Monaldi Archives for Chest Disease

Monaldi Archives for Chest Disease 2025; 95:3203
doi: 10.4081/monaldi.2024.3203

Diffuse alveolar hemorrhage: a retrospective study from a tertiary care center

Sanchit Mohan, Rohit Kumar, Pranav Ish, Rajnish Kaushik, Tanmaya Talukdar, Neeraj Gupta, Nitesh Gupta

Department of Pulmonary Medicine, VMMC & Safdarjung Hospital, New Delhi, India

Abstract

Diffuse alveolar hemorrhage (DAH) is characterized by a syndrome of alveolar bleeding, a fall in hemoglobin, and respiratory failure. It can occur because of various immunologic and non-immunologic conditions. The etiology of DAH is important, as treatment varies with the etiology. This retrospective observational study evaluates the diverse etiologies, time to diagnosis from symptom onset, management strategies, and outcome of DAH in a span of 12 months at our tertiary care center. A total of 8 patients were identified with 8 different etiologies. 6/8 (75%) patients had immunologic causes, and 2/8 (25%) had non-immunologic causes of DAH. 6/8 (75%) patients were females, the mean time to DAH diagnosis was 4.25 months from symptom onset, 6/8 (75%) patients improved, and 2/8 (25%) died due to complications. It is necessary to differentiate between the etiologies of DAH and establish an early diagnosis to plan management and improve outcomes.

Key words: pulmonary hemorrhage, alveolar hemorrhage, hemoptysis, bronchoscopy, pulmonary-renal syndromes.

Correspondence to: Nitesh Gupta, Department of Pulmonary Medicine, room number 612, super speciality block, VMMC & Safdarjung Hospital, New Delhi, 110029, India. E-mail: niteshgupta2107@gmail.com

Introduction

Diffuse alveolar hemorrhage (DAH) is characterized by bleeding in the alveoli of the lungs, resulting in the accumulation of blood within the lung parenchyma, leading to potentially life-threatening respiratory compromise. It is associated with a spectrum of diverse etiologies, including autoimmune diseases, vasculitis, infectious agents, cardiac causes, and drugs [1].

The most common conditions associated with DAH include anti-glomerular basement membrane antibodies (anti-GBM), anti-neutrophil cytoplasm antibody (ANCA) related vasculitis, systemic lupus erythematosus (SLE), and, rarely, anti-phospholipid antibody syndrome (APLA), idiopathic pulmonary hemosiderosis (IPH), and other collagen vascular diseases may also be found [2]. Among ANCA-associated vasculitis, granulomatosis with polyangiitis (GPA) is the common cause of DAH, followed by microscopic polyangiitis (MPA) and eosinophilic GPA (EGPA) [3].

Patients with DAH typically present with symptoms such as cough, hemoptysis, dyspnea, hypoxemia with new pulmonary infiltrate on chest radiology, and anemia. Although the presentation may vary, diagnosis often involves a combination of clinical assessment, laboratory tests, imaging studies, bronchoscopy, and sometimes lung biopsy to confirm the presence of alveolar hemorrhage [4]. DAH is a life-threatening condition with a poor prognosis; about 20-50% of hospital mortality has been reported [2]. Hence, rapid diagnosis and early initiation of treatment are necessary to prevent mortality.

Treatment includes immunosuppressive therapy, including systemic steroids and steroid-sparing agents. These may be harmful in patients where the cause of DAH is due to infection; therefore, the infection must be ruled out before starting immunosuppressive therapy [2].

This 1-year study explores the diverse etiologies, clinical presentation, time to diagnosis from symptom onset, management strategies, and outcome of DAH. By examining individual cases, we aim to shed light on the varied causes, diagnostic challenges, and treatment approaches encountered in the management of DAH.

Materials and Methods

This was a retrospective observational study analyzing medical records of patients admitted to the Department of Pulmonary Critical Care and Sleep, at a tertiary care center between April 2023 to March 2024 (12 months).

