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ORIGINAL ARTICLE

Rheumatic diseases associated with alveolar hemorrhage: analysis of the national inpatient sample

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Abstract

Objective Diffuse alveolar hemorrhage (DAH) is a severe pulmonary complication of numerous diseases, including rheumatic conditions. We have conducted an observational study using inpatient data from the National Inpatient Sample to study the relationship of DAH with rheumatic conditions along with their descriptive characteristics.

Methods An observational study was conducted on hospitalizations in 2016–2018 with a principal diagnosis of DAH from the United States National Inpatient Sample database. A multivariate logistic regression analysis was performed to calculate adjusted odds ratios (OR_{adj}) for risk factors of DAH.

Results A total of 5420 DAH hospitalizations were identified among 90 million hospitalizations. Mortality in this group was found to be 24.3%. Majority of patients admitted with DAH were white and male, with a mean age of 61.8 years and a mean LOS of 10.6 days. Multivariate analysis showed that multiple rheumatic diseases were associated with DAH, including anti-neutrophil cytoplasmic antibody–associated vasculitis (AAV) (OR_{adj} 72.56) (95% *C.I.* 50.607–104.043), antiphospholipid antibody syndrome (APLS) (OR_{adj} 6.51) (95% *C.I.* 3.734–11.366), eosinophilic granulomatosis with polyangiitis (EGPA) (OR_{adj} 7.13) (95% *C.I.* 1.886–26.926), Goodpasture's (OR_{adj} 30.58) (95% *C.I.* 16.360–57.176), rheumatoid arthritis (RA) (OR_{adj} 1.60) (95% *C.I.* 1.158–2.212), sarcoidosis (OR_{adj} 3.99) (95% *C.I.* 2.300–6.926), and systemic lupus (SLE) (OR_{adj} 5.82) (95% *C.I.* 3.993–8.481).

Conclusion Although DAH is a relatively rare entity, it carries a very high mortality. Multiple rheumatic diseases were associated with DAH hospitalizations including AAV, APLS, EGPA, Goodpasture's, RA, sarcoidosis, and SLE.

Key points

- *It is known that DAH carries a high morbidity and mortality based on prior literature. However, large datasets on the association of rheumatic diseases with DAH are lacking*
- *This study identifies the descriptive characteristics of patients admitted to the hospital with DAH*
- *This study also identifies the strength of association of rheumatic diseases with DAH*

Keywords Alveolar hemorrhage · ANCA vasculitis · Lupus

Introduction

Diffuse alveolar hemorrhage (DAH) is a severe pulmonary complication of numerous diseases and carries a significant morbidity and mortality. DAH requires prompt diagnosis and aggressive treatment [1]. DAH has been shown to be a complication of multiple rheumatic conditions. A recent retrospective observational study by Bhushan et al. that was conducted at a tertiary-care academic center showed that 37.5% of DAH patients over a 12-year period had underlying immune causes, with granulomatosis with polyangiitis (GPA) (10.2%), microscopic polyangiitis (MPA) (9%), and

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systemic lupus erythematosus (SLE) (9%) being the most common [2]. Other reports also show DAH to be associated with various immune and non-immune diseases including vasculitis [3–8], Goodpasture syndrome [9, 10], antiphospholipid antibody syndrome (APLS) [11–15], SLE [16, 17], infections [8], toxic exposures [8], cardiac conditions [18], idiopathic pulmonary hemosiderosis [19–22], and post-transplantation [10, 22–24]. However, large studies on DAH and its triggers are lacking. Here, the objective of our study is to obtain the descriptive characteristics of patients with DAH, and also to determine the strength of association of DAH with rheumatic conditions using a large population–based data set.

Methods

Data source

An observational study was conducted on hospitalizations in 2016–2018 with a diagnosis of DAH in acute-care hospitals across the USA. Hospitalizations were selected from the National Inpatient Sample (NIS) database (online at https://www.hcup-us.ahrq.gov). Diagnoses are divided into two categories in the NIS: principal and secondary diagnoses. A principal diagnosis was the main ICD-10 code for the hospitalization. Secondary diagnoses were any ICD-10 code other than the principal diagnosis. Institutional Review Board approval was not sought for our study as all the patient data are de-identified and publicly available.

