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Original Research Article

Comparison of survivors and nonsurvivors of diffuse alveolar hemorrhage: risk factors for in-hospital death

Swathi Sangli[1]*, Misbah Baqir[2], Jay Ryu[2]

[1]Department of Pulmonary and Critical Care, Drexel University College of Medicine, Allegheny Health Network, Pittsburgh, PA, USA
[2]Department of Pulmonary and Critical Care, Mayo Clinic, Rochester, Minnesota, USA

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***Correspondence:**
Dr. Swathi Sangli,
E-mail: swathisang@gmail.com

ABSTRACT

Background: The objective of this study was to identify the predictors of in-hospital mortality among patients with diffuse alveolar hemorrhage (DAH).
Methods: We conducted a retrospective review of 89 patients hospitalized for DAH at our institution. 49 patients who died during hospitalization and 40 patients who survived were compared. We reviewed their clinical course, radiologic and pathologic findings, along with medical management. We then performed univariate and multivariate analyses to identify the risk factors associated with in-hospital mortality.
Results: We identified 12 factors to be associated with mortality when comparing survivor versus non-survivor cohorts: smoking (67 versus 42%, p=0.02), malignancy (17 versus 49%, p=0.002), interstitial lung disease (0 versus 14%, p=0.01), liver failure (2 versus 28%, p=0.001), autoimmune diseases (40 versus 8%, p=0.0006), thrombocytopenia (7 versus 71%, p<0.0001), ICU admission (57 versus 85%, p=0.004), mean ICU stay (p=0.4), steroid use (90 versus 63%, p=0.003), plasma exchange (15 versus 0 %, p=0.005), mechanical ventilation (37 versus 75%, p=0.0007) and acute respiratory distress syndrome (22 versus 77%, p<0.0001). On multivariate analysis, thrombocytopenia (p<0.0001) and ARDS (p=0.0013) were associated with higher odds of mortality in DAH while steroid use (p=0.0004) was associated with a lower risk of in-hospital mortality in patients with DAH.
Conclusions: In DAH, thrombocytopenia and ARDS were predictors of in-hospital mortality whereas the use of steroid was associated with a more favorable prognosis.

Keywords: Diffuse alveolar hemorrhage, Diffuse alveolar infiltrates, Mortality

INTRODUCTION

Diffuse alveolar hemorrhage (DAH) is a life-threatening condition. The presenting features usually include dyspnea with or without hemoptysis and bilateral pulmonary infiltrates on chest imaging. Bronchoscopy with bronchoalveolar lavage (BAL) is usually needed to establish the diagnosis. DAH has a number of potential etiologies; however, pulmonary capillaritis is the most common histopathological finding in these patients.[1] Among those with immune-mediated DAH, systemic vasculitides are the most common cause.[2] The management of DAH includes supportive care along with targeted therapy directed toward the underlying cause, when identifiable.[3]

The reported in-hospital mortality associated with DAH ranges from 25 to 50%.[4-7] There are limited data regarding the factors contributing to mortality associated with DAH; previous studies have implicated mechanical ventilation, renal failure, shock, thrombocytopenia, and infections to be associated with higher risk of mortality.[8,9] Studies specifically pertaining to immune-mediated DAH, e.g., DAH in systemic lupus erythematosus (SLE),

have also reported a wide range of mortality rates, 0% to 60%.[10-20] In this retrospective study, we sought to identify the factors associated with in-hospital mortality of patients hospitalized with DAH by comparing patients who died to those who survived their hospitalization.

METHODS

A retrospective study was conducted with the support of a computer-assisted electronic search of medical records to identify all patients with DAH admitted to our medical center at Mayo Clinic, Rochester from January 2001 to October 2017. Selection criteria and the procedure to identify these patients included the following. Firstly, to identify these patients, we searched for the following query terms: "diffuse alveolar hemorrhage" or "alveolar hemorrhage" mentioned anywhere in the clinical notes.

