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The Prognostic Impact of Pericardial Fluid Cytology in Malignant Pericardial Effusion

ABSTRACT

Objective: Malignant pericardial effusion may affect almost 15 of the patients with underlying malignancies which deteriorates the prognosis. The prognostic significance of pericardial fluid cytology is under-represented in previous studies.

Methods: A total of 73 patients with symptomatic pericardial effusion treated with pericardiocentesis were included in this retrospective analysis. Macroscopic appearance, biochemical features, and cytological findings were obtained. Patients were divided into 3 groups: (i) without malignancy, (ii) with malignancy and negative cytology, and (iii) with malignancy and positive cytology. Survival data were searched via governmental death notification system.

Results: Mean age of the study group was 62 ± 15, and 54% (40) of the patients were female. On the cytological evaluation, 17 patients (23.3%) revealed positive cancer cytology, whereas 56 patients (76.7%) revealed negative cancer cytology. The median follow-up period was 840 days, and 34 patients (46.5%) died during follow-up. The survival rate of Group 3 was found to be significantly worse compared to Groups 1 and 2, no statistical difference was found between Groups 1 and 2 in terms of survival (Group 1 vs. Group 2 $P = .078$; Group 1 vs. Group 3 $P < .001$; Group 2 vs. Group 3 $P = .041$).

Conclusion: Cytological evaluation is an important step in patients with malignant pericardial effusion. Positive pericardial fluid cytology indicates a poorer prognosis.

Keywords: Pericardial effusion, survival, prognosis

INTRODUCTION

Primary pericardial tumor is rarely diagnosed; however, pericardial involvement in malignancies is frequently detected in almost 15% of the patients.[1] Pericardial effusion (PE) is the most common presentation of cardiac involvement in malignancies either with or without cardiac tamponade depending on the accumulation rate of pericardial fluid. Moreover, PE may be the first manifestation of an underlying malignancy.[2] Nevertheless, PE does not always demonstrate malign cell infiltration in the pericardium, and non-malignant causes like radiotherapy or opportunistic infections can also cause pericardial fluid accumulation in patients with malignancies.[3] Pericardial invasion in any malignancy reflects advanced disease stage; therefore, demonstration of malign cells in PE is of utmost importance both for diagnosis and treatment strategy.[4]

Pericardiocentesis (PC) is indicated in patients presenting with cardiac tamponade to provide hemodynamic stability, symptom relief, and establishment of diagnosis. Evaluation of pericardial fluid is essential following PC. Macroscopic appearance of fluid, biochemical analysis, culture for potential microbiological agents, and cytology should be sought in each case for definitive diagnosis and to lead treatment.[5] Pericardial effusion due to neoplasms has the highest mortality rate when compared to other causes.[6] However, prognostic significance of malign cell determination in fluid cytology is lacking. Therefore, we aimed to investigate the prognostic effect of malignancy and positive pericardial fluid cytology in patients undergoing PC.

ORIGINAL INVESTIGATION

Burak Sezenöz[1]
Feriha Pınar Uyar Göçün[2]
Emrullah Kızıltunç[1]
Salih Topal[1]
Hüseyin Murat Özdemir[1]

[1]*Department of Cardiology, Faculty of Medicine, Gazi University, Ankara, Turkey*
[2]*Department of Pathology, Faculty of Medicine, Gazi University, Ankara, Turkey*

Corresponding author:
Burak Sezenöz
✉ drburaksezenoz@gmail.com

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METHODS

We retrospectively included 73 patients who underwent PC due to hemodynamically significant PE between August 2010 and March 2021. All patients were symptomatic (dyspnea, tachypnea, reduced functional capacity, orthopnea, etc.) and hemodynamically compromised documented either by physical examination (low blood pressure, pulsus paradoxus, cold and pale skin, etc.) or by transthoracic echocardiography. Pericardiocentesis was performed under local anesthesia and fluoroscopic guidance using a subxiphoid approach. A pigtail catheter was introduced into the pericardial space. All pericardial fluid was drained which was confirmed by intraprocedural transthoracic echocardiography. Pericardial fluid (at least 50 cc) was sent for biochemical, cultural (aerobe /anaerobe/tuberculosis), and cytological analysis. The sample was centrifuged and analyzed as soon as possible by the pathology department. If any cellular infiltration was detected, specific marker staining was performed. A simultaneous blood sample was taken for discrimination of fluid content by using Light's criteria.[7] Moreover, all patients underwent routine laboratory analysis for common causes of PE such as thyroid and kidney dysfunction.

