JACC: ASIA VOL. 2, NO. 3, 2022


STATE-OF-THE-ART REVIEW

# Pulmonary Hypertension Caused by Fibrosing Mediastinitis

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## ABSTRACT

Pulmonary hypertension (PH) is a progressive and severe disorder in pulmonary hemodynamics. PH can be fatal if not well managed. Fibrosing mediastinitis (FM) is a rare and benign fibroproliferative disease in the mediastinum, which may lead to pulmonary vessel compression and PH. PH caused by FM (PH-FM) is a pathologic condition belonging to group 5 in the World Health Organization PH classification. PH-FM has a poor prognosis because of a lack of effective therapeutic modalities and inappropriate diagnosis. With the development of percutaneous pulmonary vascular interventional therapy, the prognosis of PH-FM has been greatly improved in recent years. This article provides a comprehensive review on the epidemiology, pathophysiologic characteristics, clinical manifestations, diagnostic approaches, and treatment modalities of PH-FM based on data from published reports and our medical center with the goal of facilitating the diagnosis and treatment of this fatal disease. (JACC: Asia 2022;2:218–234) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Pulmonary hypertension (PH) is a progressive, severe, and hemodynamic disorder that may cause high mortality if not well treated.[1] PH caused by fibrosing mediastinitis (PH-FM), a rare type of the condition in group 5 PH according to the World Health Organization PH classification, has a poor prognosis because of a lack of effective therapeutic modalities. Misdiagnosis and underdiagnosis of PH-FM are common.[1,2]

Fibrosing mediastinitis (FM), also known as sclerosing mediastinitis or mediastinal fibrosis, is a rare and benign fibroproliferative disease in the mediastinum.[3] Proliferative fibrous tissue gradually replaces normal fat tissue and wraps, infiltrates, and compresses the adjacent structures in the mediastinum, such as pulmonary vessels, superior vena cava (SVC), bronchus, esophagus, and pericardium. The aberrant behavior of the proliferative fibrous tissue may cause PH, SVC syndrome, atelectasis, and obstructive pneumonia, among which PH and the resulting right heart failure are the most prevalent sequels leading to death.[4] In recent years, with the development of percutaneous pulmonary vascular interventional therapy, the prognosis of PH-FM has been substantially improved.[5,6] This paper provides a comprehensive review of the etiology, epidemiology, pathophysiologic characteristics, clinical manifestations, imaging features, diagnostic criteria, and treatment modalities of PH-FM according to published reports (see the search method in Supplemental

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received July 26, 2021; revised manuscript received November 24, 2021, accepted November 25, 2021.

ISSN 2772-3747 https://doi.org/10.1016/j.jacasi.2021.11.016

**TABLE 1 The Etiologies of Fibrosing Mediastinitis**

| |
|---|
| Idiopathic[19] |
| Infection associated[7-10] |
| *Histoplasmosis capsulatum* |
| Tuberculosis |
| Aspergillosis |
| Mucormycosis |
| Blastomycosis |
| Actinomycosis |
| Nocardiosis |
| Coccidioidomycosis |
| Cryptococcosis |
| Non-infection associated[11-14] |
| Sarcoidosis |
| Immunoglobulin G4–related disease |
| Behçet disease |
| Systemic sclerosing disease |
| Rheumatic fever |
| Hodgkin disease |
| Silicosis |
| Trauma |
| Iatrogenic[15-18] |
| Radiotherapy |
| Chest surgery |
| Esophageal fistula |
| Methysergide maleate |
| Microinvasive procedures in the mediastinum (endoscopic ultrasound-guided fine-needle aspiration, drainage tube placement) |

Materials) and the data from our medical center with the goal of facilitating the standardization of the diagnosis and therapeutics of this fatal disease.

## ETIOLOGY, PATHOGENESIS, AND EPIDEMIOLOGY

FM is currently deemed as an abnormal immune proliferative reaction in the mediastinum in response to the triggering factors, including pathogens (*Histoplasma capsulatum*, *Mycobacterium tuberculosis*, *Blastomyces* and *Aspergillus* species, and so on),[7-10] sarcoidosis,[11] autoimmune diseases (immunoglobulin [Ig] G4-related diseases, Behcet's disease, and systemic sclerosing disease, among others),[12-14] iatrogenic (radiotherapy and esophageal injury, and so forth)[15-18] and idiopathic FM[19] (**Table 1**). FM is categorized into granulomatous FM (also known as the focal subtype) and nongranulomatous FM (also designated as the diffuse subtype or idiopathic FM).[20] Granulomatous FM is more prevalent, accounting for 80% to 90% of FM, and is elicited by infectious pathogens and inflammatory diseases such as sarcoidosis, whereas nongranulomatous FM is induced by autoimmune diseases, which often involve extramediastinal disorders, such as retroperitoneal fibrosis, sclerosing cholangitis, autoimmune pancreatitis, and Riedel thyroiditis[20,21] (**Table 2**).

The pathogenesis of FM remains elusive. It has been hypothesized that FM may progress through 3 stages following infection with *Histoplasma capsulatum*.[22,23] The first stage is an acute infection of *Histoplasma capsulatum*. Patients may exhibit fever, myalgia, cough, severe pneumonia, and respiratory failure; however, most patients present with covert infection and have no salient clinical manifestation. The second stage is mediastinal granuloma, a cheese-like mass formed by enlarged and fused lymph nodes. Patients in the first stage rarely progress to the second stage. The last stage is FM, which elicits clinical symptoms because of the compression of mediastinal structures by excessive proliferation of fibrous tissue. Although the pathogenesis of FM caused by *Mycobacterium tuberculosis* infection or other triggers has not been reported, it may be similar to that of FM following *Histoplasma capsulatum* infection. PH-FM is mainly ascribed to the pathogenic factors causing stenosis of pulmonary arteries (PAs) and pulmonary veins (PVs).[2,24]

The most prevalent trigger of FM is *Histoplasma capsulatum* infection (H-FM) in the United States and *Mycobacterium tuberculosis* infection (TB-FM) in China.[8,25] The median age of patients with FM is 42 years in the United States,[25] whereas the average age is 69.5 years in China from a small-sample study.[8] Although histoplasma infection is common in the United States, it is often asymptomatic and rarely progresses to FM.[26] It has been reported that 3 in 100,000 patients with histoplasma infection develop FM.[27] Dines et al[23] showed that 11 of 31 patients with mediastinal granuloma eventually developed FM. The incidence of FM caused by *Mycobacterium tuberculosis* infection has not yet been reported. Although there is no official report on the prevalence of PH in FM, it is of note that most of the FM cases recruited in previous small-sized cohort studies are accompanied by PH upon admission.[8,24,28] In our center, we registered 161 patients with FM, and 139 of them (67 men) were evaluated by echocardiography. Among the evaluated FM patients, 91 (47 men; age range: 50-90

**ABBREVIATIONS AND ACRONYMS**

**CT** = computed tomography

**CTEPH** = chronic thromboembolic pulmonary hypertension

**CTPA** = computed tomography pulmonary angiography

**CTPV** = computed tomography pulmonary venography

**ECG** = electrocardiogram

**FM** = fibrosing mediastinitis

**H-FM** = histoplasma capsulatum infection-related fibrosing mediastinitis

**Ig** = immunoglobulin

**MRI** = magnetic resonance imaging

**PA** = pulmonary artery

**PAG** = pulmonary artery angiography

**PET-CT** = positron emission tomography/computed tomography

**PH** = pulmonary hypertension

**PH-FM** = pulmonary hypertension caused by fibrosing mediastinitis

**PV** = pulmonary vein

**PVG** = pulmonary vein angiography

**RHC** = right heart catheterization

**SPECT/CT** = single-photon emission computed tomography/computed tomography

**SVC** = superior vena cava

**TB** = tuberculosis

**TB-FM** = Mycobacterium tuberculosis infection-related fibrosing mediastinitis

**V/Q** = lung ventilation/perfusion

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**TABLE 2 The Characteristics of Fibrosing Mediastinitis Caused by Different Triggers[a]**