Inclusion criteria

All patients who were admitted to the Department of Pulmonary, Critical Care and Sleep at a tertiary care center for suspected DAH.

Exclusion criteria

Patients who were repeatedly admitted for DAH with the same etiology. Patients with hemorrhage due to bronchial etiology. Patients who were already on treatment for DAH before the initiation of this study.

Criteria to define DAH: compatible clinical picture of hemoptysis/anemia, pulmonary infiltrates on chest radiograph, and bronchoalveolar lavage (BAL) fluid either showing progressive hemorrhagic returns on serial aliquots or ≥20% hemosiderin-laden macrophages on cytological examination [2]. The STROBE guidelines for observational studies were used for reporting (Figure 1).

Results

A total of 1080 patients were admitted to the Department of Pulmonary, Critical Care and Sleep, out of which 120 had suspected DAH, 100 had an endobronchial cause of hemoptysis and were excluded a total of 20 cases were diagnosed as DAH. 12/20 patients had recurrent admission, hence 8 patients were considered in the final evaluation.

The mean age of presentation was 39.87 years. 6/8 (75%) of patients in our study were female. Anemia was present in all patients (100%) at the time of presentation. 6/8 (75%) patients presented with hemoptysis. The mean time for diagnosis of DAH was 4.25 months from the symptom onset (15 days to 12 months). The predominant high-resolution computed tomography (HRCT) finding was ground glass opacities (GGO) followed by consolidation; cavitation was seen in one patient. 4/8 (50%) patients presented with acute kidney injury, explained by raised creatinine and urea. 4/8 (50%) of patients had glomerulonephritis at the time of presentation, explained by the presence of dysmorphic red blood cells (RBCs) in urine.

Histopathological diagnosis on trans-bronchial lung biopsy (TBLB) was achieved in 6/8 (75%) patients; 4/6 (66.66%) patients had capillaritis, and 2/6 (33.33%) patients had bland hemorrhage of varied etiologies. 6/8 (75%) patients had an immune cause of DAH, like SLE, ANCA-associated, APLA-associated, and anti-GBM-associated DAH, whereas 2/8 (25%) patients had a non-immune cause, like IPH and drug-induced. 6/8 (75%) patients improved and are in follow-up, and 2/8 (25%) patients died due to infection (Figures 2 and 3). Both patients who died had an immune-mediated cause of DAH. The clinical profile of all 8 cases is presented in Table 1.

Discussion

DAH associated with hemoptysis should be differentiated from other causes of hemoptysis, like infections, bronchiectasis, and neoplasm [5]. DAH is classified into immune and non-immune; immune causes of DAH are associated with capillaritis, whereas non-immune causes have bland hemorrhage on histopathology [5]. DAH associated with capillaritis is characterized by destruction of alveolar capillaries and neutrophilic infiltration, fibrinoid necrosis of the alveolar tissue, and capillary's perivascular interstitium [5]. ANCA-associated vasculitis, SLE, anti-GBM disease, collagen vascular disease, and post-lung transplantation (acute rejection) cause immune-mediated DAH, whereas DAH associated with bland hemorrhage occurs due to leakage of RBCs into the alveoli without destruction or inflammation of alveolar capillaries, venules, or arterioles.[5] It occurs due to IPH and drug-induced.

