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REVIEW

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Incidence of secondary pericardial effusions associated with different etiologies: a comprehensive review of literature

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Abstract

Pericardial effusion is a relatively common complication associated with inflammatory and non-inflammatory diseases. The primary etiology of this condition could be considered when choosing therapeutic options and factors such as effusion size and its hemodynamic consequence. In most cases, small to moderate pericardial effusions can be managed with observation and anti-inflammatory medications unless the effusion develops rapidly. However, in a small proportion of patients, large effusions lead to impaired cardiac filling with hemodynamic compromise and cardiovascular collapse due to cardiac tamponade. The rate at which fluid accumulates is the primary determinant of hemodynamic impact and thus guides the choice of treatment, irrespective of the effusion's size. Severe cases are typically treated with pericardiocentesis with echocardiographic guidance. More aggressive treatments may be necessary for cases due to purulent or malignant etiologies. These cases may require a pericardial window to allow for long-term drainage of the pericardial fluid. This comprehensive review focuses on the epidemiology of pericardial effusion and discusses pathophysiology, diagnostic approaches, and therapeutic options for different causes of secondary pericardial effusions.

Keywords Cardiovascular disease, Pericardial effusion, Pericarditis, Infections, Inflammations, Cardiac imaging

Anatomy and physiology of the pericardium and the pericardial fluid

The pericardium is a two-layered covering around the heart. The inner layer, the visceral layer, consists of a single layer of mesothelial cells, collagen, and elastin fibers in contact with the epicardial heart surface. The external layer, normally about 2 mm thick, is a fibrous parietal layer covering most of the heart [1]. The main functions of the pericardium include fixing the heart to the mediastinum, providing efficient protection against infection, and making the surrounding part of the heart lubricated to facilitate its movement [2]. The normal range of pericardial fluid volume is 15–50 ml. However, the accumulation of fluid more than this amount raises pressure in the pericardial sac, causing compression of the heart, particularly the right side, due to a thinner wall and lower

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intracardiac pressure. Venous congestion occurs when the right heart's diastolic filling is impaired. Reduced diastolic filling of the left ventricle leads to lower stroke volume. Tachycardia and enhanced contractility are the earliest compensatory responses induced by adrenergic stimulation to sustain cardiac output. However, blood pressure and cardiac output gradually fall [3].

Definitions and categorization of pericardial effusion

Pericardial effusion (PE) refers to the accumulation of excess fluid in the pericardial sac, regardless of the type of accumulated fluid, and can be seen in up to 6.5% of the general population in the United States [4]. Various indices can be used to categorize pericardial effusion (Table 1). However, this pathology is classified into two main categories based on the etiology: 1) Primary PE (Without known underlying cause): Acute inflammatory pericarditis (infectious, autoimmune), previously unknown neoplasia, or idiopathic, and 2) Secondary PE: Secondary to a known underlying disease such as acute myocardial infarction, cardiac surgery (pericardiotomy), trauma, known widespread or metastatic neoplasia, chest radiation, chronic kidney disease (uremia), invasive cardiac procedures (cardiac perforation), hypothyroidism, or autoimmune diseases [5]. The echocardiographic features can differentiate mild (small) (< 10 mm), moderate (10–20 mm), and large (> 20 mm) from each other based on the effusion size (Fig. 1) [6, 7]. Sometimes, the drainage and assessing characteristics and composition of accumulated fluid are helpful and can lead to a definite diagnosis [8]. Moderate and severe types of PE have been more thoroughly investigated in recent years. This review focuses on the etiologies of secondary PEs, their geographic patterns, symptoms, diagnostic approaches, and therapeutic options (Fig. 2).

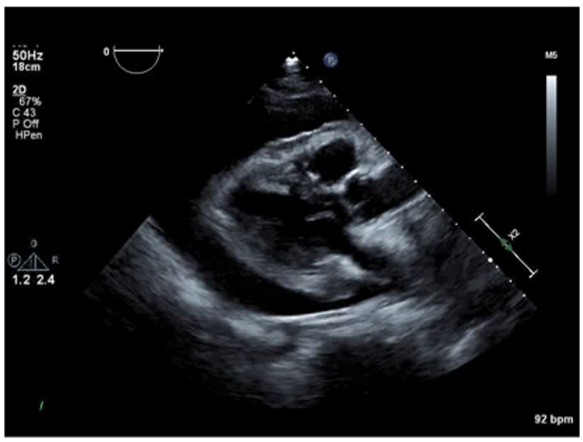

Fig. 1 Echocardiography can show the amount of fluid around the heart in pericardial effusions

Causes and epidemiology of pericardial effusion

The etiologies of PE include almost all pathologic pericardial diseases [12]. Inflammatory processes can cause exudative fluid accumulation by increasing the production of pericardial fluid. However, decreased reabsorption caused by enhanced systemic venous pressure can lead to transudative PE [6]. The main causes of pericardial effusion are different among developing and developed countries. The leading cause in developing countries is still tuberculosis. However, in the developed world, the leading causes include idiopathic pericardial effusion, inflammatory causes, malignancy-related PE, and complications of surgical and percutaneous cardiac procedures [13]. The overall leading causes of PE in the

Table 1 Overall categorization of pericardial effusions [9, 10]

Determining factor	Categorization
Size	Mild (small): < 10 mm Moderate:1–20 mm Severe (large): > 20 mm
Distribution	Circumferential Localized (or loculated)
Onset	Acute < 1 week Subacute: 1 week-3months Chronic > 3months
Composition	Transudate Exudate Hemorrhagic: Mostly due to malignancy, infections, rheumatologic disease, or trauma [11]
Hemodynamic impact	Insignificant (the hemodynamic effect of PE is often mild) Cardiac tamponade (from early signs to severe chamber collapse, Fig. 2) Effusive-constrictive

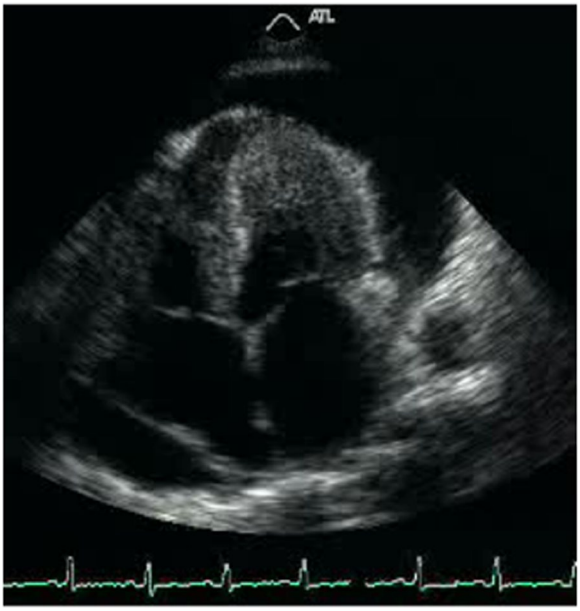

Fig. 2 Tamponade leads to increased intrapericardial pressure (holodiastolic compression), impairs ventricular filling, and consequently leads to elevated and equal left ventricular end-diastolic pressure (LVEDP) and right ventricular end-diastolic pressure (RVEDP) and reduction in stroke volume and cardiac output

developed countries, apart from up to 50%, which are idiopathic, are infections (15–30%), cancer-related causes (10–25%), iatrogenic causes (15–20%) and autoimmune or autoinflammatory causes (5–15%) [2, 14]. More recently, COVID-19 infection and vaccination (specifically mRNA vaccines) have become additional causes of PE [15, 16]. Many studies have broadly categorized PE's causes as inflammatory and noninflammatory (Table 2, Figs. 3) [17]**.** It is important to consider the point that in clinical practice, determining the exact cause of pericardial effusion often remains challenging, with many cases ultimately labeled as idiopathic [2, 18]. For instance, in a study, Abdallah R. et al. found that the most frequent etiology of large symptomatic pericardial effusion was idiopathic, accounting for 36% of cases. This highlights the importance of including idiopathic or undetermined categories in figures and tables related to pericardial effusion etiology, reflecting that the specific cause remains elusive despite thorough evaluations [2, 19].

Inflammatory pericardial effusion

Infections

Viral pericardial effusions

Viruses are the leading causes of pericarditis cases, which have known etiologies, especially adenovirus and coxsackievirus, and about 60% of viral pericarditis can cause pericardial effusions. However, most of the time, effusions are small and can be treated conservatively or with colchicine plus NSAIDs [32]. Corticosteroids and IL-1 blockers are other medical therapies [2, 12, 33, 34]. Hemorrhagic and large (hemodynamically significant) are uncommon viral causes of PE [35]. However, they are generally classified as idiopathic since a viral diagnosis needs histologic, immunologic, and or serologic evaluation, which is not usually done unless HIV or HCV infection is suspected [9].

Coxsackievirus-induced pericardial effusion

Coxsackieviruses, including types A and B, can have a wide range of clinical presentations in children and adults. Although it can cause a spectrum of symptoms from simple fever, hand-foot-mouth syndrome, up to severe life-threatening encephalitis or pericarditis, in adults, it is primarily a controllable presentation with malaise or fever, which can be treated with supportive care and NSAIDs plus colchicine [36, 37]. In the winter and fall, these infections are more observed in men [34]. Coxsackievirus B is cardiotropic and tends to involve the myocardium. This virus can involve myocardial cells chronically; it can cause severe myocarditis or even large pericardial effusions and tamponades because of myocarditis [36]. Pericardial effusion due to the Coxsackie virus can also be seen in children, and there are case reports of hemorrhagic pleural effusion in them, like the adult group [38]. Most of the time, myopericarditis, due to this virus, can be treated with anti-inflammatory medications and colchicine or other nonsteroidal anti-inflammatory treatments and steroids. However, colchicine efficacy and safety have not been approved yet in children. Massive PE and tamponade in these children are life-threatening. If needed, they should be treated aggressively with percutaneous or surgical drainage [38, 39].