| Features | H-FM[25] | TB-FM[8] | Idiopathic FM[74] |
|---|---|---|---|
| Pathophysiology | Granulomatous<br>Focal, invasive, calcified lesions in the mediastinum caused by abnormal immune reaction to pathogen | Granulomatous<br>Focal, invasive, calcified lesions in the mediastinum caused by abnormal immune reaction to pathogen | Nongranulomatous<br>Extensive, diffuse, noncalcified proliferation of fibrous tissue in the mediastinum caused by autoimmune diseases, radiotherapy, IgG4-related disease, and drugs |
| Prevalence | 3/100,000 persons | Unknown | Unknown |
| Demographics | Median age: 42 y (range: 21-75 y)<br>No sex differences<br>More common in the United States | Median age: 66 y (range: 50-90 y)<br>No sex differences<br>More common in China | Unknown<br>Unknown<br>More common in Japan |
| Symptoms (depending on affected structures) | Common symptoms are dyspnea, cough, chest pain, SVC syndrome (less in TB-FM), hemoptysis, pleural effusion (less in H-FM) | | |
| Location in mediastinum | Focal > diffuse<br>Unilateral > bilateral | Focal > diffuse<br>Bilateral > unilateral | Diffuse or focal<br>Bilateral or unilateral |
| Mainly affected mediastinal structures | Pulmonary arteries<br>Bronchi<br>SVC<br>Pulmonary veins (less) | Pulmonary arteries<br>Bronchi<br>Pulmonary veins<br>SVC (less) | Pulmonary arteries<br>Bronchi<br>Pulmonary veins<br>SVC |
| Extrathoracic involvement | None | None | Retroperitoneal fibrosis<br>Autoimmune pancreatitis<br>Sclerosing cholangitis |
| Imaging | Mediastinal widening<br>Nodal calcification<br>Atelectasis<br>Abnormal soft tissue (focal)<br>Compression of mediastinum structures including vessels, airway, and SVC | Mediastinal widening<br>Nodal calcification<br>Atelectasis<br>Abnormal soft tissue (focal)<br>Compression of mediastinum structures including vessels, airway, and SVC | Mediastinal widening<br>Nodal calcification (less)<br>Atelectasis<br>Abnormal soft tissue (diffuse)<br>Compression of mediastinum structures including vessels, airway, and SVC |
| Treatment[2,5-8,25,33,36,74,75,83] | | | |
| Medication | Antifungal and anti-inflammatory drugs are ineffective[b]<br>Rituximab may be effective[c]<br>Vasodilator drugs for pulmonary hypertension may be ineffective[d] | Anti-TB and anti-inflammatory drugs are ineffective[b]<br>Rituximab may be effective[c]<br>Vasodilator drugs for pulmonary hypertension may be ineffective[d] | Corticosteroids are of varied benefit[b]<br>Rituximab may be effective[c]<br>Vasodilator drugs for pulmonary hypertension may be ineffective[d] |
| Surgery | Uncertain efficacy and high operation-related mortality rate (20%) | | |
| Endovascular therapy | Preferred and effective for reliving pulmonary artery, pulmonary vein, and SVC stenosis, but the rate of intrastent restenosis is high in pulmonary veins and SVC | | |

[a]There may have some bias because of limited evidence, and there are some overlaps with H-FM, TB-FM, and idiopathic FM in pathophysiology, location in mediastinum, distribution of affected structures in mediastinum, symptoms, and imaging findings in some patients. [b]It may depend on whether there is active fungal or TB infection and if the fibrous lesion is active. [c]It was reported that rituximab was effective for patients with progressive FM in a small-sample case series study.[75] [d]Evidence comes from a small-sample retrospective study.[2]

H-FM = *Histoplasma capsulatum* infection-related fibrosing mediastinitis; IgG4 = immunoglobulin G4; SVC = superior vena cava; TB-FM = Mycobacterium tuberculosis infection-related fibrosing mediastinitis; TB = tuberculosis.

years; median age: 66 years) had confirmed or suggested tuberculosis (TB) infection according to the medical history, results of TB tests, and findings of imaging examinations. Furthermore, 83 of these 91 patients exhibited systolic pulmonary artery (PA) pressure of no <40 mm Hg. The prevalence of the involvement of the PAs, bronchi, PVs, and SVC were 100%, 98.9%, 94.5%, and 13.2%, respectively (Y. Cao, unpublished data, 2021) (Table 2).

Disparate preferences and extents of involvement in the mediastinal structures were also found in patients with FM. For instance, Peikert et al[25] reported that the focal subtype accounts for 95% and the diffuse subtype for 5% in the FM cases studied; 72% of the cases involved the right side, 5% the left side, and 23% both sides. Moreover, 42% of the cases involved PAs, 13% PVs, and 42% the SVC. By contrast, another report demonstrated that of the 28 patients with TB-FM, 85% presented with bilateral lesions, 3% with SVC compression, 100% with PA compression, and 66% with PV involvement.[28] Additionally, another small-sized study showed that all the patients had bilaterally involved mediastinum and none had involved SVC.[24] The differences in the scope and location of the involved structures may be due to the distinct triggering factors of this disease. Collectively, H-FM predominantly affects the structures in the right upper mediastinum, including the PAs, bronchus, and SVC, but exerts fewer effects on PVs. TB-FM mainly involves the structures at bilateral hilar regions, such as PAs, bronchi, and PVs but rarely involves the SVC (Table 2).

## CLINICAL MANIFESTATIONS

The clinical symptoms of PH-FM depend on the involved structures in the mediastinum[2,6-8,25,28-40]

(Table 3). In general, shortness of breath is the most frequent symptom of FM.[8,25] The involved mediastinal structures include PAs, PVs, the SVC, and bronchi, with the corresponding symptoms as dyspnea, hemoptysis, SVC syndrome, and coughing.[2,6,7,25,28,29] Specifically, compression of the PAs may incur PH and severe hemoptysis as a result of systemic collateral hyperplasia; compression of the PVs can lead to PH and pulmonary venous congestion, which, in turn, cause mild to moderate hemoptysis and refractory pleural effusion, and eventually, pulmonary vascular compression may lead to severe PH, right heart failure, and even death. Compression of the SVC can cause SVC syndrome. If the bronchus is involved, the patient may experience wheezing, cough, atelectasis, and obstructive pneumonia. Involvement in the recurrent laryngeal nerve and phrenic nerve may cause hoarseness or shortness of breath; involvement with the esophagus and the thoracic duct can elicit dysphagia and chylothorax, respectively; and compression of the pericardium may cause pericardial tamponade and constrictive pericarditis. The SVC syndrome is more prevalent in H-FM than in TB-FM, whereas refractory pleural effusion exhibits the opposite trend.[8,25]

**TABLE 3** The Involved Mediastinal Structures and the Associated Symptoms and Signs in Patients With Pulmonary Hypertension Caused by Fibrosing Mediastinitis

| Involved Structures | Associated Symptoms/Signs | Reference(s) |
|---|---|---|
| Pulmonary artery | Dyspnea<br>Chest pain<br>Hemoptysis<br>Pulmonary hypertension<br>Enlarged right heart<br>Prominent main pulmonary artery<br>Mosaic perfusion | 8,20,25,28,36,48 |
| Pulmonary vein | Dyspnea<br>Chest pain<br>Hemoptysis<br>Refractory pleural effusion<br>Pulmonary edema<br>Pulmonary hypertension<br>Enlarged right heart<br>Prominent main pulmonary artery<br>Mosaic perfusion<br>Thickening of interlobular septum | 20,28,31,32,36,48 |
| Bronchus | Cough<br>Dyspnea<br>Lithoptysis<br>Postobstructive pneumonia<br>Atelectasis | 20,28,34 |
| Superior vena cava | Superior vena cava syndrome | 33 |
| Esophagus | Dysphagia<br>Odynophagia | 30 |
| Pericardium | Constrictive pericarditis | 35 |
| Thoracic duct | Chylothorax | 37 |
| Recurrent laryngeal nerve | Hoarseness | 38 |
| Coronary artery | Angina<br>Acute coronary syndrome<br>Sudden death | 39,40 |

## IMAGING FINDINGS

**ELECTROCARDIOGRAM AND ECHOCARDIOGRAPHY.** The typical electrocardiogram (ECG) manifestations of PH-FM are similar to those of pulmonary arterial hypertension and PH caused by other types of PA stenosis.[41-43] The characteristic ECG includes right deviation axis, uncertain axis, R/S <1 in lead I, R/Q >1 in lead aVR, and right bundle branch block and T-wave inversion/flatness in limb and/or precordial leads, indicating enlargement of and endocardial ischemia in the right ventricle caused by pressure overload. These typical ECG characteristics are termed PAS syndrome.[44] The abnormal ECGs can be partially or totally recovered following the amelioration of pulmonary vascular stenosis (Figure 1).

Echocardiogram has no finding specific for PH-FM. All PH signs can be present in patients with PH-FM, including elevated systolic right ventricle pressure, enlarged right heart, and compressed left ventricle.[45] Proximal PV lesions can be revealed by echocardiography in some patients with PH-FM.[46,47]

**CHEST X-RAY.** Patients with PH-FM usually show signs of FM, including widening of the mediastinum, atelectasis, mediastinal masses and hilar enlargement, and pulmonary congestion or interstitial pulmonary edema in the upper lobes, as well as signs of PH, including a prominent main PA and enlarged right heart on chest radiographs.[20,21,48] The terminology "FM dyad" and "FM triad" have been used to describe the chest x-ray manifestations of PH-FM.[49] The FM dyad includes one of the signs of PH such as prominent main PA and atelectasis, whereas FM triad refers to the dyad plus refractory pleural effusion[49] (Figure 2A). Additionally, pulmonary congestion or interstitial pulmonary edema in the upper lobes, as one of the signs of upper PVs stenosis, could have the same implication as refractory pleural effusion for PH-FM with PV stenosis. Accordingly, the FM triad could be modified to an FM dyad plus refractory pleural effusion or pulmonary congestion or interstitial pulmonary edema in the upper lobes. These 4 signs could be termed as "FM tetralogy" (Figure 2A). Our preliminary data indicated that the sensitivity of atelectasis in combination with pleural effusion for diagnosing PH-FM was 50% and that the specificity was >90% (Y. Cao, unpublished data, 2021). Therefore, the FM dyad and FM triad may provide important clues for diagnosis of PH-FM.