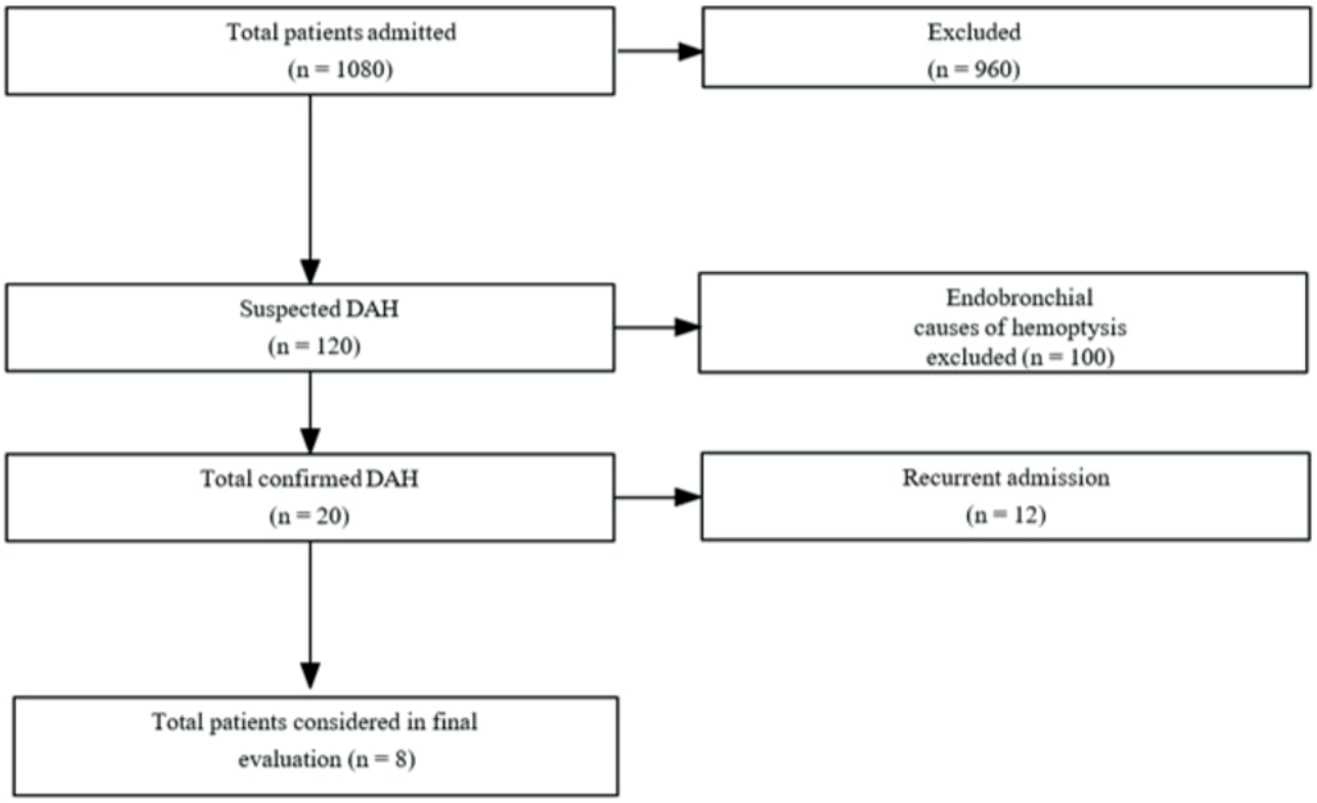

Figure 1. Flow of patient selection. DAH, diffuse alveolar hemorrhage.

