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Systematic Review/Meta-analysis

Malignant Pericardial Effusion: A Systematic Review

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ABSTRACT

Background: Malignant pericardial effusion (Eff) is often asymptomatic and has an unknown prevalence, due to its occult presentation. The condition often is identified postmortem on autopsy, and it is associated with a poor prognosis. Given the late presentation of malignant pericardial Effs, a minimal volume of literature has examined the epidemiology, clinical characteristics, and outcomes of these complex patients. We conducted a systematic review to advance present understanding of this condition.

Methods: A search of 4 databases resulted in 41 case reports meeting criteria. Inclusion criteria were being a patient aged > 18 years who presented with pericardial Eff in the setting of malignancy. Intervention was medical and/or surgical therapy, and the outcome was mortality.

RÉSUMÉ

Contexte : L'épanchement péricardique malin (EPM) est un état généralement asymptomatique, de prévalence inconnue en raison de son tableau clinique occulte. Il est souvent reconnu post-mortem, à l'autopsie, et est associé à un pronostic médiocre. En raison de la consultation tardive pour un EPM, les données publiées relatives à l'épidémiologie, aux caractéristiques cliniques et à l'issue de ces cas complexes sont limitées. Nous avons réalisé une analyse systématique dans le but d'élargir les connaissances sur cette affection.

Méthodologie : Une recherche réalisée dans quatre bases de données a permis de repérer 41 rapports de cas qui répondaient aux critères de recherche. Les critères d'inclusion étaient les suivants : être âgé de plus de 18 ans; présenter un épanchement péricardique en présence

The pericardial space is a site of metastatic spread in both solid and hematologic malignancies—most commonly those of the lung and breast, and lymphomas. Rarely, malignant pericardial effusions (Effs) result from primary cardiac and pericardial tumours.[1-4] Pericardial involvement often is identified only postmortem. The estimated prevalence of malignant pericardial Effs is still disputed, but it may be as high as 20%.[1-3] Presenting features vary with symptoms, dependent on Eff size, rapidity of accumulation, and evidence of cardiac tamponade (Tamp).

The precise mechanism of pericardial involvement remains uncertain, although it likely involves direct tumour invasion, hemorrhage, or hematogenous spread.[1-3] Furthermore, treatment modalities, including radiation, chemotherapy, and immunotherapy, generate reactive oxygen species, which, in turn, activate neutrophils and predispose patients to pericardial inflammation.[1-3]

Given the late presentation of malignant pericardial Effs, a minimal volume of literature has examined the epidemiology, clinical characteristics, and outcomes of these complex patients. Therefore, we conducted a systematic review to advance our present understanding of this condition.

Methods

The following databases were searched comprehensively on May 16, 2023: Ovid Embase, Ovid MEDLINE, Cochrane

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Results: For the 41 patients included, the median age was 54 years, and the majority were male patients (58%). Dyspnea was the leading symptom (90%), and cardiac tamponade was present in 78% of cases. Common cancers included lung, gastrointestinal, and renal neoplasms (59%). Pericardiocentesis occurred in 98% of cases, with a median fluid extraction volume of 1000 mL. Death occurred in 44%, primarily due to disease progression and/or metastasis.

Conclusions: This study presents the largest systematic review on malignancy-induced pericardial Effs to date. Notably, solid tumours, and specifically lung adenocarcinomas, are common culprits. Malignant pericardial Effs are often severe, with a majority of patients presenting with cardiac tamponade. Overall, treatment options are limited, and the associated mortality rate is high.

Résultats : L'âge médian des 41 patients inclus était de 54 ans; la majorité d'entre eux étaient des hommes (58 %). Le symptôme principal était la dyspnée (90 %), et une tamponnade cardiaque était présente dans 78 % des cas. Les cancers les plus fréquents étaient le cancer du poumon, le cancer gastro-intestinal et les néoplasmes rénaux (59 %). Une péricardiocentèse a été réalisée dans 98 % des cas. Le volume de drainage médian était de 1 000 mL. Quarante-quatre pour cent des sujets sont décédés, principalement en raison de la progression de la maladie et/ou de métastases.

Conclusions : Cette étude est la plus vaste analyse systématique réalisée à ce jour sur l'EPM. Les tumeurs solides, et plus particulièrement les adénocarcinomes pulmonaires, sont des causes fréquentes. L'EPM est souvent grave, la majorité des patients présentant une tamponnade cardiaque. Les traitements disponibles sont généralement limités, et le taux de mortalité associé est élevé.