**VENTILATION/PERFUSION SCINTIGRAPHY.** Ventilation/perfusion scintigraphy (V/Q) scan is a preferred screening method for chronic stenotic pulmonary vascular disease. V/Q scan imaging in PH-FM

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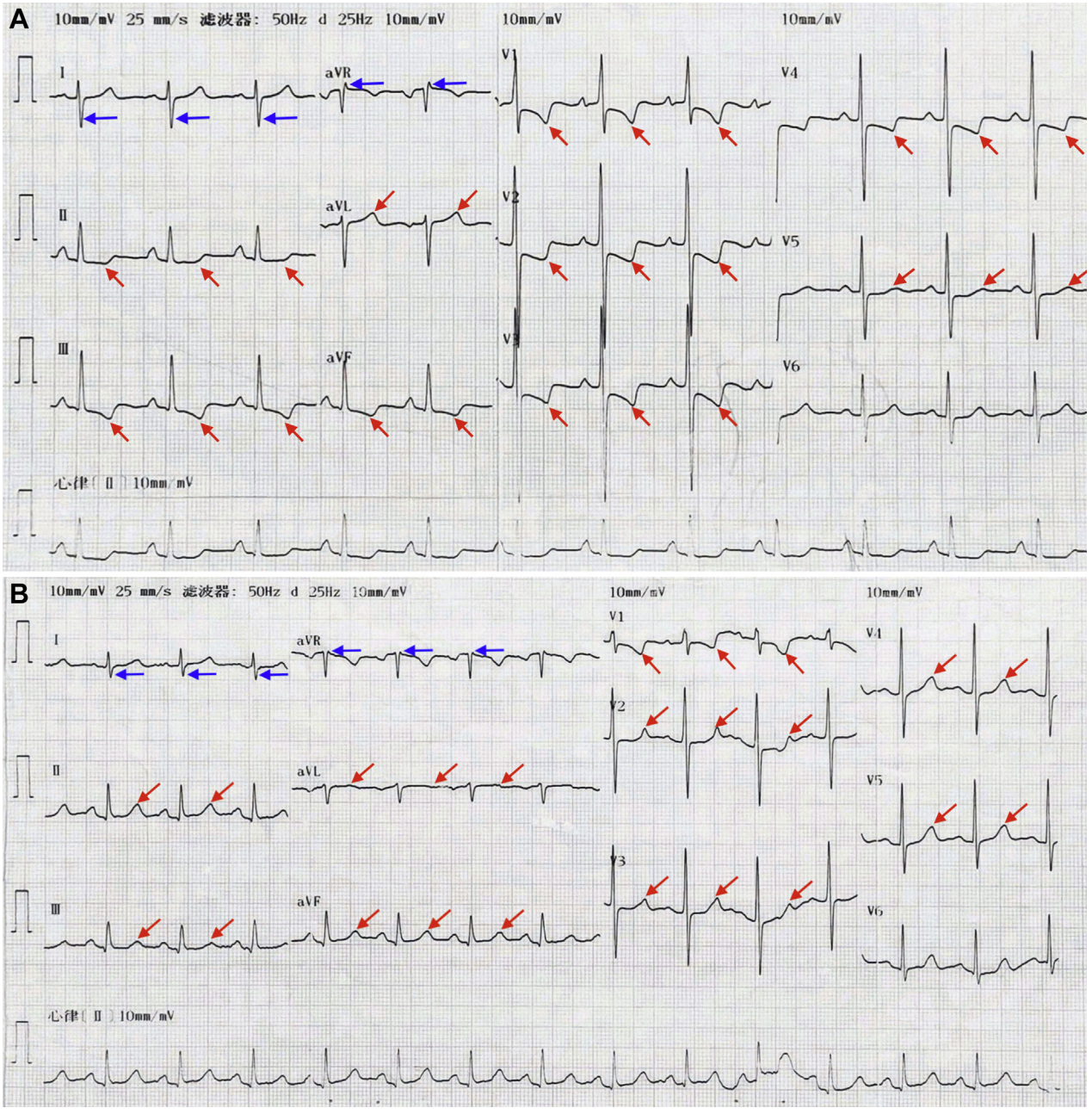
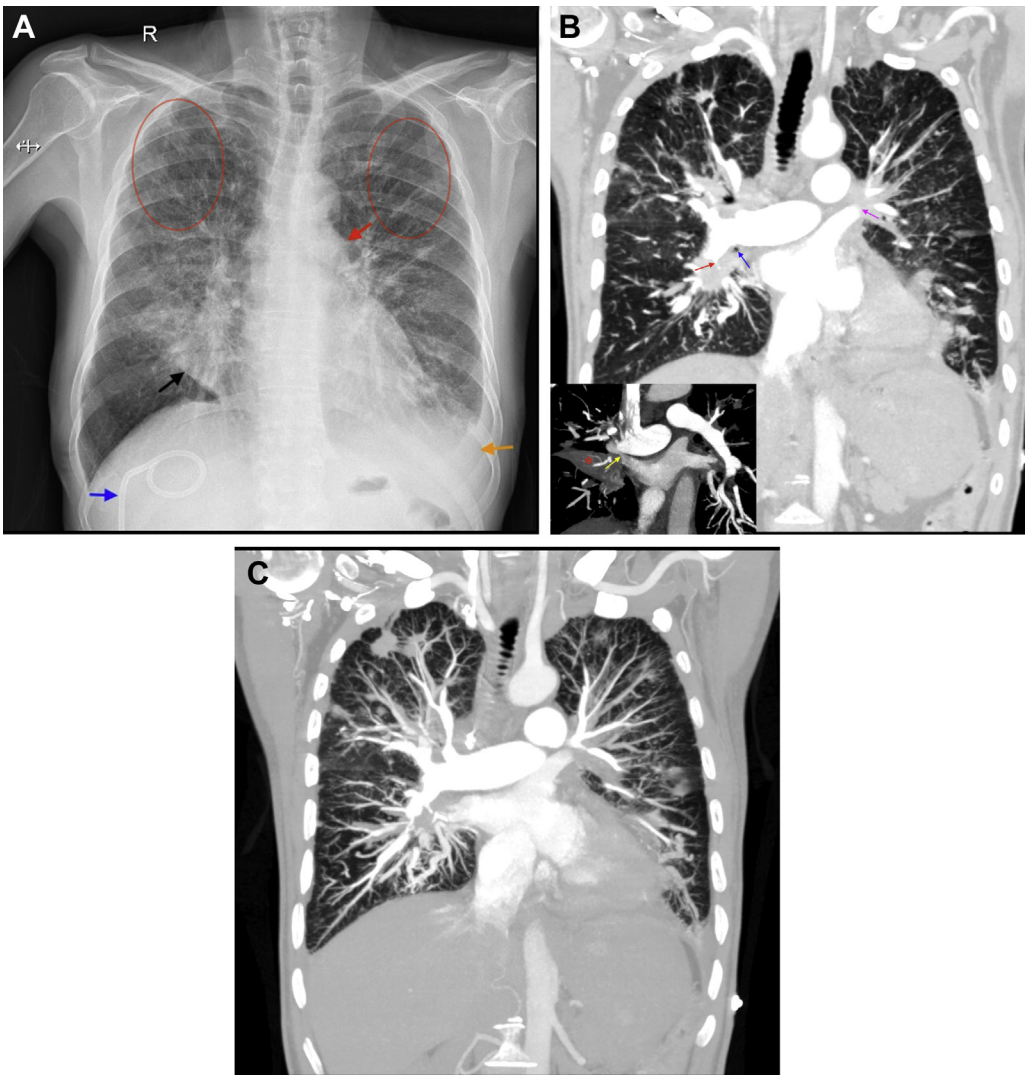
**FIGURE 1** **Representative Electrocardiogram of PH-FM**




Data from a 63-year-old woman with PH-FM. **(A)** The electrocardiogram before stenting in stenotic pulmonary arteries. **Blue arrows** refer to a prominent R-wave in lead aVR and deepened S-wave in lead I. **Red arrows** refer to inverted/flattened T waves in limb and precordial leads. **(B)** The electrocardiogram at 5 months after stenting. **Blue arrows** indicate that the S-wave in lead I and R-wave in lead aVR were smaller than the corresponding wave observed in **A**. **Red arrows** indicate that T waves in limb and precordial leads recovered except those in lead $V_1$ as compared with the T waves observed in **A**. PH-FM = pulmonary hypertension caused by fibrosing mediastinitis.