Inclusion criteria and study variables

The study group consisted of all hospitalizations recorded in the NIS from 2016 to 2018. Exclusion criteria was age ≤ 18 years. Study variables included age, gender, race, length of stay (LOS), total charges, and in-hospital mortality. DAH hospitalization was defined by the presence of a principal International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10) of DAH (R048.9 or R04.9) or a principal ICD-10 code of respiratory failure (all J96 codes) combined with a secondary ICD-10 code of DAH (R048.9 or R04.9).

We used the following ICD-10 codes to identify diagnoses/comorbidities: antineutrophil cytoplasmic antibody (ANCA) vasculitis (AAV) codes M31.30, M31.31, M31.33, and M31.7; anticoagulants D68.32; anti-phospholipid antibody syndrome (APLS) D68.61; aortic valvular disorders all I35 codes; aspergillosis B44; HIV B20; bacterial pneumonia J13, J14, and J15; Behcet's disease code M35.2; history of bone marrow transplant code Z94.81; chemotherapy codes Z51.11 and Z92.21; cocaine abuse all F14 codes; cryoglobulinemia code D89.1; cytomegaloviral (CMV) pneumonitis B.25.0; dermatomyositis (DM) and polymyositis (PM) all M33 codes; endocarditis all I33 codes; eosinophilic granulomatosis with polyangiitis (EGPA) codes M30.1; Goodpasture's M31.0; graft versus host disease (GVHD) code D89.81; Hantavirus B33.4; Henoch Schoenlein Purpura (HSP) code D69.0, hemophilia code D66; heroin abuse code T40.1; herpes infection B00.7; human immunodeficiency virus (HIV) B20; immune-mediated thrombocytopenia (ITP) D69.3; inflammatory bowel disease K50 and K51; Legionnaires' disease A48.1, leptospirosis A27; mitral stenosis I34.2; lymphangioleiomyomatosis J84.81; mixed connective tissue disease (MCTD) M35.9; myeloid leukemia all C92 codes; mycoplasma A49.3 and B96.0; myelodysplastic syndrome all D46 codes; pulmonary embolism (PE) I26; pulmonary hemosiderosis J84.03; rheumatoid arthritis (RA) all M05 and M06 codes; sarcoidosis all D86 codes; Sjogren's disease all M35 codes; SLE M32, M32.1, M32.10, M32.11, M32.12, M32.13, M32.14, M32.19, M32.8, and M32.9; systemic sclerosis all M34 codes.

Outcomes

Three outcomes were studied: (1) the prevalence of DAH hospitalizations and the in-hospital mortality, (2) description of demographic characteristics of DAH patients, and (3) identification of rheumatic conditions statistically associated with DAH hospitalizations.

Statistical analysis

We have used STATA version 16 (StataCorp, TX, USA) to perform the analyses. A univariate logistic regression analysis was used to calculate unadjusted odds ratios (ORs) for a principal diagnosis of DAH. All variables with p-values < 0.2 were included in a multivariate logistic regression model. Adjusted OR (OR_{adj}) were reported and considered significant when p-values were < 0.05. Risk factors for DAH were selected from extensive literature review.

Results

There were 90,879,561 adult hospital discharges in the combined 2016–2018 NIS database. Of those, 5420 met our case definition of DAH (Table 1). Compared to the control population, majority of the DAH patients were males (57.8% vs 44%, $p < 0.001$), were older (61.8 vs 57.9 years, $p < 0.001$), had longer LOS (10.6 days vs 4.7 days, $p < 0.001$), higher mean hospital charges ($160,898 vs $53,567, $p < 0.001$), and more likely to have in-hospital death (24.5% vs 2.2%, $p < 0.001$). Race/ethnicity were distributed among DAH patients as follows: White 71.7%, African American 13.4%, Hispanic 8.8%,

Asian or Pacific Islander 2.9%, Native American 0.9%, and other 2.3%.

Univariate analysis showed multiple variables and comorbidities were associated with DAH hospitalizations (Table 2). Several causes of DAH from the literature were not significant in our analysis. Additionally, there were zero secondary diagnoses of the following reported DAH triggers: Behcet's, Hantavirus, herpes, HSP, Legionnaires' disease, Lymphangioleiomyomatosis, mitral stenosis, or mycoplasma.

