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Prognostic Factors in Moderate-to-Large Pericardial Effusion Requiring Pericardiocentesis. A Single-Center Retrospective Study

Aim	Pericardial effusion is relatively common in daily clinical practice. To our knowledge, no study to date has been conducted on any laboratory parameter that predicts mortality in patients presenting with pericardial effusion. The present study evaluated the prognostic factors of patients with moderate to large pericardial effusions requiring pericardiocentesis.
Material and methods	This retrospective study included 156 patients who underwent pericardiocentesis in our hospital between 2013 and 2022.
Results	73 of the patients (46.8%) survived. Nonsurvivors had hypoalbuminemia more often than survivors (p<0.001). Median follow-up time in non-survivors was 274.5 [4.0–3507.0] days, while median follow-up time in survivors was 1490.0 [109.0–3209.0]. In-hospital mortality was seen in only 8 patients. The median neutrophil/lymphocyte ratio was significantly lower in survivors than nonsurvivors (p=0.005). The ROC curve analysis showed that the neutrophil/lymphocyte ratio was higher than 4.49, with sensitivity and specificity rates of 78.57% and 51.75% in predicting mortality (AUC=0.622, 95% confidence interval: 0.541–0.698, p=0.013).
Conclusions	The present study showed that the neutrophil/lymphocyte ratio and hypoalbuminemia, which are laboratory values at the time of admission, albumin in the pericardial fluid, and malignant pathology all play roles in the prognosis of pericardial effusion requiring pericardiocentesis.

Keywords	Neutrophil/lymphocyte ratio; albumin; mortality; pericardial effusion; pericardiocentesis
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Introduction

In daily clinical practice, pericardial effusion is a relatively common finding. The clinical spectrum of pericardial effusion can range between asymptomatic effusion and cardiac tamponade. The first challenge for the clinician is to try to identify the etiology. Sometimes, the condition can be easily associated with an underlying, known cause or disease, such as pericardial effusion, acute myocardial infarction, cardiac surgery, end-stage renal disease, or diffuse metastatic neoplasm. At other times, when there is no obvious cause, some clinical findings may be helpful to make a probable prognosis. Successful treatment and prognosis of pericardial effusion depend mainly on the underlying disease.

For this reason, it is essential to determine the etiology of pericardial effusion. The size of the pericardial effusion correlates with its cause, as moderate-to-large effusions are more common for a bacterial, neoplastic, or systemic inflammatory disease. Idiopathic pericardial effusion and pericarditis generally have a good prognosis and a very low risk of complications, especially if the effusion is mild-moderate [1]. Unfortunately, there is little epidemiological data on the incidence and prevalence of such effusions.

An Italian referral center for pericardial diseases at Maria Vittoria Hospital reported the mean annual incidence and prevalence of pericardial effusion as 3% and 9%, respectively, in the 6-year experience of the echocardiography laboratory [2]. Monitoring of pericardial effusion mainly relies on evaluating symptoms, the echocardiographic dimension of the effusion, and additional features such as inflammatory markers, i.e., C-reactive protein (CRP) [3]. In the present study, the purpose was to evaluate the prognostic factors of patients with moderate-to-large pericardial effusion that required pericardiocentesis.

Material and methods

156 patients who underwent pericardiocentesis in our university hospital between 2013 and 2022 were included in this retrospective study. The patients who had moderate-to-large pericardial effusion, did not respond to medical treatment, and who had an indication for pericardiocentesis, were included in the study. Patients were excluded from