HIV-virus-induced pericardial effusion

HIV can involve many aspects of the heart, including the myocardium, valve, and pericardium [40]. Pericardial effusion is seen in HIV-positive (particularly AIDS) patients more than in the average population (based on echocardiographic and autopsy studies) [41], and there is a direct correlation between the stage of the disease and the incidence of pericardial effusions. The prevalence range is between 0% in asymptomatic HIV + patients and 11% in AIDS patients. Also, the number of CD4 + lymphocytes correlates with the risk of pericardial effusion. PE is rare in non-AIDS HIV patients with normal CD4 + cells [42]. About 80% of outpatients who were HIV + have small PE (80%) and are primarily asymptomatic (87%). Hospitalized AIDS patients have a much higher prevalence of medium and large PE, attributed to its severity [41, 42].

Table 2 Inflammatory and non-inflammatory causes of pericardial effusion

Inflammatory	Infectious: Viral: enteroviruses (coxsackie B), adenovirus, herpesviruses (EBV, CMV, VZV), parvovirus B19, HIV, HCV, COVID-19 Bacterial: gram-positive cocci (Streptococcus, Staphylococcus), Mycoplasma, Neisseria (meningitides, gonorrhea), Coxiella burnetii Mycobacteria (tuberculosis, avium-intracellular) Fungal: Histoplasma species, Candida species Protozoal: Echinococcus species, Toxoplasma species
	Post-cardiac injury syndromes (PCIS): Post-pericardiotomy Post-myocardial infarction Post-electrophysiology interventions Post-coronary interventions Post-percutaneous structural interventions (Transcatheter Aortic Valve Replacement, Mitra Clip, etc.)
	Autoimmune: Systemic Lupus Erythematosus (SLE) Sjogren Syndrome Rheumatoid Arthritis (RA) Scleroderma Eosinophilic Granulomatosis with Polyangiitis (EGPA) (Churg–Straus syndrome) Familial Mediterranean Fever (FMF)
	Uremic pericarditis
	Drug hypersensitivity
Non-Inflammatory	Neoplastic: Primary tumors (rare, especially pericardial mesothelioma) Secondary metastatic tumors (lung, breast, cancer, lymphomas, and melanoma)
	Metabolic: Hypothyroidism (myxedema coma) Severe protein deficiency
	Traumatic: Iatrogenic Direct/indirect pericardial injury (penetrating or blunt chest wall injury, aortic dissection)
	Hemodynamic (Reduced Lymphatic Absorption): Congestive Heart Failure Cirrhosis Nephrotic Syndrome

Various hypotheses have been generated to try to explain the much higher prevalence of PE in AIDS patients. This difference may be due to a higher risk of malignancy such as lymphoma, Kaposi sarcoma, and other cancers. In some patients, it may be due to opportunistic infections, such as TB, bacterial, viral, fungal, cryptococcus, and protozoan infections. The correlation between low CD4 + cells and the risk of PE can explain the difference between the rate of infection between healthy and AIDS-positive populations [43–48]. There is also an indirect correlation between the progression of HIV and the level of serum albumin. It can be an independent predictor of the severity of the disease, mortality, and life expectancy [49]. An additional reason for the rise in PE occurrence is attributed to end-stage HIV capillary leak syndrome. This hypothesis is supported by autopsy investigations revealing a common presence of pericardial effusions, serous pleural effusions, and ascites. Elevated levels of cytokines like interleukin-2 and tumor necrosis factor, commonly observed in advanced HIV infection, are linked to capillary leak syndromes [42]. In a prospective 5-year study of 248 AIDS-positive patients, the annual incidence of PE was 11%/year, and the Relative Risk (RR) of death was 3 in AIDS + patients in comparison with HIV + patients without AIDS (CI:1.6–5.6). This finding indicates a statistically significant difference in the death rate among these groups [42].

COVID-19 virus-associated pericardial effusion

COVID-19 caused one of the most catastrophic health crises of our era, and there was a wide range of symptoms and signs which could be seen in the presentation of the COVID-19 patients. The manifestation can be a mild fever and respiratory discomfort or much more severe, such as rapid progression toward acute respiratory distress syndrome (ARDS) and death [50, 51]. Although many effective strategies have been introduced to combat the severity of the impact of COVID-19 on societies, during the last four years, several surges in the incidence of this disease have happened, and it has been a major

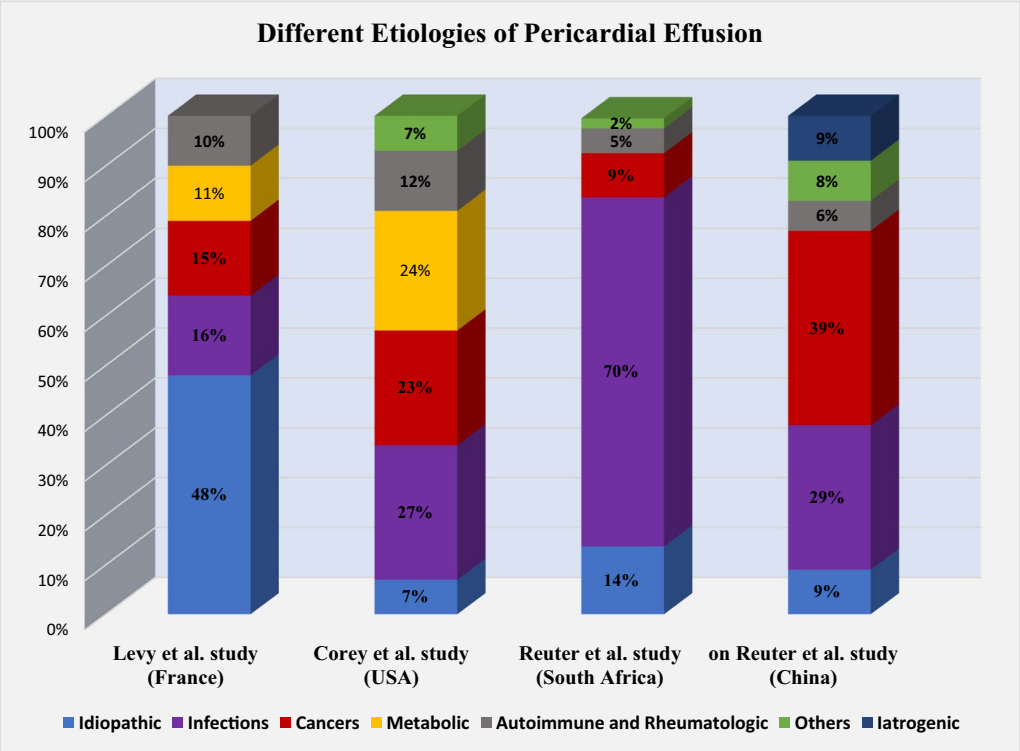

Fig. 3 Secondary causes of moderate to severe PE based on Levy et al. Study in 2003 (France) [20], Corey et al. study in 1993 (USA) [21], Reuter et al. study in 2005 (South Africa) [22], and Ma W et al. study in 2012 (China) [23]

health concern. [51]. Being well-prepared for new virus strains that might involve the population is crucial. The most vulnerable part of the population for rapid progress of the disease includes those older > 60 years, men, those with extensive lung involvement, patients with cardiac or vascular diseases, patients with a history of pericardial effusion, diabetes, and mediastinal lymphadenopathy [52–57].

Several studies have illustrated cardiac factors that can affect the prognosis or outcome of COVID-19-positive patients. In cardiac imaging, coronary vessel calcification and epicardial adipose tissue are independent prognostic factors for the worse outcome and deterioration of clinical conditions in COVID-19 patients [53, 58]. However, the prognostic effect of pericardial effusion in these patients is still a controversial issue, which has led to a lack of consistency between clinical and research studies [53].

COVID-19 can attack many kinds of tissues due to tropism through attachment to various types of receptors such as the angiotensin-converting enzyme 2 (ACE2), neuropilin-1, the tyrosine-protein kinase receptor UFO (AXL), and antibody–FcγR complexes. However, due to the high rate of asymptomatic pericardial involvement, the diagnosis of PE in this population is not adequately documented [59]. Many studies have shown that the rate of PE is much higher in COVID-19-positive patients compared to the healthy population. This difference is much more prominent in hospitalized COVID-19 patients [60]. The prevalence of PE among COVID-19-positive patients is reported to be 4% to 96% in patients with critical clinical conditions [61, 62]. Although a retrospective study showed a prevalence of 1.5% of PE among COVID-19 patients [59], another study conducted prospectively on hospitalized patients estimated this prevalence to be 15%. However, in this study, more than 90% of these PEs were mild; only 3/75 patients had moderate PE, and none of the effusions were significant [59]. There is no common consensus about the prevalence and range of severity of PE induced by COVID-19. However, the more severe the symptoms of the COVID-19 infection, the more the risk for COVID-19-associated PE [60]. Lazar M. et al. found no correlation between the severity and incidence of PE in COVID patients and the typical risk factors for severe PE, such as obesity, diabetes mellitus, and chronic kidney disease (CKD). Their results also showed among the patients with severe COVID-19 disease, 27% had PE, and all of them were mild (62.1%) or moderate (37.9%) [63].