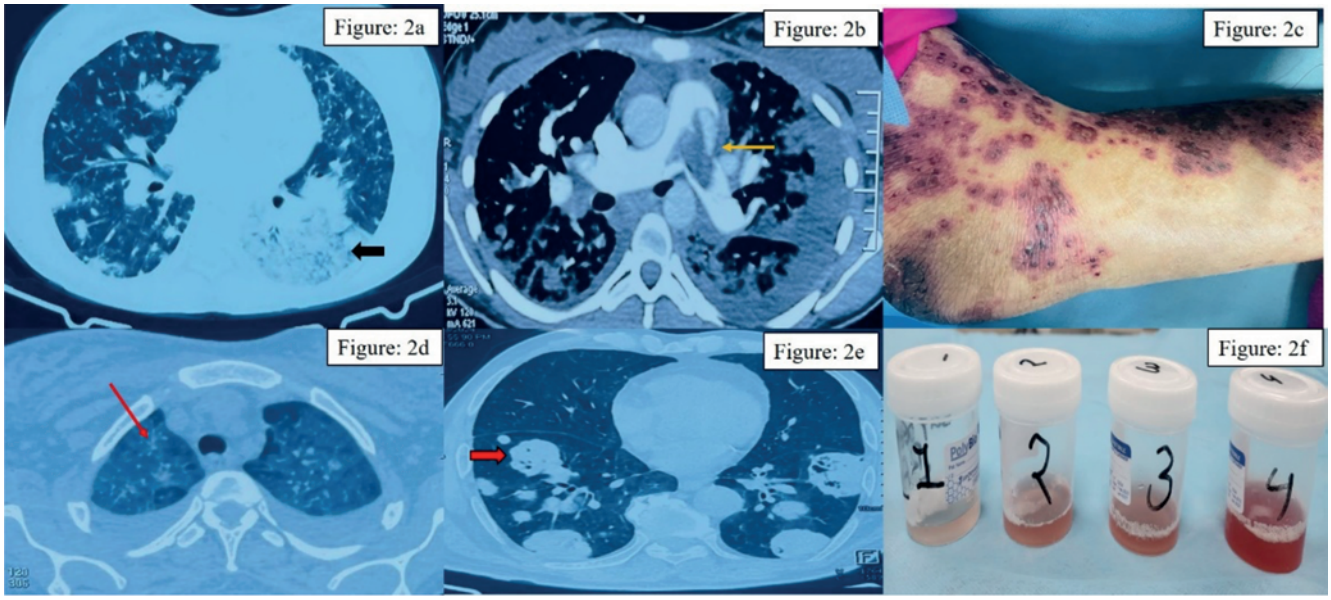

Figure 2. a) High-resolution computed tomography (HRCT) thorax showing left lower lobe consolidation (black thick arrow) with ground glass opacities (GGO) nodule in right middle and lower lobe; b) (thin orange arrow) CT pulmonary angiography showing saddle thrombus in main pulmonary artery; c) purpura on right upper limb; d) HRCT showing GGO in bilateral upper lobe (red thin arrow); e) HRCT showing cavitating masses in lower lobe (red thick arrow); f) sequential BAL showing hemorrhagic returns.

