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Original Article

Incidence of malignant pericardial effusion in pericardiocentesis patients and post-procedure care: an oncology center pilot study

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Abstract: The etiology of pericardial effusion can affect many important factors during and after pericardiocentesis. The frequency of etiologies varies among different patient populations. Pericardiocentesis is an important diagnostic and therapeutic intervention; however, data on the characteristics of malignant pericardial effusion are lacking in the United Arab Emirates (UAE). Thus, we conducted a pilot study on the incidence and post-procedure care of patients who underwent pericardiocentesis in our facility to enhance their management and treatment. This retrospective study included all cases of pericardiocentesis between 2011-2019. Epidemiological, clinical, and biochemical data were collected and analyzed. Pericardial fluid analysis, malignancy type, recurrence rate, need for a repeat procedure, and echocardiography findings were reviewed. Thirty-three patients (mean: 47.2 years) underwent pericardiocentesis, and 22 of these patients (66.7%) had malignancy. The predominant cancers were breast cancer (27.3%), lung cancer (27.3%), exudative pericardial effusion and malignant effusion (68%), and bloody fluid (73%). An average of 350 ml was drained from the patients, and the drain was retained for 4 days. Six patients (18.2%) had re-accumulation of pericardial effusion, and 4 patients required repeat procedures. All patients underwent post-procedure echocardiography, and 82% underwent follow-up echo within one week. More than two-thirds of our cancer patients had malignant pericardial effusion. The early diagnosis of the etiology of pericardial effusion may alter its management and prognosis. We would like to conduct further research to determine its influence on the prognosis of cancer patients in the UAE.

Keywords: Pericardiocentesis, malignant effusion, pericardial effusion, cancer

Introduction

Although there are many underlying etiologies of pericardial effusion, the frequency of the etiology varies among different patient populations. Therefore, previously reported studies are not necessarily representative of the diverse populations of the United Arab Emirates (UAE). Pericardial effusion requiring pericardiocentesis can have a wide variety of malignant and non-malignant causes [1, 2]. Non-malignant etiologies include effusions that are idiopathic, infectious, iatrogenic (Percutaneous Coronary Intervention (PCI), post-thoracotomy, post-radiation, and certain medications), cardiac (post-myocardial infarction and congestive heart failure), metabolic (uremia and hypothyroidism), connective tissue diseases, and traumatic [3]. A common etiology of pericardial effusion is malignancy, particularly of the breast [4]. However, malignant pericardial effusion as an initial presentation is rare [5]. The causes of pericardial effusion in cancer patients range from infectious to malignant. Data on the frequency of different etiologies and, more specifically, on primary or metastatic malignancies remain scarce and vary widely among the studied populations [6, 7].

The etiology of pericardial effusion can affect many important factors during and after pericardiocentesis, which is an important diagnostic and therapeutic intervention. Pericardial involvement in malignancy can manifest in various forms [8, 9]. The diagnosis or exclusion of pericardial involvement in malignancies is largely established by the pericardial cytology obtained by pericardiocentesis.

Our purpose was to establish the number of patients who underwent pericardiocentesis with malignant effusion, the type of cancer they had, and whether the incidence was similar to that in other areas. Additionally, we sought to examine the etiology of non-malignant pericardial effusions and the differences in the characteristics of pericardial effusions between patients who were diagnosed with malignancy and those who were not. The early recognition of the differences in pericardial fluid characteristics may aid in the management and outcomes of these patients.

Materials and methods

Study design

A retrospective observational study was conducted on all patients who underwent percutaneous pericardiocentesis over a 9-year period between 2011 and 2019 and had prospective follow-up. All patient details were de-identifi ed, and the study was conducted at Tawam Hospital, which is a leading regional oncology center in the Middle East.

Inclusion criteria

Any patient who underwent pericardiocentesis at Tawam Hospital from 2011 to 2019 and was above 18 years old were included in this study. The reporting of this study conformed to the STROBE guidelines [10].

