

# Diagnosis and Transvascular Embolization for Ruptured Pulmonary Arteriovenous Malformations: Outcomes from a 12 Years' Retrospective Study

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## Research

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# Abstract

**Background** Pulmonary arteriovenous malformations (PAVMs) are rare, and the life-threatening hemorrhagic complications, including hemoptysis and hemothorax, are extremely uncommon. However, the management of large series of ruptured PAVMs has not been described in recent years.

**Methods** We retrospectively reviewed patients who developed ruptured PAVMs between January 2008 and December 2019. We assessed the clinical and imaging data to summarize the incidence and characteristics of ruptured PAVMs, and outcomes following embolization with coils or plugs. A paired-sample t-test analysis, Kaplan–Meier method and the simple linear regression were accessed, as appropriate.

**Results** Eighteen (5.49%) of 328 patients diagnosed with PAVMs developed hemorrhagic complications. Twelve of these 18 patients were clinically diagnosed with hereditary hemorrhagic telangiectasia (HHT) (incidence, 66.67%). Eleven of 18 patients were female. Eight of the 11 females were diagnosed with HHT. Twenty-eight lesions were detected, and the simple type was more common (82.14%) than the complex type. 89.29% of lesions were located in the peripheral lung. Computed tomography angiography (CTA) showed indirect signs to predict the ruptured PAVMs in cases of hemothorax. Technical success of embolotherapy was achieved in all cases. Two days after treatment, pulmonary function was significantly improved and bleeding was controlled ( $P < 0.05$ ), and no patients showed recanalization of PAVMs. Two patients in the hemoptysis group died of other reasons during follow-up and the mean follow-up time was  $3.22 \pm 2.52$  years (range, 7 months to 10 years). The hemorrhage volume was linearly associated with the diameter of the afferent arteries in the ruptured lesions.

**Conclusions** CTA was able to diagnose ruptured PAVMs, and embolotherapy led to successful resolution of symptoms in all 18 patients who had ruptured PAVMs. Ruptured PAVMs must be considered when managing patients with hemothorax or hemoptysis, especially female patients with HHT.

## Background

A pulmonary arteriovenous malformation (PAVM) is an abnormal vascular malformation that occurs in the lung [1]. It represents an abnormal direct communication between the pulmonary arteries and veins through a thin-walled aneurysm. It results in the blood bypassing the normal capillary bed and generating an intrapulmonary right-to-left shunt [2; 3]. Most PAVMs are closely associated with hereditary hemorrhagic telangiectasia (HHT), which exhibits autosomal dominant inheritance [3–6]. The incidence of PAVMs is low worldwide [7–9]. Females are more often affected than males, and a unilateral or single lesion is more common than bilateral or multiple lesions [10–12].

Most PAVMs do not cause obvious clinical symptoms [13]. A few PAVMs may cause hypoxemia, cyanosis, or dyspnea because of the continuous presence of a right-to-left shunt [6; 14]. Other complications such as stroke and brain abscess formation also occur in a few cases because of the deficient filtration function in the pulmonary capillary bed [6; 15; 16].

In the fully developed PAVM, the sac of the PAVM is markedly dilated and convoluted, and has excessive layers of smooth muscle without elastic fibers. The vessel wall of the sac is fragile and cannot be constricted. Once the sac of PAVM ruptures, high blood flow from the afferent artery will result in massive hemorrhage in the thorax. Therefore, although hemoptysis and hemothorax rarely occur following rupture of PAVMs, they are the most life-threatening complications if they are not diagnosed and treated in a timely manner [8; 17–20].

Endovascular management of PAVMs has been the first-line treatment in lieu of surgery over the last few decades [6; 21; 22]. A ruptured PAVM is a life-threatening situation, but this complication is exceedingly rare and its treatment has only been described in isolated case reports in recent years [23].

The present study was performed to retrospectively evaluate cases of ruptured PAVMs treated at our institution and to highlight their incidence, diagnosis, and treatment.

## Methods

This present study is a retrospective observational study. It has been approved by the institutional review board of our hospital, and the informed consent can be waived because of its retrospective nature.

### Characteristics of patients and PAVMs

This study involved 328 patients who were diagnosed with PAVMs based on multi-detector computed tomography (CT) or multi-detector CT angiography (CTA) in our hospital between January 2008 and December 2019. Among these 328 subjects, patients who presented to the emergency department with symptoms of hemoptysis or hemothorax and received embolotherapy were analyzed in detail for purposes of this study (Fig. 1). A clinical diagnosis of HHT was made according to the Curacao criteria: 1) spontaneous, recurrent epistaxis; 2) multiple telangiectasias, especially in the superficial mucosa; 3) visceral lesions such as in gastrointestinal mucosa, liver, and brain; 4) first-degree relatives with HHT. Clinical diagnosis of HHT was confirmed when at least two of the criteria were met (two for probable HHT, three or more for definite HHT) [18].

The classification of PAVMs has been described in previous studies [3; 6]. In the present study, PAVMs were classified as either simple and complex according to their imaging manifestations (on CTA or pulmonary angiography) [9; 24]. A simple PAVM was defined as the presence of one segmental afferent artery, and a complex PAVM was defined as the presence of two or more segmental afferent arteries. The PAVMs were also divided into three groups according to their location and quantity: solitary PAVMs, unilateral multiple PAVMs, and bilateral multiple PAVMs.

### Treatment process

Emergency transvascular embolization was performed by three experienced interventional radiologists with 10, 12, and 15 years of experience, respectively. A pre-procedural plan involving emergency CTA was available for all patients, and the diameter of the afferent arteries was measured for all PAVMs, especially

those suspected to have ruptured. Embolotherapy was performed from a transfemoral vein approach with placement of embolization coils (Cook Medical, Bloomington, IN, USA) or plugs (AGA Medical, Plymouth, MN, USA) in the distal aspect of all PAVMs according to the standard technique previously described [25-27].

The oxygen pressure, oxygen saturation, hemoglobin concentration, leukocyte count, and clinical symptoms were respectively recorded before and 2 days after the procedure. Antibiotics and oxygen therapy were given after embolization in all patients. Closed thoracic drainage was performed in patients with hemothorax when necessary.

## **Follow-up**

The procedure was considered successful if continuous pulmonary hemorrhage was absent after the treatment process. After treatment, all patients were followed up as directed. CTA was performed in the first month after treatment, and a chest CT scan was performed at the next follow-up if the CTA at the first follow-up showed no evidence of PAVM recurrence. Follow-up was terminated if symptoms recurred or the patient died.

## **Statistical analysis**

All results are expressed as mean  $\pm$  standard deviation, and the statistical analysis was performed using SPSS version 19.0 (IBM Corp., Armonk, NY, USA). The survival time was analyzed with Kaplan–Meier curves and the log-rank test. A paired-sample t-test was applied to assess the statistical significance of differences. The impact of the afferent arterial diameter on the hemorrhage volume was examined by simple linear regression and variable correlation scatter plots. For all analyses, a P-value of  $< 0.05$  was considered statistically significant.

## **Results**

The study population consisted of 18 patients with ruptured PAVMs out of the 328 patients overall who were diagnosed with PAVMs from January 2008 to December 2019.

### **Clinical features**

The patients' basic characteristics are shown in Table 1. Thirteen patients had hemoptysis and five had hemothorax. The incidence of these hemorrhagic complications caused by acute rupture of PAVMs was 5.49% (18/328). Eleven (61.11%) of all 18 patients were female (eight with hemoptysis and three with hemothorax). A clinical diagnosis of definite or probable HHT was made in 12 patients. One patient in the hemoptysis group had hepatic cirrhosis, and this lesion was considered to be the only case of acquired PAVM in our study. Before treatment, all patients had a low oxygen pressure, oxygen saturation, and hemoglobin concentration without serious inflammation. Twelve of the 18 patients (66.7%) had no underlying diseases.

Table 1  
Baseline characteristics of patients with acute ruptured PAVMs

	Hemoptysis	Hemothorax
<b>Subjects n</b>	13	5
<b>Age in years</b>	48.69 ± 15.84	53.4 ± 23.70
<b>Female/Male</b>	8/5	3/2
<b>HHT (F/M)</b>		
definite	7 (4/3)	3 (2/1)
probable	2 (2/0)	0
<b>Oxygen Saturation (%)</b>	95.21 ± 2.76	90.74 ± 6.88
<b>Oxygen Pressure (mmHg)</b>	76.28 ± 13.02	61.3 ± 10.23
<b>Hemoglobin (g/L)</b>	102.38 ± 24.59	100.68 ± 10.94
<b>Leukocyte (10<sup>9</sup>/L)</b>	8.03 ± 3.48	5.31 ± 1.18
<b>Concomitant Diseases</b>		
tuberculosis	1	0
bronchiectasis	2	1
chronic bronchitis	0	2
none	10	2
Data are presented as n or mean ± standard deviation. PAVM: pulmonary arteriovenous malformation; HHT: hereditary hemorrhagic telangiectasia		

### Characteristics of PAVMs

Six lesions were detected in the hemothorax group: a solitary lesion in four patients and unilateral multiple lesions in two patients. All lesions were the simple type (Table 2). Twenty-two lesions were detected in the hemoptysis group: a solitary PAVM in seven patients, unilateral multiple PAVMs in one patient, and bilateral multiple PAVMs in five patients. Seventeen of the 22 lesions were the simple type, and the rest were the complex type.

Table 2  
Characteristics of detected PAVMs

Patient	Number	Type (S/C)	Location distribution	Largest diameter of afferent artery (mm)
Hemothorax				
1	unilateral multiple (2)	S	RLL A6 subpleural	6.4
		S	RLL A7 subpleural <sup>#</sup>	5.8
2	solitary	S	LLL A9 subpleural <sup>#</sup>	5.6
3	solitary	S	RLL A10 subpleural <sup>#</sup>	4.5
4	solitary	S	LLL A9 subpleural <sup>#</sup>	6.1
5	solitary	S	LLL A9 subpleural <sup>#</sup>	8.2
Hemoptysis				
1	solitary	C	RLL A9 + 10 subpleural <sup>#</sup>	4.4
2	solitary	S	RLLA9 subpleural <sup>#</sup>	3.2
3	solitary	C	LUL A1 + 2 subpleural <sup>#</sup>	5.3
4	bilateral multiple (4)	S	RML A4 + 5 subpleural	4.4
		S	RLL A10 outer 1/3 <sup>#</sup>	3.7
		C	LUL A1 + 2 outer 1/3	5.9
		S	LLL A7 + 8 inner	3
5	solitary	S	LUL A5 subpleural <sup>#</sup>	3.1
6	bilateral multiple (2)	S	RLL A9 subpleural	3.9
		S	LLL A10 outer 1/3 <sup>#</sup>	6.4

PAVM: pulmonary arteriovenous malformation; S: simple type; C: complex type; RUL: right upper lobe; RML: right middle lobe; RLL: right lower lobe; LUL: left upper lobe; LLL: left lower lobe; A: artery of pulmonary segment; <sup>#</sup>ruptured lesions.

