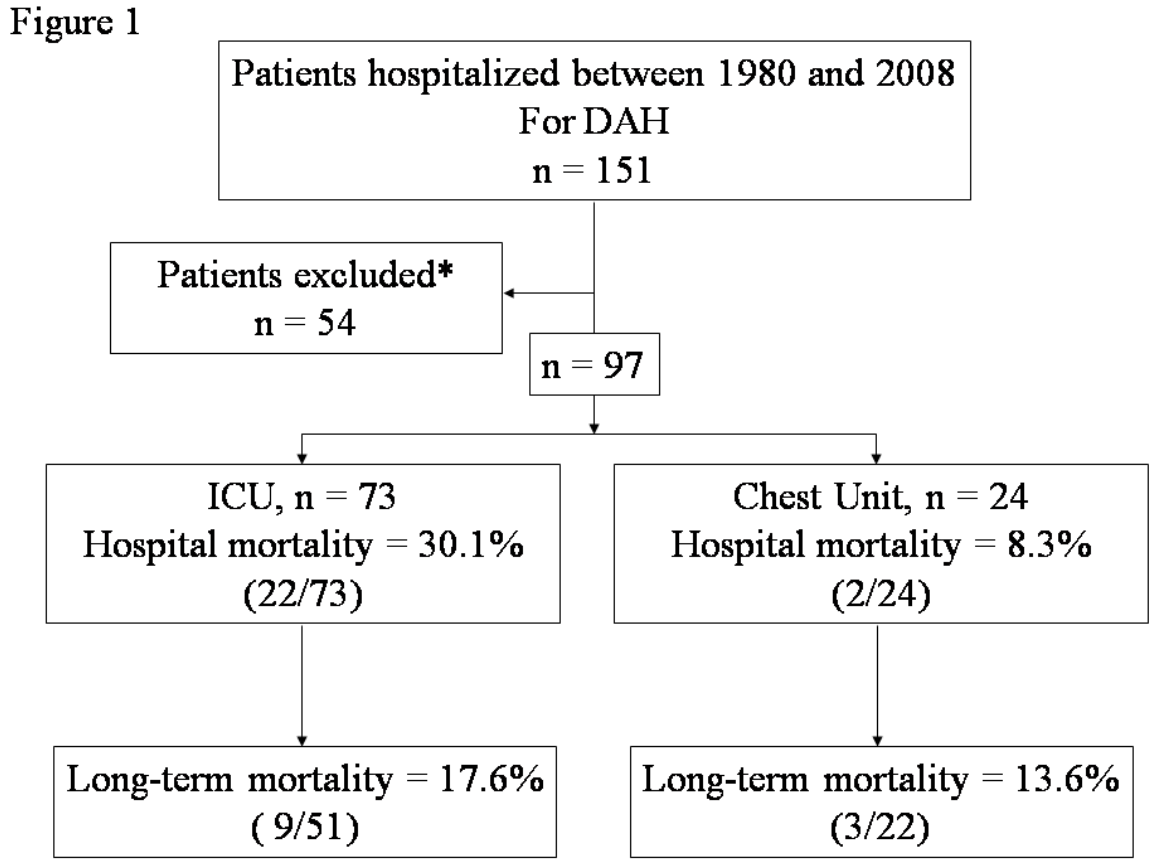


Figure 2. Causes of DAH for patients hospitalized over 4 time periods. IPCP, increased pulmonary capillary pressure.