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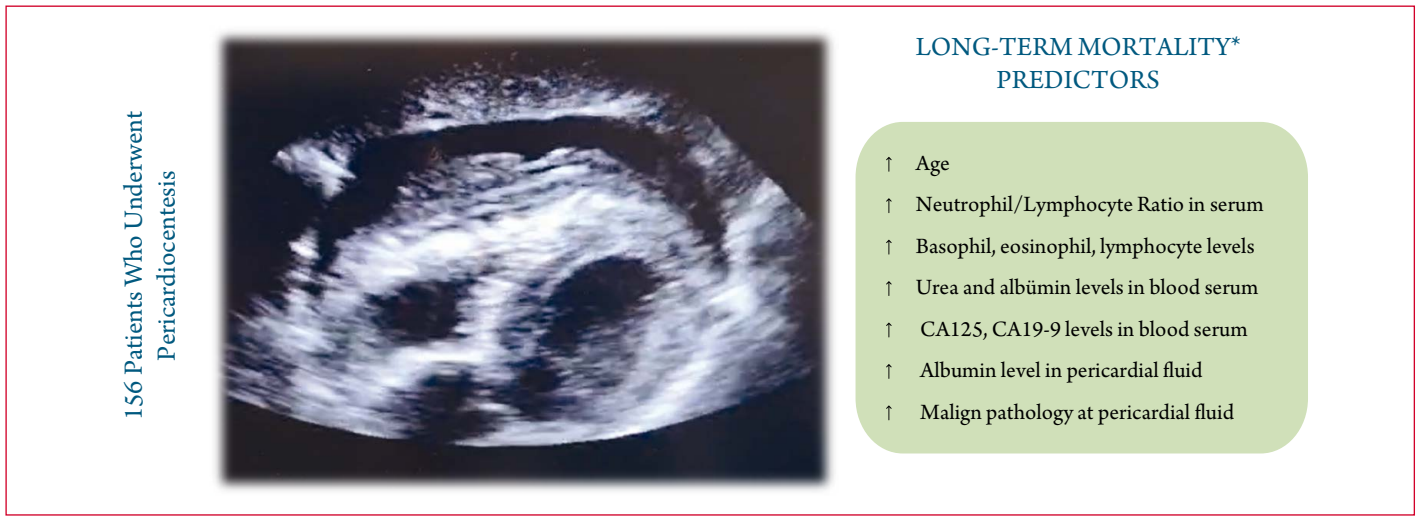
Central illustration. Prognostic Factors in Moderate-to-Large Pericardial Effusion Requiring Pericardiocentesis. A Single-Center Retrospective Study



* Median follow-up time in non-survivors was 274.5 [4.0–3507.0] years, while median follow-up time in survivors was 1490.0 [109.0–3209.0]. In-hospital mortality was seen in only 8 patients.

the study if they: 1) required surgical treatment because of pericardiocentesis failure, 2) had pericardiocentesis contraindications, 3) had constrictive pericarditis, 4) were under 18 yrs of age, or 5) had no indication for pericardiocentesis.

Regarding the biochemical parameters, blood samples taken from the upper extremity venous route and pericardial fluid samples taken during pericardiocentesis were studied during the same period, and the data were recorded. Hospital records provided the patients' demographic characteristics, clinical results, and biochemical and echocardiographic data.

All procedures involving human participants complied with the ethical standards of the institutional and/or the national research committee and the principles of the 1964 Declaration of Helsinki and its later amendments or with comparable ethical standards. The study was approved by the Clinical Research Ethics Committee (Date: 01.03.2023; No: 2022–219).

Statistical analysis

Jamovi (version 2.3.24.0) and JASP (version 0.17.1) software were used for statistical analyses. The significance level (p-value) was set at 0.05 for all statistical analyses.

Shapiro-Wilk, Kolmogorov-Smirnov, and Anderson-Darling tests were used to analyze the distribution of the numerical variables. Continuous data with a normal distribution are presented as mean ± standard deviation (SD). Continuous data without a normal distribution are presented as median (minimum – maximum values). Categorical variables are presented as numbers and percentages. Pearson Chi-Square and Fisher's Exact tests were used to compare the differences between categorical variables in 2×2 tables. The Fisher-Freeman Halton test was used for tables larger than 2×2. The t-test was used to compared two means of independent groups if numerical values were normally distributed. Mann-Whitney U tests were applied in the absence of normal distributions.