Patient	Number	Type (S/C)	Location distribution	Largest diameter of afferent artery (mm)
7	solitary	S	RML A5 subpleural <sup>#</sup>	4.2
8	unilateral multiple (3)	S	LUL A3 subpleural	3.2
		S	LUL A5 inner	3
		S	LLL A7 + 8 subpleural <sup>#</sup>	4.9
9	solitary	S	RML A5 outer 1/3 <sup>#</sup>	5
10	unilateral multiple (2)	S	RML A5 subpleural	3.1
		S	RLL A9 outer 1/3 <sup>#</sup>	4.2
11	bilateral multiple (2)	C	RUL A3 inner	6.5
		S	LUL A5 subpleural <sup>#</sup>	5.7
12	bilateral multiple (2)	C	RLL A10 outer 1/3	5.2
		S	LLL A10 subpleural <sup>#</sup>	7.1
13	solitary	S	LLL A6 subpleural <sup>#</sup>	3.8

PAVM: pulmonary arteriovenous malformation; S: simple type; C: complex type; RUL: right upper lobe; RML: right middle lobe; RLL: right lower lobe; LUL: left upper lobe; LLL: left lower lobe; A: artery of pulmonary segment; <sup>#</sup>ruptured lesions.

In the hemothorax group, all lesions were located in the subpleural areas. In the hemoptysis group, nineteen of the 22 (86.36%) of the detected PAVMs were pulmonary peripheral lesions, and 15 (68.18%) were located at the middle or lower lobes (Table 2). Additionally, in the hemothorax group, ruptured PAVMs presented as an “anomalous bulge” on CTA, and this characteristic manifested as the “double shadow sign” on angiography (Fig. 2). We observed this manifestation in all five lesions (Fig. 3).

### Treatment process

Eighteen patients were treated for 28 lesions, and the success rate of embolotherapy was 100%. Four lesions (two lesions in the hemothorax group and two in the hemoptysis group) were embolized with

plugs, and the remaining lesions were embolized with coils (Fig 4). Closed thoracic drainage was performed in four patients with hemothorax. No patients developed complications during the peri-procedural period.

There were significant differences in the oxygen pressure, oxygen saturation, hemoglobin concentration, and leukocyte count before and after therapy in both the hemoptysis group ( $P=0.004$ ,  $P<0.001$ ,  $P=0.009$ , and  $P=0.048$ , respectively) and hemothorax group ( $P<0.001$ ,  $P<0.02$ ,  $P=0.003$ , and  $P<0.001$ , respectively) (Fig 5A, B). The mean post-procedure hospital stay was  $3.92\pm 1.50$  days in the hemoptysis group and  $6.40\pm 2.97$  days in the hemothorax group.

Three patients with hemoptysis had previously undergone one session of ineffective bronchial artery embolization (BAE) without pre-procedural CTA in other institutions. One patient with hemoptysis had undergone a session of ineffective BAE with a neglected PAVM in our institution (Fig 6). One patient with hemothorax was misdiagnosed as having lung cancer on non-contrast CT at another institution.

No patients had developed recurrence of symptoms by 1 week after therapy, and the mean follow-up time was  $3.22\pm 2.52$  years, ranging from 7 months to 10 years (Fig 5C). Two patients in the hemoptysis group died during follow-up. One patient with an acquired PAVM due to liver cirrhosis died of severe hepatic failure 8 months after embolotherapy. One patient died of heart failure 12 months after embolotherapy. The diameter of the afferent arteries in ruptured PAVMs had a significant linear correlation with the hemorrhage volume in all patients ( $P=0.029$ ) (Fig 5D). No patients showed recanalization of PAVMs at the first follow-up.

## Discussion

To the best of our knowledge, the present study is the largest series of ruptured PAVMs to date. In recent years, only isolated case reports have described this condition [8; 15–18; 20]. We identified 18 patients who developed pulmonary hemorrhage associated with ruptured PAVMs. The incidence of ruptured PAVMs was 5.49% in our study, which is similar to the incidence observed by Ference et al. (8%) [20]. Significantly more patients in our study than in the study by Ference et al. were diagnosed with hemoptysis as the first symptom. Thus, we consider that ruptured PAVMs are more likely to present with hemoptysis.

According to previous studies, the incidence of PAVMs increased to 0.038% as the use of CT became more widespread, and the use of this imaging modality is more common than previously thought [9]. In addition, CTA can clearly reveal afferent arteries, draining veins, and the sac of PAVMs. Therefore, we recommend the use of CTA to achieve a definitive diagnosis of PAVM before therapy [3; 6; 13].

In the present study, four patients in the hemoptysis group had undergone ineffective BAE, and one patient in the hemothorax group had been initially misdiagnosed with lung cancer. We believe that the cause of the misdiagnosis in these patients was the absence of a pre-procedural plan established by CTA. To our knowledge, no data are currently available to predict which PAVMs are most likely to rupture.

However, we have observed that ruptured PAVMs exhibited a regular pattern on imaging examinations. Most lesions were located at the peripheral area of lower lobes, especially in patients with acute hemothorax. Furthermore, ruptured PAVMs in the hemothorax group manifested as the “anomalous bulge sign” on CTA and “double shadow sign” on angiography, which were helpful for confirming rupture. Therefore, we consider that CTA is conducive to the detection of ruptured PAVMs, contributes to classification of the lesions, and directs the next step of treatment [28; 29]. Even for patients in unstable conditions, we strongly recommend performance of CTA after endotracheal intubation and airway protection prior to therapy.

In addition to the CTA findings, the patients’ clinical histories are also helpful. In our study, 12 of the 18 patients had HHT, and 58.33% of these 12 patients were female. Therefore, we consider that HHT, especially HHT in female patients, is a significant risk factor for the occurrence of PAVM rupture. This is in line with previous studies [3; 6; 30]. Furthermore, we found that one patient with HHT had a history of massive hemoptysis during pregnancy. We believe that pregnancy is also a potential risk factor for spontaneous rupture of PAVMs, as previous studies have described [6; 20]. Although the probability of spontaneous rupture of PAVMs is low, we strongly recommend that PAVM rupture must be considered when managing patients with hemothorax or hemoptysis, especially female patients with a clear family history of HHT [31–33].

Treatment of PAVMs includes surgical resection, endovascular embolization, and conservative medical treatment [21; 23; 28]. Patients with active massive hemorrhage have a high mortality rate during surgical resection because of hemorrhagic anemia, respiratory insufficiency, or unconsciousness. Therefore, we recommend emergency embolotherapy instead of thoracoscopic surgery for patients with ruptured PAVMs [21; 23]. In addition, a longer period of time is usually required to prepare for emergency thoracoscopic surgery, and the PAVM might re-rupture during that time. In contrast, emergency embolotherapy may be more convenient and easily repeatable, and it facilitates immediate and adequate hemostasis. In addition to its safety and effectiveness, embolotherapy involves the use of recent embolic devices and materials that do not significantly influence any special examinations, especially magnetic resonance imaging.

If multiple PAVMs are found during embolotherapy, we recommend embolization of all suitable PAVMs regardless of whether they have ruptured. Embolization of a ruptured PAVM might influence the pulmonary arterial pressure, and whether this can induce rupture of other PAVMs is unknown. In line with previous research, we recommend embolization of all PAVMs with feeding arteries  $\geq 3$  mm in diameter besides the ruptured PAVM [3; 6; 34; 35].

In the present study, we observed varying degrees of hemorrhagic anemia and respiratory insufficiency in all patients before embolotherapy, and an inflammatory reaction occurred 2 days after embolotherapy. Therefore, our experience indicates that post-procedural antibiotics and oxygen therapy are indispensable. These treatment measures vastly shorten the average duration of hospitalization by timely

adequate hemostasis combined with proper supportive treatment, thus assisting in the recovery of patients with ruptured PAVMs.

Our study did have some limitations. Because of the rare nature of ruptured PAVMs, our study was a relatively small, retrospective single-center analysis, although it was the largest to date to our knowledge. A family history of HHT was not confirmed in all 328 patients with PAVMs, and genetic tests for HHT were not available in all 18 patients enrolled in our study. We did not measure the pulmonary artery pressure before and after embolization under the emergency conditions in this study.

## **Conclusion**

This study revealed that CTA was able to diagnose ruptured PAVMs, and that embolotherapy led to successful resolution of symptoms in all patients who had ruptured PAVMs. This conclusion suggests that acute rupture of PAVMs must be considered when managing patients with hemothorax or hemoptysis, especially female patients with a clear family history of HHT. A pre-procedural plan involving CTA is essential before embolotherapy.

## **Abbreviations**

PAVMs: Pulmonary arteriovenous malformations; HHT: hereditary hemorrhagic telangiectasia; CTA: Computed tomography angiography; BAE: bronchial artery embolization

## **Declarations**

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### **Authors' contributions**

The conception of the study was done by XM, SJ and BJ. LLL and DY examined the hospital clinical statistics. All analysis was done by all authors. Majority of the paper was written by XM and BJ. XM, BJ and SJ were involved in revising the paper critically. All authors read and approved the final manuscript.

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### **Availability of data and materials**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

## Ethics approval and consent to participate

The research protocol was approved by the Ethics Committee of the Shanghai Pulmonary Hospital(K20-410). Informed consent can be waived after full discussion by the institutional review board.

## Consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

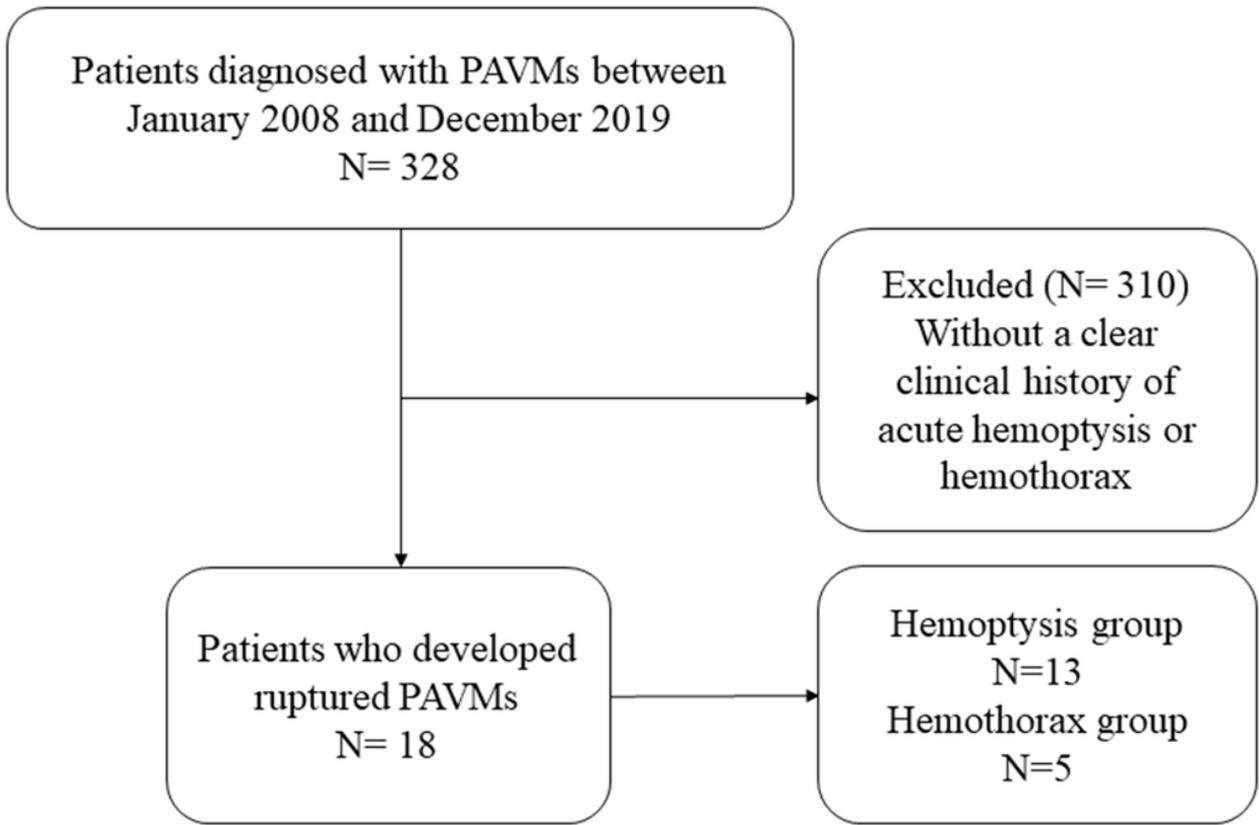
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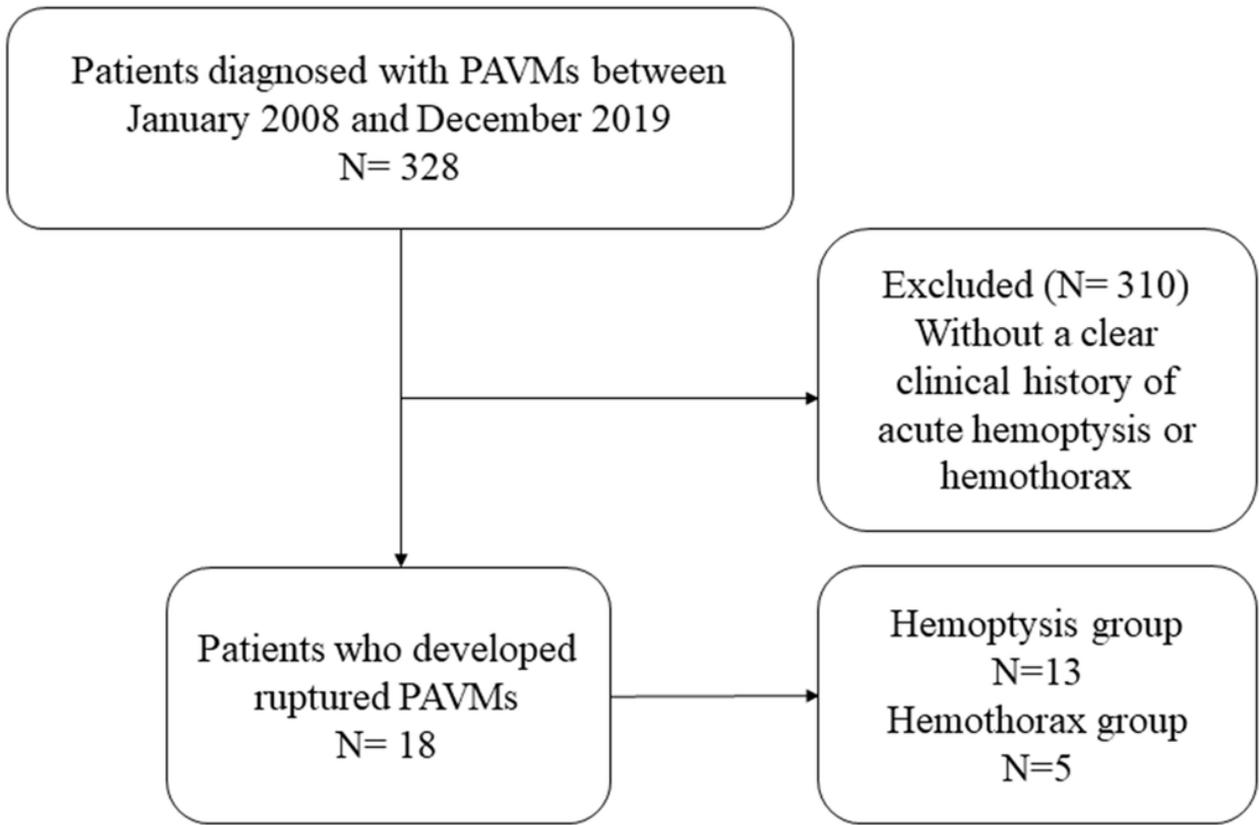
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## Figures



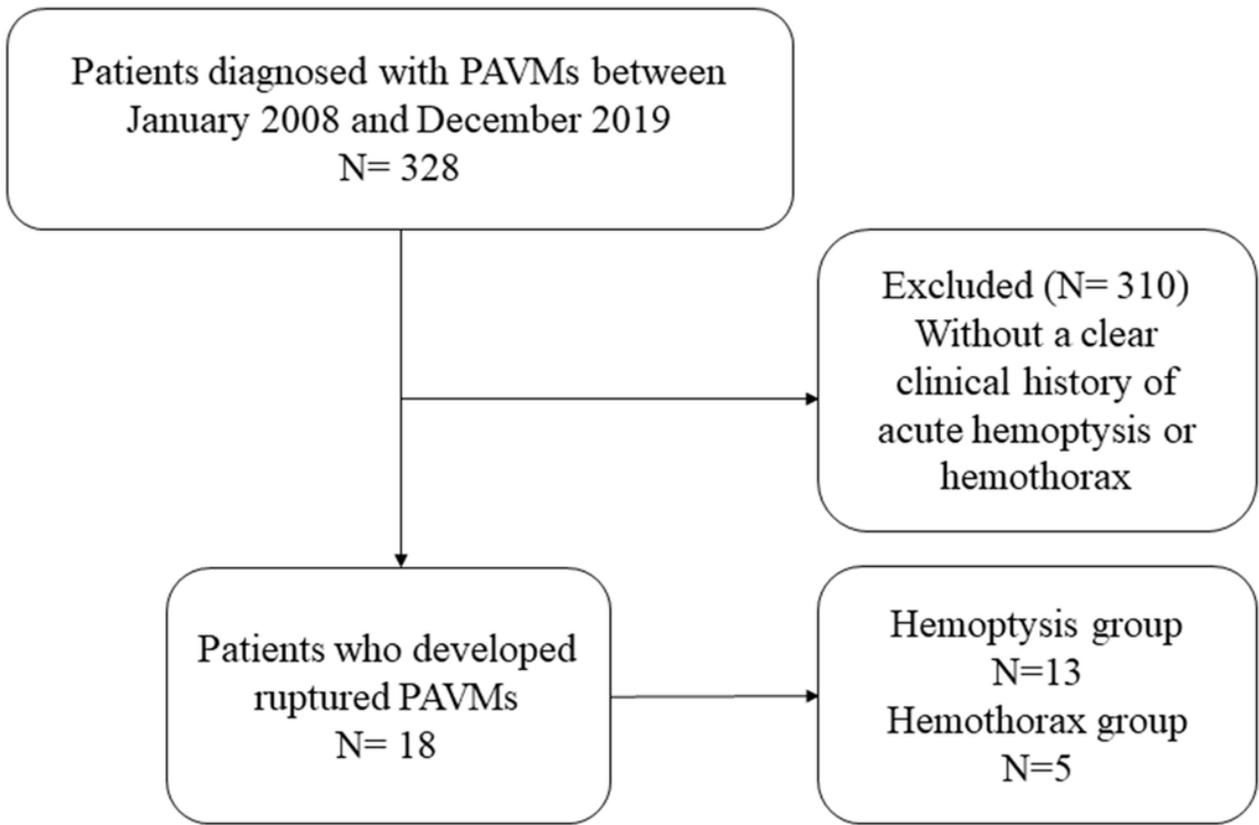
**Figure 1**

Flow diagram shows inclusion and exclusion criteria. PAVMs = Pulmonary arteriovenous malformations.



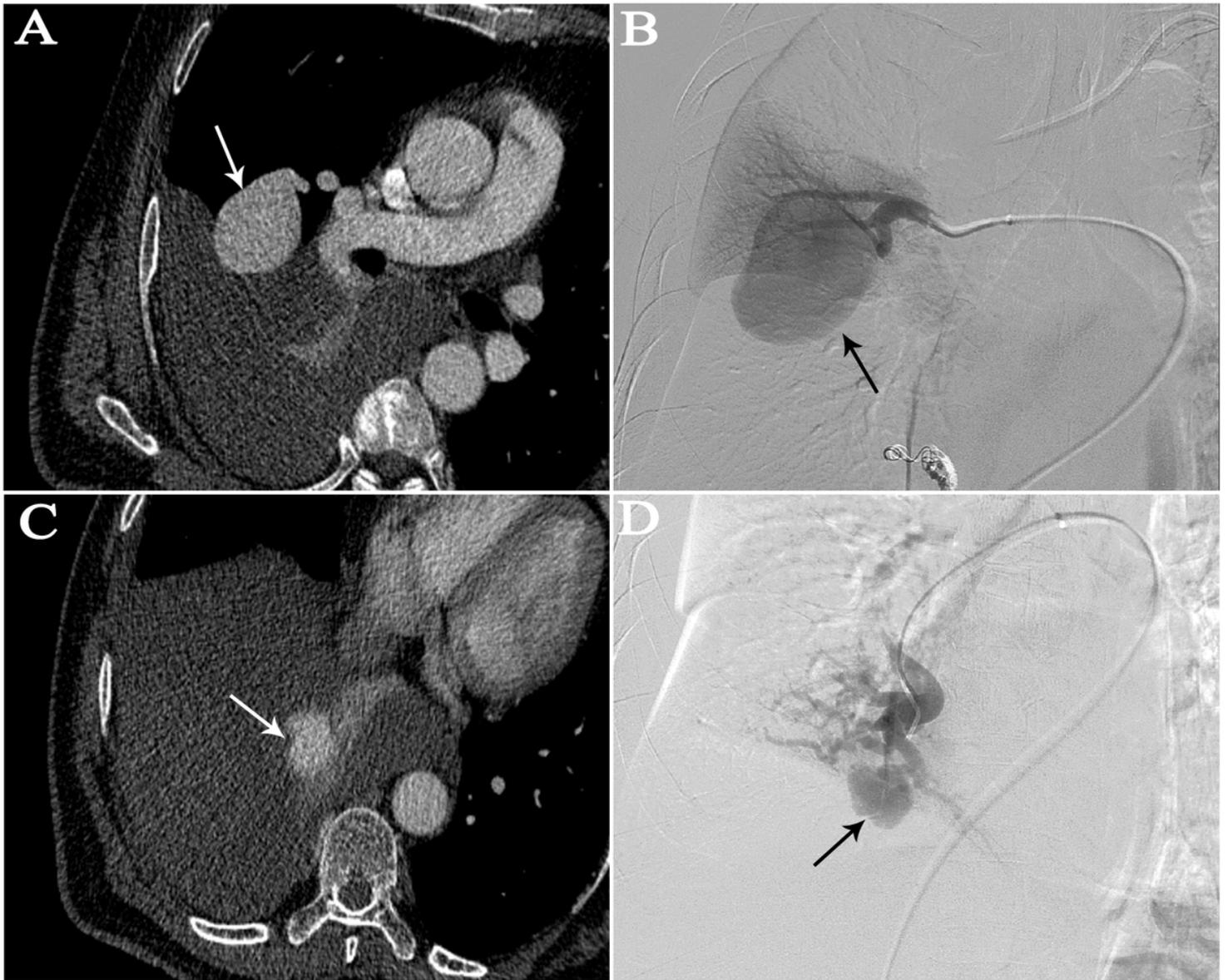
**Figure 1**

Flow diagram shows inclusion and exclusion criteria. PAVMs = Pulmonary arteriovenous malformations.