The mechanism for developing PE in COVID-19 patients has been hypothesized, but a sole definite cause

has not been identified. Several studies have demonstrated that the pericardial effusion associated with COVID-19 follows the mechanism of other cardiotropic viruses, activating systemic inflammation [64]. Elevated components of IL1 and TNF-α in these patients and the correlation between increased C-reactive protein (CRP) and the severity of PE can verify this hypothesis [65]. Other mentioned theories include the tendency of the COVID-19 virus to attach to ACE receptors in the myocardium and [63, 64] epicardial adipose tissue and elevated PAH and respiratory distress caused by this infection [66, 67]. Several factors were associated with the incidence of PE, such as the severity of pulmonary involvement, RV dysfunction, and raised BNP; however, there was a weak association between PE and mortality rate among hospitalized COVID-positive patients [16, 68]. There are reports from COVID-positive patients who had progressive PE, which resulted in tamponade [69, 70]; however, in the prospective cohort study, the rate of progression of PE among hospitalized patients was insignificant, and none of them experienced death because of PE [60].

Although there is no general agreement about the severity of the effect of PE on the prognosis of COVID-19-positive patients, it has been reported that pericarditis, which does not necessarily occur in PE, is associated with a significantly higher rate of mortality in COVID-positive patients [59]. Moreover, Lezar M. et al. noted that patients with COVID and PE had a 60% greater mortality than patients with COVID but without PE [63]. Another research found PE as a frequent finding, seldom attributable to acute pericarditis or myocarditis in hospitalized COVID-19 patients, although it was potentially linked with cardiac dysfunction and increased mortality [60]. COVID-related PE can also lead to bacterial pericarditis and purulent PE, which can result in severe clinical conditions. They should be promptly treated with pericardial drainage and potent antibiotics [71, 72]. Table 3 summarizes studies investigating PE's association with COVID-19 infection so far.

Treatment of COVID-19 and PE is complicated, and the choice depends on several factors. In a study by Imazio M. et al., it was concluded that, unlike NSAIDS, for the treatment of pericarditis in COVID-19 patients, taking of corticosteroids, colchicine, and anakinra is not harmful with close monitoring for probable bacterial super-infectious [78].

There have been echocardiographic prognostic factors that showed an association with the death rate in patients with PE and COVID-19, such as 1) low forward flow, 2) high RV and LV filling pressure, and 3) high RV afterload [79, 80]. Based on several studies and recommendations of the European Association of Cardiovascular Imaging and the American Society of Echocardiography,

Table 3 An overview of research that has explored the prevalence of PE and its relationship with outcomes in COVID-19-positive patients

Study and Authors	Type of study and sample size	Prevalence of PE in COVID-positive patients	Correlation between COVID and PE
1. Bucher et al. [51]	Multicenter, retrospective study in Germany with 1197 patients	13.3%	The presence of PE is a predictive factor for 30-day mortality, more density of involvement, and the need for ICU admission in males; no significant role in female patients
2. Adams et al. [73]	Systematic Review and Meta-Analysis, 3,466 patients, 28 studies	2.7%	PE is an atypical finding in COVID-19 patient's chest CT scans
3. Zhu et al. [74]	A retrospective meta-analysis was conducted with 4121 patients, including 34 studies and 2738 patients	0%	PE was an atypical incidence in COVID patients. No correlation was identified between PE and the outcome of COVID
4. Bao et al. [75]	Systematic review and meta-analysis on 13 studies	4.55%	It was an atypical incidence in COVID-19 patients. No correlation was identified between PE and the outcome of COVID
5. Eslami et al. [76]	Prospective cohort with 87 patients	–	The presence or absence of PE has no predictive role in the survival and outcome of COVID-19-positive patients
6. Abkooh et al. [77]	Retrospective cohort study of 129 COVID-positive patients	13%	PE was a strong independent predictor of survival and short-term mortality
7. Kermani-Alghoraishi et al. [16]	A case-report-based systematic literature review on moderate to severe PEs. And they are reporting a severe tamponade due to COVID-19	–	COVID-19 virus was found in PE fluid. Emergency percutaneous pericardiocentesis often showed exudative patterns: hemorrhagic, serous, and serosanguinous

PE, pericardial effusion; CT, computed tomography; ICU, intensive care unit

significant prognostic factors in PE and COVID-Positive patients are found using focused cardiac ultrasound. Evaluating different studies, Ghantous E. et al. concluded that a combination of three factors: 1) LVEF, 2) Four-chamber Tricuspid annular plane systolic excursion (TAPSE), and 3) the presence of PE can provide an accurate prognostic factor for hospitalized COVID-Positive patients. It is more valuable than subjective clinical assessment, and in cases of overwhelming healthcare systems, this indicator can help prioritize patients with the least bias [79, 81–83]. Moreover, it is observed that an increase in serum myoglobin in patients with COVID-19 and PE is correlated with mortality, and myoglobin's serum level is more predictive of the incidence of PE [63, 84].

TB-related pericardial effusion

The three main cardiovascular structures of tuberculosis are the pericardium, myocardium, and aorta. TB is the leading cause of pericardial effusion in low- or middle-income countries, accounting for 40–70% of PE cases. Most of these cases belong to southern Asia, sub-Saharan Africa, and the western Pacific (roughly 87% of worldwide tb-pericardial involvement cases) [85, 86]. Involvement of pericardial tissue in TB is highly associated with participation with HIV or other immune deficiency diseases [87, 88]. In a study, it has been shown that 40–75% of large pericardial effusions in TB-endemic regions are in HIV-positive patients [88, 89]. However, less than 5 percent of pericardial involvement in immunocompetent patients is due to TB [90].

Tuberculosis-related pericardial involvement can be seen in four types: 1) acute pericarditis, 2) pericardial effusion, 3) myopericarditis, and 4) constrictive pericarditis. Some patients might have two or more types of these pericardial involvements [91]. The pattern of symptoms in TB-related pericarditis depends on the severity of the involvement and the rate of fluid accumulation. When pericardium is involved, the dominant initial symptoms are fever and tachycardia. In the absence of a compensatory mechanism, if the fluid accumulates progressively and rapidly in pericardial space, it can cause severe pleural effusions, tamponade, and even death in up to 85% of cases [92, 93].

The first step in treating TB-induced pericardial effusion is the effective elimination of mycobacterium tuberculosis. Four anti-tuberculous drug regimens (rifampicin, isoniazid, ethambutol, and pyrazinamide) are the main ways to achieve this goal. They should be taken for a minimum of six months. The optimal combination of therapy depends on geographical and epidemiological features. Corticosteroids are also effective in reducing death from cardiac involvement by tuberculosis [94]. In cases of TB-related tamponade, urgent pericardiocentesis should be done. Since no favorable evidence has been reported for open surgical drainage, the treatment choice is needle pericardiocentesis and leaving a pericardial catheter in place until the effusion is stabilized [95–97].

Purulent pericardial effusion (bacterial and fungal)

Purulent pericardial effusion was more commonly seen before the emergence of antibiotics and was primarily seen in children and young adults. Nowadays, with the presence of antibiotics, advances in cardiothoracic surgeries, and widespread vaccination, its prevalence has declined dramatically [98]. The most common causes of purulent pericardial effusions are bacterial causes such as Streptococcus pneumonia, Staph aureus, Streptococcus viridians, tuberculosis, and less commonly atypical organisms such as candida and salmonella can also be detected [99, 100]. Most of the cases are immunocompromised patients with a recent history of pneumonia, cardiothoracic surgeries, bacterial endocarditis, infection in other parts of the chest or neck, intracardiac device, mediastinitis and intrathoracic cancers or septicemia [101].

The clinical manifestation of the disease might be subtle and non-specific and then change to a severe, dramatic manifestation of tamponade or CV collapse [102]. In other studies on purulent PE in children, the most presenting symptoms were fever, breathlessness, chest pain, and cough. Tachycardia, tachypnea, hepatomegaly, and distant heart sounds were dominant in their examination. In the study by Agrawal et al., tamponade was seen in 27.3% of cases, while it was more common in other previous studies (36%) [103–105]. The most common sources of infection (concomitant infections) are listed in Table 4

Table 4 Concomitant Infections and Complications in Purulent Pericardial Effusion [103]

Associate infections	Frequency (%)
Empyema	59
Pneumonia	22.7
Arthritis	18
Pneumothorax	9
Para vertebral abscess	9
Infective endocarditis	9
Peritonitis	9
Liver Abscess	4.5
Osteomyelitis	4.5
Deep Vein Thrombosis	4.5
Intestinal Obstruction	4.5
Pancreatitis	4.5
Septic Shock	4.5

below. The outcome of this condition depends on medical care since it can rapidly progress to life-threatening arrhythmia and tamponade [106]. The treatment options should be promptly evaluated and performed (surgical evacuation of PE, targeted antibiotic therapy, pericardiotomy, intrapericardial streptokinase) [107]. The mortality rate with all possible treatments can be reduced to lower than 20%. However, in survivors, pericardial constriction is one of the most common complications [103, 106].

Post-cardiac injury syndrome pericardial effusion (PCIS)

Post-pericardiotomy syndrome (PPS)-related pericardial effusion

An inflammatory-related condition can be commonly seen after cardiac surgeries due to pericardial and pleural damage and pericardial bleeding [110]. It typically presents a few days to several weeks after cardiac surgery with radiating pleuritic chest pain (worse with movement and breathing and causing shallow rapid breath) and intermittent low-grade fever in half of the cases [107, 110], and a friction rub in 20–30% of cases [110]. There might also be a relapse of PE 2–11 weeks after the resolution of the initial episode [111, 112]. Incidence has been reported between 21 and 29% in recent studies depending on the target population, diagnostic criteria, and type of procedure [113, 114]. It is considered an inflammatory process due to fever and the rise of inflammatory markers [115].