Multivariate analysis showed that many rheumatic diseases were associated with DAH including AAV (OR_{adj} 72.56, 95% *CI* 50.607–104), APLS (OR_{adj} 6.51, 95% *CI* 3.734–11.366), EGPA (OR_{adj} 7.13, 95% *CI* 1.886–26.926), Goodpasture's (OR_{adj} 30.58, 95% *CI* 16.360–57.176), RA (OR_{adj} 1.60, 95% *CI* 1.158–2.212), sarcoidosis (OR_{adj} 3.99, 95% *CI* 2.300–6.926), and SLE (OR_{adj} 5.82, 95% *CI* 3.993–8.481) (Table 3).

Additionally many non-rheumatic diseases were associated with DAH in multivariate analysis including age (OR_{adj} 1.01; *CI* 1.002–1.008), anti-coagulants (OR_{adj} 20.31, 95% *CI* 14.822–27.834), Aspergillosis (OR_{adj} 9.45, 95% *CI* 5.172–17.283), bacterial pneumonia (OR_{adj} 8.26, 95% *CI* 6.742–10.126), chemotherapies (OR_{adj} 2.18, 95% *CI* 1.548–3.082), CMV (OR_{adj} 14.44, 95% *CI* 4.114–50.714), female gender (OR_{adj} 0.60, 95% *CI* 0.525–0.679), hemophilia (OR_{adj} 7.47, 95% *CI* 1.883–29.639), history of bone marrow transplant (OR_{adj} 4.73, 95% *CI* 1.857–12.065), ITP (OR_{adj} 2.47, 95% *CI* 1.169–5.230), Leptospirosis (OR_{adj} 54.44, 95% *CI* 3.696–801.724), MDS (OR_{adj} 2.63, 95% *CI* 1.419–4.892), pulmonary embolus (OR_{adj} 3.23, 95% *CI* 2.241–4.645), pulmonary hemosiderosis (OR_{adj} 177.97, 95% *CI* 49.625–638.274), African American (OR_{adj} 0.68, 95% *CI* 0.511–0.898), Hispanic (OR_{adj} 0.63, 95% *CI* 0.466–0.859), Other race (OR 0.59, 95% *CI* 0.375–0.941), White (OR_{adj} 0.75, 95% *CI* 0.596–0.955).

Discussion

DAH is often a catastrophic clinical syndrome. Ideally, the underlying cause should be identified to improve treatment choices and outcomes [10]. Our study identified a significant association of rheumatic conditions with inpatient DAH. AAV patients had a 72-fold increased odds of being hospitalized with DAH. One study found that 19% of patients admitted to the ICU for DAH were found to have vasculitis. Seventy-one percent of those vasculitis patients had AAV; the remaining were due to SLE or other causes [8]. Another study also showed that the most common cause of pulmonary vasculitis is AAV [25]. Studies have reported varying incidences in AAV, but DAH seems to be more frequent in MPA affecting 25–60% of the patients [26] compared to GPA (22–30%) and EGPA (4%) [27, 28]. A variety of mechanisms has been shown to cause disruption in the alveolar capillaries, eventually leading to DAH. These can be immune or non-immune mechanisms [10, 25]. A single-center cohort study of AAV-associated DAH patients found that the severity of hypoxia on initial presentation was shown to be the most significant predictor of impending

Table 1 Weighted descriptive characteristics of adult DAH and non-DAH hospitalizations from the 2016 to 2018 national inpatient sample