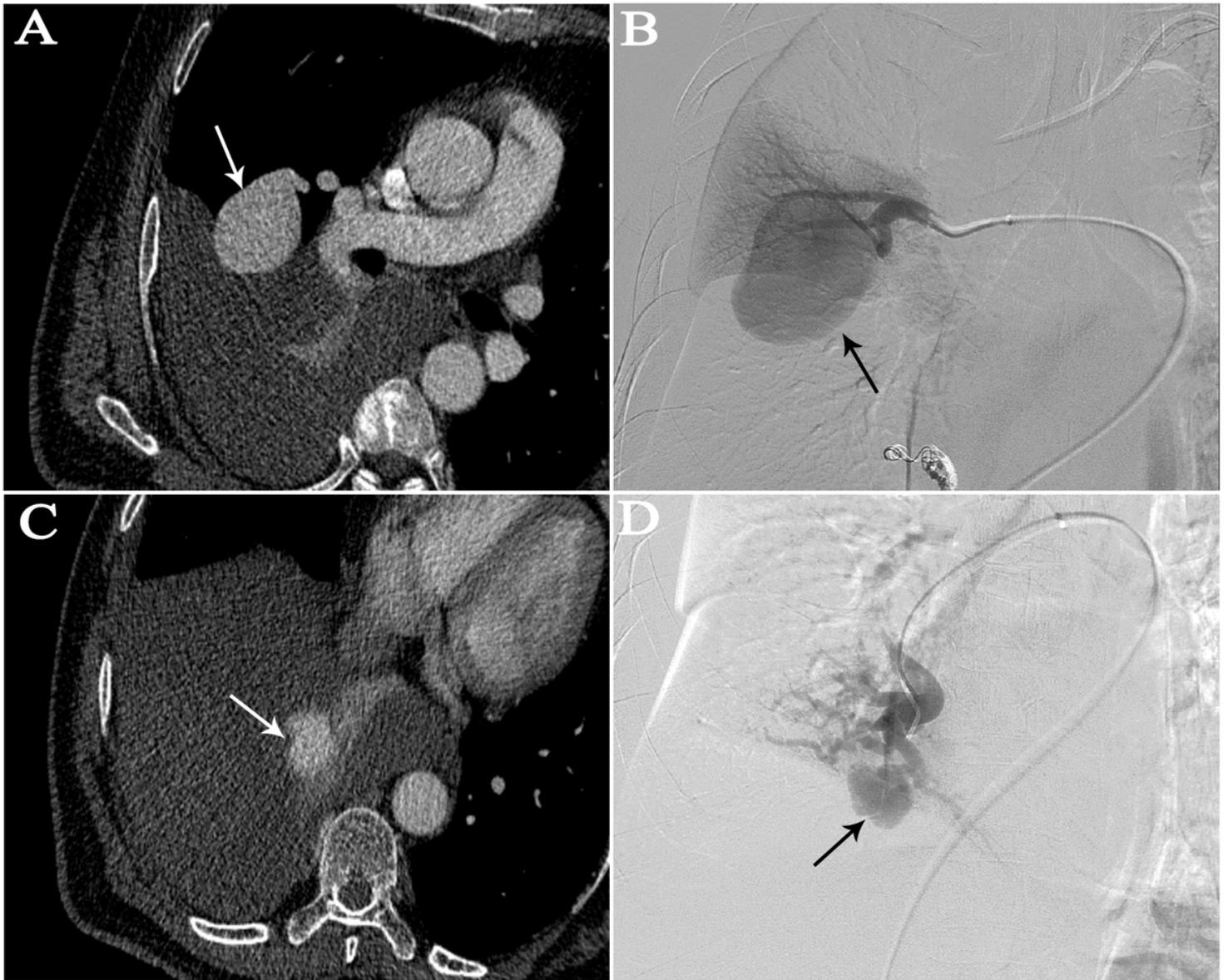
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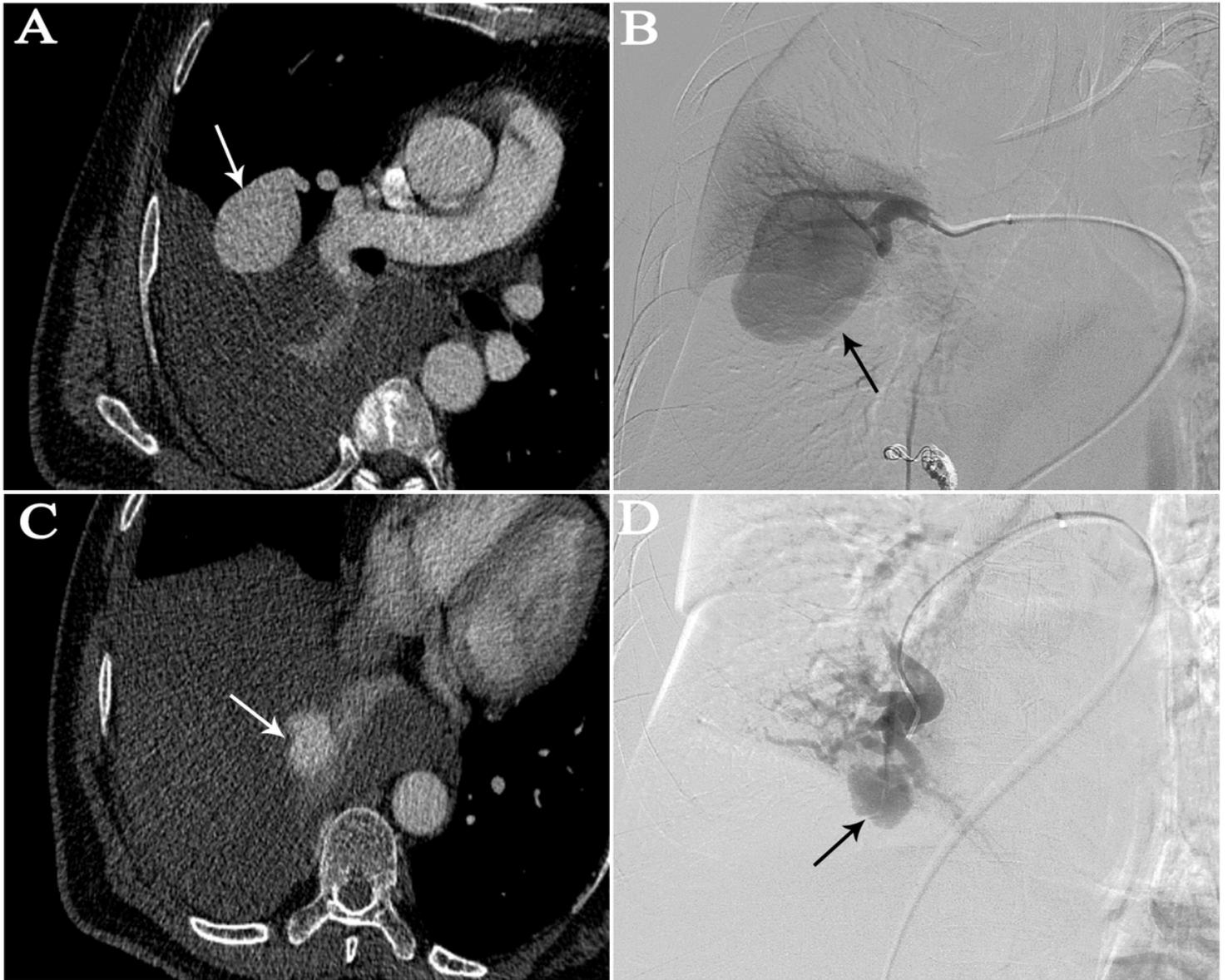
**Figure 2**

Unilateral multiple PAVMs were detected in a 52-year-old man with hemothorax. A, B, One smooth PAVM located in the interlobar pleural area was not considered to be ruptured based on its appearance on multi-detector CTA and pulmonary angiography (arrows). C, The lesion located in the subpleural area manifested as an “anomalous bulge” on CTA (arrow). D, This characteristic presented as the “double shadow sign” on angiography, as indicated by the arrow.