This condition's most definitive risk factor is the age between 2 and 30 years (lowest incidence below two years old, highest after 2, declining after that). Other patient-related risk factors include female sex, seasonal variation (highest in the summer), lower platelet count, lower weight, halothane anesthesia, corticosteroid use, and pulmonary disease. Another important risk factor is the type of surgery. Although there is no definite agreement between studies, it has been shown that there is a correlation between the complexity and duration of the procedures and a higher incidence of PPS. Manipulation of the heart and its adjacent structures during invasive procedures is one of the reasons for pericardial bleeding and, in severe cases, hemopericardium. It can be caused by myocardial rupture or other structural trauma and lead to severe blood loss and hemodynamic deterioration [116, 117]. A more complex surgery can result in more pericardial damage, longer duration in cardiopulmonary bypass, and increased exposure to foreign materials [115]. The highest rate has been seen in aortic surgeries (especially when emergent or urgent) compared to CABG, AVR, or MVR surgeries [115]. Interestingly, diabetes mellitus appears to have a protective effect, as illustrated in prior studies, and it might have been affected by many confounders [111, 118].

Most of the time, the pericardial fluid appearance is straw-colored or serosanguinous and can contain lymphocytes, RBCs, and granulocytes [119, 120]. Due to the presence of physiologic fluid accumulation after these surgeries, differentiation of PE from the normal fluid can be difficult, but the rate of PE can be as high as 88–92% in most cases, which is primarily mild (83%), rather than moderate (13%) or significant (4%) [121]. PPS treatment, most of the time, is limited to colchicine, with or without NSAIDs. Additional therapy is needed—we generally use an IL1-inhibitor, rilonacept [122]. However, others often use corticosteroids, which can increase the risk of recurrence. However, percutaneous drainage of the accumulated fluid should be considered insignificant pericardial or pleural effusion cases [118, 121]. Although needle pericardiocentesis under the guidance of fluoroscopy or echocardiography is the treatment of choice, in selected cases, a surgical approach might be recommended in complex cases or in those in which needle aspiration might be difficult [2, 118]. A strong association exists between severe PPS and mortality, specifically the first two-year mortality [111, 123].

Post-myocardial infarction pericardial effusion

Sterile pericarditis after myocardial injury, called Dressler syndrome, is an inflammatory process due to necrosis of myocardial cells and activation of the immune system against released intracellular components [124, 125]. Although it had a high prevalence of about 3–5% in the past, with the development of revascularization techniques, the incidence is now less than 1% [126]. It usually presents nonspecific symptoms such as pleuritic chest pain (exacerbated by lying flat), fever, shortness of breath, and ECG changes. However, it can rarely become complicated with PE or even tamponade [127, 128].

Dressler's syndrome typically manifests with pericardial effusion occurring between two to eight weeks after an acute myocardial infarction [126, 129]. The optimal management involves using nonsteroidal anti-inflammatory drugs (NSAIDs) to reduce inflammation and alleviate symptoms. In cases where NSAIDs are ineffective or contraindicated, corticosteroids may be considered. However, their use is generally reserved for more severe cases due to potential side effects. Early recognition and appropriate anti-inflammatory treatment are essential for managing symptoms and preventing complications [126, 129]. The rapid accumulation of fluid compresses the chambers. It limits the filling and expansion of the right and left heart chambers, which limits forward stroke volume and cardiac output. The consequence of the accumulation of intra-pericardial fluid and reduced stroke

volume can lead to tachycardia, low blood pressure, muffled heart sounds, elevated jugular venous pressure, and CV collapse [130].

Post-electrophysiology or coronary interventions pericardial effusion

Even minor traumas to the heart, such as percutaneous coronary intervention (PCI), pacemaker insertion, or radiofrequency ablation, can result in PCIS [131–134]. While the risk of PCIS can be as high as 90% in post-pericardiotomy syndrome, it is as low as 1–5% in the implantation of heart devices and 0.2% in PCI (Fig. 4) [132–134]. The majority of PCIS cases have PE, but not all of them are symptomatic or need to be treated. In a study with 968 participants for permanent pacemaker implantation, about 10% of patients had PE a day after the procedure, less than 2% were symptomatic, and about 1.5% needed to be treated [135]. Interventional procedures such as implantable cardioverter-defibrillator (ICD) placement, Cardiac Resynchronization Therapy (CRT), and PCI can uncommonly cause severe pericardial bleeding and, in some patients, result in hemopericardium. The patient's hemodynamic condition can deteriorate remarkably and lead to irreversible complications and death [116, 117] (Fig. 5). Although the risk factors for PCIS following PCI are unclear, some studies have shown that female gender, transvenous temporary pacemaker, insertion in the right atrium, using anti-platelet medications, and steroid use during the last seven days before the procedure are associated with an increased risk of PCIS incidence [135, 136]. The overall treatment of PCIS following these procedures is not different from the PCIS types discussed before [131].

Autoimmune-related pericardial effusion:

Many autoimmune diseases, including rheumatologic pathologies, can present themselves with a pericardial effusion as the first presentation [17]. The most common correlation between rheumatologic diseases and pericardial effusion can be seen in Systematic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA), and Sjogren's syndrome (SS) [11].

Pericardial effusion caused by systematic lupus erythematosus (SLE):

Lupus mainly presents with fatigue, fever, arthralgia, malaise, malar rash, photosensitivity alopecia, and weight loss [137]. The cardiac manifestations, including pericarditis, myocarditis, coronary artery disease, conduction system abnormalities, and arteritis, can commonly (up to 50%) be seen as a presentation of SLE [138]. Studies have shown the prevalence of up to 75% of pericarditis in SLE, which might be diagnosed by symptoms or incidentally. It is also one of the diagnostic criteria of SLE [138]. However, pericardial effusion is not a common initial presentation of SLE [139]. However, some studies have reported cases of women younger than 35 years old whose SLE was diagnosed after the presentation of PE as the initial complication [140, 141]. Reports of large PE or tamponade in SLE showed an incidence of about 1–2.5% [142].

In SLE, PE is often exudative. The fluid is usually clear but also serosanguinous and rarely hemorrhagic [143].

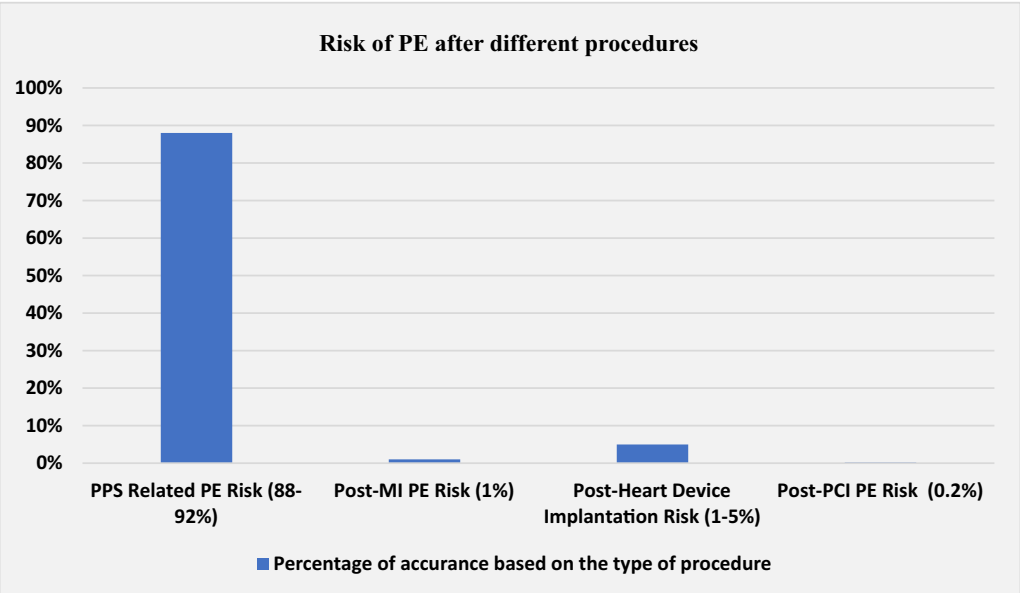

Fig. 4 Risk of PE after different cardiovascular events [134]

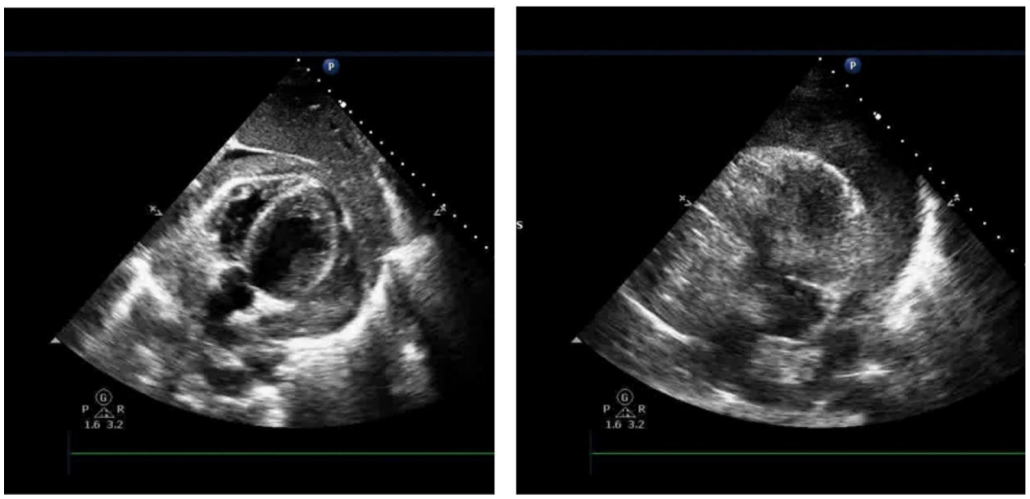

Fig. 5 Hemopericardium can be caused by interventional or surgical cardiac procedures and, in severe cases, can lead to hemodynamic deterioration, cardiovascular collapse, and even death

In a study, the incidence and potential contributing factors were detected by evaluating 50 asymptomatic SLE patients; 24% had PE, and there was a direct correlation between low albumin, higher proteinuria, higher CRP, higher pulmonary arterial pressure, and a higher tendency to have PR-segment depression [144]. Although 7% had large PE and 2% had tamponade reported among SLE patients, most of the cases have chronic mild to moderate PE [143]. Weich et al. evaluated eight SLE-positive large PE or tamponade patients among 258 cases and noticed a correlation between large PE, nephritis, Liebman-Sacks vegetations on echocardiography, and myocardial dysfunction [138]. In another study by Rosenbaum et al., 29% of SLE-positive patients who had PE were diagnosed with tamponade. Interestingly, some of these patients had two mutual characteristics: female gender and having lower levels of C4. Renal involvement, hemolytic anemia, and pleurisy are other predictor factors for the risk of having PE in SLE-positive patients [145, 146]. The primary diagnostic modality for pericardial effusion diagnosis in these patients is transthoracic echocardiography [146]. However, the treatment is based on the severity of the condition.