Hospitalization characteristics	DAH ($n=5420$)	Non-DAH ($n=90{,}874{,}141$)	*p*-value
Women, number (%)	2385 (44%)	52,467,357 (57.8%)	< 0.001
Age, mean in years	61.8	57.9	< 0.001
Number (%) hospitalizations			
Age 18–40 years	710 (13.1%)	21,949,436 (24.2%)	< 0.001
Age 40–60 years	1375 (25.4%)	21,700,077 (23.9%)	0.256
Age 60–80 years	2615 (48.2%)	32,357,086 (35.6%)	< 0.001
Age > 80 years	720 (13.3%)	14,867,542 (16.4%)	0.006
Race (%)			
(a) White	71.7%	67.3%	0.040
(b) African American	13.4%	15.2%	0.079
(c) Hispanic, number	8.8%	11.1%	0.014
(d) Asian or Pacific Islander	2.9%	2.7%	0.812
(e) Native American	0.9%	0.6%	0.346
(f) other	2.3%	3.0%	0.176
Length of stay, mean days	10.6	4.7	< 0.001
Total charges, mean	$160,898	$53,567	< 0.001
Inpatient mortality, number (%)	1330 (24.5%)	2,019,004 (2.2%)	< 0.001

DAH, diffuse alveolar hemorrhage

Table 2 Univariate analysis: DAH associations

	Odds ratio	*p*-value	95% *C.I*
Non-rheumatologic variables			
Age	1.01	< 0.001	1.007–1.013
Anticoagulants	29.83	< 0.001	22.207–40.065
Aortic valvular disease	1.66	0.004	1.173–2.351
Aspergillosis	33.25	< 0.001	20.255–54.573
Pneumonia	11.85	< 0.001	9.880–14.219
Chemotherapy	2.47	< 0.001	1.768–3.441
CMV	120.42	< 0.001	45.085–321.624
Cocaine	0.81	0.479	0.462–1.437
Endocarditis	2.37	0.082	0.895–6.291
Female	0.57	< 0.001	0.509–0.649
GVHD	3.61	0.069	0.903–14.408
Hemophilia	8.89	0.002	2.222–35.575
Heroin	3.64	0.197	0.512–25.855
HIV	0.87	0.806	0.279–2.695
History of BMT	8.24	< 0.001	3.431–19.809
IBD	1.07	0.843	0.555–2.057
ITP	4.81	< 0.001	2.401–9.624
Leptospirosis	136.45	< 0.001	19.053–977.159
MDS	4.30	< 0.001	2.385–7.751
Multiple myeloma	1.74	0.175	0.781–3.887
Myeloid leukemia	3.68	< 0.001	1.909–7.101
Pulmonary embolus	4.99	< 0.001	3.538–7.048
Pulmonary hemosiderosis	395.96	< 0.001	147.093–1065.900
African-American	0.85	0.079	0.711–1.019
Asian/Pacific Islander	1.05	0.812	0.726–1.504
Hispanic	0.76	0.014	0.611–0.945
Native American	1.37	0.346	0.712–2.633
Other Race	0.76	0.176	0.507–1.132
White	1.15	0.040	1.006–1.308
Rheumatologic variables			
ANCA vasculitis	165.08	< 0.001	128.380–212.278
APLS	17.67	< 0.001	10.973–28.469
Cryoglobulinemia	24.80	< 0.001	6.199–99.250
DM and PM	4.69	0.029	1.172–18.808
EGPA	51.41	< 0.001	16.516–160.045
Goodpasture	191.64	< 0.001	127.716–287.566
MCTD	8.99	0.002	2.245–35.984
Rheumatoid arthritis	2.31	< 0.001	1.715–3.105
Sarcoidosis	5.10	< 0.001	3.004–8.659
Sjogren's	3.28	< 0.001	2.035–5.300
SLE	8.20	< 0.001	6.091–11.028
Systemic sclerosis	3.70	0.009	1.385–9.871

ANCA, antineutrophil cytoplasmic antibody; *APLS*, antiphospholipid antibody syndrome; *BMT*, bone marrow transplant; *C.I.*, confidence interval; *CMV*, cytomegalovirus; *DAH*, diffuse alveolar hemorrhage; *DM*, dermatomyositis; *EGPA*, eosinophilic granulomatosis with polyangiitis; *GVHD*, graft versus host disease; *HIV*, Human immune deficiency virus; *IBD*, inflammatory bowel disease; *ITP*, immune-mediated thrombocytopenia; *MDS*, myelodysplastic syndrome; *MCTD*, mixed connective tissue disease; *PM*, polymyositis; *SLE*, systemic lupus