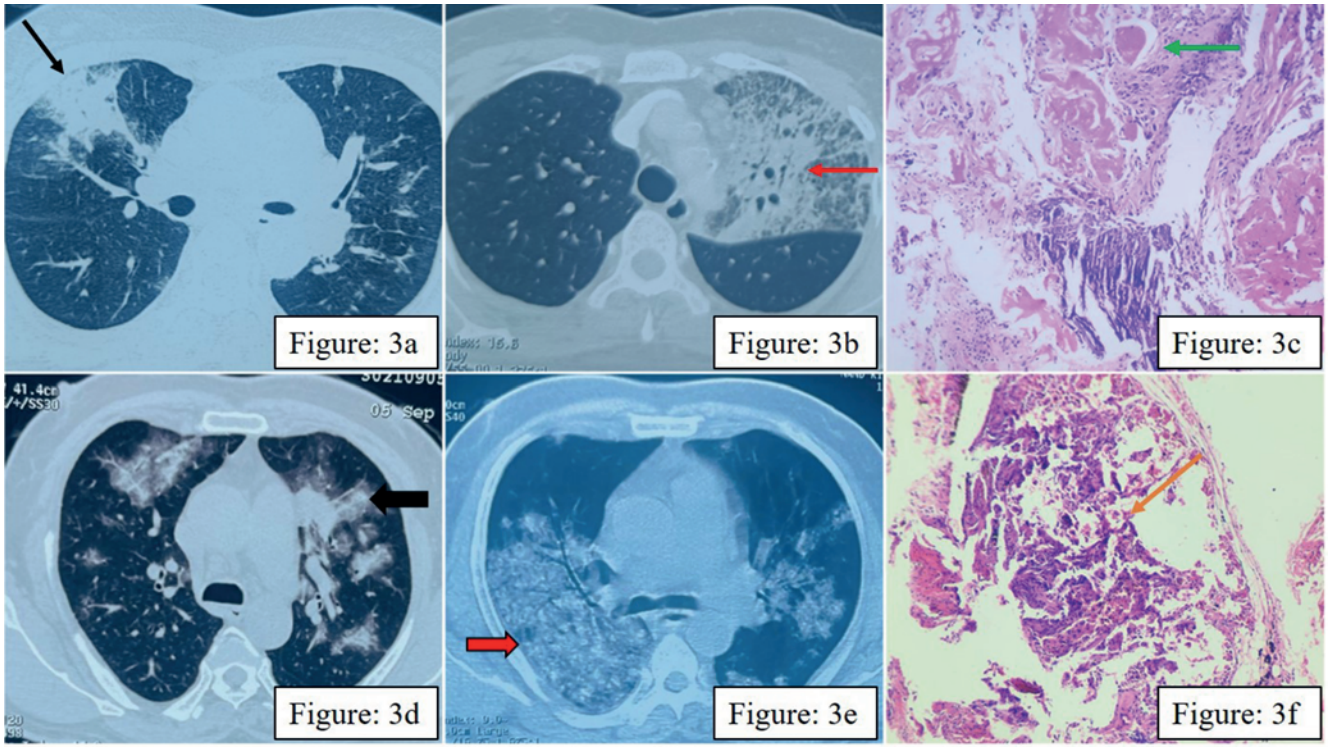

Figure 3. a) High-resolution computed tomography (HRCT) showing right upper lobe consolidation (black thin arrow); b) HRCT showing left upper lobe consolidation of same patient after 6 months (red thin arrow); c) bland hemorrhage (eosin and hematoxylin stain original magnification 10×); d) HRCT showing bilateral upper lobe consolidation left>right (black thick arrow); e) HRCT showing bilateral consolidation right>left of same patient 2 years back; f) histopathology of trans-bronchial lung biopsy showing neutrophilic inflammation suggestive of capillaritis (eosin and hematoxylin stain, original magnification 10×).

SLE and anti-GBM can induce DAH with capillaritis and bland pulmonary hemorrhage [5]. One-third of the patients with DAH do not have hemoptysis as a presenting complaint. Our findings are in concordance with a case series by De Prost *et al*. [6]; one-fourth of patients (25%) in this study did not present with hemoptysis. Anemia is usually present in patients with DAH; our findings concord with the study by Alexandre *et al*. [7], who showed 19/24 (79%) of patients with DAH present with anemia.

Chest radiology in the present study showed GGO, consolidation, and cavitation. 8/8 (100%) patients had one or the other radiological abnormalities; however, in a study by Albelda *et al*. [8], 20 to 50% of cases of DAH can have normal radiology in the acute stage. These findings indicate that a high index of suspicion is required in the absence of radiological abnormalities and normal hemoglobin levels.

In their study, Kumasaka *et al*. described a hyperdense consolidation sign characterized by a consolidation density higher than that of the aorta [9]. The specificity of the hyperdense consolidation sign was 100% in distinguishing DAH from other alveolar diseases. In the present study, 4/8 (50%) patients had hyperdense consolidation on chest radiology. A hemorrhagic BAL that does not clear after sequential aliquots indicates DAH. While BAL can diagnose DAH, it cannot identify its underlying cause, but it can help rule out infectious and neoplastic causes [1].

In the present study, BAL diagnosed DAH in all cases, and infections were excluded in all patients. Systemic vasculitis is most commonly associated with DAH among immune causes [7].

In the present study, 3/8 (37.5%) patients had DAH secondary to ANCA-associated vasculitis, and 6/8 (75%) patients had an immune-related DAH. In a study by Quadrelli *et al.* [3], 75% of patients of DAH due to immune mechanisms were secondary to ANCA-associated vasculitis, GPA being the most common among them. Connective tissue diseases (CTD) accounted for the rest. In the present study, only 1 patient had CTD-related DAH.