patients usually shows multiple adjacent segmental perfusion defects with mismatched ventilation impairment (Figure 3). These imaging characteristics, known as mismatched perfusion defects (Figure 3), are similar to those exhibited by pulmonary embolism. Therefore, misdiagnosis between PH-FM and pulmonary embolism should be avoided.[37-39] In addition, the PH-FM patients with severe bronchus

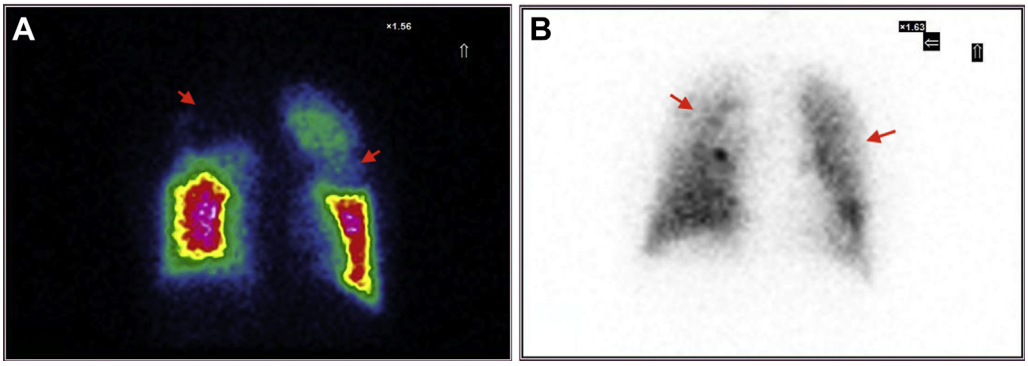
**FIGURE 2** **Typical Chest X-Ray and Contrast-Enhanced Computed Tomography of PH-FM**




Data from a 63-year-old man with PH-FM. **(A)** Chest radiograph showed the dyad, triad, and tetralogy of PH-FM. The FM dyad includes predominant main PA **(red arrow)** and right middle lobe atelectasis **(black arrow)**. FM triad refers to the FM dyad plus pleural effusion **(orange arrow)** or upper lobe pulmonary congestion/interstitial pulmonary edema **(circles)**. FM tetralogy includes the mentioned 4 signs. **Blue arrow** indicates a chest tube for pleural effusion drainage. **(B)** Coronal computed tomography angiography image demonstrates the concentric stenosis of multiple lobular/segmental PAs **(red arrow)**, stenosis of the right middle lobe bronchus **(blue arrow)**, and occlusion of the left upper PV **(pink arrow)**. The inset image in the lower left shows severe stenosis of the right upper PV **(yellow arrow)**. Thickening secondary pulmonary lobule margins and interlobular septal thickening were related to the occlusion or stenosis of PV. **Asterisk** refers to atelectasis. **(C)** Coronal computed tomography angiography MIP image shows many ill-defined small nodules in the upper lobes, which is consistent with the history of pulmonary tuberculosis infection. FM = fibrosing mediastinitis; MIP = maximum intensity projection; PA = pulmonary artery; PH-FM = pulmonary hypertension caused by fibrosing mediastinitis; PV = pulmonary vein.

stenosis and atelectasis may have impaired ventilation, which could be matched with the perfusion defects induced by the stenosis of corresponding PAs. Single-photon emission computed tomography/computed tomography (SPECT/CT) integrates functional imaging with anatomic imaging and has been proven as effective as V/Q scan in diagnosing chronic thromboembolic PH (CTEPH).[50] In view of the definite imaging characteristics such as FM dyad and triad, SPECT/CT might have advantages over V/Q scan in the differential diagnosis of PH-FM from other stenotic pulmonary vascular diseases.

**FIGURE 3 Representative Lung Ventilation/Perfusion Scan of PH-FM**




Data from a 67-year-old woman with PH-FM. The **(A)** perfusion views revealed the defects **(arrows)** mismatched with the **(B, arrows)** ventilation views in the right upper lobe and the left superior lingula. PH-FM = pulmonary hypertension caused by fibrosing mediastinitis.

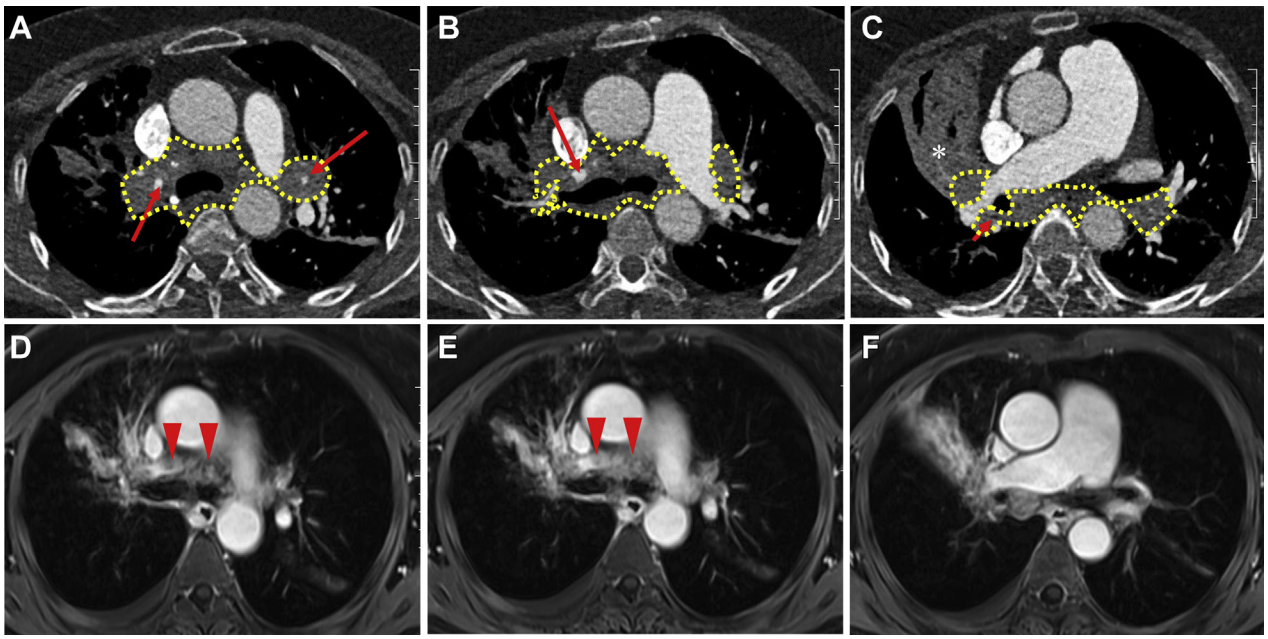
**CONTRAST-ENHANCED CHEST COMPUTED TOMOGRAPHY.** PH-FM usually manifests as focal or diffuse hyperplasia of fibrous tissues compressing adjacent structures with or without calcification on chest computed tomography (CT) (**Figures 2B, 2C, and 4A to 4C**). Other findings on CT include atelectasis, mosaic perfusion, ground glass density shadow, thickening of the interlobular septum, and hyperplasia of the systemic collateral vessels.[20,21,51] The FM dyad and triad can be observed in typical chest CT[49] (**Figures 4A to 4C**). Contrast-enhanced chest CT is the first option of imaging examination to diagnose suspected PH-FM, evaluate the extent of involvement in mediastinum structures (**Figures 2B, 2C, and 4A to 4C**), and detect hyperplasia of the collateral vessels. The results of this examination suggest the clinical classification of PH-FM and facilitate the determination of a therapeutic regimen. In particular, the multiplanar and virtually reconstructed images further illustrate the length and diameter of target lesions and provide the best projection view during interventional therapy, thereby subserving an important reference for making a strategy of intervention. In addition, contrast-enhanced chest CT is also crucial for evaluating right heart function and identifying other types of PH, such as Takayasu arteritis–related PH, CTEPH, and PA tumors.[52-57]

**MAGNETIC RESONANCE IMAGING.** The benefits of magnetic resonance imaging (MRI) are similar to CT in determining the extent of fibroproliferative lesions, but CT is more accurate than MRI in evaluating trachea and bronchus involvement and identifying calcification.[51,58] Fibrous tissue is usually exhibited as a moderately enhanced signal on T1-weighted images and a differently enhanced signal on T2-weighted images[51,58-60] (**Figures 4D to 4F**). Moreover, metal artifacts of vascular stents on MRI influence the evaluation of intrastent restenosis; hence, CT pulmonary angiography and venography (CTPA and CTPV, respectively) could be the first choice of examination during follow-ups after interventional therapy.[6,60,61] However, MRI is still the gold standard for evaluating right heart function.[62]

**POSITRON EMISSION TOMOGRAPHY/CT.** Positron emission tomography/CT (PET-CT) is rarely used for the diagnosis and evaluation of PH-FM. The published reports on the use of PET-CT in FM diagnosis are all case reports and showed substantial variability in fluorodeoxyglucose uptake by mediastinal lesions[20,63-65] (**Figure 5**).