Statistical analysis

Epidemiological, clinical, and biochemical data were collected from the patients' electronic medical records in Cerner. Data were analyzed using descriptive analysis in SPSS software. Data were extracted and analyzed using Stata version 16.1. Qualitative variables were tabulated as frequencies with corresponding percentages (%), and quantitative variables were summarized as medians with corresponding minimum and maximum values. Both qualitative and quantitative variables were cross-tabulated for malignant (and) non-malignant pericardial fluid. Fisher's exact test was used to compare qualitative variables with the malignancy status. Wilcoxon rank sum tests were used to compare quantitative variables with the malignancy status. A *P*-value <0.05 was chosen to determine significance.

The clinical variables evaluated included the prevalence of malignancy, frequency of different types of malignancy, amount of pericardial fluid drained during pericardiocentesis (mL), duration of post-pericardiocentesis chest drain (days), pericardial effusion recurrence rate requiring a repeat procedure (including pericardiocentesis and/or pericardial window), rate of follow-up echocardiogram after the procedure, outcome and laboratory pericardial fluid analysis. The components of the pericardial fluid analysis from which the data was collected included macroscopic appearance, cytology (red blood cell [RBC] count [cells/mm^3], white blood cell count [WBC] count [cells/mm^3], absence or presence of malignant cells), and biochemistry (protein levels [g/L], LDH level [U/L], glucose level [mmol/L]). The test was not performed uniformly in all patients on certain components of the pericardial fluid samples, but was reported if applicable.

The etiology of the pericardial effusion was determined on the basis of certain criteria. Effusions were labeled idiopathic in patients for whom no clear evidence was found for any etiology via routine clinical care. Effusion was defined as malignant when the pericardial fluid cytology included atypical or malignant cells. Bacterial effusion was identified using positive pericardial fluid cultures. Uremic pericarditis was diagnosed when the blood urea nitrogen level was >60 mg/dL or when dialysis dependency was present in the absence of other identifiable causes. Inflammatory pericardial effusion was caused by pericarditis.

Exudative effusions versus transudative effusions were classified on the basis of Light's criteria [11].

Results

After the initial review of the patient data, 10 cases were omitted from the present retrospective analysis because of the unavailability of laboratory results. A total of 33 patients (14

Table 1. Characteristics of participants with pericardial effusion, overall and by malignancy status (n=33)

Characteristic	All	Patients with malignancy N=22	Patients without malignancy N=11	*P*-value
Age (years) - n (%)	--			
≤25	3 (9.1)	1 (33.3)	2 (66.7)	0.019
26-50	18 (54.5)	13 (72.2)	5 (27.8)	
51-75	9 (27.3)	8 (88.9)	1 (11.1)	
>75	3 (9.1)	0 (0.0)	3 (100.0)	
Sex - n (%)	--			
Male	14 (42.4)	10 (71.4)	4 (28.6)	0.710
Female	19 (57.6)	12 (63.2)	7 (36.8)	
Previous diagnosis of malignancy - n (%)				
Yes	21 (63.6)	21 (100.0)	0 (0.0)	<0.001
No	12 (33.3)	1 (8.3)	11 (91.7)	
Malignant cells - n (%)				
Yes	15 (45.5)	15 (100.0)	0 (0.00)	<0.001
No	18 (54.5)	7 (38.9)	11 (61.1)	
Color of effusion - n (%)				
Bloody	22 (66.7)	16 (72.7)	6 (27.3)	0.391
Turbid	9 (27.3)	5 (55.6)	4 (44.4)	
Straw	1 (3.0)	1 (100.0)	0 (0.0)	
Clear	1 (3.0)	0 (0.0)	1 (100.0)	
Type of effusion - n (%)				
Exudative	28 (84.8)	22 (78.6)	6 (21.4)	0.002
Transudative	5 (15.2)	0 (0.0)	5 (100.0)	
Re-accumulation of fluid - n (%)				
Yes	6 (18.2)	4 (66.7)	2 (33.3)	1.00
No	27 (81.8)	18 (66.7)	9 (33.3)	
Repeat pericardiocentesis - n (%)				
Yes	5 (15.1)	3 (60.0)	2 (40.0)	1.00
No	28 (84.9)	19 (67.9)	9 (32.1)	
Duration of drain (days) - Median (Min - Max)	3 (1-7)	4 (1-7)	3 (1-4)	0.319
Amount of fluid drained (ml) - Median (Min - Max)	500 (60-1500)	350 (60-1200)	600 (300-1500)	0.009
RBC count (cells/mm^3) - Median (Min - Max)	51300 (72-3430000)	396000 (2500-3430000)	25625 (72-1800000)	0.155
WBC count (cells/mm^3) - Median (Min - Max)	1699 (6-515000)	2004 (6-515000)	1274 (31-8894)	0.382
Protein (g/l) - Median (Min - Max)	46 (22-67)	45 (22-67)	49 (28-62)	0.047
Glucose (mmol) - Median (Min - Max)	5 (0.1-12)	4.0 (0.1-8)	6 (4-12)	0.088
LDH (u/l) - Median (Min - Max)	524 (83-4999)	826 (248-4999)	363 (83-1416)	0.013