Anti-phospholipid antibody syndrome (APS) is an autoimmune disease characterized by thromboembolic events with obstetric morbidity along with anti-phospholipid antibodies. Pulmonary thromboembolism and pulmonary artery hypertension are frequent pulmonary complications [10]. Rarely has DAH been found to be associated with APS [11]. In the present study, 1/8 (12.5%) of patients had APS as a cause of DAH, and APS was diagnosed after the diagnosis of DAH. In a case series by Deane *et al*., 9/79 (11%) patients had DAH as the initial presentation of APS [12].

On the other hand, in studies by Scheiman Elazary *et al*. and Cartin-Ceba *et al*., in 18 and 13 patients of APS, the median time to DAH onset was 5.9 and 5.8 years, respectively, after the diagnosis of APS [13,14]. APS patients in the present study had capillaritis on histopathology; however, the largest case series on APS-associated

Table 1. Clinical profile of all 8 cases.

Case	Age (years)/ sex	Hemoglobin (g/dL)	Creatinine (mg/dL)	Hemoptysis	Urine dysmorphic RBC	HRCT findings	TBLB	Time to diagnosis	Diagnosis	Treatment/ Outcome
1	75/M	9.6	0.8	Yes	Negative	GGO in RLL	Bland hemorrhage	6 months	Drug-induced	Stop clopidogrel/ improved
2	17/F	9	2.0	No	Negative	Left consolidation, cardiomegaly, bilateral pleural effusion; saddle thrombus in MPA	Capillaritis	40 days	SLE	Enoxaparin, steroids, rituximab/ succumbed to infection
3	50/F	7.0	0.6	Yes	Positive	Bilateral pleural effusion; right > left GGOs	Capillaritis	15 days	EGPA with skin manifestation (purpura)	Steroids, rituximab/ improved
4	30/F	6.7	0.7	No	Negative	Bilateral upper lobe consolidation, surrounding GGO	Capillaritis	1 month	Anti-phospholipid antibody syndrome	Anticoagulation, steroids, rituximab, apixaban/improved
5	20/F	7.5	1.8	No	Positive	Cavitating lesions in bilateral lung fields	Capillaritis	3 months	GPA	Steroids, rituximab/ improved
6	35/F	6.8	0.6	Yes	Negative	Left upper lobe consolidation	Bland hemorrhage	12 months	Idiopathic pulmonary hemosiderosis	Prednisolone/ improved
7	66/M	11.0	2.6	Yes	Positive	Bilateral GGO and consolidation	Not done	2 months	Life-threatening microscopic polyangiitis	Steroids, rituximab/ improved
8	26/F	7.0	2.2	Yes	Positive	Bilateral GGO predominantly in lower lobes	Not done	8 months	Goodpasture syndrome	Could not be treated/ succumbed to infection

F, female; M, male; HRCT, high-resolution computed tomography; TBLB, trans-bronchial lung biopsy; GGO, ground glass opacities; RLL, right lower lobe; MPA, microscopic polyangiitis; SLE, systemic lupus erythematosus; EGPA, eosinophilic granulomatosis with polyangiitis.

DAH by Cartin-Ceba *et al*. showed that only 3/18 (16%) patients had capillaritis [14].

Treatment of immune DAH includes pulse methylprednisolone (MPS) followed by oral prednisolone 1 mg/kg (maximum 60 mg) for 1 week, followed by tapering along with other immunosuppressive therapy, *i.e.*, cyclophosphamide or rituximab [3,14]. 6/8 (75%) patients in the present study had an immune mediated cause of DAH; 5/6 (83%) were treated with pulse MPS 1 g/day for 3 days along with intravenous rituximab 375 mg/m^2 weekly or 4 weeks followed by maintenance 1 gm rituximab 6 monthly; and 1/6 (17%) patient could not be treated as patient succumbed to infection before treatment could be initiated.