Patients with low-volume PE and minimal symptoms are observed, and most effusions in these cases spontaneously resolve. Considering the clinical and echocardiographic features, the therapeutic options in small asymptomatic cases can be observed whereas aligned with the severity of symptoms and (size of the effusion), NSAIDs, colchicine, rilonacept corticosteroids, or pericardiocentesis (in cases of tamponade) are used as potential treatments [113, 147, 148].

Sjogren syndrome-induced pericardial effusion

SS is one of the most common rheumatologic diseases, primarily seen in women (9/1 ratio), and it is caused by lymphocytic infiltrates of the exocrine glands, which cause typical xerostomia and keratoconjunctivitis sicca. It can be divided into two types: 1) Primary SS (pSS) and 2) Secondary to other rheumatologic diseases [149]. One of the most lethal complications of this disease is cerebrovascular and cardiovascular involvement [150, 151]. One of the common complications of pSS is high pulmonary arterial pressure (PAP), which is a prevalent condition in all connective tissue diseases. A study shows that 12.5% of pSS patients have high PAP, and this is highly associated with PE [152]. In a study evaluating associated factors with pulmonary arterial HTN (PAH), PE has become one of the independent risk factors, with a 31% prevalence in the PAH-positive group compared to 12.1% in the PAH-negative group. Therefore, the presence of pericardial effusion in pSS patients should alert the clinician about an increased risk for the development of PAH in the future. In another study by Farrukh et al. PE was one of the most common cardiac manifestations of pSS, with a 19.3% prevalence (following atrioventricular block and myocarditis). Most of these patients presented with chest pain, dyspnea, fever, and palpitations [150].

Pericardial effusion caused by rheumatoid arthritis (RA)

Rheumatoid arthritis (RA) shows a strong association with the occurrence of pericardial effusions. Pericardial effusion is seen in 3.6% of women and 1.7% of men with rheumatic arthritis [153]. However, diagnosis is not always straightforward due to nonspecific symptoms and a lack of agreement on a definite laboratory test to

confirm the disease. It is estimated that 30% of patients with confirmed RA have concomitant pericardial effusion [154]. In a study of RA patients without any cardiovascular disease symptoms, the most common echocardiographic features in a screening study were 1) pericardial effusion, 2) aortic root dilation, and 3) valvular thickening [155]. In an echocardiographic and autopsy study, PE was prevalent in up to 50% of the RA population. [156].

Although there are typical features of PE fluid in RA, such as 1) exudative, 2) low glucose, 3) low C3 and C4 complement, 4) high lactate dehydrogenase, gamma globulin levels, and leukocytes, these diagnostic features may not be reliable as they are absent in many cases. In RA patients, the severity of joint manifestations does not reflect the incidence or likelihood of PE [157, 158]. Moreover, once occurring, TNF-alpha inhibitors cannot decrease the incidence risk of PE [158]. Recurrent PE in RA increases the risk of developing tamponade [154]. Since there is often a gradual and asymptomatic accumulation of fluid in the pericardial, an episode of RA can result in a rapid accumulation of pericardial effusion and lead to tamponade faster and more clinically catastrophic in comparison with the general population.

Although uncomplicated RA-induced pericarditis is mostly manageable with colchicine, NSAIDs, corticosteroids, and immunosuppressive medications [159], progressive PE and life-threatening tamponade should be approached by catheter-based pericardiocentesis for therapeutic and diagnostic reasons. Moreover, tamponade is an indicator of poor prognosis, severity of disease, and the necessity of controlling inflammation in this disease [160].

Scleroderma-induced pericardial effusion

Scleroderma is one of the most prevalent rheumatologic diseases in the US [161], primarily seen in women, and has a cardiac manifestation that can occur before or simultaneously with other manifestations of the disease in 32.5% of the patients [162]. The overall incidence of PE in scleroderma is about 17%. The risk of death in scleroderma patients complicated with PE is about 2.8 times higher than in cases without PE [162] and mainly occurs due to arrhythmia and severe heart failure [163]. Most of the cases of scleroderma-induced PE are manageable with anti-inflammatory medications, and percutaneous or surgical drainage should be reserved for those unresponsive to medications or with severe, life-threatening symptoms.

In systemic sclerosis, PE is mainly detected in the first year of disease diagnosis (while skin tightness and internal organ involvement are detected in the first 3–5 years) and are associated with higher mortality [164, 165]. Pericardial effusion features are less studied due to the higher risk of pericardiocentesis in this population, considering PAH and the increased elasticity of chest skin [166]. However, in a study of nine patients in Thailand, most of the patients' PE fluid had exudative features with a low cell count and high protein and lactate dehydrogenase. The outcome of treatment for pericardial disease in these patients was poor. There was a direct correlation between pericardial effusion incidence and the rate of anti-SCL-70 positivity. Most of the PE detected were moderate, and the large effusions often developed into tamponade [167].

Eosinophilic granulomatosis with polyangiitis (EGPA) or Churg–Strauss syndrome (CSS)-related pericardial effusion:

EGPA, or CSS**,** is an autoimmune disease characterized by asthma, necrotizing vasculitis of small vessels, inflammation with extravascular granuloma, and hypereosinophilia. It mostly starts with pulmonary symptoms. However, it can involve other organs, such as the gastrointestinal and nervous (mostly peripheral neuropathy in the vasculitis phase) and cardiovascular systems [168–170]. Cardiac involvement in EGPA can take various forms, and the pericardium is one of the targets of this disease. This involvement can be in the form of pericarditis or variable (but mostly mild) amounts of PE. Large PE and tamponade were rare manifestations of this disease despite being reported in some cases [171]. According to some studies, cardiomyopathy and PE were the most common cardiac presentations of EGPA [172]. Pericardial involvement was reported in about 20% of these patients [173], and it was more common in ANCA-positive patients, but tamponade was rarely reported [174]. PE can seldom manifest as the first presentation of EGPA [175, 176].

Familial mediterranean fever (FMF) and pericardial effusion

FMF is an inherited (autosomal recessive) autoinflammatory disease primarily seen in Arabs, Turks, Armenians, and Jewish populations. It presents with periodic fever, pleuritis, pericarditis, and arthritis [177]. Pericardial involvement is one of FMF's most common cardiac presentations, while a rare overall presentation (0.7–1.4%) can be pericarditis, pericardial effusion, or constrictive pericarditis [178]. Pericarditis mainly occurs as a 4-day attack and resolves spontaneously [179, 180]. Although a study demonstrated that during FMF attacks, the rate of pericarditis and PE is much higher (27%) [179], other studies show that the overall involvement of pericardium in FMF is very low (0.7% to 1.4%) [181]. This complication does not require regular monitoring. It has been reported that colchicine, NSAIDs, and corticosteroids effectively prevent and treat FMF-induced pericardial effusion [182]. However, other trials have emphasized

restricting colchicine's effectiveness to the recurrent FMF-induced PEs. They have reported cases of pericardial effusion occurrence, even in the severe form and tamponade, despite taking colchicine as a primary prevention for PE [183, 184]. Sometimes, massive PE can be a life-threatening initial presentation of FMF and should be approached with transcatheter pericardial drainage as a diagnostic and therapeutic procedure [182].

Uremic pericardial effusions

Following the increasing prevalence of hypertension, diabetes mellitus, and consequently, end-stage renal disease (ESRD), the pericardial complications of this condition have had a growing trend. The pericardial complications include pericarditis, pericardial effusions, and constrictive pericarditis. Large pericardial effusions can have significant hemodynamic complications [183]. The effusions are categorized into two categories: 1) uremic pericarditis, which starts before the initiation or during the first eight weeks of dialysis, and 2) dialysis pericardial complications, which usually start after eight weeks of dialysis [185].

Pathophysiology and the treatment of PE due to uremia and dialysis are complicated. These patients have many comorbidities, such as cardiovascular disease, inflammatory and rheumatologic processes such as lupus and hypoalbuminemia (which can alter the water loss from the body), susceptibility to various viral infections, and accumulation of nitrogen oxidative components due to kidney dysfunction, which can put them at greater risk of PE [186, 187]. The incidence of pericardial effusions is different in various studies. In one study, PE was seen in 12.9% of patients, with 6.1% and 0.7% being moderate and severe, respectively. The incidence in women was about 50% higher than men's [188]. Another study showed an incidence of 14.3% among ESRD patients [189]. Ravi et al. estimated that dialysis-related pericardial effusions were about 44% [190]. It has been shown that most of the PEs in CKD patients are found incidentally, and most have no clinical symptoms or ECG changes. Therefore, diagnosis of PE in these patients based on their clinical condition is not feasible, and the rate of PE in CKD patients seems to be underdiagnosed [191].