Figure 2

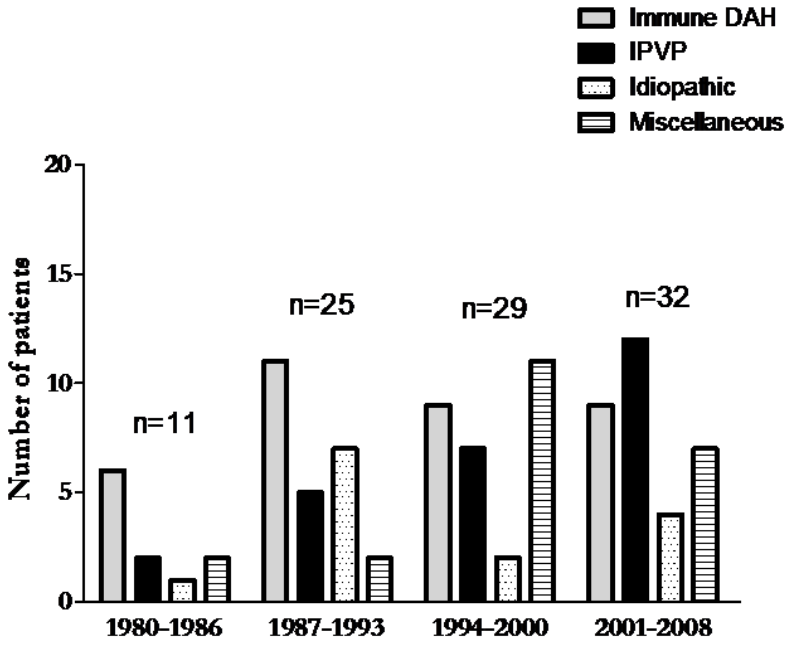


Figure 3. Kaplan-Meier curves of the probability of survival during the median follow-up period. Dashed line shows the separation between in-hospital mortality and mortality in discharged patients. (A) Kaplan-Meier curve showing the probability of survival for all patients. (B) Kaplan-Meier curve showing the overall probability of survival for patients with (dashed curve) or without (continuous curve) DAH related to increased pulmonary capillary pressure (IPCP). p=0.019 (log-rank test). DAH non related to increased pulmonary capillary pressure include immune and idiopathic DAH and DAH of miscellaneous causes. (C) Kaplan-Meier curve showing the overall probability of survival for patients with immune (dashed curve) or non-immune (continuous curve) related DAH. p=0.735 (log-rank test). Non-immune DAH include DAH related to increased pulmonary capillary pressure, idiopathic DAH and DAH of miscellaneous causes.

Figure 3A

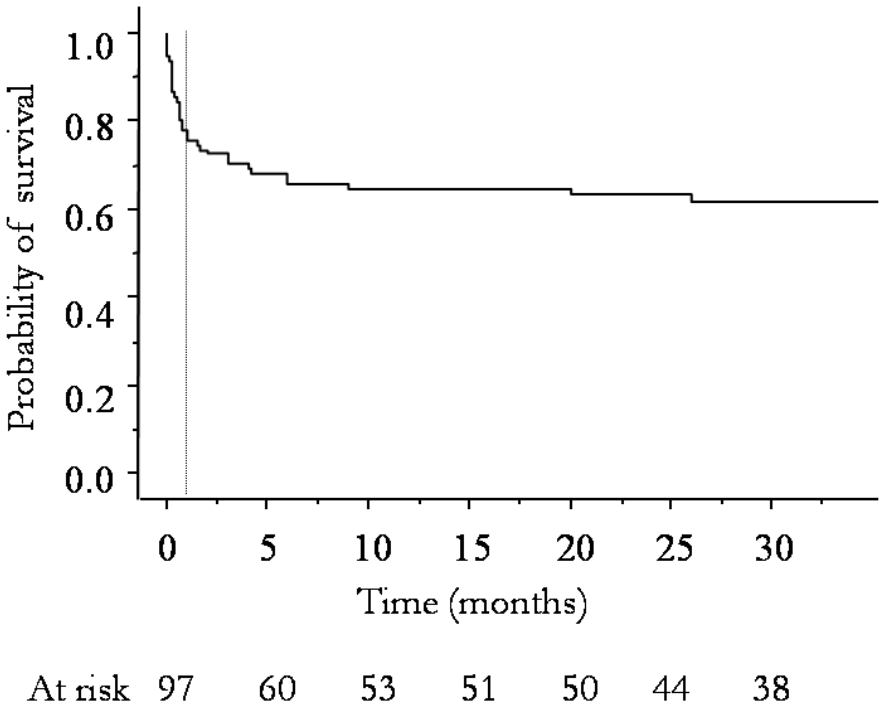
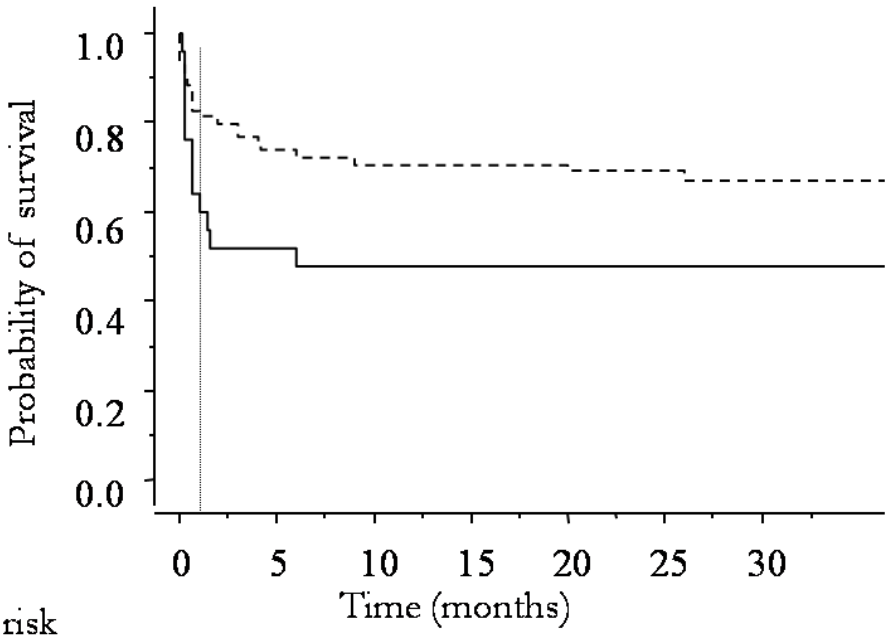
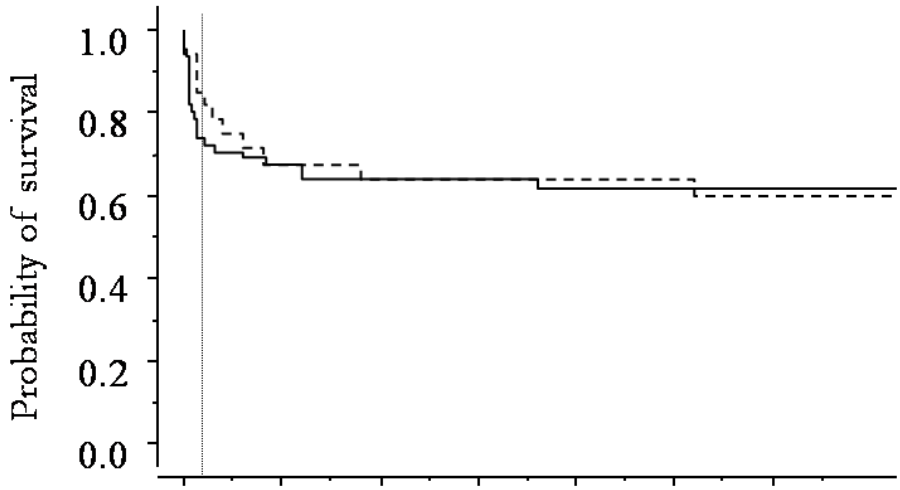