Central Register of Controlled Trials, and Web of Science. Results were limited to sources written in English and published from 2010 to the present. Eventually, 1174 citations were organized and uploaded to the online systematic review management system Covidence. After removal of duplicates (n = 387), 787 citations remained for screening.

Two independent researchers (A.K.K., A.A.) assessed and screened data in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Fig. 1).[5] Another reviewer (D.R.) adjudicated any conflicts during the screening process. Excluded items included the following: letters to the editors, conference proceedings, animal studies, pediatric population studies, review articles, and articles in languages other than English. A total of 81 studies underwent a full-text review. Overall, 41 studies were identified for final inclusion (Supplemental Table S1). Studies were excluded because of either insufficient data regarding diagnosis and management or insufficient follow-up data regarding mortality. Information from text, tables, and figures was extracted for use.

Qualitative analysis employed the patient intervention, control, and outcome framework. Inclusion criteria included patients aged > 18 years who presented with pericardial Eff in the setting of malignancy. Our intervention included medical and/or surgical therapy. Our outcome was mortality. To our knowledge, no prior observational studies have been undertaken; therefore, no comparison groups were included in the analysis.

Extracted data were pooled for analysis and reporting. No comparison group was included, given the nature of the study. Continuous variables were described using mean or median, whereas categorical variables were described as proportions (%). Statistical analysis was accomplished using SPSS 23.0 software (IBM, Armonk, NY).

Results

Epidemiology and clinical characteristics

A total of 41 cases were included. Patient demographics included a median age of 54 years (interquartile range [IQR]: 43-67), with a predominance of those of male sex (n = 24; 58%). Most cases identified were from the US (n = 13; 32%). The most common comorbidities were hypertension (n = 10; 24%) and hyperlipidemia (n = 4; 10%). The most-frequent initial presenting symptoms were dyspnea (n = 37; 90%), pleuritic chest pain (n = 13; 32%), and edema (n = 9; 22%). Findings of pericarditis on electrocardiogram were absent in 71% of cases (n = 30). Patients presented with cardiac Tamp in 78% of cases (n = 32). Pericardial Effs or cardiac Tamp was the initial presentation among 85% of patients (n = 33; Table 1).

Imaging

The most frequent finding of Eff on chest radiograph was cardiomegaly (n = 18; 43%). Definitive diagnosis of pericardial Eff with echocardiogram occurred in 90% of patients (n = 37). The majority of patients presented with large pericardial Effs on echocardiogram (n = 23; 55%). Among those who underwent chest computed tomography (CT), Effs were classified as large in 29% of cases (n = 12; Table 2).

Outcomes

The most-common cancers identified were solid neoplasms of lung, gastrointestinal, and renal origin (n = 24; 59%); primary cardiac tumours (n = 10; 24%); and leukemia and/or lymphoma (n = 7; 17%). Of the identified primary cardiac tumours, 5 cases were intracardiac (4 angiosarcoma, 1 primary cardiac lymphoma), and 5 cases were identified as being primary pericardial mesotheliomas. Pericardiocentesis or pericardial window occurred in 40 patients (98%). The median fluid volume extracted during pericardiocentesis, or pericardial window, was 1000 mL (IQR: 700-1500). Cytologic analysis yielded malignant cells in 39% of the cohort (n = 16). In patients with negative or inconclusive cytology, diagnosis was confirmed via pericardial biopsy in 10 patients (24%). The most frequently identified cancer on cytology was adenocarcinoma (n = 5; 12%). After diagnosis, patients underwent chemotherapy (n = 27; 66%) and radiation and/or surgery (n = 5; 12%). The majority of pericardial Effs occurred in the metastatic setting (n = 20; 67%). Death occurred in 44% of patients (n = 18), with death occurring at a median of 45 days