The receiver operating characteristic (ROC) analysis using the DeLong method with the Youden index was used to determine the optimum neutrophil/lymphocyte ratio that predicts mortality. The area under the ROC curve (AUC) and the corresponding 95% confidence interval (CI) were calculated. Based on the appropriate cut-off value of the neutrophil/lymphocyte ratio, specificity and sensitivity were also calculated.

To analyze the factors impacting mortality, univariate and multivariate Cox proportional hazard logistic regression analysis was performed. The hazard ratio (HR) with a 95% confidence interval (CI) was calculated.

Results

There were 156 pericardial effusion patients, 86 male (55.1%) and 70 female (44.9%). Their mean age was 64.2±15.7 yrs. Hypertension (30.3%) and diabetes mellitus (17.4%) were the most frequent two comorbidities. Pericarditis and malignancy-related and idiopathic pericardial effusions were seen in 51 (32.7%), 46 (29.5%), and 41 (26.3%) patients, respectively. Lung cancer was the most frequent cancer type (15.4%) that led to malignant pericardial effusion. The other clinical characteristics of pericardial effusion are given in Table 1.

Of 156 patients, 73 patients (46.8%) survived. Nonsurvivors were significantly older than the survivors (p=0.003). The frequencies of comorbidities differed between the survivors and nonsurvivors (p<0.05). The incidence of malignant pericardial effusion was significantly higher in the nonsurvivors patients (p=0.005).

Table 1. Demographic and clinical characteristics of the patients

Characteristic	Overall (n = 156)	Groups		p
		Survivors (n = 73)	Nonsurvivors (n=83)	
Age (yr)	64.2 ± 15.7	60.2 ± 15.6	67.7 ± 14.9	0.003
Sex				
Male	86 (55.1)	38 (52.1)	48 (57.8)	0.574
Female	70 (44.9)	35 (47.9)	35 (42.2)	-
Comorbidities				
Hypertension	47 (30.3)	23 (31.9)	24 (28.9)	0.815
Diabetes mellitus	27 (17.4)	18 (25.0)	9 (10.8)	0.035
Chronic renal failure	13 (8.4)	2 (2.8)	11 (13.3)	0.040
Rheuma-tological diseases	9 (5.8)	8 (11.0)	1 (1.2)	0.013
Chronic heart failure	4 (2.6)	1 (1.4)	3 (3.6)	0.623
Etiology				
Pericarditis	51 (32.7)	32 (43.8) a	19 (22.9) b	<0.001*
Malignancies	46 (29.5)	7 (9.6) a	39 (47.0) b	-
Idiopathic	41 (26.3)	19 (26.0) a	22 (26.5) a	-
Dressler syndrome	7 (4.5)	5 (6.8) a	2 (2.4) a	-
Connective tissue diseases	6 (3.8)	5 (6.8) a	1 (1.2) a	-
Viral/candidal infections	3 (1.9)	3 (4.1) a	0 (0.0) a	-
Iatrogenic	2 (1.3)	2 (2.7) a	0 (0.0) a	-
Type of malignancy	42 (26.9)	5 (6.8)	37 (44.6)	<0.001
Lung cancer	24 (15.4)	3 (4.1)	21 (25.3)	0.001
Breast cancer	5 (3.2)	1 (1.4)	4 (4.8)	0.372
Gastrointestinal system cancer	4 (2.6)	1 (1.4)	3 (3.6)	0.623
Urogenital system cancer	2 (1.3)	0 (0.0)	2 (2.4)	0.499
Other cancer	3(1.9)	0	3 (3.6)	-
Carcinoma of unknown primary	4 (2.6)	0	4 (4.8)	-
History of pericardial effusion	15 (9.6)	4 (5.5)	11 (13.3)	0.170
Number of pericardial effusion attacks				
1	11 (73.3)	2 (50.0)	9 (81.8)	0.516
2	4 (26.7)	2 (50.0)	2 (18.2)	-
Presentation with cardiac tamponade	64 (44.8)	29 (43.3)	35 (46.1)	0.870
Fluid at echocardio-graphy (§)	2.5 [0.9 – 7.0]	2.3 [0.9 – 7.0]	2.7 [1.2 – 6.0]	0.112