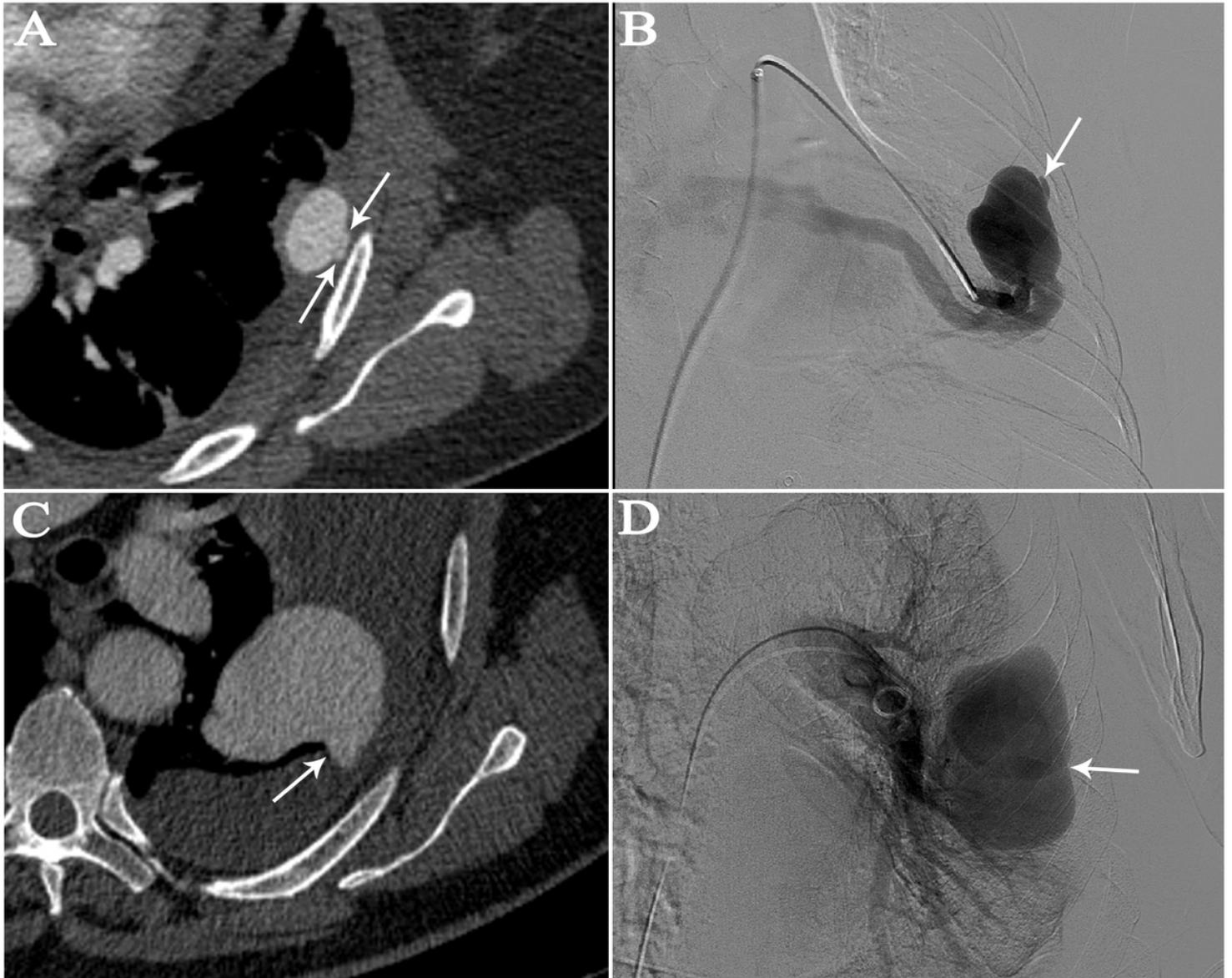
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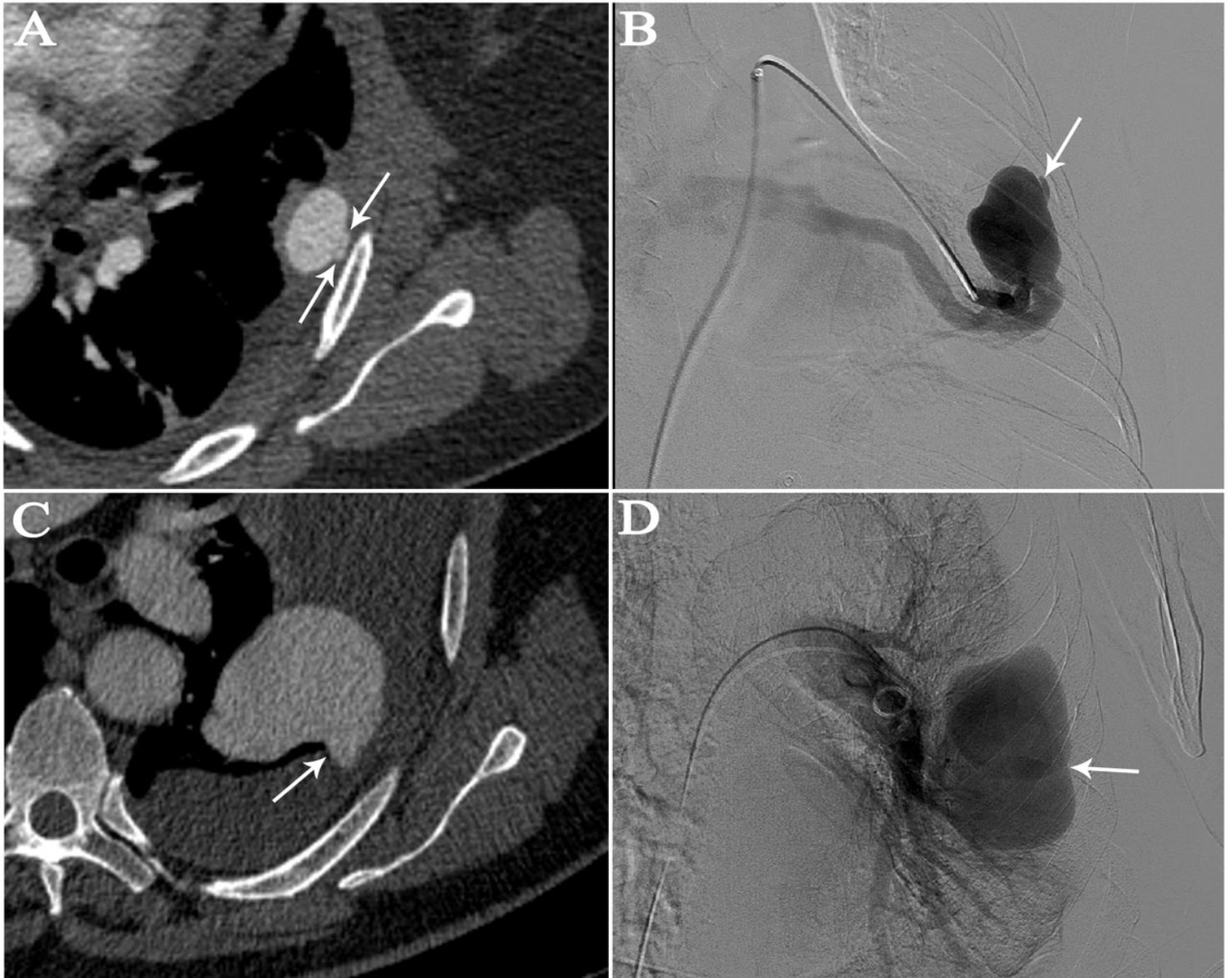
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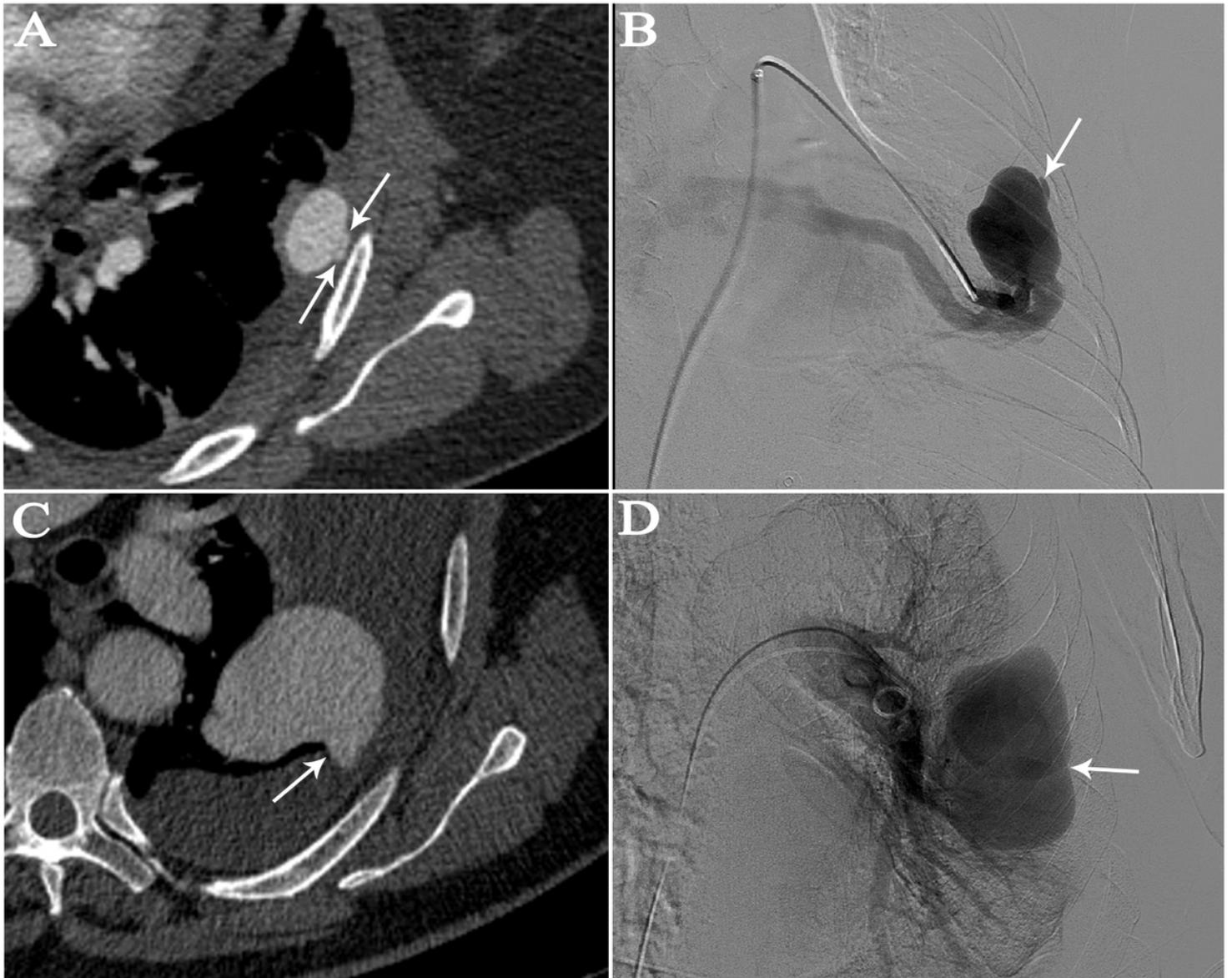
**Figure 3**

An “anomalous bulge” and the “double shadow sign” in A, B, a 47-year-old woman and C, D, a 72-year-old man in the hemothorax group. A, C, The ruptured PAVMs had a bulging surface near the subpleural area on CTA, as shown by the arrow. B, D, The bulging surface of the ruptured PAVMs manifested as the “double shadow sign” on angiography (arrow).