Patients were divided into 3 subgroups: Patients (1) without malignancy, (2) with malignancy and negative cytology, and (3) with malignancy and positive cytology.

Patients with iatrogenic PE, recent myocardial infarction (<30 days), and decompensated heart failure were excluded from the analysis. All data were extracted from our hospital's database. The study was approved by our Institutional Ethical Committee.

Survival Data

The time from PC to death or last follow-up visit was considered as follow-up duration. Survival data were searched via the governmental death notification system. Mortality data were extracted in September 2021.

Statistical Analysis

Statistical Package for Social Sciences 25.0 software for Windows (SPSS Inc., Chicago, Ill, USA) was used for data analysis. The Kolmogorov–Smirnov test was used to test the normality of distribution for continuous variables. The results are presented as mean ± standard deviation and as median (interquartile range, 25th-75th percentage). The comparisons of categorical variables were performed using the chi-square test. For comparison of more than 2 groups, the Kruskal–Wallis H test or one-way analysis of variance tests were used. Tukey and Bonferroni adjustments were used as a post hoc test for multiple comparisons among the groups. The impact of underlying disease on survival was investigated using the log-rank test. The Kaplan–Meier survival estimates were calculated. The possible factors identified in univariate analysis were further entered into Cox regression analysis to determine the independent predictors of survival of CT patients. A P value of <0.05 was considered statistically significant.

HIGHLIGHTS

- Cytological evaluation in pericardial effusion (PE) provides valuable information about the underlying cause and prognosis.
- Conventional pericardial analysis may fail to differentiate the underlying cause of PE.
- Cytological evaluation may improve diagnostic accuracy and may help us to identify underlying primary malignancies.
- Positive pericardial cytology is associated with poorer outcomes in patients with malignant pericardial effusion.

RESULTS

We included 73 patients who underwent fluoroscopy-guided PC in our department since May 2013. The mean age of the study group was 62 ± 15, and 54% (40) of the patients were female. A total of 35 patients (47.9%) had a known cause of PE; however, 38 patients (52.1%) had no history of PE-related disease on admission. Further evaluation revealed lung cancer (4), other malignancies (2), tuberculosis pericarditis (2), rheumatologic disorders (2), postpericardiotomy syndrome (1), and viral pericarditis (1) in patients without previous history of PE causing disease. There was no specific underlying cause in 26 patients (68.4%). The underlying causes of the patients at the time of admission and the underlying causes identified during the follow-up of the patients who were not previously diagnosed at the time of admission are shown in Table 1.

Biochemical and Cytological Findings

On the cytological evaluation, 17 patients (23.3%) revealed positive cancer cytology, whereas 56 patients (76.7%) revealed negative cancer cytology. Fifteen patients with negative cytology were found to be related to underlying

Table 1. Distribution of Underlying Causes of Pericardial Effusion

Underlying causes in patients with a previous diagnosis (n = 35)

- Lung cancer: 10 (28.51%)
- Lymphoid and hematological cancer: 12 (34.28%)
- Breast cancer: 4 (11.42%)
- Other cancer: 3 (8.57%)
- Romatological disorders: 3 (8.57%)
- Postpericardiotomy syndrome: 2 (5.71%)
- Chronic renal failure: 1 (2.85%)

Diseases identified during follow-up in undiagnosed patients (n = 38)

- Unknown origin: 26 (68.42%)
- Lung cancer: 4 (10.52%)
- Other cancer: 2 (5.26%)
- Rheumatological disorders: 2 (5.26%)
- Tuberculosis: 2 (5.26%)
- Postpericardiotomy syndrome: 1 (2.63%)
- Viral pericarditis: 1 (2.63%)