**PA AND PV ANGIOGRAPHY.** PA angiography (PAG)/PV angiography (PVG) is the gold standard for evaluating vascular stenosis but not for tracing the etiology of pulmonary vascular stenosis. PH-FM is mainly manifested as localized stenosis at the origin of the second and third branches of the PA in PAG and at the first drainage branches of the PV in PVG around the hila (**Figure 6**, Video 1). However, PAG and PVG cannot accurately determine the cause of vascular stenosis, whether there are hyperplastic soft tissues or tumors in the mediastinum, whether the trachea/bronchus is involved, and whether calcification exists. In addition, the transeptal puncture entailed by direct PVG adds operational difficulties. Therefore, CTPA, CTPV, and MRI are the major diagnostic methods for PH-FM.[62] Once the diagnosis is secured, either PAG or PVG or both are then used for evaluation before angioplasty and/or venoplasty.

**FIGURE 4** **Representative Contrast-Enhanced Computed Tomography and Magnetic Resonance Imaging of PH-FM**




Data from a 67-year-old woman with PH-FM. **(A to C)** Contrast enhanced computed tomography images. Multiple low-density nodules and patchy soft tissue shadow in the mediastinum and on both hila **(yellow dotted lines)** compressed the left and right pulmonary arteries **(red arrows in A and B)**. The bronchus of the right middle lobe was also compressed and became narrowed **(arrow in C)**, thereby leading to atelectasis **(asterisk in C)** of the middle lobe of the right lung. Also, the widened main pulmonary artery was observed. **(D to F)** were contrast-enhanced magnetic resonance imaging with fat-suppression T1WI images. These images demonstrate the heterogeneity of the enhanced nodules, reflecting the characteristic of necrotic lymph nodes **(arrowheads)**. Also, the widened main pulmonary artery, stenotic pulmonary arteries, stenotic bronchus, and atelectasis could be observed in the magnetic resonance images at the same places shown in the corresponding computed tomography images. PH-FM = pulmonary hypertension caused by fibrosing mediastinitis.

## PATHOLOGIC STUDY

Biopsy is the gold standard for pathologic diagnosis of FM and a critical approach to rule out malignancy. However, biopsy is not necessary for issuing a diagnosis of FM because of its invasive nature and the complications it may incur.[6] The pathologic analysis reports nodular or diffuse hyperplastic fibrous tissues surrounding and infiltrating mediastinal structures.[25,66] In addition, Peikert et al[25] found that infiltration in proliferative fibrous tissues of the mixed lymphocytes, in which CD20-positive B lymphocytes accounted for a considerable portion, implicating an association of these B lymphocytes with FM (**Figure 7**).

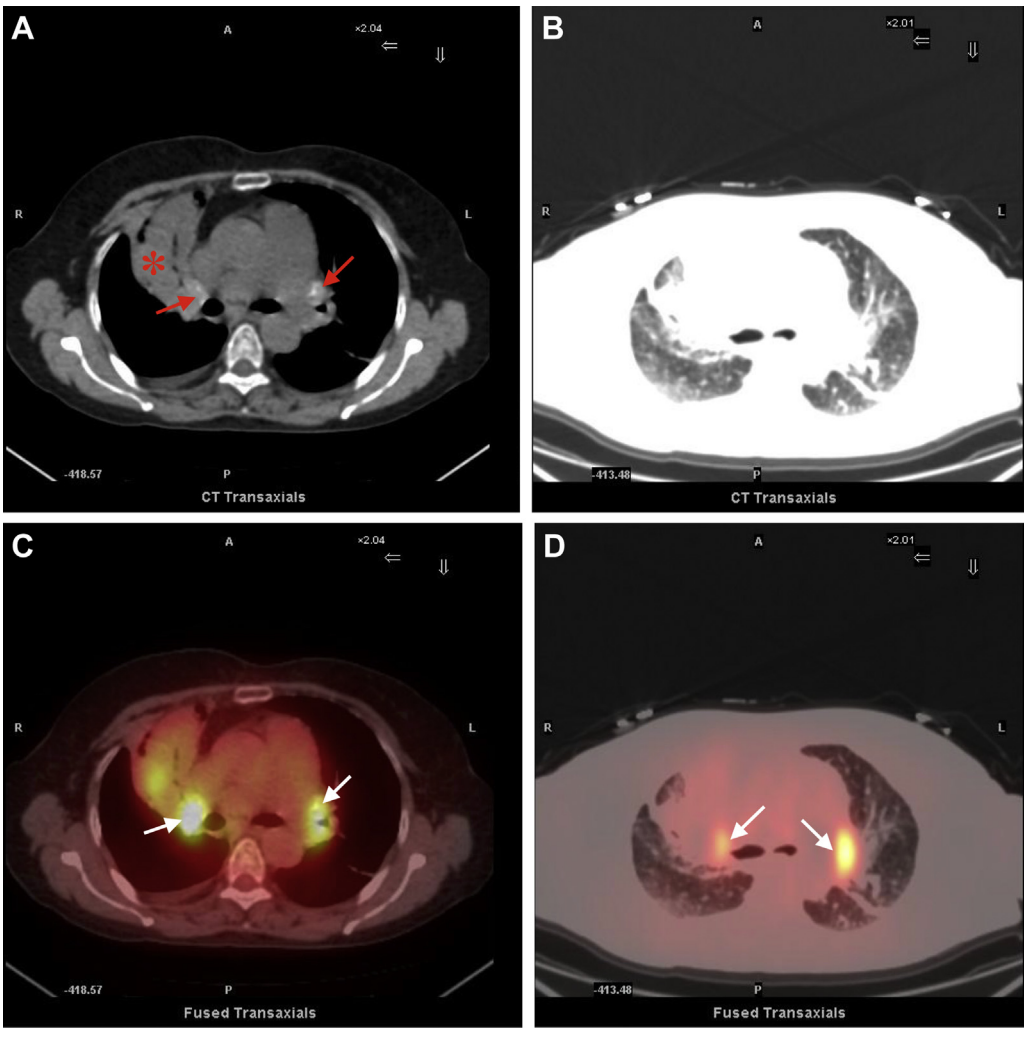
## HEMODYNAMICS

Right heart catheterization (RHC) is the gold standard for diagnosing PH. PH-FM mostly belongs to precapillary PH.[2] Although some patients have PV stenosis, their PA wedge pressure measured by Swan-Ganz catheter is mostly normal. This is because the involved PVs are predominantly located at the proximal first drainage branches, which are usually smaller in size than the balloon of a Swan-Ganz catheter.[67] This scenario is comparable to the apparently normal PA wedge pressure exhibited during PV occlusive disease.[68] RHC can also measure the pressure gradient across the stenotic site in pulmonary vessels, evaluate the functional impairment of stenotic vessels, and provide detailed hemodynamic information for interventional modality.

## CLINICAL CLASSIFICATION

PH-FM is categorized into 3 types based on the involved pulmonary vessels.[49] Type I refers to the FM that mainly causes stenosis in the PAs, mostly accompanied by the stenosis of anatomically adjacent bronchi but not the PVs; type II refers to the FM that predominantly induces stenosis of the PVs without involvement of the PAs, and bronchus involvement is