Non-immune-mediated causes of DAH include infections (dengue, leptospirosis, malaria, *Staphylococcus aureus*, *Mycoplasma*, *Legionella*, cytomegalovirus, adenovirus, invasive aspergillosis, *Strongyloides*), heart diseases (mitral stenosis, left ventricular dysfunction, left atrial myxoma), drug-induced (amiodarone, antiplatelets, cannabis smoking), and IPH [7]. In the present study, 2 patients had a bland hemorrhage on histopathology, one of whom was associated with a drug (clopidogrel), which improved after stopping the culprit drug.

The other was associated with IPH, which improved with tab. prednisolone 0.75mg/kg and iron supplements. BAL was done in both cases, and infections were ruled out. There was no evidence of cardiac abnormality on echocardiography. A case report published by Onuk *et al.* has shown the occurrence of DAH on the second day of clopidogrel use; however, in the present study, it occurred after 3 years of use [15]. Soriano *et al.* published a case report in 2021 describing clopidogrel as a culprit of DAH after 6 months of its use [16]. In both cases published in the literature, histopathology suggested bland hemorrhage; stopping the culprit agent has led to the resolution of symptoms.

IPH may be present with celiac disease known as Lane-Hamilton syndrome [17], where the patient presented with DAH and on further evaluation, he was diagnosed with celiac disease and was treated with a gluten-free diet; however, in the present case, there was no history of diarrhea and serum anti tissue transglutaminase antibody titers were 1 U/mL (Normal <3 U/mL), hence the diagnosis of isolated IPH was made.

Treatment of acute DAH without respiratory failure requiring invasive mechanical ventilation (IMV) is oral prednisolone 0.5 mg/kg to 0.75 mg/kg for 4-8 weeks followed by tapering; however, treatment in patients requiring IMV is pulse dose of MPS (500-2000 mg/day for 3-5 days), followed by oral prednisone 0.5-1 mg/kg/day [18].

A case report published by Iwasaki *et al.* diagnosed isolated IPH without TBLB and treated with MPS 1 gm/day for 3 days followed by MPS 80 mg/day for 9 days, and the patient was successfully weaned off from non-invasive ventilation on the 10th day [19]. 6/8 (75%) patients improved from the current study; one died of complications of immunosuppressive therapy, and the other died due to complications of the disease. Immunosuppressive therapy remains the mainstay of treatment in patients with immune-mediated DAH. Reported mortality in DAH is 20-50% [20]. DAH secondary to SLE has shown 50% mortality [20]. Our findings are in line with those by de Prost *et al*. [5], who stated 25% mortality in patients with DAH. De Prost *et al*. reported 17.9% mortality with immune DAH [21].

Clinical outcomes and prognosis

Despite the varied etiologies and treatment approaches, outcomes differed among the cases. While some patients achieved resolution of symptoms and disease control with treatment, others faced complications such as infections, leading to adverse outcomes. The heterogeneity in outcomes underscores the importance of early recognition, prompt intervention, and individualized management strategies based on underlying pathology.

Limitations

Our study is limited by its retrospective nature and the small sample size. The diversity in etiologies highlights the complex nature of DAH, necessitating a multidisciplinary approach involving pulmonologists, rheumatologists, and intensivists for optimal management.

Conclusions

In conclusion, our study underscores the diverse etiologies and clinical presentations associated with DAH. Timely recognition of underlying conditions and tailored therapeutic interventions can help improve outcomes in patients presenting with this challenging clinical entity.