Based on the absence of suggestive signs and symptoms for diagnosing PE in CKD patients, having laboratory data helps physicians as a guide for detecting more vulnerable patients to PE. It seems to be very practically useful [191–193]. Unexpectedly, none of the kidney function (BUN, CR, GFR) indicators have demonstrated any significant correlation with the incidence of PE [191, 193]. Ravi et al. identified that heart rate > 100, potassium level > 5 mEq/L, and corrected calcium level < 8 mEq/dL were the predictors of the occurrence of PE, while only corrected calcium level < 8 was the only highly sensitive predictor of moderate to severe PE. Concerning the progression of hyperkalemia and hypocalcemia with deterioration of renal failure, increased incidence and volume of PE are expected [190]. This would be a helpful information for screening of the patients with CKD. If they have any of these three factors, they will be a candidate for TTE, which is not feasible for all patients [190].

Interestingly, the presence or absence of PE does not significantly affect the survival rate or complications. If PE is not life-threatening or reducing the quality of life, treatment for these patients is still chosen based on kidney functions, not pericardial effusion [193]. The mainstay of the treatment of PE due to uremia is initiating dialysis, and more than half of these patients respond to intensive hemodialysis [2, 194]. Moreover, if the response is unsatisfactory, other methods, such as pericardiocentesis, pericardial window, and pericardiectomy, should also be considered [2, 195]. As with different types of PE, whenever the PE is severe or the symptoms of tamponade are seen, treatment should be conducted as soon as possible and opted based on the available facilities, the patient's clinical condition, and the expertise of available physicians.

Drug-related pericardial effusion

Several medications can cause pericarditis and pericardial effusions, but the incidence of this type of PE is infrequent [6]:

1. Procainamide, hydralazine, isoniazid, and phenytoin (lupus-like syndrome),
2. Penicillin's (hypersensitivity pericarditis with eosinophilia),
3. Doxorubicin and daunorubicin (although often associated with a cardiomyopathy, they can also involve pericardial tissue and space).
4. Minoxidil.
5. Immunosuppressive therapies (methotrexate, cyclosporine).

Non-inflammatory pericardial effusions

Neoplastic pericardial effusions:

Malignancies are the second leading cause of etiology-established pericardial effusion in developed countries (10–25%). The leading cause of neoplastic pericardial effusions is the spread of metastatic cells through the blood or lymphatic circulation system into the pericardium. Alternatively, inflammation involving the pericardium, radiation or chemotherapeutic therapy toxicity, or opportunistic infections following immunocompromised can result in pericardial [196, 197]. Pericardial effusions

can be seen in up to 15–30% of patients with cancer at autopsy, while this percentage of people without cancer is roughly 4% [197]. Lung (35%), breast (25%), and lymphoma and leukemia (15%) are the most common metastatic cancers that can cause PE, and other malignancies such as the esophagus, Kaposi's sarcoma, and melanoma are the next causes [198, 199].

The clinical manifestations of neoplastic PE vary widely depending on the volume and rate of filling of the pericardium. PE can be asymptomatic when the fluid volume is minimal and is slowly accumulating. On the other hand, a high volume and rapid accumulation results in symptomatic cases such as arrhythmia, cardiovascular collapse, and death due to tamponade [200]. Neoplastic diseases can cause cardiac pathologies with different acuities and consequences. The cardiac presentation can be rapid and fulminant such ass tamponade. Such complications need to be approached emergently as potential causes of cardiovascular collapse and death. Constrictive pericardial disease is a condition that is generally chronic, but it needs to be diagnosed, and it is usually treated with pericardiectomy. Mild and moderate pericardial effusion or pericarditis are less acute and give more time to patients and physicians to treat or control them [198]. The treatment of pericardial effusion due to cancer includes relieving the symptoms and preventing the reaccumulating of fluid [201]. Percutaneous pericardiocentesis is the mainstay of the treatment and, at the same time, an excellent diagnostic procedure [202, 203]. Pericardial effusion has significant prognostic implications for cancer patients. There is a high risk of recurrence of PE (about 90% in 90 days) if pericardiocentesis is done without prolonged pericardial drainage. In a study from Cedars-Sinai Medical Center, the overall recurrence rate of 11.8 ± 0.6 months after pericardiocentesis was 20%, and the mean interval to recurrence was 1.2 ± 2.1 months. However, patients with extended catheter drainage had a reduced recurrence rate of 12% compared to 52% in patients without extended drainage ($p < 0.001$) [202, 204, 205].

Metabolic pericardial effusions

Hypothyroidism-induced pericardial effusion:

Thyroid dysfunction can affect the heart in many aspects, including contractility, rate and rhythm, vascular lining features, blood pressure, and the pericardium [206]. PE is one of the main cardiovascular complications of hypothyroidism. The incidence of PE ranges from 3 to 37% (Fig. 6) [207–209]. There is a direct correlation between the severity of hypothyroidism, PE incidence, and its severity [207–209]. Less than one-third of these cases are large PEs [210].

There are three main hypotheses according to the etiology of PE due to hypothyroidism:

1. Hypothyroidism causes increased vessel permeability; pericardium-supplying vessels are permeable to albumin, and albumin accumulation in the pericar-

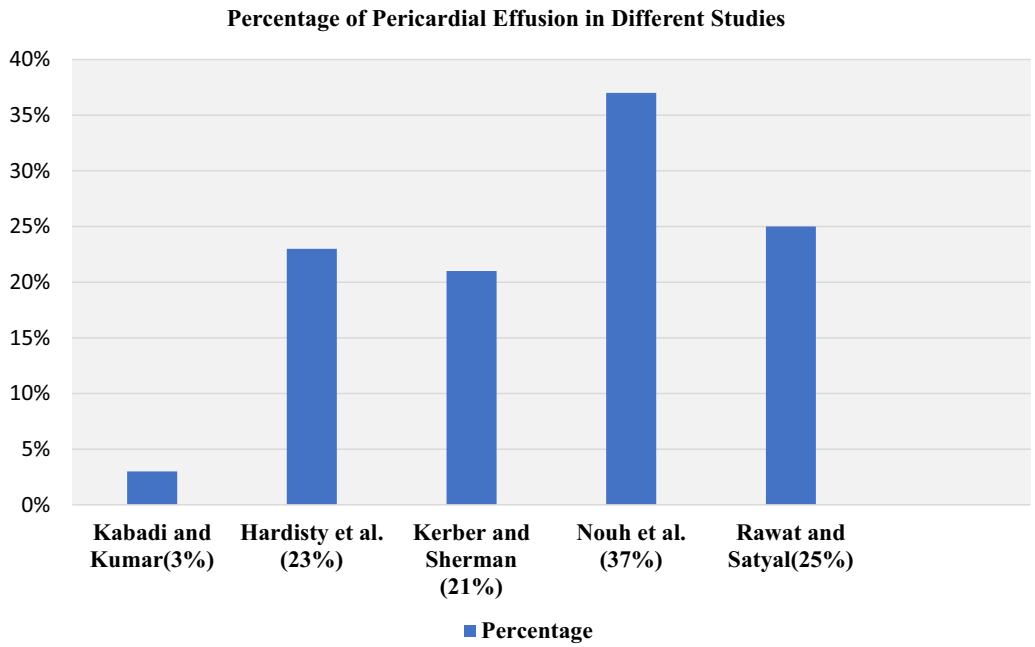

Fig. 6 Percentage of pericardial effusion among hypothyroid patients

dial space increases the space's osmolarity, causing more water to be absorbed [211].
2. Hypothyroidism causes decreased catecholamine levels (catecholamines' role is to increase lymph flow; therefore, the impaired lymphatic system cannot efficiently drain pericardial space) [210, 212].
3. Hypothyroidism can cause PAH. The pressure on the right side of the heart is elevated, and fluid accumulates in the pericardial space and is not drained [213].

The pericardial space can contain about 1000 ml of fluid without any symptoms if the accumulation is very gradual, as in the case of hypothyroidism-induced PE. Therefore, this kind of PE usually has no symptoms [209, 212]. However, after a certain amount of pericardial effusion, the symptoms emerge and become worse, even as severe as cardiovascular collapse and death, even with a small addition of fluid (Table 5) [214, 215].

The definitive treatment of PE in these patients is levothyroxine until the euthyroid state becomes established [216, 217]. However, the PE usually resolves in several weeks or months after achieving a euthyroid state. In cases of tamponade or inflammatory symptoms, drainage and anti-inflammatory medications are indicated [215, 217]. It has been reported that not all instances of tamponade need to be drained, and the hypothyroidism treatment might be enough for the treatment of tamponade; however, this situation should be carefully monitored [17, 217].

Pericardial effusion due to severe protein deficiency:

Any severe protein deficiency, such as nephrotic syndrome, cirrhosis, anorexia nervosa, and malnutrition, can cause pericardial effusion [17, 218]. Protein deficiency due to malnutrition is mainly seen in the children of sub-Saharan African countries [218]. Although the most common reason for adult PE in these regions is TB, children with a diagnosis of PE should be evaluated for malnutrition. Since malnutrition is frequently accompanied by concomitant diseases such as HIV and TB, determining which one is the cause of PE is not easy [219]. One way to differentiate malnutrition-induced PE from chronic infection-induced PE is by treating malnutrition, which will cause improvement in the first reason of PE and worsen in the latter [220]. The other distinguishing factor between these two kinds of PE is the evaluation of peripheral edema. Considering the mutual etiology between PE and peripheral edema in the case of malnutrition-induced PE, there is a direct correlation between the incidence and severity of these two. This feature would be helpful in regions such as Africa, where patients with both infections, such as HIV and TB, can have concomitant malnutrition. If the PE is accompanied by peripheral edema, it can be attributed to malnutrition. In contrast, those without peripheral edema have a higher chance of infectious PE. This means such signs and symptoms can distinguish infectious PE due to TB or HIV from malnutrition-induced PE [219].