For all identified patients, we performed a complete review of their electronic medical records and radiologic studies. DAH was diagnosed using the following criteria: clinical (dyspnea with or without hemoptysis) and radiologic presentation (bilateral pulmonary infiltrates) compatible with DAH, plus one of the following: i) BAL revealing grossly hemorrhagic fluid from multiple lobes or increasingly hemorrhagic fluid return, ii) >20% hemosiderin macrophages in BAL, or iii) DAH confirmed on surgical lung biopsy or autopsy.[21-23]

There were 49 patients who died from DAH between January 2001 and October 2017 during their hospitalization. For comparison, we selected first 40 patients with DAH who survived their hospitalization during this interval. We conducted a retrospective review of these 89 patients to extract variables including patient demographics (age and gender), smoking history, presenting clinical features, echocardiographic findings, pathology results, management, and outcomes.

Patients with acute respiratory distress syndrome (ARDS) were identified based on the presence of bilateral diffuse alveolar opacities which were not explained by heart failure with an onset of <1 week, and a PaO_2/FiO_2 <300 with a minimum requirement of 5 cmH_2O of positive end-expiratory pressure (PEEP) either on mechanical ventilation or non-invasive ventilation.[24] Renal dysfunction was defined as creatinine level >1.5 mg/dl. Thrombocytopenia was defined as platelet count below the normal level <150 × 10^9/l.

The Mayo Clinic Institutional Review Board approved this study (#16-010437-02). Patients who did not allow their medical records to be used for research purposes were excluded. The ethics approval and consent to participate was not applicable to our study.

Statistical analysis

Data was analysed by simple descriptive statistical methods. Categorical variables are expressed as number (percent) and continuous variables expressed as mean (standard deviation).

To compare the continuous variables by survivor status, we used Wilcoxon Rank sum test and Pearson chi square test to compare categorical variables. We identified variables which were independent predictors of survival. We then developed a multivariate logistic regression model from these variables to identify a predictive model and obtained odds ratio values, 95% confidence intervals and p values. Variables with p values ≤0.2 were considered for multivariate analysis. All statistical analysis was completed using JMP 15.0. P value <0.05 was considered for statistical significance.

RESULTS

Demographics and presenting clinical symptoms are summarized in Table 1. The proportion of smokers (current and former) was significantly higher in survivors versus non-survivors.

Table 1: Baseline characteristics and clinical presentation in survivors and non-survivors after DAH.

Characteristics	Survivors (n=40)	Non-survivors (n=49)	P value
Age, years, median (range)	72 (20-100)	66 (23-95)	0.12
Males	25 (62)	30 (62)	0.9
Smoking status*	27 (67)	21 (42)	0.02
Active	6 (15)	5 (10)	
Former	21 (52)	16 (33)	
Never	13 (32)	20 (41)	
Hemoptysis	23 (57)	23 (48)	0.37
Dyspnea	39 (97)	48 (98)	0.9

Values provided as No. (%), unless otherwise indicated.
Abbreviation: DAH- diffuse alveolar hemorrhage; *Smoking status was not available in 8 patients

Table 2: Causes of diffuse alveolar hemorrhage.

Cause	Survivors (n=40)	Non survivors (n=49)
Malignancy	0 (0)	14 (28)
Infection	8 (20)	13 (26)
Interstitial lung disease	0 (0)	7 (14)
Coagulopathy	5 (12)	4 (8)
Drug-induced	0 (0)	3 (6)
Anticoagulant therapy	3 (7)	1 (2)
Autoimmune disease	16 (40)	1 (2)
Thrombocytopenia	3 (7)	0 (0)
Congestive heart failure	2 (5)	1 (2)
Miscellaneous	3 (7)	5 (10)

Values provided as No. (%).

Commonly noted causes of DAH in the non-survivor DAH group were: malignancy (especially hematological) in 14 patients (28%), infections in 13 patients (26%) and interstitial lung diseases in 7 patients (14%) (Table 2). On the other hand, commonly noted causes of DAH in the survivor group included: autoimmune disease in 16 patients (40%), infections in 8 patients (20%) and coagulopathy in 5 (12%).

Table 3: Risk factors for diffuse alveolar hemorrhage.