Figure 3B



At risk							
Non IPVP	71	48	43	41	40	36	32
IPVP	26	12	10	10	9	8	6



At risk							
Non immune	62	39	35	33	32	29	25
Immune	34	19	17	17	16	15	13

Tables

Table 1. Etiology of DAH syndromes.

DAH of immune cause	**N=35**
Vasculitis*	25
AGBMAD	4
Connective tissue disease**	6
DAH of non-immune cause	**N=62**
Increased pulmonary capillary pressure	26
Systolic dysfunction of the left ventricle†	15
Diastolic dysfunction of the left ventricle	6
Valvular heart disease††	5
Miscellaneous	22
Infection§	6
Toxic- or drug-induced DAH	6
Clotting disorder	4
Barotrauma	4
Cancer	2
Idiopathic DAH	14

AGBMAD, anti-glomerular basement membrane antibody disease; * Microscopic polyangiitis (n=13); Wegener disease (n=11), Churg and Strauss disease (n=1); ** Systemic lupus erythematosus (n=4), rheumatoid polyarthritis (n=1), Sharp syndrome (n=1); † Median left ventricle ejection fraction was 40% (30.0-47.5); †† Mitral stenosis (n=4), aortic stenosis (n=1); § Panton-Valentine producing (n=3) and non producing (n=1) *Staphylococcus aureus*, unidentified anaerobic bacteria (n=1) and filariasis (n=1).

Table 2. Characteristics and initial presentation of the 97 patients.