**FIGURE 5 Representative Photon Emission Tomography/Computed Tomography of PH-FM**



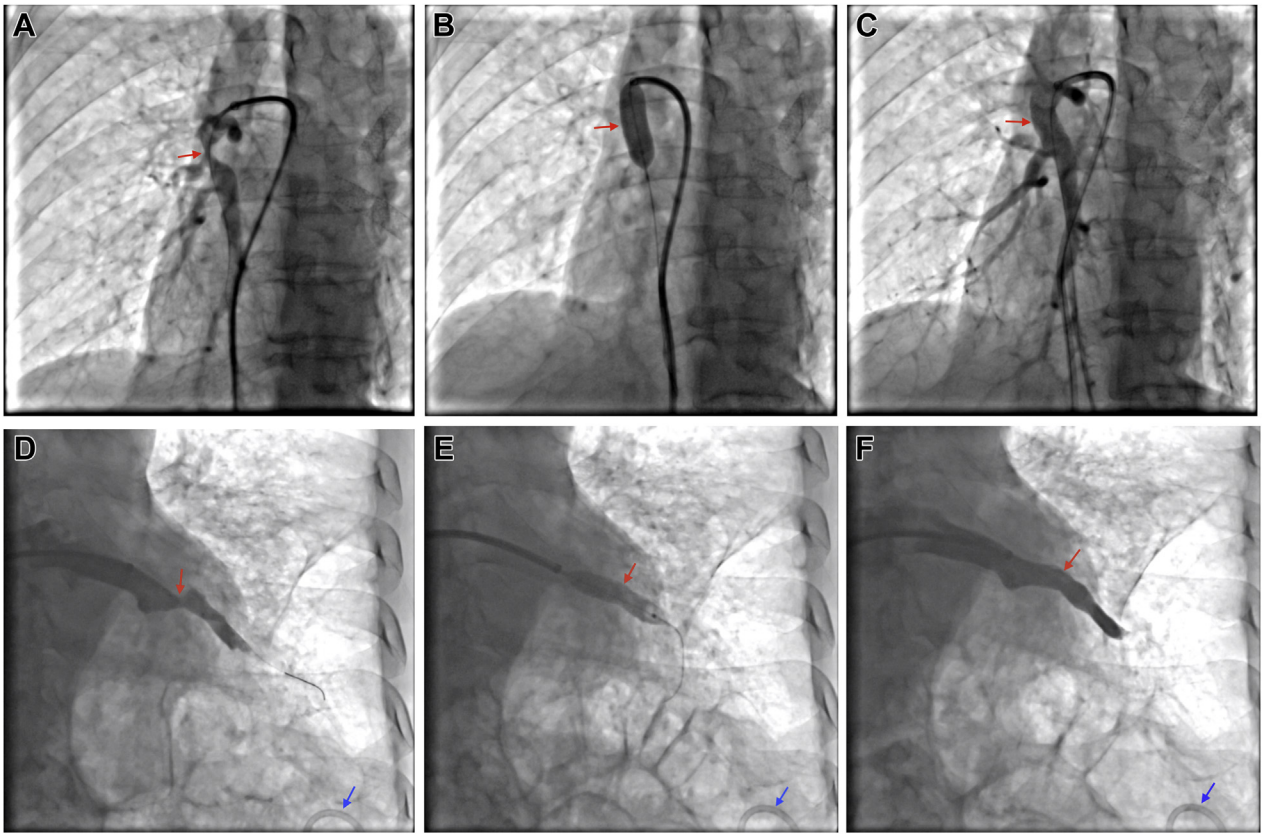

Data from the same patient as in Figure 4. **(A, B)** Multiple partially calcified lymph nodes **(arrows)** on both hila could be seen in computed tomography images. The bronchus of the right middle lobe was compressed, causing atelectasis of the middle lobe **(asterisk)**. **(C, D)** Fused photon emission tomography/computed tomography images demonstrate bilateral hilar enlarged nodes **(arrows)** with increased fluorodeoxyglucose uptake (SUV max: 6.37). **Asterisk** refers to the atelectasis in the middle lobe of the right lung with slightly increased fluorodeoxyglucose uptake (SUV max: 3.2). PH-FM = pulmonary hypertension caused by fibrosing mediastinitis; SUV = standardized uptake value.

rare; type III refers to the FM eliciting stenosis of the PAs, PVs, and bronchi (Figure 8). Furthermore, if other structures, such as the SVC and esophagus, are involved, the first letter of the involved structure is used as a subscript to specify the categorization. For example, type I plus involvement of the SVC is designated as type $I_s$.[49] The prevalence of different types may depend on the triggering factors of the disease. In our center, most cases were triggered by TB. Among these cases, type III accounted for about 92%, and only 1% were type II (Y. Cao, unpublished data, 2021).

## DIAGNOSTIC FLOW CHART

The clinical manifestations, FM dyad and triad, as well as PAS syndrome of ECG provide useful clues for diagnosis. V/Q scan is an important screening tool. Contrast-enhanced CT is the major examination for diagnosing PH-FM, identifying the involved

**FIGURE 6** **Representative Images of Pulmonary Artery and Pulmonary Vein Angiography of PH-FM**



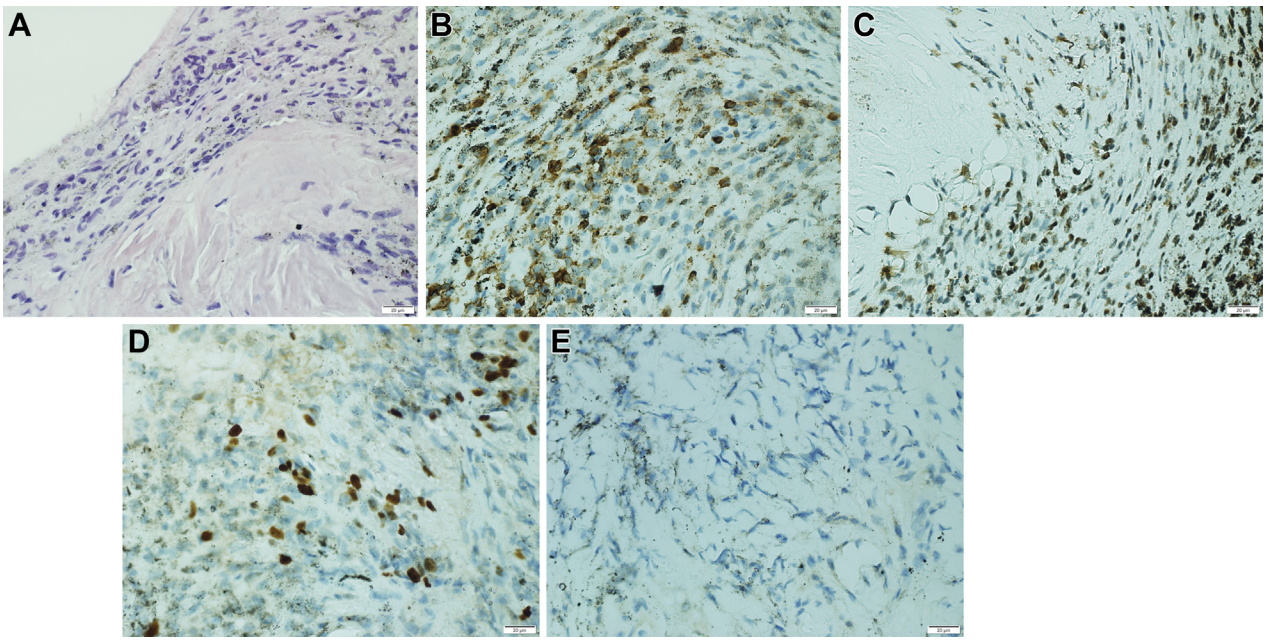

**(A to C)** Pulmonary artery angiography. **(D to F)** Pulmonary vein angiography. **(A, D)** The images taken before stenting. **Arrows** indicate the stenosis in **(A)** the right intermediate pulmonary artery and **(D)** left inferior pulmonary vein. **(B, E)** The images taken during stenting. **Arrows** indicate **(B)** pulmonary artery stenting and **(E)** pulmonary vein stenting. **(C, F)** The images taken after stenting. **Arrows** indicate the stents implanted in the **(C)** pulmonary artery and **(F)** pulmonary vein. **Blue arrows** in the **(D to F)** indicate the chest tube for pleural effusion drainage. PH-FM = pulmonary hypertension caused by fibrosing mediastinitis.

mediastinal structures, and determining the clinical classification. RHC should be performed to measure hemodynamic parameters. PH-FM should be distinguished from other types of PH, especially from other types of chronic stenotic pulmonary vascular diseases, including chronic thromboembolic disease, CTEPH, PV thrombosis, PV stenosis after radiofrequency ablation, pulmonary vascular stenosis caused by vasculitis, pulmonary vascular stenosis after surgical repair of congenital heart disease, and compressive pulmonary vascular stenosis caused by mediastinal tumor. For patients with PH as the chief complaint, doctors should follow the diagnostic flow chart described in the guidelines for PH.[69] For patients with mismatched perfusion defects, the possibility of PH-FM as one of the diagnoses should be considered; for PH patients with atelectasis, widened mediastinum, and/or refractory pleural effusion, PH-FM is highly suspected, and CTPA and CTPV are required to verify the suspicion. After confirmed diagnosis of PH-FM, clinical classification should be determined and the distribution of involved mediastinal structures demarcated, whereby the appropriate therapeutic strategy can be selected. Thorough medical histories should be taken, and the immune parameters, such as IgG4 levels and tuberculosis antibodies, should be tested for routinely to identify the disease triggers. Retroperitoneal fibrosis, sclerosing cholangitis, and other clinical conditions need to be examined (**Figure 9, Central Illustration**).

## TREATMENT

**MEDICATION.** The general treatment for patients with PH-FM includes oxygen therapy, diuretics, and digoxin. Antifungal, anti-TB, and anti-inflammatory

**FIGURE 7 Representative Pathology Pictures of PH-FM**




**(A)** Hematoxylin and eosin staining revealed lymphocyte infiltration in the proliferative fibrous tissue of hyaloid degeneration. **(B to E)** Immunohistochemical staining. **(B, C)** Dispersed CD3-positive T lymphocytes and CD20-positive B lymphocytes, respectively. **(D)** Ki-67 staining shows a proliferation index of 20% to 30% in infiltrating lymphocytes. **(E)** pan-cytokeratin staining was negative, indicating no epithelial cells. PH-FM = pulmonary hypertension caused by fibrosing mediastinitis.