Variable	Survivors (n=40)	Non survivors (n=49)	P value
Malignancy	7 (17)	24 (49)	0.002
Sepsis	16 (41)	22 (45)	0.7
Interstitial lung diseases	0 (0)	7 (14)	0.01
Idiopathic	3 (7)	4 (8)	0.8
Drug-induced	1 (2)	3 (6)	0.3
Anticoagulation	16 (41.03)	15 (30.61)	0.31
Congestive heart failure	10 (27)	9 (19.5)	0.4
Renal dysfunction	19 (47)	30 (61)	0.2
Liver failure	1 (2)	14 (28)	0.001
Connective tissue diseases	16 (40)	4(8)	0.0006
SLE	1 (2)	1 (2)	1
Mixed connective tissue disease	3 (7)	3 (6)	0.8
Microscopic polyangiitis	7 (18)	0 (0)	0.001
Granulomatosis with polyangiitis	2 (5)	0 (0)	0.1
Antiphospholipid syndrome	2 (5)	0 (0)	0.1
Dermatomyositis	1 (2)	0 (0)	0.3
Thrombocytopenia	3 (7)	35 (71)	<0.0001
Coagulopathy INR>1.5	15 (37)	22 (45)	0.5

Values provided as No. (%), unless otherwise indicated.
Abbreviations: SLE- systemic lupus erythematosus; INR- international normalized ratio

The risk factors for DAH are summarized in Table 3. The factors which significantly differ between survivors vs. non-survivors, respectively, were: malignancy in 7 patients (17%) versus 24 (49%) (p=0.002), interstitial lung disease (ILD) in 0 versus 7 (14%) (p=0.01), liver failure in 1 (2%) versus 14 (28%) (p=0.001), connective tissue disease in 16 (40%) versus 4 (8%) (p=0.0006), and thrombocytopenia in 3 (7%) versus 35 (71%) (p<0.0001).

Management of DAH in survivor and non-survivor is shown in Table 4. The statistically significant different factors between survivors and non-survivors were: ICU admission in 23 (57%) versus 40 patients (85%) (p=0.004), steroid administration in 36 (90%) versus 31 (63%) (p=0.003). Mechanical ventilation was required in 15 (37%) versus 36 patients (75%) (p=0.0007); those who developed ARDS were noted to be 9 (22%) versus 37 (77%) (p<0.0001). One of the non-survivors underwent extracorporeal membrane oxygenation (ECMO). Medical management also included cessation of the potentially offending drugs and reversal of coagulopathy. Autopsy was performed in 12 patients (24%); most common histopathologic finding (in addition to DAH) was diffuse alveolar damage (58%, n=7).

Table 4: Management of diffuse alveolar hemorrhage in survivors and non-survivors.

Variable	Survivors (n=40)	Non survivors (n=49)	P value
ICU admission, n (%)	23 (57)	40 (85)	0.004
ICU length of stay, days, mean±SD	3.5±6.7	5.5±5.5	0.4
Duration of hospitalization, days mean±SD	11±8.8	10±9.3	0.5
Antibiotics, n (%)	34 (85)	43 (90)	0.5
Steroids, n (%)	36 (90)	31 (63)	0.003
Immuno-suppression, n (%)	6 (15)	9 (18)	0.7
Plasma exchange, n (%)	6 (15)	0 (0)	0.005
ECMO, n (%)	0 (0)	1 (2)	0.3
ARDS, n (%)	9 (22)	37 (77)	<0.0001
Mechanical ventilation, n (%)	15 (37)	36 (75)	0.0007

Values provided as No. (%), unless otherwise indicated.
Abbreviations: ICU- intensive care unit; ECMO- extracorporeal membrane oxygenation; ARDS- acute respiratory distress syndrome

Table 5: Predictors of mortality after DAH (adjusted for age and sex).

Variable	Odds ratio (95% CI)	P value
Age		0.21
Sex		0.74
Thrombocytopenia	52.08 (8.59-315.71)	<0.0001
ARDS	11.71 (2.60-52.67)	0.0013
Steroid use	0.05 (0.007-0.39)	0.0004

Abbreviations: ARDS- acute respiratory distress syndrome; DAH- diffuse alveolar hemorrhage

On multivariate analysis (Table 5), thrombocytopenia (OR 52.08: 95% CI, 8.59-315.71; p<0.0001) and ARDS (OR 11.71: 95% CI, 2.60-52.67; p=0.0013) were associated with higher odds of mortality in DAH, while

steroid use (OR 0.05: 95% CI, 0.007-0.39; p=0.0004) was associated with a lower risk of mortality in patients with DAH.