* – Pearson Chi-Square, Fisher's Exact, or Fisher Freeman Halton test.
§ – median [min-max]. Data are mean ± standard deviation, number (%), or median [minimum – maximum].
a, b – significant differences between the groups.

Table 2. Prognostic outcomes of the study groups

Parameters	Groups		p
	Survivors (n=73)	Nonsurvivors (n=83)	
Follow-up time (day) §	1490.0 [109.0–3209.0]	274.5 [4.0–3507.0]	<0.001
In-hospital mortality ‡	0 (0.0)	8 (9.6)	0.007

‡ – n (%), § – median [min-max].

Pericarditis-related pericardial effusion was seen more frequently in the patients who survived (p<0.001). The other demographic and clinical characteristics of the survival and nonsurvival patients were similar (Table 1).

Median follow-up time in non-survivors was 274.5 [4.0–3507.0] days, while median follow-up time in survivors was 1490.0 [109.0–3209.0]. In-hospital mortality was seen in only 8 patients. Minimum follow-up time was 4 days, and no procedure-related mortality was observed. (Table 2)

Table 3 compares of the laboratory parameters of the groups. There were significant differences in lymphocytes, eosinophils, basophils, urea, albumin, CA-125, and CA-19–9 between the survivors and nonsurvivors (p<0.05). The median neutrophil/lymphocyte ratio was significantly lower in the survivors than in the nonsurvivors (p=0.005). The receiver operating characteristics (ROC) curve (Figure 1) showed that the neutrophil/lymphocyte ratio was higher than 4.49 had sensitivity and specificity rates of 78.6% and 51.8% for predicting mortality (AUC=0.622, 95% confidence interval: 0.541–0.698, p=0.013).

Figures 1. The receiver operating characteristics (ROC) curve analysis showing the cut off value of neutrophil/lymphocyte ratio in predicting mortality (AUC: the area under the ROC)

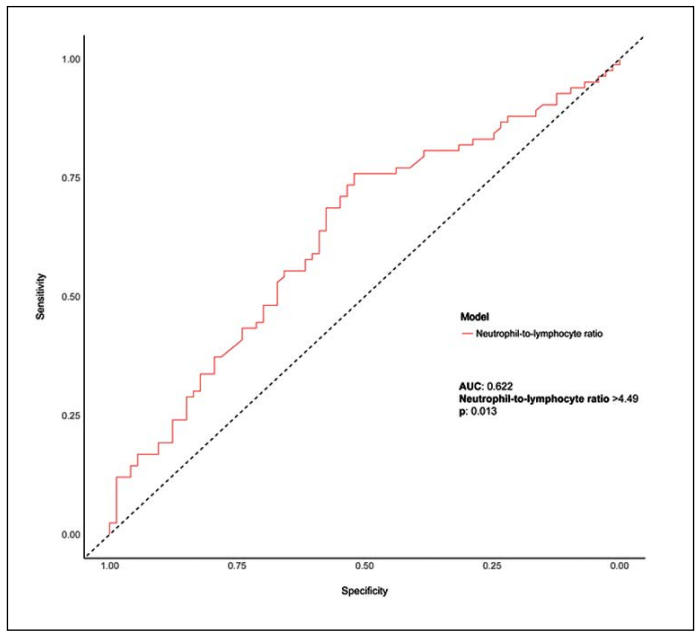


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Table 3. Comparison of the laboratory parameters of the survivors and nonsurvivors