The reasons why protein deficiency can cause PE are numerous, such as hypoalbuminemia-caused extravasation of fluid from vessels, increased permeability of fluids due to decreased osmotic pressure, congestive heart failure, and changes in the hemostasis of water and salt in the kidneys [219]. One of the theories is that muscle waste and consequent heart failure are due to the lack of micronutrients. Therefore, deficiency of thiamin and selenium, reversible causes of congestive heart failure, has shown to be partially effective in these cases [221–223].

Table 5 Clinical findings in patients with hypothyroidism-induced Severe PE

Variable	Finding
Symptoms	Shortness of breath (61%) Chest pain (25%) Paradoxical pulse (22%) Cough (14%)
Electrocardiogram	Low voltages (42–50%) T wave Inversion (22%) or Flattening (47%) Sinus Bradycardia (20%)
Chest X-Ray	Cardiomegaly
Echocardiography	Large Pericardial Effusion (30%) Tamponade Physiology (50%)
Laboratory	Increased TSH

Traumatic pericardial effusion

Traumatic PEs are the next cause of noninflammatory pericardial effusion. The leading cause among this group is iatrogenic PE (15–20% of overall cases) [2, 14]. The management of traumatic pericardial effusion primarily focuses on prompt drainage to prevent cardiac tamponade, a life-threatening condition. While medical therapy is essential for treating underlying causes of pericardial effusion, its role in traumatic cases is limited [2]. Treatment for pericardial effusion depends on factors such as the amount of fluid buildup, the cause of the effusion, and the presence or risk of cardiac tamponade. In cases of traumatic pericardial effusion, immediate drainage procedures like pericardiocentesis or surgical creation of a pericardial window are often necessary to relieve pressure on the heart. Medical therapies, such as anti-inflammatory medications, are more applicable in non-traumatic pericardial effusions where inflammation is the primary cause. Therefore, in the context of traumatic pericardial effusion, medical therapy serves a supportive

role, with surgical intervention being the cornerstone of effective management [2, 224].

Iatrogenic pericardial effusion

Almost one-fifth of tamponade cases are due to iatrogenic reasons, including surgical and nonsurgical. These reasons can be categorized as 1) nonprocedural, such as fibrinolytic therapy, antithrombotic therapy, or anti-cancer drugs, and 2) procedural cases, including percutaneous coronary interventions, percutaneous valvuloplasty, ablation with a catheter, and implantation of a pacemaker [223, 225]. Considering the increasing number of cardiac catheterizations, the rate of iatrogenic causes of pericardial effusion due to these procedures has become more prevalent [225]. A study in China showed that almost 10% of moderate and severe PEs are due to iatrogenic causes [23]. The difference between these types of PEs and others is that these are rapidly expanded and changed to cardiac tamponade, primarily due to the perforation of the coronary sinus or atrium during catheter ablation. The risk is higher in women and patients with tachycardia [23, 217].

Another procedure that can lead to cardiac tamponade or severe pericardial effusion is central venous catheter insertion. Pericardial effusion occurs in less than 1% of adults and 1–3% of infants undergoing these procedures [217]. The smaller dimension of the body and the length of the catheter, which are larger and have a greater risk of causing injury to the cardiac cavities or inner cardiac wall, seem to be the reasons for this remarkably higher incidence in children [226]. The main factor associated with the increased risk of this incident is accessing a cephalic, basilic, or brachial vein compared with less risk in central veins. Moreover, inappropriate skin fixation and suturing of the catheter, angle, and positioning (more risk with 90 degrees to the wall), non-curved and metallic guidewire type, and rigid catheter material are other factors that can influence the risk of these events [226].

There are non-cardiovascular iatrogenic causes of PEs and tamponade, mainly caused by injury to the diaphragm's dome, such as hiatal and anti-reflux surgeries, graft fixation, mechanical hernia repairs, and laparoscopic surgeries [223, 227]. Generally, iatrogenic PE and tamponade can occur due to a physician's negligence, inexperience, malpractice, or even an unavoidable surgical complication. Although more experienced surgeons might experience cardiac tamponade in their operating room. The risk factors of iatrogenic PE or tamponade include urgency to finish the procedure, human errors, and limited operator experience and/or skill. Therefore, post-incidence evaluation to determine the cause is crucial to avoid the recurrence of these complications [223].

Penetrating trauma-caused pericardial effusions

Most patients with traumatic PEs die at the scene or during transportation, and their survival rate is estimated at 6% [228]. Those who reach the hospital alive have almost always small tears in the cardiac wall, a clot that occludes the rupture, or an opening from the pericardium to other spaces in the chest that prevents the accumulation of blood in the pericardial space [224]. Based on the higher mortality before reaching the hospital, this condition also remained frequently undiagnosed due to severe concomitant injuries. Therefore, the statistics about the occurrence of these conditions remain inconsistent and inaccurate [229, 230]. One of the reasons for the catastrophic mortality rate of penetrating heart traumas is the anatomic position of the heart, which makes it vulnerable to even abdominal traumas. The frequency of rupture among various heart parts is different [231]. The right and left ventricles are injured approximately 40% of the time, the right atrium approximately 24%, and the left atrium approximately 3% of the time [230]. Various diagnostic and therapeutic approaches exist for those who reach the hospital alive. Among those, Focused Assessment with Sonography in Trauma (FAST) is the optimal diagnostic, and pericardial window is the optimal therapeutic method [228].

Blunt trauma-caused pericardial effusions

The incidence of heart wall rupture in blunt chest trauma is reported to be ranging from 0.5 to 2% in various studies [232–234]. Moreover, studies have shown that moderate-to-severe significant post-traumatic PE, delayed PE, and tamponade can occur following blunt chest trauma [235, 236]. The central pillar of treatment in blunt-trauma-caused PEs has been surgical methods due to the high probability of cardiac rupture (by subxiphoid, thoracotomy, or sternotomy approach) [224]. On the other hand, some studies recommend non-surgical treatments in selected patients with stable hemodynamics and have shown that this approach is not inferior compared to surgical choices [224, 237, 238]. Although traumatic aortic rupture to the free space of the chest is a fatal condition with a mortality of 97–100% [239], traumatic aortic rupture or dissection can also occur in retrograde expansion and cause confined bleeding into the pericardium and pericardial effusion. Detection of ascending aorta aneurysm and pericardial effusion after trauma should make the physician suspicious of aortic rupture or dissection, which needs immediate surgical evaluation management of the aortic dissection as pericardial drainage may result in a higher BP and lead to a worsening of the effusion/tamponade [239].

Hemodynamic pericardial effusions

It is important to note that these types of pericardial effusions are often mild due to gradual and limited progression [240, 241].

Heart failure

Approximately 12–20% of heart failure (HF) cases can be accompanied by pericardial effusions [242]. Branches of the internal mammary arteries and the musculophrenic arteries provide arterial supply to the pericardium. Venous drainage of the pericardium is via the pericardiophrenic vein, which empties into the internal thoracic vein, the left superior intercostal vein, or directly into the left brachiocephalic vein [242].

Fluid can accumulate in the pericardium space due to increased venous pressure. Conditions such as HF and cirrhosis can cause congestion of venous returns, dysfunction of lymphatic drainage, and decreased fluid reabsorption, which can finally result in pericardial effusion. Since these patients experience chronic fluid accumulation in the pericardium space, they are mostly asymptomatic, and PE diagnosis occurs as an incidental finding during evaluation for other reasons [242].

Pulmonary hypertension

With the same mechanism, the pressure on the right ventricle will also be raised when the PAP is increased. This pathologic condition is called PAH and is one of the five groups of pulmonary hypertension [243]. PAH can be divided into two subgroups: Idiopathic PAH, which is caused without any known specific reason, and secondary PAH, due to connective tissue disorders, HIV, and other reasons [244]. It has been shown that echocardiographic features such as right ventricle dysfunction and moderate and severe PE presence can be associated with a higher mortality rate. PAH can be accompanied by fluid accumulation in the pericardial space, lack of appropriate drainage by the reabsorbing system, and various degrees of PEs [244]. The treatment of PE in these cases depends on the cause of increased PE, and there is a wide inconsistency between the results of various studies [244]. Those with primary PAH will benefit from medications that can decrease this pressure, such as sildenafil and bosentan; anti-inflammatory medications may reduce inflammation and improve rheumatologic causes. Some evidence emphasizes the better outcome of transcatheter drainage of pericardial effusion. The medical team should decide based on the patient's condition and after considering all therapeutic strategies [245].

Nephrotic syndrome

Hypoalbuminemia is one of the most common conditions in critically ill patients. It can be caused by decreased nutrient intake, insufficient albumin synthesis, loss of protein more than usual, such as nephrotic syndrome, and other causes, such as burns or sepsis [246]. In cases such as nephrotic syndrome, it can cause increased hydrostatic pressure in the venous drainage of the body. Therefore, fluid reabsorption can be disturbed, and fluid accumulation in various spaces is typical in these cases. PE is one of the consequences of this condition [247]. Therefore, to resolve the PE caused by this condition, the underlying cause of the process should be treated, and albumin in the serum should be regulated as much as possible. On the other hand, like other cases of large PEs or tamponade, transcatheter pericardiocentesis is the mainstay of therapy, with surgical drainage as an option in those not amenable to the less invasive approach for pericardial drainage [247].