Qualitative variables are presented as frequencies with corresponding percentages (%). Quantitative variables are presented as medians with corresponding minimum and maximum. Fischer Exact tests were applied to compare qualitative variables with malignancy status. Wilcoxon rank-sum tests were applied to compare quantitative variables with malignancy status.

were male [42%]) who underwent primary pericardiocentesis from 2011 to 2019 were included in the study. The female-to-male ratio was 1.4:1. The age range was 18 to 103 years, with a mean age of 47.2 years. Twenty-one patient who underwent pericardiocentesis for diagnostic and therapeutic purposes were known to have an established malignancy, whereas 1 patient was diagnosed following the procedure, thus bringing the total number of patients with malignancy to 22 (66.7%) (**Table 1**).

The predominant cancer types in our cohort were breast cancer (27.3%), lung cancer (27.3%), gastrointestinal tract cancer (13.6%), and other types of cancer (13.6%). Cancers of the reproductive system and hematological malignancies comprised 9.1% of the cohort (**Table 2**).

Most patients with malignancy drained bloody fluid (73%), followed by turbid effusions (23%, 5 patients) and straw-colored fluid (4%, 1 patient).

Table 2. Types of cancer with presence of malignant cells in pericardial fluid

Type of cancer	N% (n)	Malignant cells in pericardial fluid/N% (n)
Breast	27.3% (6)	66.7% (4)
Lung	27.3% (6)	66.7% (4)
colon	1	100% (1)
rectal	1	100% (1)
gastric	1	100% (1)
GI	13.6% (3)	100% (3)
cervical	1	100% (1)
ovarian	1	100% (1)
Reproductive	9.1% (2)	100% (2)
leukemia	1	0% (0)
lymphoma	1	100% (1)
Hematological	9.1% (2)	50% (1)
mesothelioma	1	100% (1)
synovial	1	0% (0)
nasopharyngeal	1	0% (0)
Other	13.6% (3)	67% (2)

Table 3. Color of pericardial effusion

Color of Effusion	All/n (N%)	Patients with malignancy/n (N%)	Patients without malignancy/n (N%)	*P* value
Bloody	22 (66.7%)	16 (72.7%)	6 (54.5%)	0.339
Turbid	9 (27.3%)	5 (22.7%)	4 (36.4%)	
Straw	1 (3%)	1 (4.5%)	0 (0.0%)	
Clear	1 (3%)	0 (0.0%)	1 (9.1%)	

Patients with non-malignant disease also mostly drained bloody fluid (55%, 6 patients), followed by turbid fluid (36%, 4 patients) and clear fluid (9%, 1 patient) (**Table 3**).

The etiologies of effusion in the patient sample were as follows: malignancy, 21 (63.6%); idiopathic, 6 (18.2%); inflammatory, 3 (9.1%); infectious, 2 (6.1%); and traumatic, 1 (3.0%) (**Figure 1**).