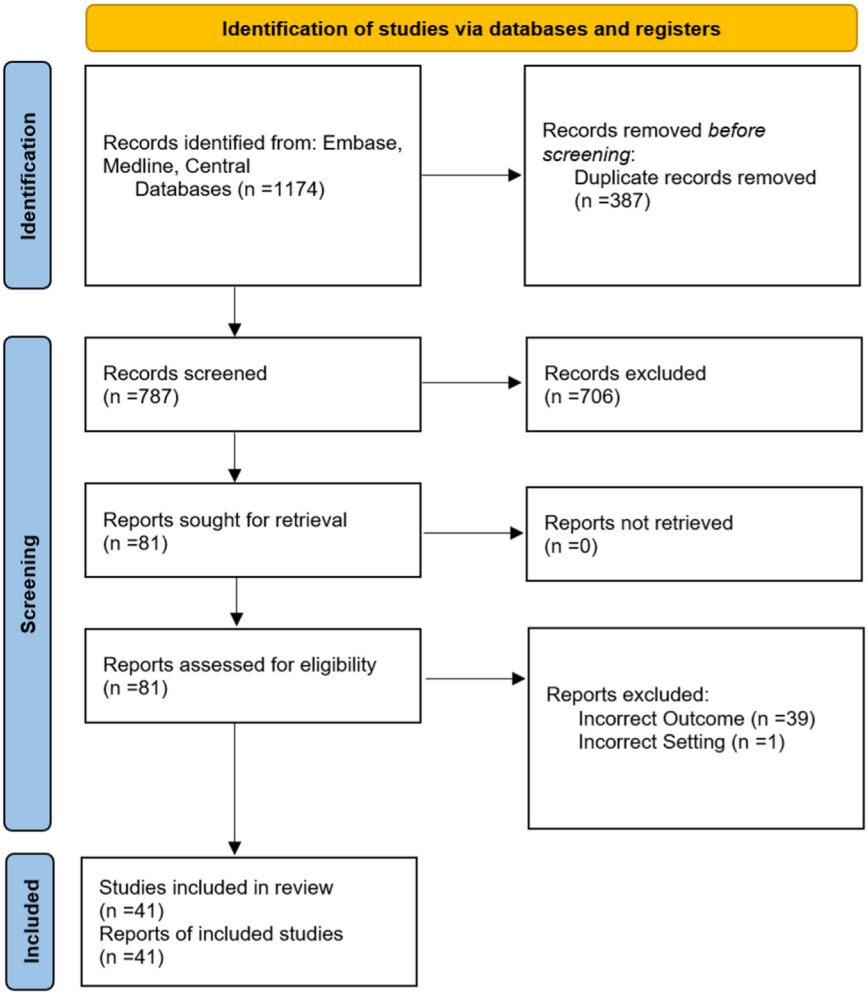

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram demonstrating the included studies. CENTRAL, Cochrane Central Register of Controlled Trials.

(IQR: 1-495) following initial presentation. The most common cause of death was disease progression and/or metastasis (n = 13; 68%; Table 3).

Discussion

To our knowledge, this systematic review of malignancy-induced pericardial Effs is the largest conducted to date. Overall, this systematic review analyzes the epidemiology, clinical presentation, and outcomes of patients with malignant pericardial Effs.

Pericardial disease is commonly seen in malignancies.[6] Although the exact prevalence is unknown, as cardiac involvement is frequently asymptomatic, large postmortem studies have revealed pericardial involvement in 8%-12%.[7-11] In this analysis, malignant pericardial Effs were caused primarily by metastatic disease, rather than by primary cardiac malignancies. Solid tumours were the type most often identified, with lung cancer being the most frequent. Breast cancer, lymphoma, leukemia, melanoma, and gastrointestinal cancers also have been reported as common causes of malignant pericardial Effs in the literature.[8,10-12] Notably, adenocarcinoma was identified most frequently via cytologic analysis, likely reflecting the predominance of lung adenocarcinoma.[12]

Pericardial involvement can occur in several ways. Frequently, malignant cells may directly invade the pericardium from localized tumour burden (primarily lung and breast cancers) or through lymphatic spread.[3] Other less common causes of pericardial involvement include chemoradiation and opportunistic infections in the setting of immunosuppression[3] (Fig. 2).