References

1. Lara AR, Schwarz MI. Diffuse alveolar hemorrhage. Chest 2010;137:1164-71.
2. Gallagher H, Kwan JT, Jayne DR. Pulmonary renal syndrome: a 4-year, single-center experience. Am J Kidney Dis 2002; 39:42-7.
3. Quadrelli S, Dubinsky D, Solis M, et al. Immune diffuse alveolar hemorrhage: clinical presentation and outcome. Respir Med 2017;129:59-62.
4. Collard HR, Schwarz MI. Diffuse alveolar hemorrhage. Clin Chest Med 2004;25:583-92.
5. Park MS. Diffuse alveolar hemorrhage. Tuberc Respir Dis 2013; 74:151-62.
6. de Prost N, Parrot A, Picard C, et al. Diffuse alveolar haemorrhage: factors associated with in-hospital and long-term mortality. Eur Respir J 2010;35:1303-11.
7. Alexandre AT, Vale A, Gomes T. Diffuse alveolar hemorrhage: How relevant is etiology? Sarcoidosis Vasc Diffuse Lung Dis 2019;36:47-52.
8. Albelda SM, Gefter WB, Epstein DM, Miller WT. Diffuse pulmonary hemorrhage: a review and classification. Radiology 1985;154:289-97.
9. Kumasaka S, Kumasaka Y, Jingu A, Tsushima Y. Diagnostic value of "hyperdense consolidation sign" as a characteristic new computed tomography sign of diffuse alveolar hemorrhage. Sci Rep 2022;12:21143.
10. Garcia D, Erkan D. Diagnosis and management of the antiphospholipid syndrome. N Engl J Med 2018;378:2010-21.
11. Yachoui R, Sehgal R, Amlani B, Goldberg JW. Antiphospholipid antibodies-associated diffuse alveolar hemorrhage. Semin Arthritis Rheum 2015;44:652-7.
12. Deane KD, West SG. Antiphospholipid antibodies as a cause of pulmonary capillaritis and diffuse alveolar hemorrhage: a case series and literature review. Semin Arthritis Rheum 2005; 35:154-65.
13. Scheiman Elazary A, Cohen MJ, Aamar S, et al. Pulmonary hemorrhage in antiphospholipid antibody syndrome. J Rheumatol 2012;39:1628-31.
14. Cartin-Ceba R, Peikert T, Ashrani A, et al. Primary antiphospho-

lipid syndrome–associated diffuse alveolar hemorrhage. Arthritis Care Res 2014;66:301-10.
15. Onuk T, İpek G, Karataş MB, et al. Diffuse alveolar hemorrhage after clopidogrel use. Balkan Med J 2016;33:719-20.
16. Soriano R, Al-Rawaf S, Diab K. Diffuse alveolar haemorrhage: a rare complication of clopidogrel use. BMJ Case Rep 2021;14:e244314.
17. Khilnani GC, Tiwari P, Goyal A, Singh L, Arora A, Guleria R. A rare case of pulmonary alveolar hemorrhage with cardiomyopathy. Chest 2018;142:463A.
18. Saha BK. Idiopathic pulmonary hemosiderosis: A state of the art review. Respir Med 2021;176:106234.
19. Iwasaki K, Matsuzawa Y, Wakabayashi H, et al Diffuse alveolar haemorrhage with suspected idiopathic pulmonary hemosiderosis and decrease in lung diffusing capacity and chronic respiratory failure BMJ Case Rep 2021;14:e242901.
20. Zamora MR, Warner ML, Tuder R, Schwarz MI. Diffuse alveolar hemorrhage and systemic lupus erythematosus: clinical presentation, histology, survival, and outcome. Medicine 1997; 76:192-202.
21. de Prost N, Parrot A, Cuquemelle E, et al. Diffuse alveolar hemorrhage in immunocompetent patients: etiologies and prognosis revisited. Respir Med 2021;106:1021-32.

Received: 13 September 2024; Accepted: 17 September 2024; Early view: 28 October 2024.

Contributions: Sanchit Mohan, Rohit Kumar, Pranav Ish, Rajnish Kaushik, Tanmaya Talukdar, Neeraj Gupta, Nitesh Gupta: literature search, planning, conduct, writing the original draft of manuscript, literature search, and editing; Nitesh Gupta, Rajnish Kaushik: involved in review and editing. All the authors have agreed with the submitted manuscript.

Conflict of interest: the authors declare that they have no conflicts of interest regarding the current study.

Ethics approval and consent to participate: no ethical clearance required.

Informed consent: written informed consent taken.

Patient consent for publication: obtained.

Availability of data and materials: the clinical data and the study materials are available from the corresponding author on reasonable request.

Publisher's note: all claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.