A total of 68% of cancer patients (n=15) had malignant cells in their effusion, and 1 cancer patient had an infectious effusion (**Figure 2**).

A total of 91% of oncology patients (n=20) had metastatic disease at the time of pericardiocentesis. Among the two patients who did not have metastatic disease, one had an infection as the source of their pericardial effusion (**Figure 3**). **Figure 4** shows the incidence of malignancy and malignant pericardial effusion in the study population.

Patients who had a malignancy drained 350 ml on average, whereas patients who did not have a malignancy drained 600 ml on average (P=0.009). One patient (4.5%) who had a malignancy drained <100 ml, 14 patients (64%) drained 100-500 ml, 6 patients (27%) drained 501-1000 ml, and 1 patient (4.5%) drained >1000 ml. In non-cancer patients, 3 patients (27.3%) drained 100-500 ml, 5 patients (45.4%) drained 501-1000 ml, and 3 patients (27.3%) drained >1000 ml (**Table 1**).

Drainage cannulas were inserted for an average of 4 days in cancer patients and 3 days in non-cancer patients. For approximately 9.1% (n=2) of cancer patients, drainage was performed for 1 day, followed by 22.7% (n=5) for 2 days, 18.2% (n=4) for 3 days, 13.6% (n=3) for 4 days, and 36.4% (n=8) for more than 4 days. In non-cancer patients, 9.1% (n=1) underwent drainage for one day, 27.2% (3) for 2 days, 18.2% (2) for 3 days, and 45.5% (5) for 4 days (**Table 1**).

Pericardial fluid analysis was performed in 30 patients: in 18.8% (n=3) of cancer patients RBC levels >10^3/mm^3, in 25% (n=4) levels were >10^4/mm^3, in 18.8% (n=3) levels were >10^5/mm^3, and in 37.5% (n=6) levels were >10^6/mm^3. Ten percent (n=1) of patients without cancer had RBC levels of <100/mm^3 or <10^3/mm^3, 20% (n=2) had levels >10^3/mm^3, 30% (n=3) had levels >10^4/mm^3, 20% (n=2) levels >10^5/mm^3, and in 10% (1) levels were >10^6/mm^3. Data were available for seven patients (**Table 1**).

There were 6.3% (n=1) cancer patients with WBC levels of <100/mm^3, 25% (n=1) had WBC levels <10^3/mm^3, 68.8% (n=11) WBC were <10^4/mm^3, and 6.3% (n=1) WBC were <10^6/