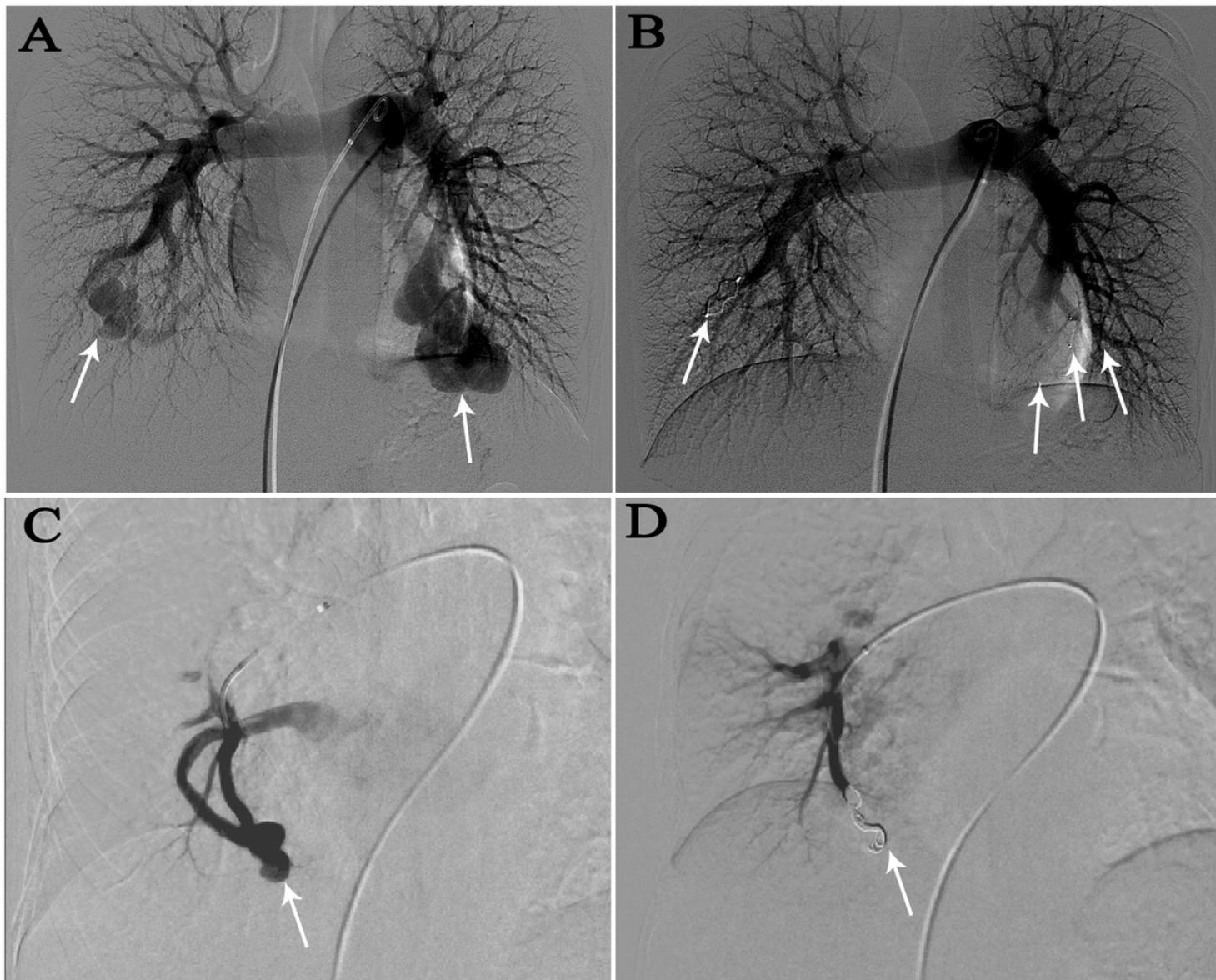
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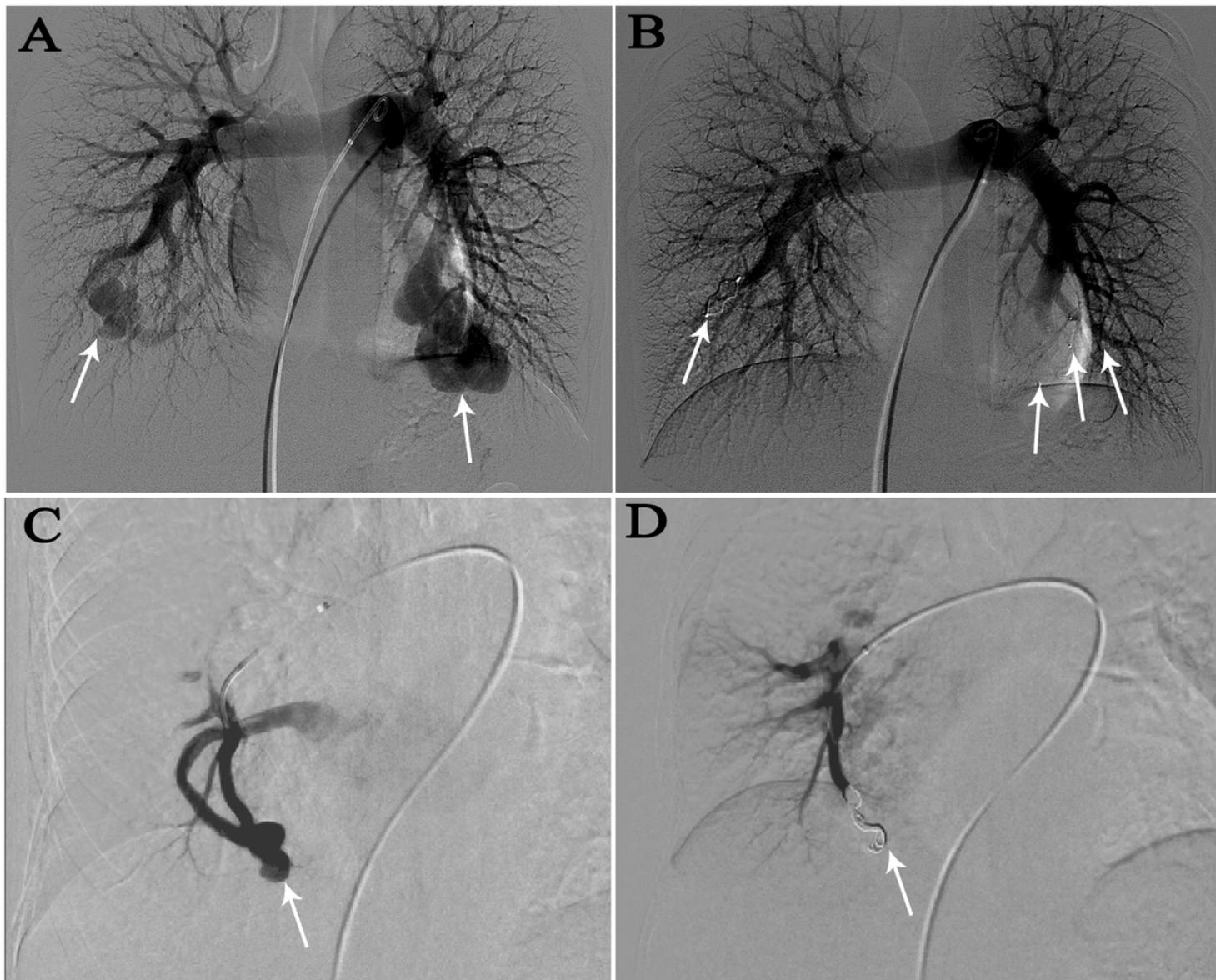
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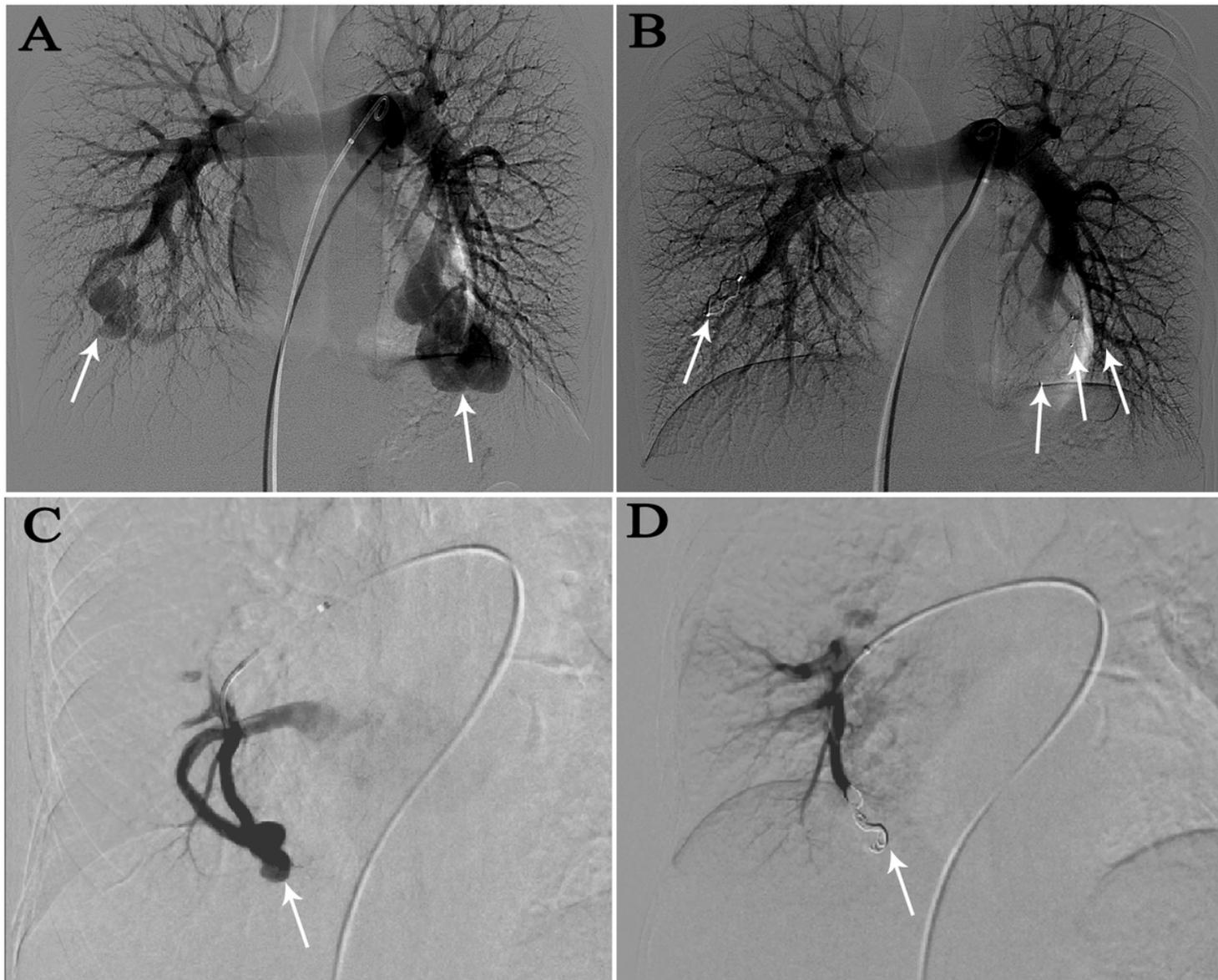
**Figure 4**

A, B, Pulmonary angiogram of a 17-year-old man with hemoptysis. A, Bilateral multiple PAVMs were detected in the lower lobe (arrows). B, Embolization was performed with four plugs (arrows). C, D, Pulmonary angiogram of a 67-year-old woman with hemoptysis. C, A solitary PAVM was detected in the right middle lobe (arrow). D, Embolization was performed with multiple coils (arrow).