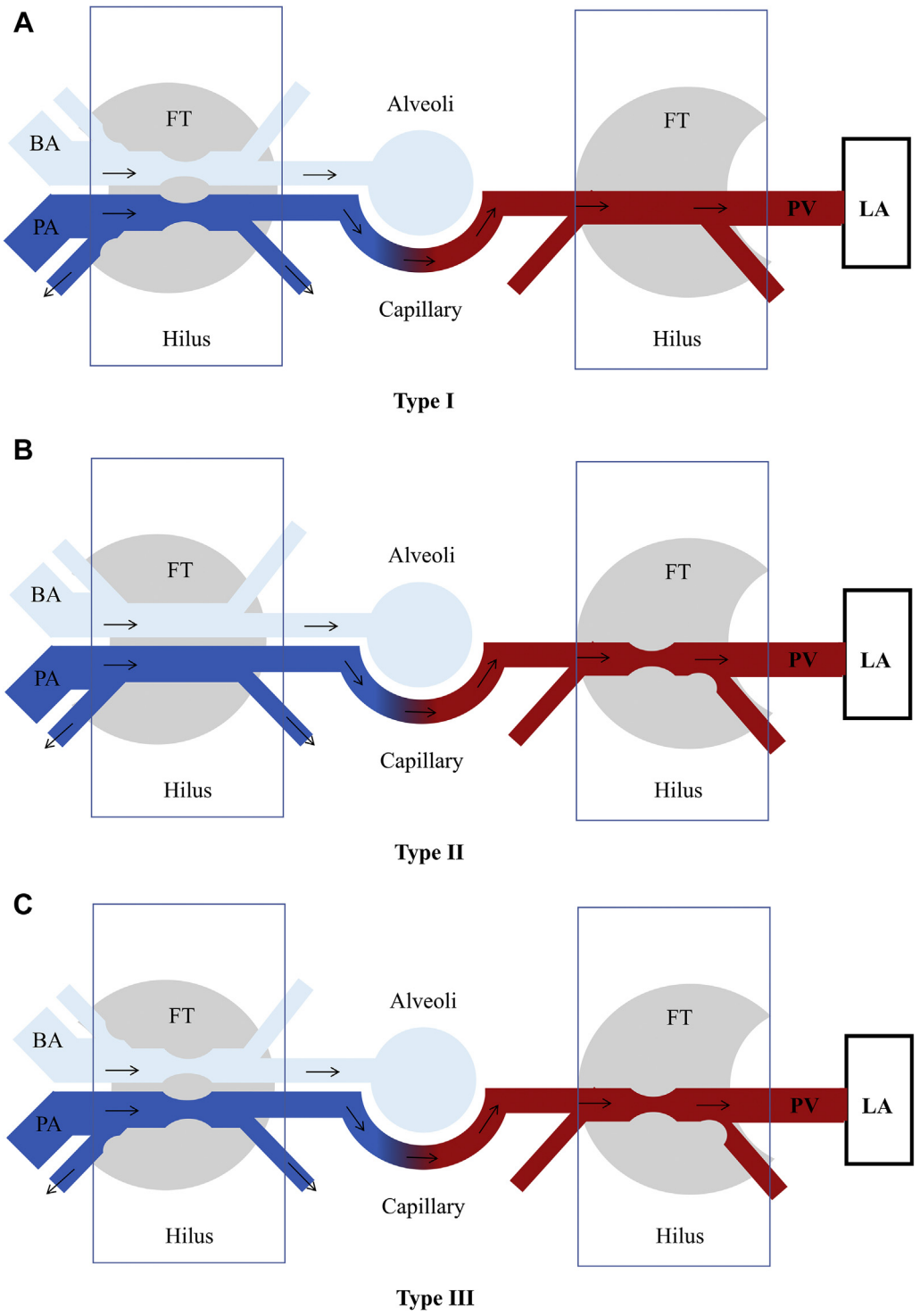
drugs are ineffective, although there is an association of histoplasmosis and TB infection with the occurrence of FM.[7,8,23,25,70] Unless there is evidence of active infection with *Histoplasma*, such as mediastinal granuloma or the H or M band in immunodiffusion tests, the administration of itraconazole may not be effective.[71,72] For sarcoidosis- or IgG4-related FM, glucocorticoid therapy may be effective.[11,73] In addition, the efficacy of hormone therapy varies among individuals with idiopathic FM.[74]

Furthermore, Westerly et al[75] reported the administration of rituximab to 3 FM patients whose pathologic biopsy specimens showed abundant infiltration of CD20-positive B lymphocytes in proliferative fibrous tissues and in whom PET-CT revealed high uptake of fluorodeoxyglucose and active lesions in the mediastinum. Following rituximab administration, the patients' symptoms were relieved, the sizes of the lesions shrank, and the metabolic activities of the lesions diminished. However, the safety and efficacy of rituximab as a therapeutic modality for PH-FM needs to be further investigated by multicenter, large-sample, randomized controlled clinical trials.

In patients with PH-FM, the experience of using vasodilators for PH is scant. A small-sized study has shown the limited efficacy.[2] However, some patients with sarcoidosis-related FM were included in this study; the New York Heart Association functional classification was used as the primary outcome during the follow-up, and the evidence strength was limited. Therefore, the efficacy of vasodilators for PH in the patients with PH-FM has to be further studied (Table 2).

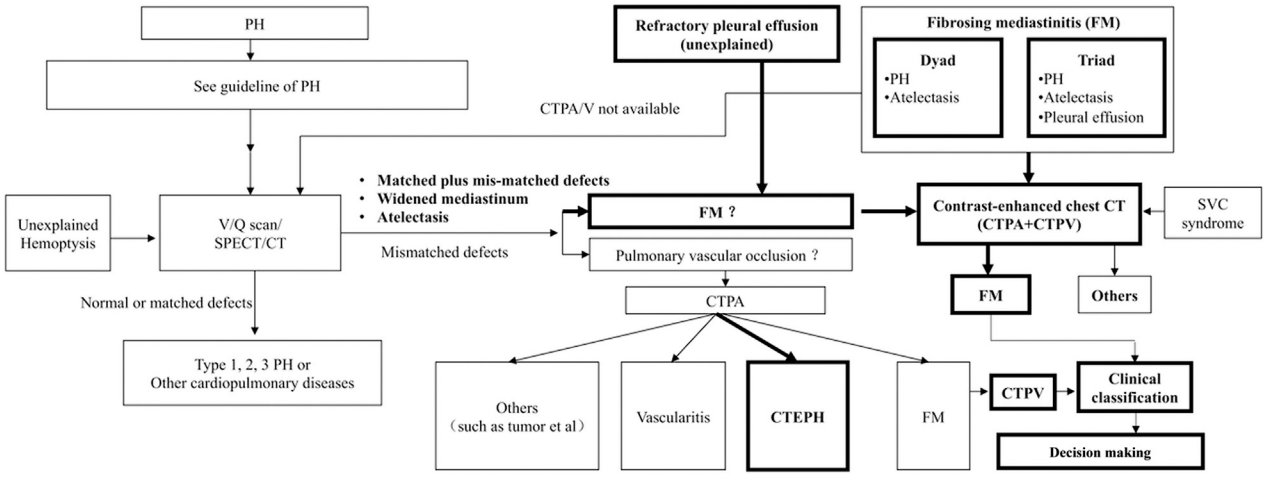
**SURGERY.** The purpose of surgical treatment is to relieve the compression of mediastinal structures by proliferative fibrous tissues and ameliorate the compression-related symptoms (Table 2). Common surgical procedures include mediastinal tissue resection, SVC bypass grafting, airway reconstruction, pulmonary revascularization, lobectomy, and segmentectomy.[7,25,76-79] As a result of the complexity of FM pathology, surgical treatment has a mortality rate as high as 20%.[7] Moreover, the clinical benefits of these surgeries are not yet clear. Studies have shown that 42% of FM patients subjected to surgical treatment relapse during follow-up and require other interventions.[25] The cause of recurrence may be related to residual obstruction and progression of fibrous lesions in the mediastinum, and this awaits further investigation.

**FIGURE 8** **Scheme of Clinical Classification of PH-FM**




**(A)** Type I. The PA and bronchus are compressed by proliferative fibrous tissues. **(B)** Type II. Only the PV is compressed by proliferative fibrous tissues. **(C)** Type III. The PA, PV, and bronchus are compressed by proliferative fibrous tissues. BA = bronchus airway; FT = proliferative fibrous tissues; LA = left atrium; PA = pulmonary artery; PH-FM = pulmonary hypertension caused by fibrosing mediastinitis; PV = pulmonary vein.