General diagnostic methods of pericardial effusions

Electrocardiographic features such as electrical alternans, low-voltage QRS waves, and tachycardia, along with CXR findings, can be helpful for the diagnosis of PE. However, transthoracic echocardiography (TTE) is still the first line for diagnosis, considering its availability, lack of radiation exposure, and relatively low cost. [198]. It is also very helpful for determining the size of the PE. However, based on the patient's condition and the suspected diagnosis, other methods such as transesophageal echocardiography (TEE), computer tomography scan (CT scan), and magnetic resonance imaging (MRI) might also be performed to assess the size. These methods all have their indications, positive and negative points (Table 6). Both CT scans and MRI have an excellent capability to differentiate the pericardium and its pathologies from the adjacent tissues. They are also very useful in measuring the thickness of the pericardium [24–26].

Differentiation between pericardial effusion and pericarditis

In many cases, pericardial effusion and pericarditis coexist. Their management often requires addressing the underlying etiology and monitoring for complications such as cardiac tamponade or chronic pericardial constriction [2, 19]. However, there are essential differences between these two pathologic circumstances (Table 7).

Role of autoimmune markers in the diagnosis and follow-up of pericarditis

Biomarkers have shown practical application in diagnosing, determining prognosis, and treating pericarditis. The study highlights the significant role of autoimmune markers, particularly anti-heart autoantibodies (AHA) and anti-intercalated disk autoantibodies (AIDA), in the etiology and recurrence of idiopathic recurrent acute pericarditis (IRAP). These markers were significantly

Table 6 Positive and negative aspects of diagnostic modalities for PE

Imaging modality	Main indications and advantages	Main disadvantages
Echocardiography	First and most common diagnostic method due to: Availability, Safety, low cost, applicability at the bedside Widely used for follow-up of PE	Not well-performed in tissue characterization Dependent on the skills of the operator Restricted ability in cases of obesity, obstructive lung diseases, and after cardiothoracic surgery Limited window and narrow field of view
CT scan	Better anatomical visualization compared to echocardiography Suitable in cases of the possibility of the presence of pathology in adjacent tissues or organs, such as cancers Used for the planning before cardiothoracic surgeries High performance in the detection of pericardial calcifications	Use ionizing radiation or contrast (in cases needing anatomical evaluation). Therefore, it is mostly possible for retrospective gated studies It is only practical in hemodynamically stable patients and those who can hold their breaths The temporal resolution is limited
MRI	It is mostly used for better anatomical evaluation and characterization	Specific features are required, such as hemodynamic stability, being able to hold breaths, and GFR ≥ 30 in cases of Gadolinium-contrast need Not possible in some cases with metal devices in the thorax, such as some pacemakers or defibrillators Not capable of visualizing lung tissue or calcification with an appropriate sensitivity and quality High cost and lower availability

Table 7 Depicts a summarized comparison between pericardial effusion and pericarditis features

Features	Pericarditis	Pericardial Effusion
Primary pathology	Inflammation of the pericardium	Fluid accumulation in the pericardial sac
Chest pain	Sharp, pleuritic, positional	Dull, non-positional
Friction rub	Present	Absent
ECG findings	Widespread ST-elevation, PR-depression	Low voltages or electrical alternans
Imaging	Pericardial thickening/enhancement (CT/MRI)	Fluid detection (echo)
Inflammatory markers	Elevated	Normal or elevated
Management focus	Anti-inflammatory therapy	Fluid drainage if severe; treat cause

more prevalent in IRAP patients compared to controls, supporting an autoimmune mechanism underlying the disease. AIDA positivity was associated with increased recurrences, hospitalizations, and refractory symptoms, while high-titer AHA correlated with prolonged disease duration and frequent relapses. These findings suggest that AHA and AIDA are valuable non-invasive biomarkers for diagnosing IRAP, predicting disease severity, and potentially guiding personalized immunosuppressive treatments [108].

The management of pericarditis involves a guideline-based approach primarily endorsed by the European Society of Cardiology (ESC) [2, 19]. First-line therapy includes nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and aspirin, combined with colchicine, which is pivotal in reducing recurrence rates. Corticosteroids are reserved for specific scenarios, such as NSAID intolerance or contraindications. For cases resistant to colchicine or dependent on steroids, anti-interleukin-1 (anti-IL-1) therapies, such as anakinra, are recommended. These agents have shown efficacy in colchicine-resistant and refractory pericarditis. Adherence to proper dosages and tapering protocols as per ESC guidelines significantly impacts treatment success and recurrence prevention. Recent evidence underscores the need for careful patient selection for anti-IL-1 therapy, particularly in recurrent, colchicine-resistant cases, to achieve stable remission and avoid overtreatment [109].

General therapeutic approach towards pericardial effusions

Treatment of pericardial effusion is planned based on the size, consequences, and etiology (Fig. 7). If the fluid volume exceeds a determined threshold, the filling process of the heart chambers and cardiac output declines [27]. In 2015, ESC guidelines stated that pericardiocentesis was the class I recommended for moderate to large PEs. It can be performed under local anesthesia with fluoroscopic or echocardiographic guidance [2]. Echocardiographic guidance is widely accessible, straightforward, and safe when done by experienced operators.

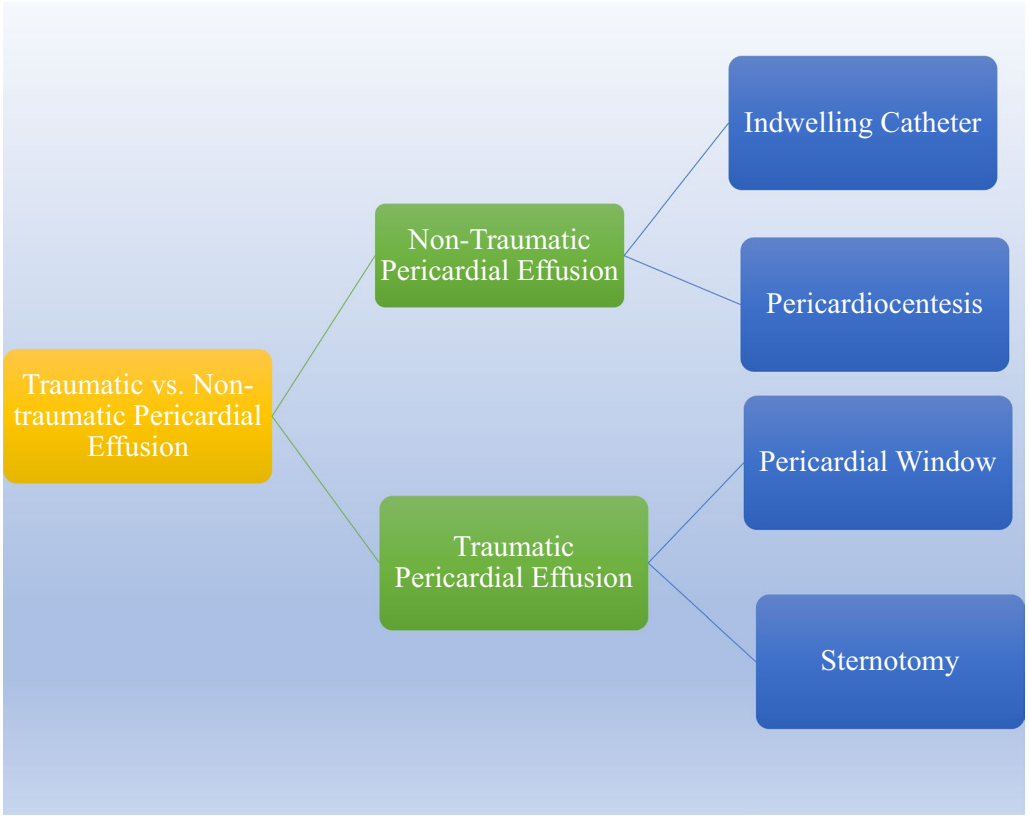

Fig. 7 General therapeutic approach to traumatic and non-traumatic PE [27]

It is most safely done at the bedside in the ICU or the cardiac catheterization lab. The common complications of this therapeutic method are related to trauma from the pericardiocentesis needle and include 1) ventricular tachycardia, 2) injury to intercostal vessels, 3) chamber laceration, and 4) pneumothorax, and rarely 5) iatrogenic infection [28].

However, in a small percentage of cases with a high risk of pericardiocentesis or previously failed pericardiocentesis, another therapeutic option is the placement of a pericardial window. This surgical approach is usually performed to prevent reaccumulation of fluid in cases with recurrent pericardial effusions but can also be the only feasible approach in loculated posterior effusions. By removing a portion of the pericardium, pericardial fluid is drained into the pleural (transpleural drainage) or mediastinal space (subxiphoid drainage). The latter method is preferred because it is associated with less post-surgical pain, although the recurrence risk may be higher than trans-pleural drainage [27]. Both open-surgical and video-fluoroscopic approaches are options [29–31].

Conclusion

Pericardial effusions are primarily categorized into inflammatory and non-inflammatory cases. This classification and the severity of the conditions determine the therapeutic plan. An essential consideration in understanding the epidemiology of the disease is the geographical region and country of residence. Not all pericardial effusions require evaluation to determine the cause. In developed countries, they are mainly categorized as idiopathic, believed to be associated with temporary viral infections. The second and third most common reasons are diagnosed diseases and malignancies. Conversely, in developing countries, tuberculosis remains the primary cause of the disease. These epidemiological factors can assist health decision-makers in approaching disease prevention and treatment. On a smaller scale, they empower physicians to make informed decisions for patient treatment when there is insufficient time to investigate the cause of pericardial effusion or when such investigation is not rationalized based on cost–benefit considerations. History, physical examination, and echocardiography constitute the main pillars of diagnosis. Treatment can

range from observation to percutaneous or surgical procedures depending on the etiology and severity of fluid accumulation.

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