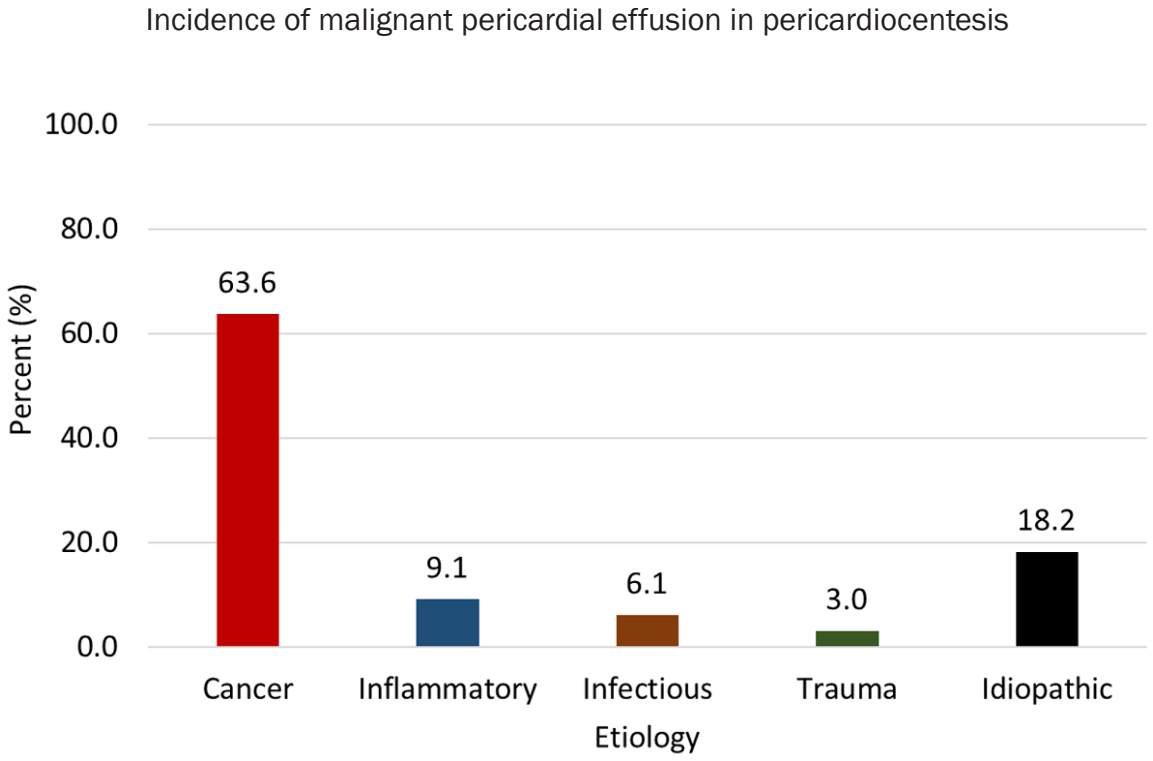

Figure 1. Etiologies of pericardial effusion (N=33).

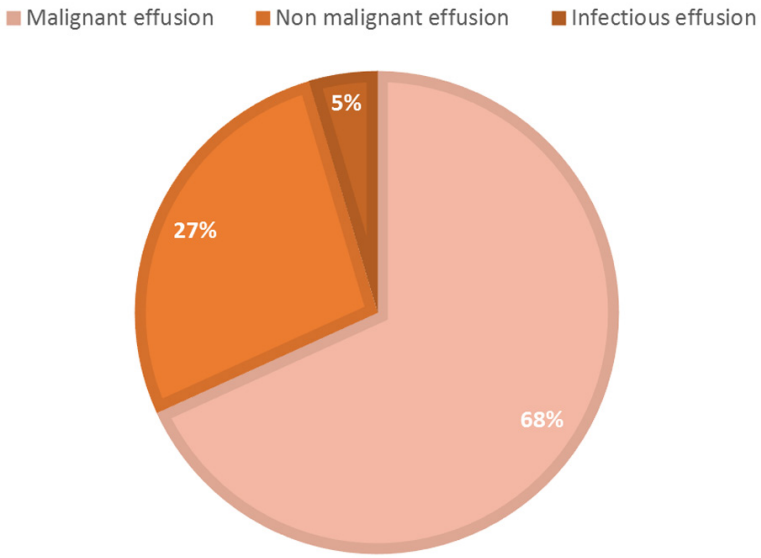

Figure 2. Type of effusion in oncology patients who underwent pericardiocentesis (N=22).

mm^3. Twenty percent (n=2) of patients without cancer had WBC levels <100/mm^3, while 10% (n=1) had levels <10^3/mm^3; and 70% (n=7) had levels >10^4/mm^3. Data were available for seven patients (**Table 1**).

Protein levels in patients with malignancy were 20-40 g/L in 38.9% (n=7) of the patients, 41-60 g/L in 55.5% (n=10), and 61-80 g/L in 5.6% (n=1). Among patients with non-malignant causes, 18.2% (n=2) had protein levels of 20-40 g/L, 63.6% (n=7) protein levels ranged from 41-60 g/L, and in 18.2% (n=2) from 61-80 g/L. No data were available for four patients. There was a significant difference in the median protein levels of pericardial fluid between the two groups (P=0.047) (**Table 1**).