**FIGURE 9 Diagnostic Chart for PH-FM**



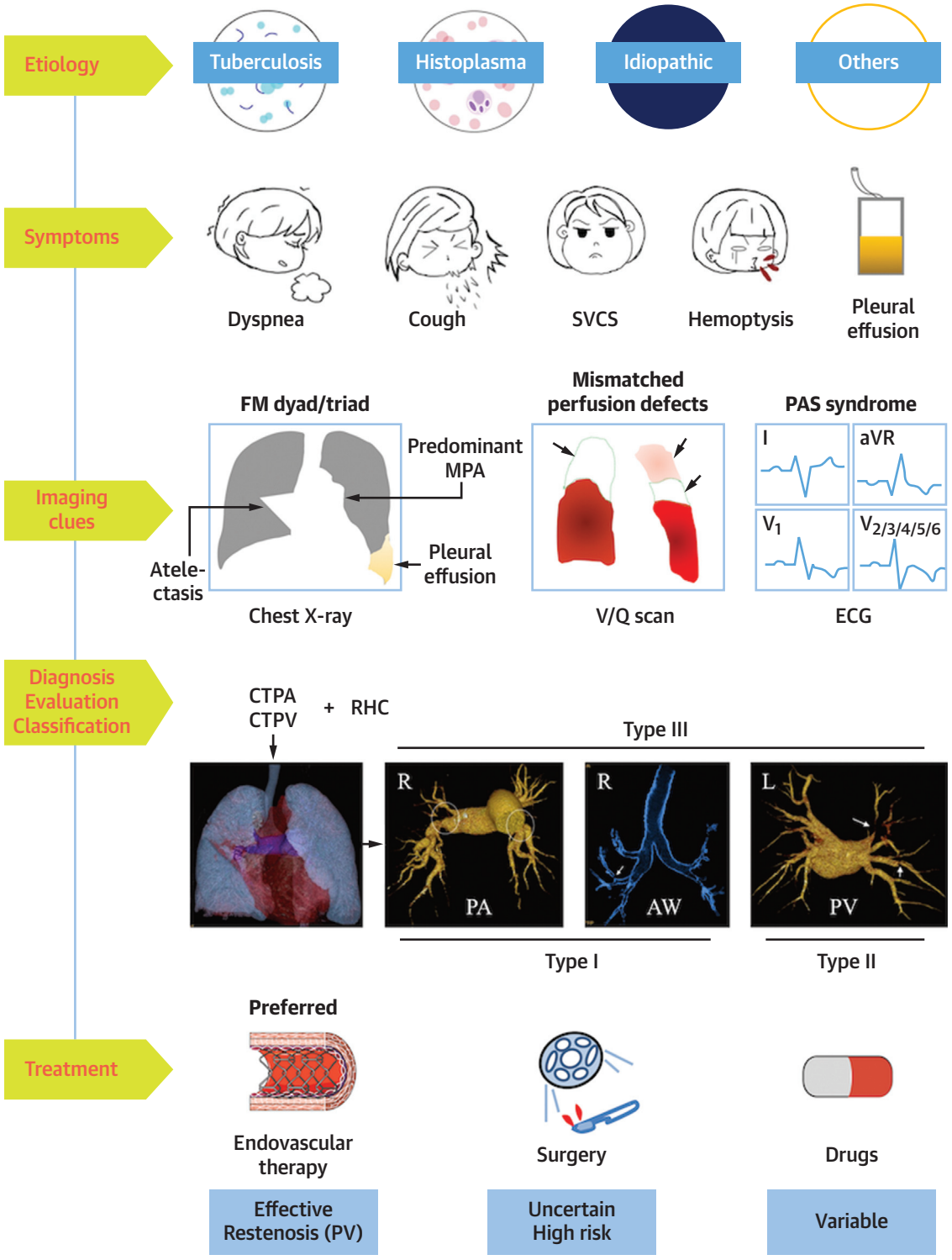

CT = computed tomography; CTEPH = chronic thromboembolic pulmonary hypertension; CTPA = computed tomography pulmonary angiography; CTPV = computed tomography pulmonary venography; FM = fibrosing mediastinitis; PH = pulmonary hypertension; PH-FM = pulmonary hypertension caused by fibrosing mediastinitis; SPECT/CT = single-photon emission computed tomography/CT; SVC = superior vena cava; V/Q = lung ventilation/perfusion.

**ENDOVASCULAR INTERVENTIONS.** Interventional therapy has been used to relieve symptoms caused by obstruction of the pulmonary vessels in PH-FM patients (Table 2, Video 1). It is the preferred treatment for such diseases.[5,6,36,80-84] Different interventional modalities have been proposed according to the patient's clinical classification. In general, PV intervention should be performed first. After the stenosed PV has regained patency, the PA intervention may be performed soon; if the PV occlusion cannot be removed, the PA intervention should be avoided. Also, if the PA occlusion is prejudged not to be alleviated, the PV intervention should not be performed. A study with the largest sample size so far showed that 59 stents in 47 pulmonary vessels (26 PAs and 21 PVs) were implanted in 30 patients with FM.[36] Symptoms were relived significantly after the procedure; however, during the median 115-month follow-up period, symptomatic restenosis occurred in 1 case of PA (5%) and 4 cases of PV (25%).[36] Moreover, 8 patients with FM-induced PV stenosis underwent percutaneous pulmonary venoplasty, and their symptoms were ameliorated, but 50% of the patients experienced restenosis.[83] Notably, owing to the stiff, rigid, and brittle pulmonary vessel wall formed during the pathophysiologic process of this disease, PH-FM incurs a higher rate of complications than other types of pulmonary vascular stenosis during interventions. The complications include vessel injury, lung injury, lung edema, stent displacement, stent underexpansion, and intrastent restenosis.[5,6,36,80-87] Therefore, although interventional treatment can significantly ameliorate symptoms and improve the hemodynamics of the patients with PH-FM in small-sized case studies, its efficacy and safety should be thoroughly assessed in the future. Importantly, perioperative management should be strengthened to avoid fatal complications. In addition, intrastent restenosis, especially restenosis of the PV stent, is a prevalent and recalcitrant issue to which close attention should be paid following interventional modalities of PH-FM. The specific mechanisms underlying and preventative schemes for intrastent restenosis warrant further study.

**INTERVENTIONAL MODALITIES TO SVC STENOSIS AND BRONCHIAL STENOSIS.** Interventional modalities can relieve SVC syndrome caused by FM-induced SVC stenosis, but restenosis is prone to occur after intervention (Table 2).[33,36] For bronchial stenosis caused by FM, the stent strategy is difficult and perilous and, hence, is more challenging than the strategy for other benign lesions in the mediastinum (Table 2).[34]

Collectively, there is limited experience in the treatment of PH-FM, and no guideline or expert consensus has been established. Therefore, it is recommended that patients with PH-FM be referred to an experienced pulmonary vascular center for effective and safe treatment after careful evaluation by multidisciplinary approaches.

**CENTRAL ILLUSTRATION** **Pulmonary Hypertension Caused by Fibrosing Mediastinitis**




**Wang A, et al. JACC: Asia. 2022;2(3):218–234.**

AW = airway; CTPA = computed tomography pulmonary angiography; CTPV = computed tomography pulmonary venography; ECG = electrocardiogram; L = left; PA = pulmonary artery; PAS = pulmonary artery stenosis; PV = pulmonary vein; R = right; RHC = right heart catheterization.

## HIGHLIGHTS

- PH-FM, as a type of rare condition in group 5 PH, has a poor prognosis because of a lack of effective therapeutic modalities and frequent misdiagnosis and underdiagnosis.
- The most prevalent trigger of FM is infection of *Histoplasma capsulatum* in the United States and infection of *Mycobacterium tuberculosis* in China.
- Imaging findings, including mismatched perfusion defects in the V/Q scan, FM dyad, and FM triad are important diagnostic clues, and clinical classification facilitates decision making in diagnosis and therapeutics.
- Because of the limited efficacy of drug therapy as well as the uncertain effectiveness and high risk of surgical treatment, endovascular interventional modality is currently the preferred therapeutic option, although procedure-related complications and intrastent restenosis after PV intervention need to be addressed.

## PROGNOSIS

Because of the limited reports with limited sample sizes in the past, the prognosis of patients with PH-FM is not clear. Peikert et al[25] conducted a retrospective study of 80 patients with FM admitted to the Mayo Clinic from 1998 to 2007; 2 patients (2.5%) died of FM during the follow-up period of a median of 68 months. Another study summarized the clinical data of 71 patients with FM and showed that the mortality rate was as high as 30% based on incomplete follow-up data.[70] In 2015, Seferian et al[2] followed up 27 patients with PH-FM and found that survival rates at 1, 3, and 5 years postdiagnosis were 88%, 73%, and 56%, respectively.

## CONCLUSIONS

In summary, the pathogenesis of PH-FM is still unclear, and there is no curable modality for it. The clinical manifestations of PH-FM lack specificity, and the rates of clinical misdiagnosis and underdiagnosis are high. For patients with PH, especially those with mismatched perfusion defects, SVC syndrome, FM dyad, and FM triad, doctors should consider the possibility of PH-FM. Contrast-enhanced chest CT can confirm the initial diagnosis and determine the clinical classification. In view of the limited efficacy of drug therapy as well as the uncertain effectiveness and high risk of surgical treatment, the endovascular interventional modality is currently the preferred therapeutic option, although procedure-related complications and intrastent restenosis after PV intervention remain concerns (**Central Illustration**).

## FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was supported by the National Natural Science Foundation of China (82070052 and 81860059). The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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**KEY WORDS** clinical classification, fibrosing mediastinitis, FM, FM dyad, FM triad, interventional therapy, pulmonary hypertension

**APPENDIX** For supplemental videos and the search strategy, please see the online version of this paper.