Table 2. Demographic and Laboratory Findings of Subgroups

	Group 1 (n = 41)	Group 2 (n = 15)	Group 3 (n = 17)	*P*
Age	66 ± 13	54 ± 16	56 ± 15	.035
Gender (female)	24 (58.5)	6 (40.0)	10 (58.8)	.434
Hb (g/dL)	11.2 ± 1.8	10.4 ± 2.4	11.2 ± 2.0	.391
Platelet count (1000/m^3)	294 (178-381)	234 (69-376)	290 (189-369)	.553
WBC (1000/m^3)	7.3 (5.8-9.6)	8.0 (4.7-10.6)	9.0 (6.7-12.4)	.665
Creatinine (mg/dL)	0.90 (0.77-1.23)	0.88 (0.56-1.02)	0.86 (0.58-1.20)	.272
LDL (mg/dL)	76 (62-103)	85 (66-91)	95 (60-121)	.295
HDL (mg/dL)	30 (25-38)	30 (26-34)	37 (32-46)	.058
Triglyceride (mg/dL)	99 (73-141)	111 (78-140)	94 (73-130)	.997

Hb, hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; WBC, white blood cell.

Table 3. Macroscopic and Biochemical Features of Pericardial Fluid Among Groups

	Group 1 (n = 41)	Group 2 (n = 15)	Group 3 (n = 17)	*P*
Macroscopy				
Serose	16 (39.0)	6 (40.0)	5 (29.4)	.634
Serohemorrhagic	3 (7.3)	3 (2.0)	2 (11.8)	
Hemorrhagic	22 (53.7)	6 (40.0)	10 (58.8)	
Glucose (mg/dL)	110 (87-123)	104 (75-122)	107 (79-124)	.889
Total protein (g/dL)	5.4 (4.9-5.8)	5.2 (4.8-5.5)	4.8 (3.9-5.3)	.071
Albumin (g/dL)	3.2 (2.9-3.5)	2.8 (2.7-3.4)	2.8 (2.4-3.1)	.016
LDH (U/L)	340 (212-617)	449 (174-1150)	717 (242-1420)	.247
Fluid protein/serum protein ratio	0.78 (0.72-0.82)	0.85 (0.76-0.94)	0.75 (0.65-0.85)	.340
Fluid LDH/serum LDH ratio	1.39 (0.79-2.37)	1.33 (0.71-2.96)	2.61 (0.81-3.74)	.627
Albumin gradient	0.38 (0.20-0.65)	0.35 (0.15-0.65)	0.60 (0.15-0.90)	.883

LDH, lactate dehydrogenase.

malignancy. Most of the patients (41.1%) had lung cancer with PE with positive pericardial cytology, whereas 3 patients (17.6%) had no specific diagnosis at the time of death. Cellular analysis of pericardial fluid guided the final diagnosis in 5 patients (29.4%) with specific cellular marker determination. Demographic features, laboratory, and survival findings of the study subgroups according to diagnosis and cytological findings are shown in Table 2. The macroscopic and biochemical findings of pericardial fluid are depicted in Table 3, and the cytological findings are shown in Table 4. Pericardial fluid albumin level was found to be significantly higher in Group 1 compared to Groups 2 and 3. The macroscopic and biochemical properties of the pericardial fluid were similar between Groups 2 and 3.

Follow-Up Data

The median follow-up period was 840 (3-4036) days in this study. A total of 34 patients (46.5%) died during follow-up. Figure 1 depicted the Kaplan–Meier curve of survival in subgroups. The survival rate of Group 3 was found to be significantly worse compared to Groups 1 and 2, and no statistical difference was found between Groups 1 and 2 in terms of survival (Group 1 vs. Group 2 $P = .078$; Group 1 vs. Group 3 $P < .001$; Group 2 vs. Group 3 $P = .041$). There was repeated pericardiocyntesis in 2 patients, and both of them died during follow-up. Table 5 shows that Group 3 has the worst prognosis after adjustment for age, gender, serum HDL, protein, and albumin values.