Clinical manifestations of malignant pericardial Eff vary widely. Patients may be asymptomatic or may present with hemodynamic compromise secondary to cardiac Tamp.[1] In our study, the majority of patients presented with dyspnea and evidence of cardiac Tamp. Patients who underwent pericardiocentesis or pericardial window placement had a median of 1000 mL of fluid drained, suggesting that pericardial fluid accumulation occurred insidiously and resulted in large pericardial Effs at the time of clinical presentation. In one study of 450 patients with acute pericardial disease, neoplastic causes were significantly more likely to present with severe pericardial Effs (69.7%) or cardiac Tamp (60.6%), as compared to non-neoplastic causes (20.1% and 10.3%, respectively).[6] Likewise, the presence of severe pericardial Effs significantly increased

Table 1. Clinical characteristics of the cohort

Demographics	n (%)*
Gender, male	24 (58)
Age, y, median (IQR)	54 (43–67)
Country	
US	13 (32)
Middle East	5 (12)
Europe	8 (13)
Asia	12 (29)
Other	3 (7)
Symptoms	
Fatigue	5 (12)
Shortness of breath	37 (88)
Chest pain	13 (32)
Weight loss	2 (5)
Ascites	1 (2)
Orthopnea	3 (7)
Edema	9 (21)
Elevated jugular venous pressure	8 (19)
Comorbidity	
Diabetes mellitus	1 (2)
Hypertension	10 (24)
Coronary artery disease	1 (2)
Hyperlipidemia	4 (10)
Chronic kidney disease	1 (2)
ECG findings of pericarditis and/or cardiac tamponade	
Electrical alternans	6 (14)
Diffuse ST segment elevation	1 (2)
Low voltage	4 (10)
Cardiac tamponade	32 (77)
Pericardial Eff or cardiac Tamp as initial presentation	33 (85)

Eff, effusion; ECG, electrocardiogram; IQR, interquartile range; Tamp, tamponade.

*Unless otherwise noted.

the odds of a neoplastic etiology. In another study involving 173 patients, with large symptomatic pericardial Effs, a neoplastic etiology was discovered in 33% of patients.[13]

Transthoracic echocardiography remains the first-line imaging test to detect pericardial disease. Echocardiography accurately detects pericardial Eff and is useful for assessing its hemodynamic significance.[14] Pericardial Effs also may be visualized using imaging modalities, including chest radiography and CT. Chest radiographs are largely nonspecific but may demonstrate an enlarged cardiac silhouette when at least 200 mL of pericardial fluid accumulates.[3] CT provides excellent anatomic detail of the heart and pericardium and is a useful adjunct to echocardiography to further characterize pericardial Effs.[14] CT can be used to quantitate the amount of fluid, provide information on the nature of the fluid, and

Table 2. Imaging findings of included cohort

Imaging	n (%)
Chest radiograph findings	
Cardiac enlargement	19 (45)
Computed tomography effusion size	
Large	12 (29)
Moderate	1 (2)
None	10 (24)
Transthoracic echocardiogram effusion size	
Small/Moderate	8 (19)
Large	23 (55)
None	8 (19)

Table 3. Outcomes data of included cohort

Outcomes	n (%)*
Pericardiocentesis and/or pericardial window	40 (98)
Pericardial fluid extraction, mL, median (IQR)	1000 (700–1500)
Type of primary malignancy	
Lung tumours	10 (24)
Lymphoma and/or leukemia	7 (17)
Primary cardiac tumour	10 (24)
Non-lung solid tumours	14 (33)
Chemotherapy	27 (64)
Radiation and/or surgery	5 (12)
Confirmed metastasis	20 (67)
Confirmed death	18 (44)
Cause of death	
Disease progression	13 (68)
Other causes	6 (32)
Time to death, d, median (IQR)	45 (1–495)

IQR, interquartile range.

*Unless otherwise noted.

elucidate the underlying etiology of the effusion.[14] Electrocardiography may reveal low voltage in cases of pericardial Eff or electrical alternans in cases of cardiac Tamp.[14,15] However, as seen in our analysis, electrocardiography findings frequently are absent.

If malignant pericardial Eff is suspected, pericardial drainage is indicated for further cytologic analysis.[14] Cytologic evaluation remains the gold standard for diagnosing malignant pericardial Effs, with a sensitivity of 92%, and a specificity of nearly 100%, although the diagnosis may be made with pericardial or epicardial biopsy as well.[14]

Immediate treatment with pericardiocentesis is indicated if cardiac Tamp is present. Even in instances in which Tamp is absent, current guidelines recommend pericardial drainage for large definitive or suspected malignant pericardial Effs.[14] Definitive treatment, however, requires systemic treatment of the underlying malignancy with chemotherapy, radiation, and surgery (Fig. 3). Unfortunately, the overall prognosis remains poor in those with oncologic-related Effs, with a median survival duration as short as 15 weeks.[16] In cases in which cytology identified malignant pericardial Effs, this median duration of survival was reduced further to 7 weeks.[16]