Table 3 Multivariate analysis, DAH associations

	Odds ratio	*p*-value	95% *C.I*
Non-rheumatologic variables			
Age	1.01	0.001	1.002–1.008
Anticoagulants	20.31	< 0.001	14.822–27.834
Aortic valvular disease	1.32	0.127	0.924–1.882
Aspergillosis	9.45	< 0.001	5.172–17.283
Bacterial pneumonia	8.26	< 0.001	6.742–10.126
Chemotherapy	2.18	< 0.001	1.548–3.082
CMV	14.44	< 0.001	4.114–50.714
Endocarditis	1.01	0.984	0.367–2.781
Female	0.60	< 0.001	0.525–0.679
GVHD	0.65	0.572	0.150–2.854
Hemophilia	7.47	0.004	1.883–29.639
Heroin	3.87	0.177	0.543–27.594
History of BMT	4.73	0.001	1.857–12.065
ITP	2.47	0.018	1.169–5.230
Leptospirosis	54.44	0.004	3.696–801.724
MDS	2.63	0.002	1.419–4.892
Multiple myeloma	1.11	0.797	0.493–2.516
Myeloid leukemia	1.91	0.078	0.930–3.936
Pulmonary embolus	3.23	< 0.001	2.241–4.645
Pulmonary hemosiderosis	177.97	< 0.001	49.625–638.274
African American	0.68	0.007	0.511–0.898
Hispanic	0.63	0.003	0.466–0.859
Other Race	0.59	0.027	0.375–0.941
White	0.75	0.019	0.596–0.955
Rheumatologic variables			
ANCA vasculitis	72.56	< 0.001	50.607–104.043
APLS	6.51	< 0.001	3.734–11.366
Cryoglobulinemia	6.37	0.139	0.548–73.949
DM and PM	2.57	0.194	0.619–10.706
EGPA	7.13	0.004	1.886–26.926
Goodpasture	30.58	< 0.001	16.360–57.176
MCTD	3.23	0.138	0.686–15.166
Rheumatoid arthritis	1.60	0.004	1.158–2.212
Sarcoidosis	3.99	< 0.001	2.300–6.926
Sjogren's	1.66	0.073	0.953–2.899
SLE	5.82	< 0.001	3.993–8.481
Systemic sclerosis	1.99	0.190	0.710–5.602

ANCA, antineutrophil cytoplasmic antibody; *APLS*, Antiphospholipid antibody syndrome; *BMT*, bone marrow transplant; *C.I.*, confidence interval; *CMV*, cytomegalovirus; *DAH*, diffuse alveolar hemorrhage; *DM*, dermatomyositis; *EGPA*, eosinophilic granulomatosis with polyangiitis; *GVHD*, graft versus host disease; *ITP*, immune-mediated thrombocytopenia; *MDS*, myelodysplastic syndrome; *MCTD*, mixed connective tissue disease; *PM*, polymyositis; *SLE*, systemic lupus

respiratory failure. Other indicators included serum CRP and high number of neutrophils in the bronchoalveolar lavage. The AAV phenotype (GPA vs MPA) or the ANCA type did not influence the outcomes [3]. Unfortunately, relapses in AAV-associated DAH are high, ranging from 22 to 58% [7, 29–32].

In our study, SLE patients were nearly six times more likely to be hospitalized with DAH. The reported incidence of DAH in SLE is 3.7% [17] and it carries a high mortality. Older studies reported a mortality of 91% [33] but this seems to have improved over the years. A systematic review study performed by Christina Ednalino et al. [34] showed that survival rates improved from 25% in the 1980s to 67% over the last decade. Increased use of cyclophosphamide appears to be associated with better survival (71% vs 49%). Although the use of plasmapheresis increased from 0 to 68% in the last two decades, it did not seem to account for the better survival rates.

In our study, patients with APLS were nearly seven times more likely to be hospitalized with DAH. Prior studies have shown that incidence of DAH in APLS ranged from 0.7 to 2% [15, 35], whereas the incidence is higher in catastrophic APLS at nearly 12% [36]. APLS can affect the lung in a variety of ways. The inherent hypercoagulability of this disease can cause thrombotic complications like PE, microthrombosis, and resultant infarction [12], but it can also result in adult respiratory distress syndrome (ARDS) [11], likely from pulmonary capillaritis. There have been case reports of perivascular immune-complex deposition leading to pulmonary capillaritis and resultant DAH [37]. Cartin-Ceba et al. conducted a retrospective review of primary APLS-associated DAH at the Mayo clinic over a 15-year period. In total, 3 of the 5 people who underwent lung biopsy showed capillaritis and DAH with no evidence of thrombosis which in part supports a non-thrombotic mechanism for DAH [13]. Case series show that almost all APLS patients presenting with DAH require immunosuppression with corticosteroids in addition to other agents such as cyclophosphamide or rituximab[11, 13].