DISCUSSION

Pericardial effusion may occur during the course of malignancies or it may be the first presentation which consequently leads to the diagnosis of underlying cancer. The data about the prognostic significance of positive cytology in patients with malignant PE are scarce. This study shows us that positive pericardial cytology has poorer survival compared to cytology negative cases. Moreover macroscopic or biochemical analysis revealed no significant difference among groups. Interestingly, cytology negative patients had similar survival rates compared to non-malignant patients.

Transthoracic echocardiography is the mainstay evaluation test in patients with PE; however, additional imaging

Table 4. Cytological Findings of the Patients

Type of Malignity (n)	Cellular Type	Additional Markers
Lung cancer (8)	Malign epithelial cell	TTF-1, Keratin-7, CK-7, p63
Breast cancer (4)	Adenocarcinoma cell	GATA-3, MOC-31
Lymphoid and hematologic cancer (4)	Malign epithelial cell	TTF-1
Malign mesothelioma (1)	Epithelioid type mesothelioma	EMA

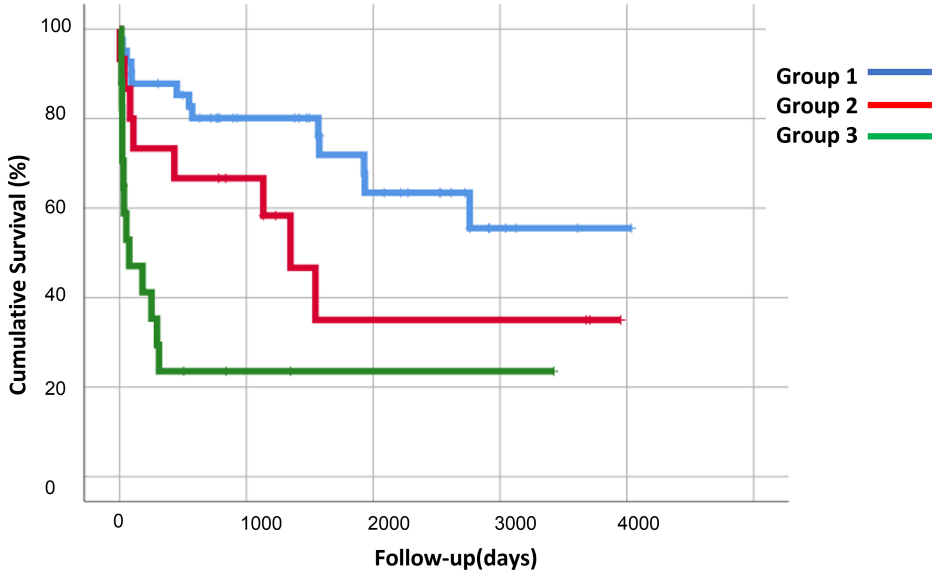

Figure 1. Kaplan–Meier curve of the survival in each group.

modalities may be utilized to differentiate the underlying causes.[8,9] Besides, several laboratory parameters need to be tested in the setting of pericardial fluid analysis, and cytological evaluation is a major determinant of malign involvement.[10] Diagnostic accuracy of pericardial cytology is considerably high compared to pericardial biopsy.[11] Presence of positive cytology supports pericardial involvement; however, negative cytology may fail to rule out malignant PE.[11] Thus, positive pericardial cytology as in our study has a poorer prognosis compared to negative cytology.

Pericardial effusion is a common and possibly life-threatening complication during malignancies especially when it results in cardiac tamponade. Pericardiocentesis may be considered as a diagnostic and treatment tool for these patients. Since our population consist of patients with a different kind of underlying malignity, overall this may affect our results. However, PC is only effective for symptomatic relief and has no benefit on underlying malignancy.

Table 5. Cox Regression Analysis for the Predictors of Mortality

		95% CI for HR		
	HR	Lower	Upper	*P*
Age	1.011	0.978	1.045	.516
Gender (male)	1.227	0.537	2.802	.627
HDL	0.974	0.925	1.025	.313
Serum protein	0.886	0.422	1.860	.749
Serum albumin	1.936	0.634	5.907	.246
Study groups				.001
Group 2 vs. Group 1	1.210	0.323	4.539	.777
Group 3 vs. Group 1	8.087	2.619	24.957	<.001
Group 3 vs. Group 2	5.570	1.353	22.933	.017

Group 1, patients without malignancy; Group 2, patients with malignancy and negative cytology; Group 3, patients with malignancy and positive cytology; HDL, high-density lipoprotein.