DISCUSSION

In this retrospective single-center study we attempted to identify the predictors of in-hospital mortality of patients hospitalized for DAH. Malignancy followed by infections were the two most common underlying causes in this cohort. We found 12 factors (smoking, malignancy, ILD, liver failure, autoimmune diseases, thrombocytopenia, ICU admission, ICU length of stay, steroid therapy, plasma exchange, ARDS and mechanical ventilation) to be associated with in-hospital mortality in this cohort. On multivariate analysis there were three factors (thrombocytopenia, ARDS and steroid use) which were independently associated with in-hospital mortality when adjusted for age and sex. Thrombocytopenia and ARDS were associated with in-hospital mortality, whereas steroid use was found to be protective.

Our study reports the outcome of 89 patients hospitalized at a tertiary care center for DAH and was designed to assess the predictors of in-hospital mortality. Limited literature exists regarding the predictors of in-hospital mortality in this population, but varying survival rates have been reported.[25] Patients whose DAH stems from immunological mechanisms appear to have a higher survival rate than those with DAH related to malignancy or sepsis.[26] Strongest association as independent risk factors of in-hospital mortality was identified in our patients with autoimmune diseases; thrombocytopenia, development of ARDS, ICU admission, and requirement of mechanical ventilation.

Previous studies have shown predictors such as mechanical ventilation, renal failure and bacterial or fungal infections to be associated with higher risk of mortality in DAH.[27] Severe hypoxia was also found to be a predictor of respiratory failure from DAH.[28] Our results corroborate some of these findings from earlier studies in that we found increased mortality in patients who developed ARDS and those requiring mechanical ventilation, reflecting the overall severity of the disease process. We did not find renal failure and sepsis to be associated with in-hospital mortality while the majority of our patients manifested these features. The definition of renal failure varied among these studies.

Interestingly, there are inconsistent reports about the prognosis of DAH patients, particularly in those with underlying autoimmune diseases. Possible explanations for the discrepant mortality rates associated with DAH in the latter population could be differences in the underlying autoimmune conditions. Whilst there are studies that show mortality rate associated with DAH in autoimmune diseases to be declining, there are also studies that show that mortality risk remains alarmingly high in those with systemic lupus erythematosus, anti-glomerular basement membrane antibody disease, and vasculitis.[29-32] In our study, the presence of autoimmune condition was associated with better survival and steroid use to be one of the favorable prognostic predictors with lower in-hospital mortality (as used commonly in DAH associated with autoimmune conditions).

A previous study reported poor survival in in patient with DAH who manifested thrombocytopenia, especially in the setting of cancer or sepsis.[33] Similarly, we found malignancy in nearly one-half of those in our non-survivor group. It has been reported that DAH in patients with hematological malignancies is often fatal. There are multiple contributory factors in this population including hematopoietic stem cell transplant, bone marrow transplant, opportunistic infections, thrombocytopenia, and other coagulopathies.[34] Amongst these, thrombocytopenia was independently associated with higher risk of mortality in our study. In fact, the odds of dying from DAH in the setting of thrombocytopenia was found to be 52 times higher when compared to those with no thrombocytopenia.

Our study has several limitations. Firstly, this is a retrospective single-center study with a small sample size, which may limit the significance and generalization of the results. Given the nature of the large electronic database and challenges involved to establish the true denominator of the total number of DAH patients, the data selection for the control group was sequentially identified within the specified time frame. The study data was collected from 16 years' study period under varying practices. This study is mainly on patients admitted in medical floor and medical ICU. The results of this study may not be generalized to surgical or trauma patients.

CONCLUSION

The most common underlying cause for in-hospital mortality in patients with DAH was malignancy. Steroid administration was associated with lower risk of in-hospital mortality. Those patients who manifested thrombocytopenia or developed ARDS during their hospitalization experienced a high mortality rate.

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