LDH levels in cancer patients were 100-1000 U/L in 37.5% (n=6), followed by 1001-2000 U/L in 31.2% (n=5), and >2000 U/L in 31.2% (n=5). In noncancer patients, 18.2% (n=2) had an LDH levels <100 U/L, followed by 72.7% (n=8) in the range 100-1000 U/L range. Approximately 9.1% (n=1) had an LDH levels between 1001-2000 U/L. Data were available for six patients. There was a significant difference in the median LDH level in the pericardial fluid between the two groups (P=0.013) (**Table 1**).

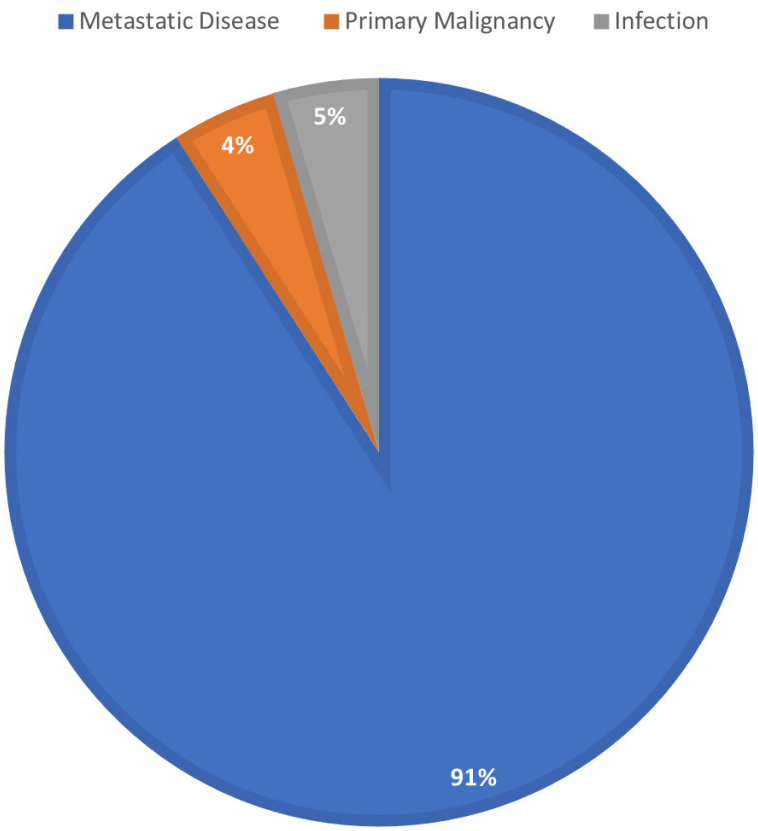

Figure 3. Presentation of oncology patients who underwent pericardiocentesis (N=22).

All oncology patients presented exudative pericardial effusions (P=0.002) (**Table 1**). Four cancer patients (18.2%) had re-accumulation of pericardial effusion and three patients (75%) required a repeat procedure (50% underwent pericardial window and 25% underwent repeat pericardiocentesis). Two non-cancer patients presented re-accumulation of pericardial effusion, one of whom underwent pericardial window creation (**Table 1**).

All patients underwent post-procedure echocardiography, and 87.9%, 60.6%, 27.3%, and 9% had a follow-up echocardiography within one week, within a week to a month, within a year, and after more than a year, respectively (**Table 4**).

However, patients who did not have a malignancy were followed up for a longer period (36.4% versus 22.7% had a follow-up echo after >1 month) possibly because of the mortality rate and metastatic nature of the malignancies found in our cohort.

Discussion

In the Western world, malignancy is the most common cause of large pericardial effusions [12]. Data on malignant pericardial effusion is lacking in the Middle East. The confirmation of malignant effusion and pericardial involvement in patients with cancer leads to changes to their management and prognosis [13, 14]; therefore, it is crucial to establish the etiology of the effusion [7, 15]. Research on the prevalence of malignancy-related pericardial effusions is minimal. The significance of malignancy-related effusion in patients with malignancies has not been well studied.