Thus, additional specific treatment modalities should be adopted in these patients in light of recent pharmacological advancements to overcome recurrences.[12,13] In this manner, cytology specimens may help us to aid diagnosis for further interventions.

There are several mechanisms responsible for PE in oncological patients: direct tumoral invasion or metastasis, adverse effects of antineoplastic treatment, and concomitant opportunistic infections.[14] As the underlying mechanism of the PE might be different in malignancy patients, a difference with regard to survival would be expected according to the cause of PE. Previous reports demonstrated conflicting results about the prognostic value of positive pericardial fluid cytology in cancer patients. Few studies suggested positive cytology as a negative prognostic factor; on the contrary, some studies reported no effect on survival.[15,16] Our results demonstrated that survival is significantly poorer in patients with positive pericardial cytology compared to non-malignant PEs and malign PEs without positive cytology. It is expected to see a survival difference between non-malignant and malignant PEs. But the mortality difference between cytology positive and negative malign PEs in our study needs some explanations. One possible explanation can be the underlying mechanism of PE. Pericardial effusion can develop as a side effect of chemotherapy or radiotherapy in cytology negative malign patients, and relief of cardiac tamponade with PC would have a beneficial effect on survival in this patient group. The other possible explanation can be the low patient number in the malignancy-related PE groups. Kaplan–Meier curves exhibited divergence between all 3 groups, but log-rank analysis showed a statistical difference only for the cytology positive group. The low patient number can explain why the cytology negative malignant PE group had similar mortality compared to the non-malignant PE group. Additionally, there can be some confounding factors that we cannot remove. For example, better survival in

the cytology negative malignant PE group may be attributable to novel cancer treatment modalities.[17]

Biochemical analysis is the mainstay in the evaluation of possible PE causes. We routinely apply Light's criteria which is helpful to distinguish exudative and transudative fluid content. However, none of the biochemical parameters of pericardial fluid is helpful for the discrimination of benign and malignant PE. Tumor markers may have a potential role in this setting; however, their clinical utility is limited.[18] Our findings are compatible with the literature since there was no significant difference among groups in terms of macroscopic appearance and biochemical content.

We also found that patients with malignancy but negative cytology in the pericardial fluid have a similar prognosis compared to patients without malignant effusion. This finding may be incidental, and also PE may be accepted as a more advanced stage of non-malignant conditions which in return may increase the likelihood of increased mortality.[19] Positive pericardial fluid cytology was associated with significantly higher mortality rates compared to cytology negative malignant and non-malignant PE.

Study Limitations

We have several study limitations. Our study was a retrospective, single-center study being the major limitation. Our study population consisted of patients from different underlying diseases, and their heterogeneity may be another limitation. We cannot provide results of pericardial specimens in our group which we do not perform routinely; however, diagnostic utility of pericardial biopsy is limited in malignant effusion. Limited number of patients is another limitation of our study. We do not have information about the cancer treatment protocols which can be a conflicting factor for the prognosis. On the other hand, we can only present the data about massive PE needed intervention which may generate an inclusion bias. Despite all the limitations, our study's follow-up period is quite long compared to previous studies, and we provide the long-term prognostic impact of pericardial cytology in malignant PE.

CONCLUSION

Cytological evaluation is an important step in patients with malignant PE. Positive fluid cytology indicates a poorer prognosis. The presence of malign cells in pericardial fluid may reflect an advanced stage of malignancy and has a negative impact on staging. It may influence both prognosis and treatment strategy once detected. Moreover; cellular content along with specific markers may facilitate and guide the diagnostic pathways when PE is the initial presentation. Macroscopic appearance and biochemical content of the fluid have no benefit for the discrimination of malign and benign causes.

Ethics Committee Approval: This study was approved by Institutional Ethics Committee (Gazi University, Date: 28.06.2021/ Decision number: 615).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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