Variables	All patients (N=97)	Immune DAH (N=35)	Non-immune DAH (N=62)	P
Age, year	52 (32-67)	48 (24-64)	52 (36-68)	0.37
Male gender	61 (62.9)	17 (48.6)	44 (71.0)	0.28
BMI, kg/m^2	24.1 (20.8-26.0)	23.3 (19.7-24.6)	24.3 (22.3-26.7)	0.052
Weight loss > 5%	34 (35.0)	21 (60.0)	13 (21.0)	0.009
Tobacco > 20 packs.years	33 (34.0)	8 (22.8)	25 (40.3)	0.21
Alcohol use	18 (18.5)	6 17.1)	12 (19.3)	0.82
Previous cardiovascular disease*	42 (43.3)	12 (34.3)	30 (48.4)	0.39
Previous respiratory disease†	20 (20.6)	8 (22.8)	12 (19.3)	0.74
Anticoagulant treatment	13 (13.4)	0 (0.0)	13 (21.0)	0.009
Antiagregant treatment	16 (16.5)	4 (11.4)	12 (19.3)	0.39
SAPS II	22 (12-35)	19 (12-35)	23 (13-36)	0.70
LOD score	3 (0-5)	3 (1-5)	2 (0-4)	0.088
First symptom-admission, days**	10 (3-21)	18 (10-30)	5 (2-15)	<0.001
Hemoptysis	66 (68.0)	21 (60.0)	45 (72.6)	0.57
Use of accessory muscles	26 (26.8)	9 (25.7)	17 (27.4)	0.89
Crackles	77 (79.4)	27 (77.1)	50 (80.6)	0.71
PaO_2/FiO_2 ratio	252 (195-352)	286 (205-333)	219 (170-355)	0.33
Mechanical ventilation	17 (17.5)	4 (11.4)	13 (21.0)	0.41
Pulmonary infiltrates on chest x-ray	90 (92.8)	32 (91.4)	58 (93.5)	0.94
Shock	17 (17.5)	2 (5.7)	15 (24.2)	0.054
Extra-pulmonary symptoms				
Cutaneous	30 (30.1)	19 (54.3)	11 (17.7)	0.011
Bone-joint	16 (16.5)	13 (37.1)	3 (4.8)	<0.001
Gastro-intestinal	10 (10.3)	3 (8.6)	7 (11.3)	1.0
Neurological	21 (21.6)	10 (28.6)	11 (17.7)	0.33
Nose-ear-throat	26 (26.8)	17 (48.6)	9 (14.5)	0.013
Ocular	11 (11.3)	7 (20.0)	4 (6.4)	0.10
Urinalysis reagent strip				
Hematuria	25 (25.8)	22 (62.8)	3 (4.8)	<0.001
Proteinuria	29 (29.9)	24 (68.6)	5 (8,1)	<0.001
Glomerular filtration rate, mL/min	64 (39-101)	48 (17-65)	83 (49-105)	<0.001
Hemoglobinemia, g/dL	10.7 (8.3-13.2)	8.6 (7.5-11.1)	12.5 (10.0-14.2)	<0.001
White blood cells count, $10^3/\mu L$	10.2 (7.5-15.2)	9.7 (7.4-13.1)	10.4 (7.5-16.5)	0.71
Platelets count, $10^3/\mu L$	280 (199 -394)	322 (247-422)	277 (183-353)	0.036

Date are presented as median (25 to 75 interquartile range), or No (%). BMI, body mass index; * Hypertension (n=30), coronary heart disease (n=15), atrial fibrillation (n=11), oblitering arteriopathy of the lower limbs (n=6), stroke (n=3); † COPD (n=8), respiratory tract infection (n=8), miscellaneous (n=4). ** Time elapsed between the first symptom of DAH and hospital admission.

Table 3. Univariate and multivariate analysis of variables associated with in-hospital mortality available within the 24 hours following admission.

Variables	N	Hospital Mortality N (%)	Univariate analysis		Multivariate analysis	
			OR (95%CI)	P	OR (95%CI)	P
Age > 60 years						
No	63	9 (14)	1	0.002	-	ns
Yes	34	15 (44)	4.4 (1. 8-12.6)			
AAT						
No	69	14 (20)	1	0.115	-	ns
Yes	28	10 (36)	2.2 (0.8-5.8)			
Previous or current respiratory disease						
No	77	18 (23)	1	0.542	-	ns
Yes	20	6 (30)	1.4 (0.5-4.2)			
Previous or current CVD						
No	55	8 (15)	1	0.009	-	ns
Yes	42	16 (62)	3.6 (1.4-9.6)			
Tobacco > 20 packs.yr						
No	64	11 (18)	1	0.019	-	ns
Yes	33	13 (39)	3.1 (1.2-8.1)			
IMV						
No	80	12 (15)	1	<0.001	-	ns
Yes	17	12 (71)	13.6 (4.0-45.6)			
Shock						
No	80	9 (11)	1	<0.001	1	<0.001
Yes	17	15 (88)	59.2 (11.6-302.1)		77.5 (8.9-677.2)	
Hb < 10 g/dL						
No	57	11 (19)	1	0.141	-	
Yes	40	13 (32)	2.0 (0.8-5.1)			
LDH > 2 UNV						
No	71	12 (17)	1	<0.001	1	0.012
Yes	15	10 (67)	9.8 (2.8-34.0)		12.1 (1.7-84.3)	
GFR < 60 mL/min						
No	54	6 (11)	1	<0.001	1	0.009
Yes	43	18 (42)	6.5 (2.3-18.6)		11.2 (1.8-68.4)	

Abbreviations: AAT, anticoagulant or antiagregant treatment; RD, respiratory disease; CVD, cardiovascular disease; IMV, invasive mechanical ventilation; UNV, upper normal value; Hb, hemoglobin; GFR, glomerular filtration rate. The Pearson goodness of fit test showed good calibration of the model (for four degrees of freedom: χ^2=0.75, p=0.94).