Malignant pericardial effusion is a common problem in oncology; however, it is rare as an initial presentation [16]. In the present cohort, there were no patients who were initially diagnosed because of malignant pericardial effusion. Most patients (>90%) were previously established oncology patients with metastasis, thus further supporting the evidence of pericardial effusion as a hallmark of progressive disease.

Lung cancer is the primary tumor that most frequently affects the pericardium [17]. In the present cohort, the incidence of lung and breast cancer was the highest at 27.3%. This finding is similar to that of other studies. Despite treatment, median overall survival in patients with malignant pericardial effusion is reported to be in the range of two to four months and is influenced mainly by the nature of the underlying malignancy [18]. Overall outcomes are poor in cancer patients with pericardial effusions requiring drainage, particularly in those with carcinoma or sarcoma [19]. The development of a pericardial effusion remains a grave occurrence in malignant disease, and this has improved little in contemporary oncological practice [20]. No epidemiological or clinical parameters were useful in differentiat-

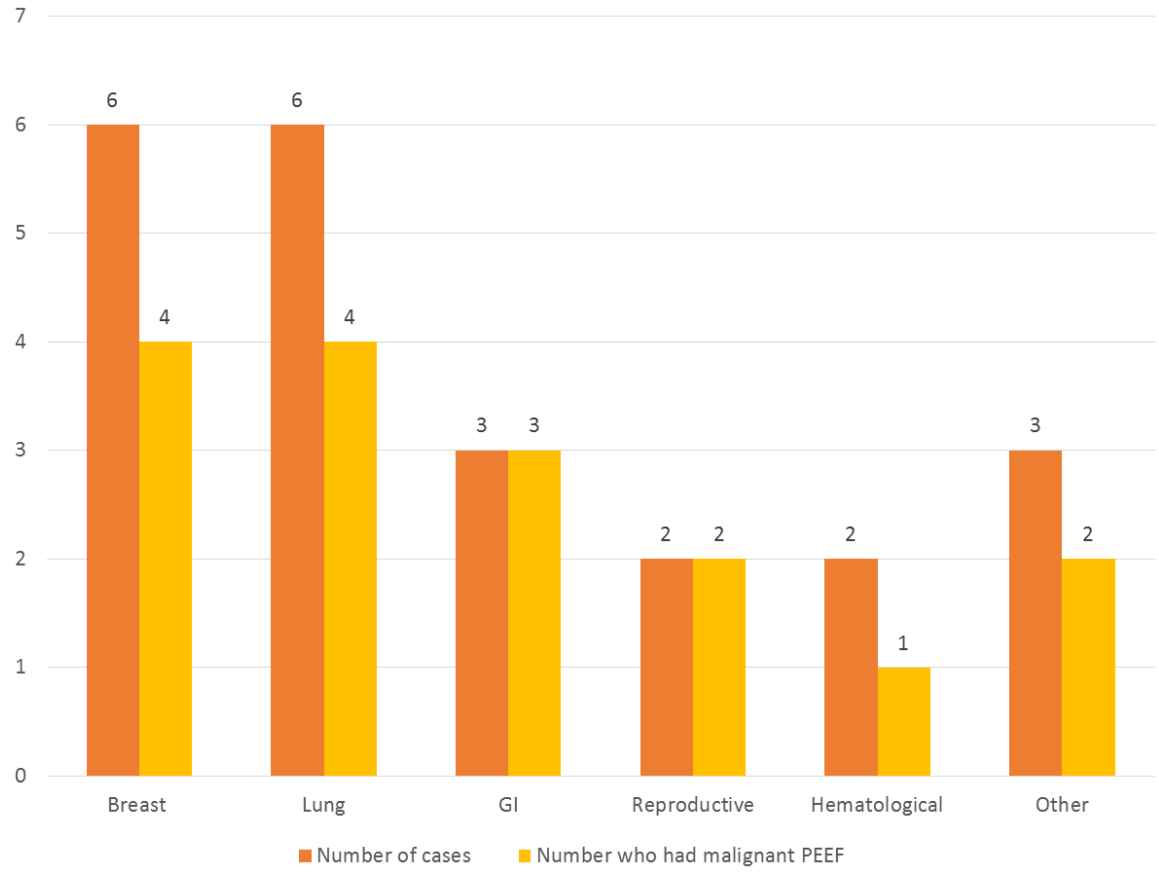

Figure 4. Incidence of malignancy and malignant pericardial effusion.