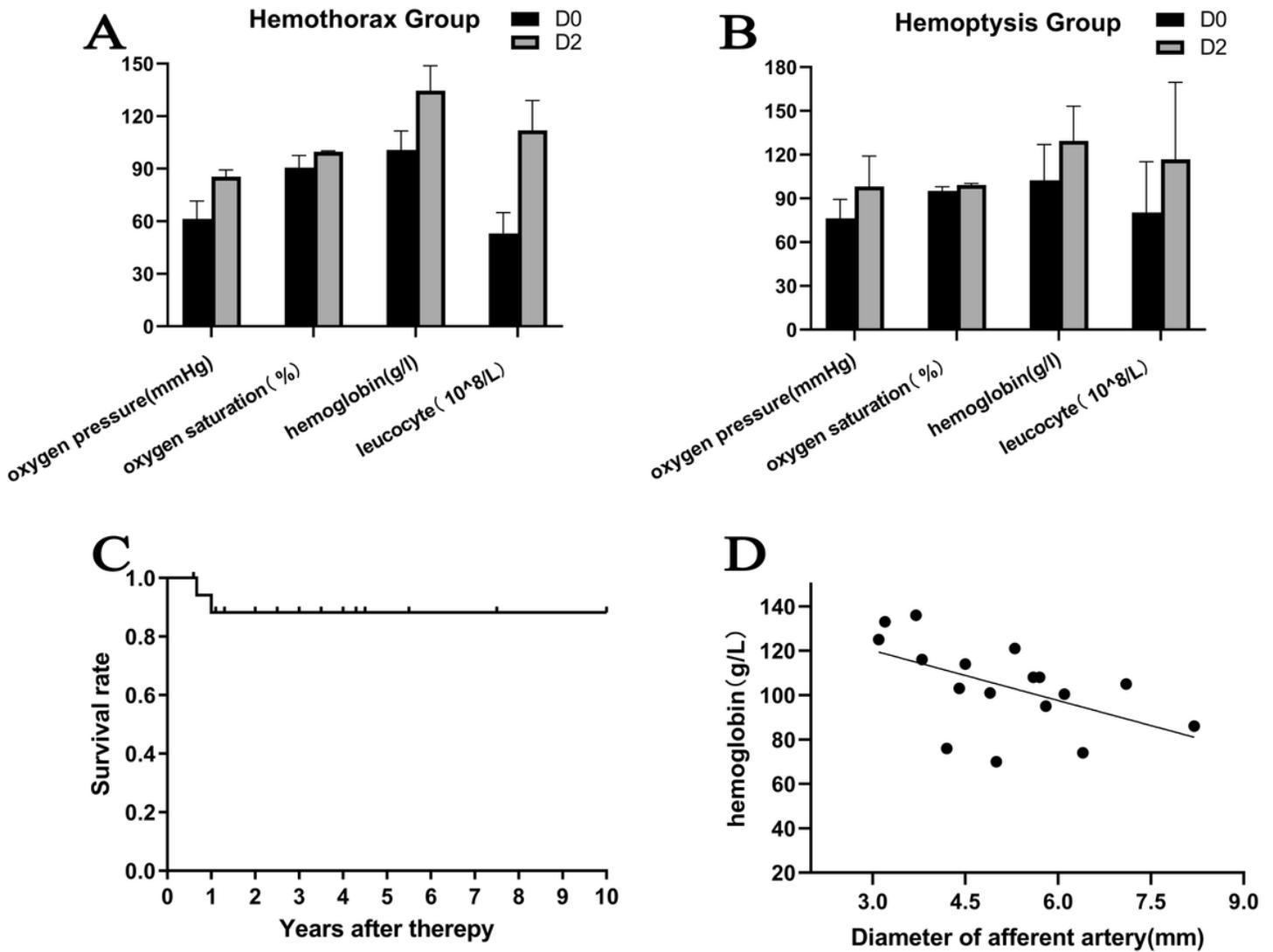
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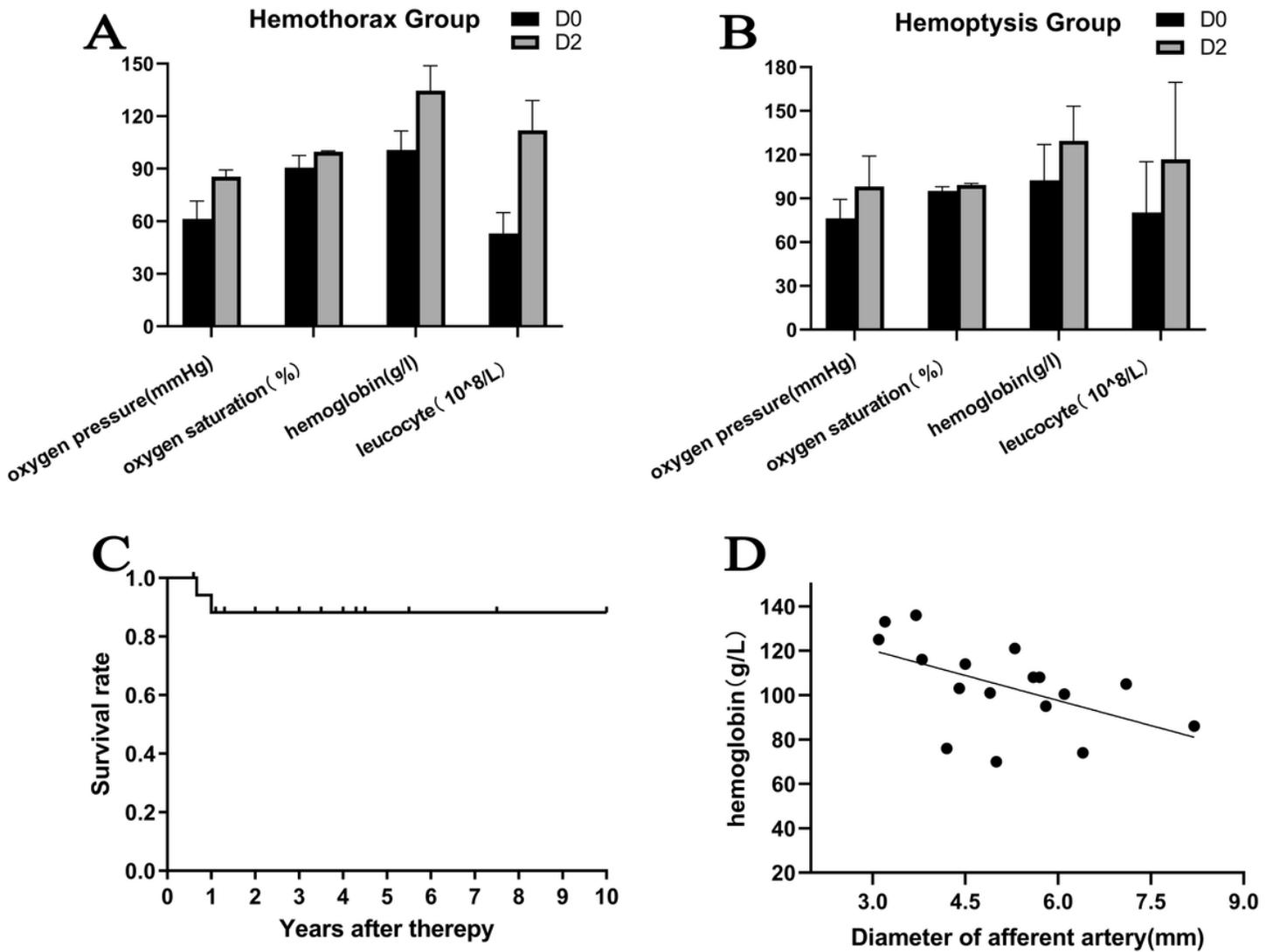
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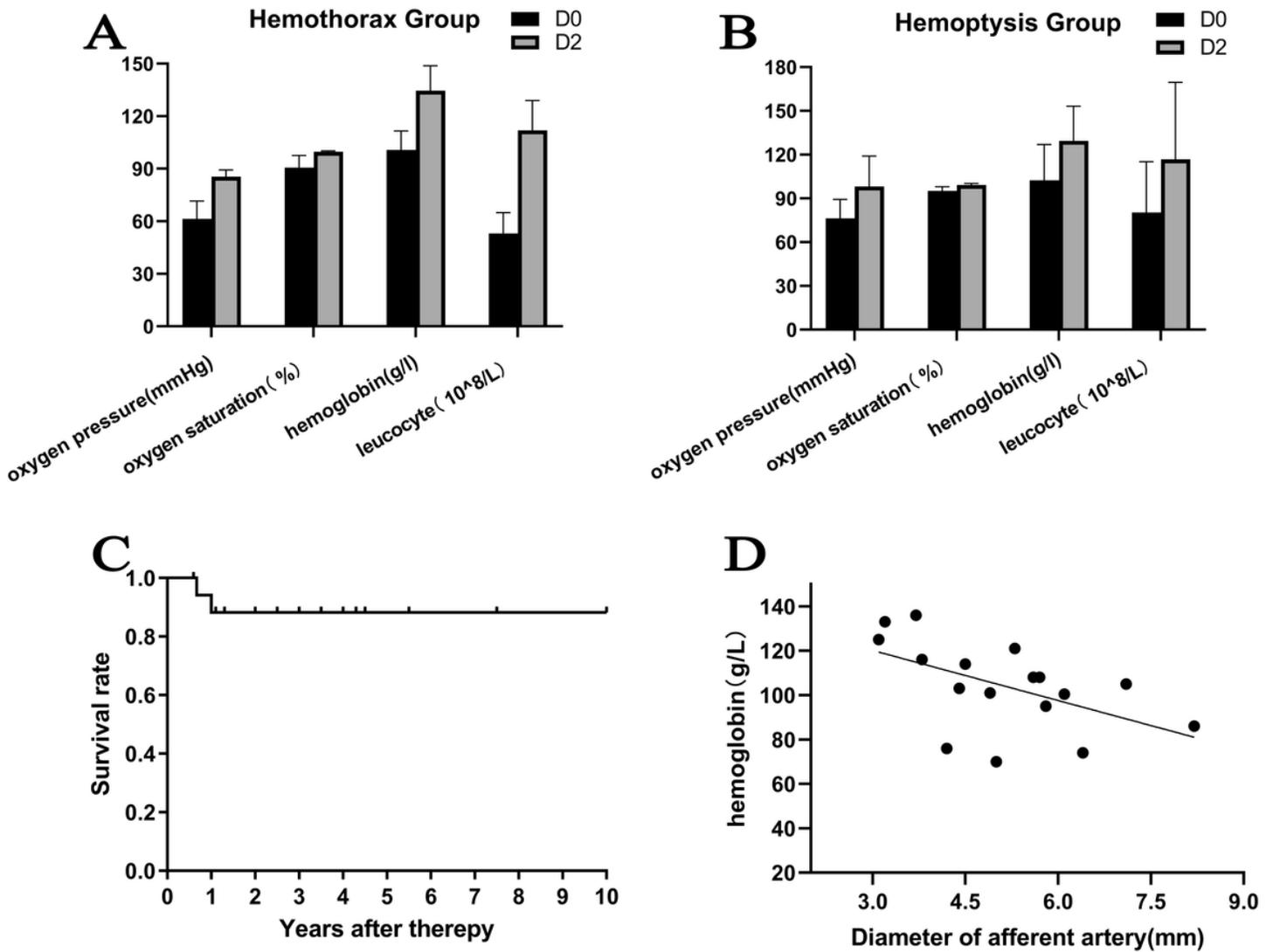
**Figure 5**

A, B, In the hemoptysis and hemothorax groups, the oxygen pressure, oxygen saturation, hemoglobin concentration, and leukocyte count significantly increased after therapy. C, Kaplan–Meier analysis for overall survival. The mean survival time was  $3.22 \pm 2.52$  years, ranging from 7 months to 10 years. D, The hemorrhage volume was linearly associated with the diameter of the afferent arteries in the ruptured lesions ( $P=0.029$ ).