In our study, we found that patients with Goodpasture's disease were 30 times more likely to be hospitalized with DAH. Goodpasture's disease is an autoimmune disease with both renal and pulmonary manifestations. This is due to expression of the auto-antigen on the basement membrane of glomerular and alveolar capillaries [38]. DAH can occur in Goodpasture's without renal involvement in about 10% patients [39]. The prognosis for Goodpasture's disease has improved over the last several years due to the aggressive management with plasmapheresis, glucocorticoids, and immunosuppressants. One study showed improved survival rates, exceeding 80% at 5 years with less than 30% of them requiring chronic dialysis [40].

Despite frequent pulmonary involvement in sarcoidosis, literature review revealed only rare reports of DAH in this disease [41]. Unexplainably, our study showed sarcoidosis patients were nearly four times more likely to be hospitalized with DAH.

Several non-rheumatic conditions reported in the literature to produce DAH [8, 10] [18–22] were confirmed in our study including idiopathic pulmonary hemosiderosis, infections, use of anti-coagulants, hemophilias, BMT, and PE.

This study was aimed to obtain the descriptive characteristics of patients hospitalized with DAH and quantify the association of rheumatic diseases with DAH. One of the main strengths of our study is that it leveraged a nationwide dataset to provide a large sample size. This is the first such study to report a comprehensive estimate of in-hospital incidence and mortality of DAH. The findings in our study support prior case series and case reports showing a strong association of rheumatic diseases with DAH. An additional strength is that we utilized a comprehensive list of DAH risk factors from the literature to build our multivariate model.

Limitations

The study also has some limitations. First, the study relies solely on coding without clinical details pertaining to the hospitalization. Second, most ICD-10 billing codes do not grade disease severity or duration. Thus, it is difficult to discern if underlying disease severity or duration resulted in DAH. Third, NIS does not contain data on individual patients but rather shows data on total hospitalizations. Multiple hospitalizations of the same individual for DAH could not be separated. Fourth, smoking was not included in our multivariable regression model. Smoking can cause hemoptysis and could possibly be misdiagnosed as diffuse alveolar hemorrhage. Also, the smoking ICD-10 code is underutilized in US hospital admissions. And finally, NIS lacks data from outpatient setting, medications utilized, and radiological data.

Conclusion

Our study represents the largest sample to date to assess the incidence, mortality, and disease associations of DAH. The mean age of patients admitted with DAH was 61.8 years; a majority of patients were white (71.7%), majority of them were males (57.8%), and the average LOS was 10.6 days. Nearly 1 out of 4 suffered in-hospital mortality. Numerous rheumatic diseases were associated with inpatient DAH including AAV, APLS, EGPA, Goodpasture's, RA, sarcoidosis, and SLE. A non-rheumatic condition, pulmonary hemosiderosis, showed the strongest association with inpatient DAH. With this knowledge, physicians might better recognize DAH in the early stages and hopefully improve outcomes. Further research is required to identify the factors that are resulting in such high mortality of DAH.

Author contribution Author contributions in accordance with the ICMJE four authorship criteria are as follows:

(1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: Soumyasri Kambhatla, MD; Augustine Manadan, MD; Sharath Vipparthy, MD

(2) Drafting the work or revising it critically for important intellectual content: Soumyasri Kambhatla, MD; Augustine Manadan, MD; Sharath Vipparthy, MD

(3) Final approval of the version to be published: Soumyasri Kambhatla, MD; Augustine Manadan, MD; Sharath Vipparthy, MD

(4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: Soumyasri Kambhatla, MD; Augustine Manadan, MD; Sharath Vipparthy, MD

Compliance with ethical standards

Disclosures None.

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