Furthermore, management is complicated by recurrence of the malignant effusion, especially among those with lung or breast cancer.[17] Intrapericardial instillation of cytotoxic or sclerosing agents and percutaneous balloon pericardiotomy have been posited as mechanisms to prevent recurrence, with limited success.[14] Other methods to prevent recurrence include extended catheter drainage and the creation of a pericardial window. In a systematic review of 31 observational studies, isolated pericardiocentesis was associated with a recurrence rate of 38%, and extended catheter drainage, pericardial sclerosis, and balloon pericardiotomy had recurrence rates of 12.1%, 10.8%, and 10.3%, respectively.[18] A pericardial window was associated with the lowest rate of recurrence ($< 7\%$).[18] Important to note is that these methods have not been studied against each other in randomized controlled trials.[19] Guidelines recommend management of malignant pericardial disease with systemic antineoplastic therapy, pericardiocentesis, and extended pericardial drainage.[14,20] Pericardiotomy and sclerosing agents may be used adjunctively.[14] However, many

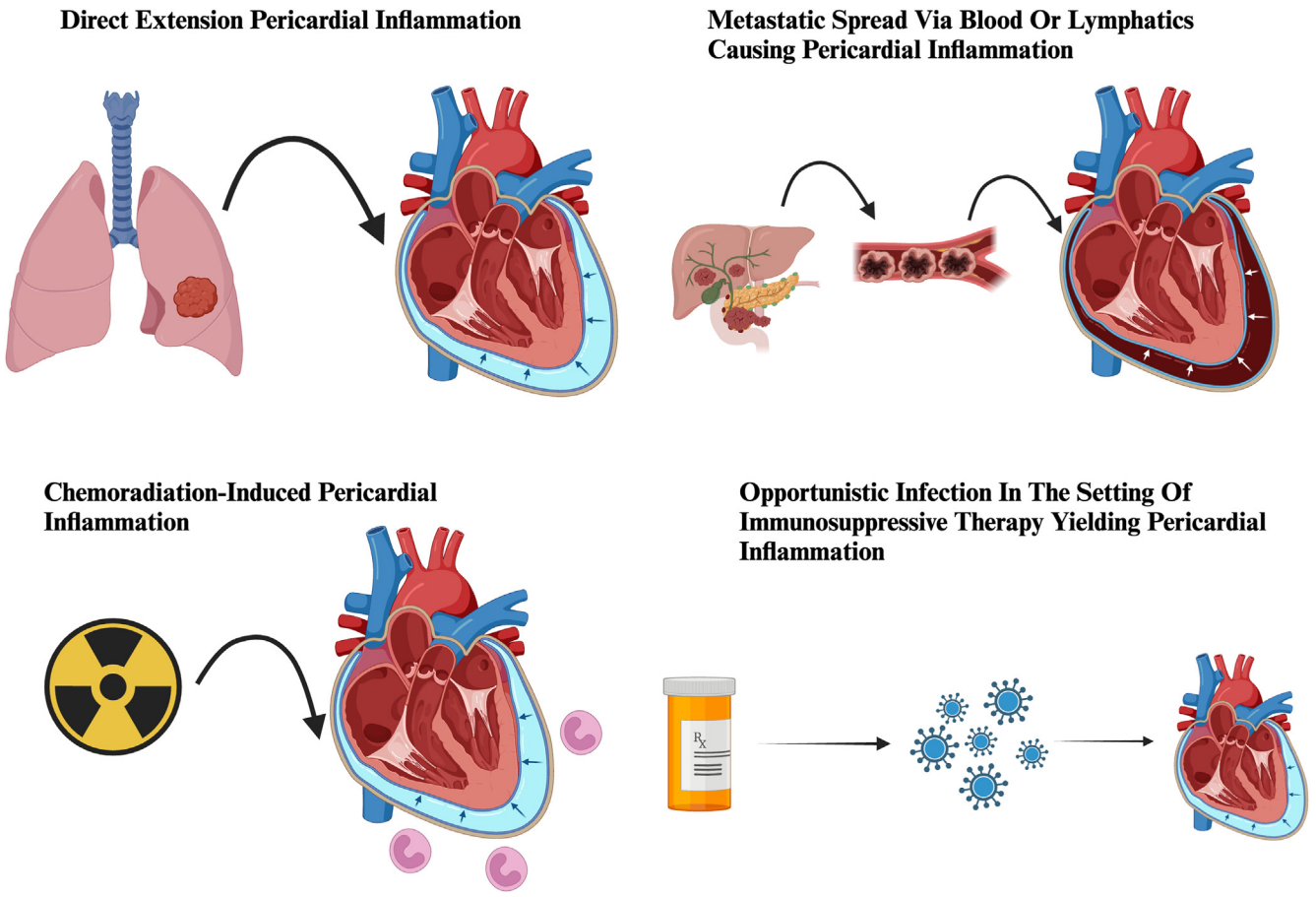

Figure 2. Pathophysiology of malignant pericardial effusion. Created with BioRender (BioRender.com).

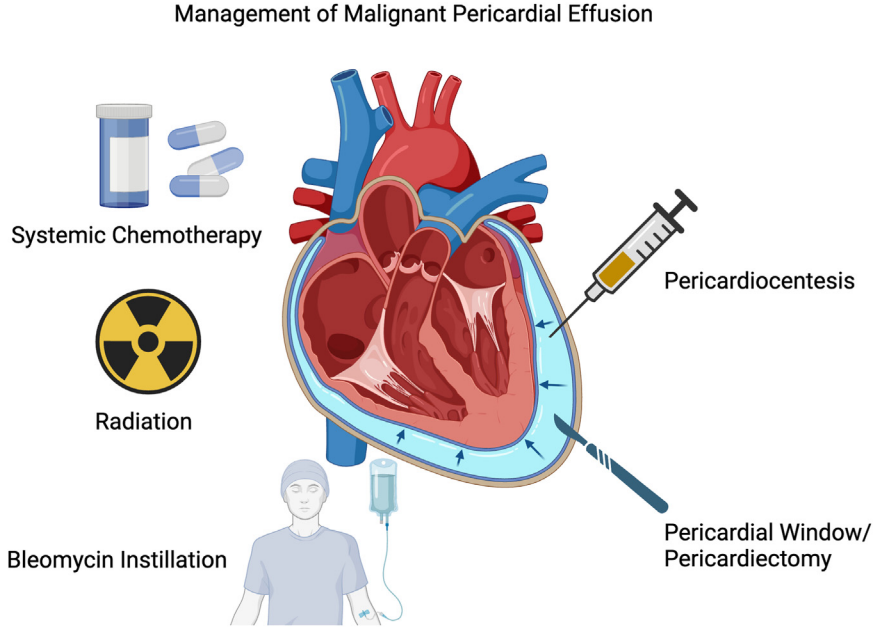

Figure 3. Management of malignant pericardial effusion. Created with BioRender (BioRender.com).

providers avoid the use of pericardial sclerosing agents, given the high rates of chest pain and constrictive pericarditis associated with these therapies.[18,20]