Table 4. Follow-up Echo in pericardiocentesis patients

Follow-up Echo	All/n (N%)	Patients with malignancy/n (N%)	Patients without malignancy/n (N%)	*P* value
Within 1 Week	29 (87.9%)	20 (90.9%)	9 (81.8%)	0.451
1 Week-1 Month	20 (60.6%)	13 (59.1%)	7 (63.6%)	0.801
1 Month-1 Year	9 (27.3%)	5 (22.7%)	4 (36.4%)	0.700
1 Year+	3 (9.1%)	2 (9.1%)	1 (9.1%)	1.000

ing between cancerous and non-cancerous effusions [21].

The underlying diagnoses of pericardial effusion in the patient cohort were made on the basis of pericardial fluid analysis obtained via pericardiocentesis and laboratory tests, including cytology and biochemistry, which have high sensitivity and specificity when utilized appropriately [22, 23]. In our chart analysis, we found that more than two-thirds of patients diagnosed with malignancy had malignant pericardial effusion, and all of which were exudative. Pericardial fluid protein levels were significantly lower in oncology patients, whereas pericardial fluid LDH were significantly higher. There is a recognized link between LDH level and malignancy. These values may benefit clinicians as diagnostic tools [24]. The amount of fluid drained from patients without malignancies was significantly higher than that drained from patients with malignancies. This may indicate a more insidious nature of accumulation in other etiologies, thus posing a threat to early drainage and tamponade prevention.

Percutaneous needle pericardiocentesis remains the most common therapeutic procedure for early management of symptomatic effusions and continues to be used as a diag-

nostic procedure [25, 26]. A surgical approach to pericardial drainage is effective and improves the quality of life in these patients [27]; however, it does not improve clinical outcomes compared to pericardiocentesis [28]. Percutaneous balloon pericardiotomy has been shown to be highly effective and may be particularly useful in managing recurrent effusions [29, 30]. One study found that systemic chemotherapy plus a pericardial window was a more effective treatment option than systemic chemotherapy alone or systemic chemotherapy plus drainage for patients with malignant effusions [31]. The optimal therapy for the management of malignant pericardial effusion remains to be determined [32].

Follow-up after pericardiocentesis is also important because this population is at an increased risk of recurrence of pericardial effusion [33, 34]. Among our patients, all underwent post-procedure echo, and 87.9% had follow-up within a week. However, only 27% of these patients had follow-up after one month. This may be due to multiple factors and shows that there is a need to convey the importance of follow-up to patients and explain its significance.

The limitations of our study include the possibility of selection bias due to the cohort size and the research being performed in a leading Middle Eastern oncology center.

The early diagnosis of the etiology of pericardial effusion based on fluid analysis may have a marginal effect on long-term outcomes, particularly in patients with cancer. We would like to expand our pilot study and conduct further research to determine how the presence of pericardial effusion affects the prognosis of patients with cancer, especially in the UAE, where there is a multiracial population that will benefit from this information. Additionally, these data will help regional oncologists in their daily practice and in the workup of pericardial effusion in patients with cancer.

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This study was conducted in accordance with the Declaration of Helsinki and was reviewed and approved by the Human Research Ethics Committee of Tawam Hospital, UAE, (IRB Approval: CRD 10/60) on the basis of relevant guidelines and regulations. Informed consent was waived by the Human Ethics Committee of Tawam Hospital, UAE, (IRB Approval: CRD 10/60) because of the retrospective nature of the study.

Disclosure of conflict of interest

None.

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