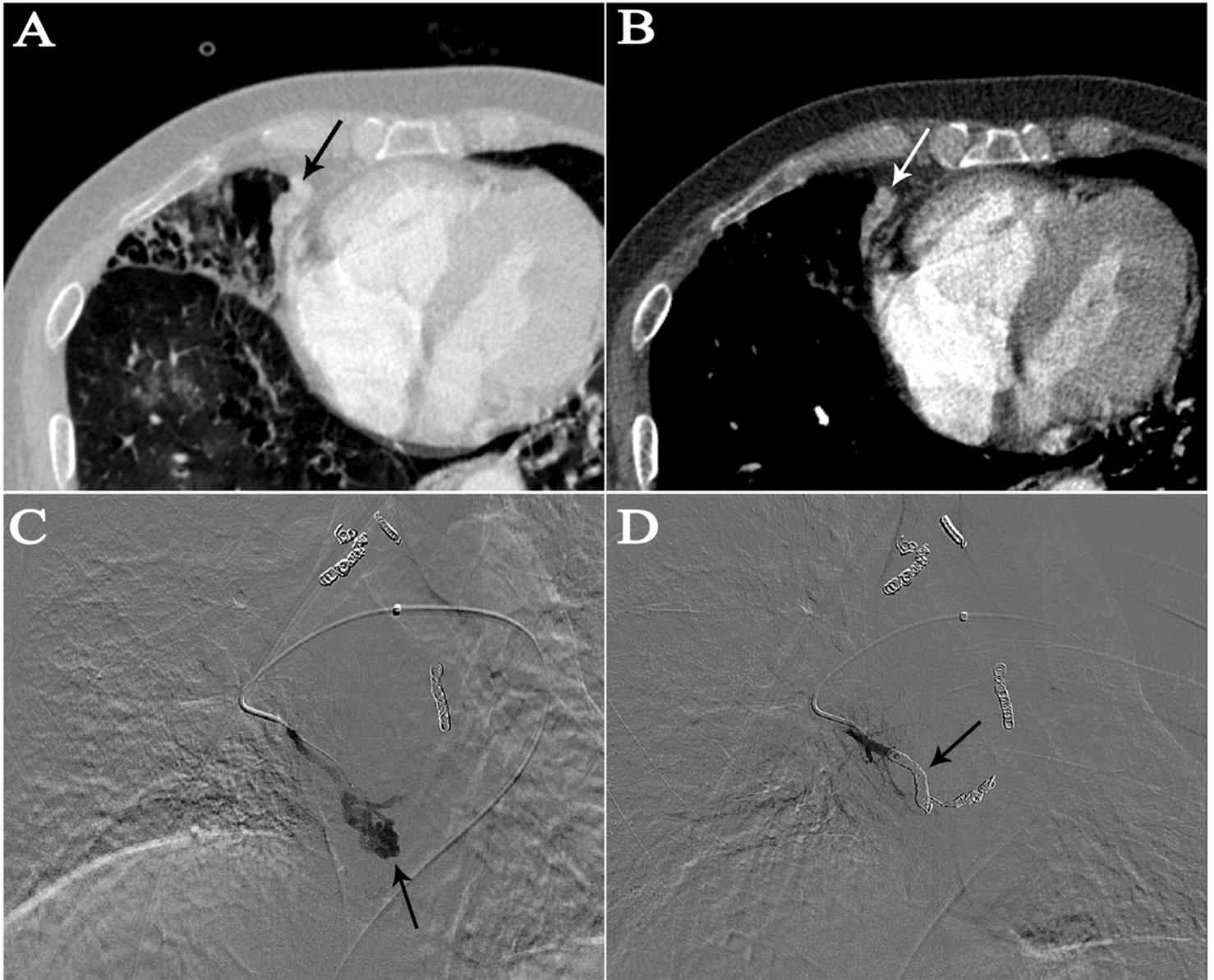
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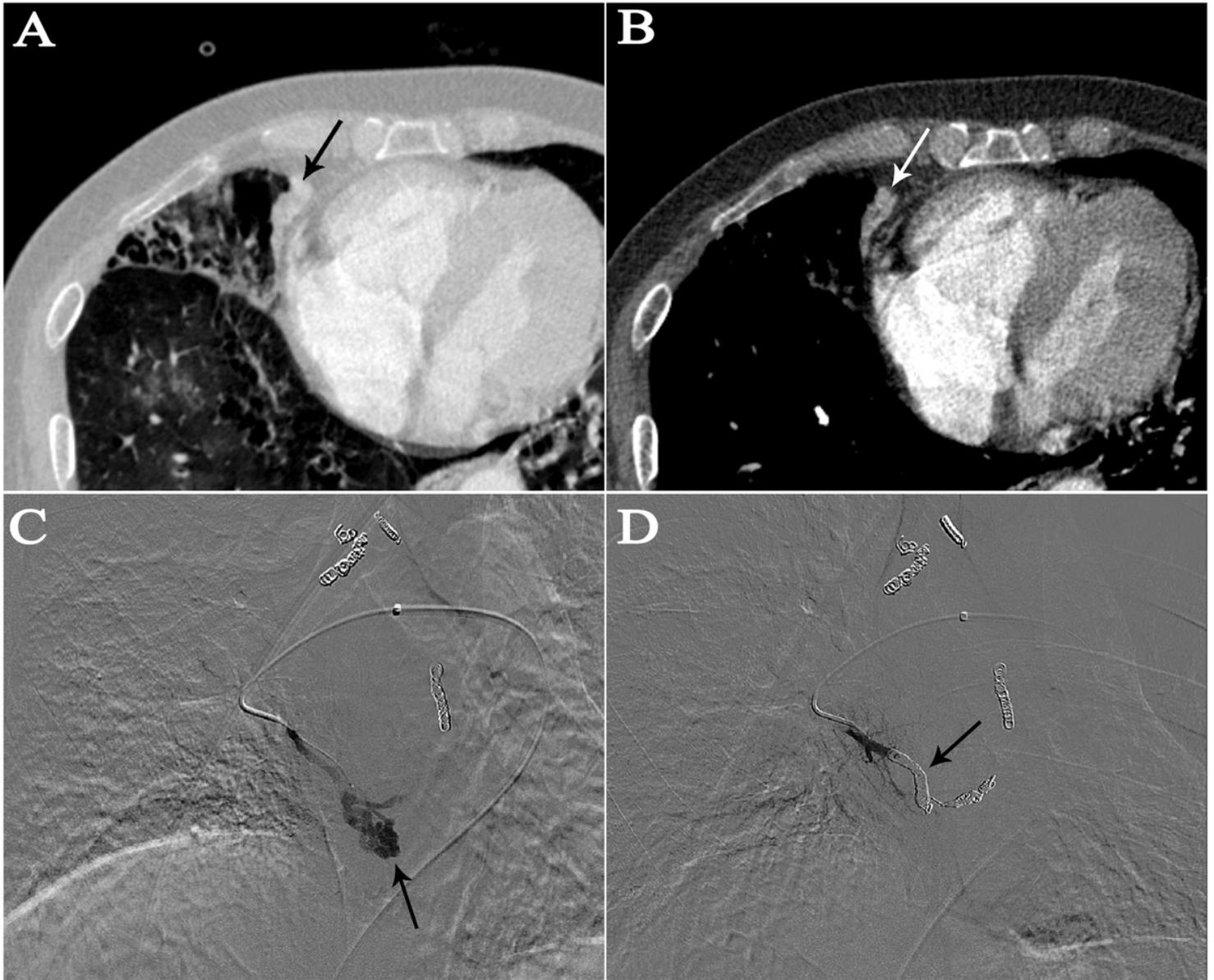
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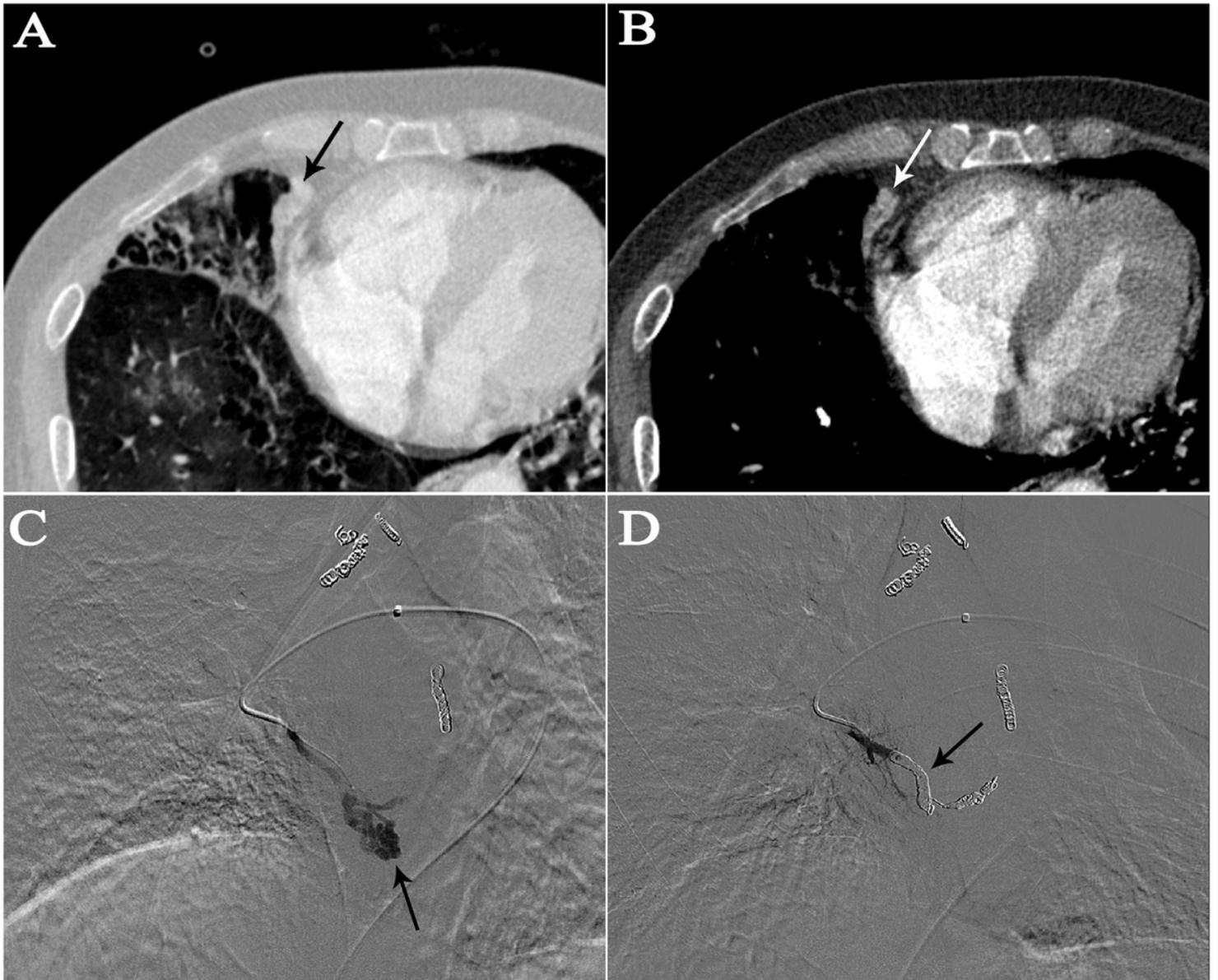
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A 61-year-old man with hemoptysis due to liver cirrhosis had previously undergone one session of ineffective bronchial artery embolization (BAE). A, B, CTA showed a hidden PAVM located in the right middle lobe (arrows). C, The PAVM was clearly revealed during pulmonary angiography (arrow). D, Embolization was performed with multiple coils (arrow).



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