This systematic review poses several limitations. Chiefly, our cohort was drawn entirely from case reports, with resulting publication bias. This analysis likely represents only the most-severe cases, particularly as a majority presented with evidence of pericardial Tamp. Additionally, these data are limited by the small sample size and variations among cases in the quality and quantity of data reported. Due to the paucity of data available for examination, this analysis also lacks a control group. Despite these limitations, these data represent the largest systematic review to date of the epidemiology, clinical presentation, and outcomes in a single set of patients with malignant pericardial Eff. As data continue to emerge, further investigation in these areas will be needed in a larger, more representative clinical dataset.

Conclusion

Malignant pericardial Effs are a late presentation of either primary cardiac tumours, or more commonly, metastatic cancer, and they portend a poor overall prognosis. In this dataset, most patients presented symptomatically with dyspnea or pleuritic chest pain and with evidence of cardiac Tamp. Diagnosis is determined via a combination of echocardiography and pericardial fluid analysis. The most common underlying etiology of malignant pericardial Effs is solid tumours, with a predominance of lung adenocarcinomas. Overall, treatment options are limited, and the associated mortality rate is high.

Ethics Statement

The research reported has adhered to the relevant ethical guidelines.

Patient Consent

Patient consent was not obtained, as this is a systematic review of previously reported case reports, and therefore IRB consent and patient consent were not required.

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Disclosures

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Supplementary Material

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