Variable	Groups		p
	Survivors (n = 73)	Nonsurvivors (n = 83)	
Hemoglobin (g/dl)	11.2 ± 2.0	11.1 ± 2.0	0.687
Hematocrit (%)	34.4 ± 5.5	34.5 ± 6.2	0.851
Leukocyte count (x 10^3/l)	8930 [2970 – 27990]	8650 [1065 – 25380]	0.755
Neutrophil count (x 10^3/l)	6390 [500 – 23910]	6340 [1760 – 21970]	0.722
Monocyte count (x 10^3/l)	720 [170 – 1910]	690 [220 – 4180]	0.982
Lymphocyte count (x 10^3/l)	1580 [440 – 3710]	1140 [200 – 8770]	0.001
Eosinophil count (x 10^3/l)	90.0 [0.0 – 960.0]	60.0 [0.0 – 790.0]	0.012
Basophil count (x 10^3/l)	40 [10 – 120]	30 [0 – 70]	<0.001
Platelet count (x 10^6/l)	279 [64– 563]	266 [33 – 613]	0.243
Neutrophil/ lymphocyte ratio	4.0 [0.5 - 27.7]	5.5 [0.3 - 48.1]	0.005
Sodium (meq/l)	139 [128 – 146]	138 [104 – 147]	0.284
Potassium (meq/l)	4.2 ± 0.5	4.3 ± 0.6	0.712
Calcium (meq/l)	8.7 [1.7 – 9.9]	8.5 [6.2 – 9.8]	0.378
Magnesium (meq/l)	1.9 [1.1 – 3.2]	1.9 [1.0 – 2.7]	0.225
Urea (mg/dl)	36 [18– 211]	43 [4.0 – 321]	0.015
Creatinine (mg/dl)	0.8 [0.5 – 14.0]	0.9 [0.5 – 4.9]	0.063
Glucose (mg/dl)	114 [69 – 420]	106 [71 – 250]	0.265
Total protein (mg/dl)	6.4 ± 0.7	6.2 ± 0.8	0.062
Albumin (mg/dl)	3.5 [2.6 – 4.4]	3.3 [2.0 – 4.4]	<0.001
Lactate dehydrogenase (U/l)	244 [105 – 1496]	242 [123 – 5236]	0.584
C-reactive protein (mg/dl)	36 [2.0 – 284]	47 [2.0 – 376]	0.346
Neutrophil/albumin ratio	1762[143 – 8539]	2168 [518 – 7422]	0.096
CRP/albumin ratio	11.9 [0.5 – 97.9]	15.2 [0.5 – 71.5]	0.313
RBC sedimentation rate (ml/hr)	55.5 [8.0 – 118]	42 [5.0 – 123]	0.301
CA-125 (U/l)	48 [10 – 550]	118 [7.1 – 1978]	<0.001
CA-15-3 (U/l)	13.0 [2.0 – 31.0]	16.0 [4.2 – 272.0]	0.055
CA-19-9 (U/l)	4.0 [2.0 – 40.0]	10.0 [2.0 – 1200000]	0.008
Adenosine deaminase positivity ‡	0 (0.0)	2 (2.4)	0.499
SII	1245 [98.6 – 6249]	1513 [88.8 – 14831]	0.282

Data are mean ± standard deviation or median [minimum – maximum].
CRP, C-reactive protein; RBX, erythrocyte; SII, systemic immune-inflammation index.

Table 4. Comparison of the groups based on selected laboratory parameters

Variable	Groups		p
	Survivors (n=73)	Nonsurvivors (n=83)	
Anemia (hemoglobin <13.7 g/dl)	65 (89.0)	74 (89.2)	0.999
Hyponatremia (sodium <136 meq/l)	13 (17.8)	22 (26.5)	0.268
High creatinine (creatinine >1.25 mg/dl)	9 (12.3)	24 (28.9)	0.020
Hypoalbuminemia (albumin <35 mg/dl)	26 (40.0)	56 (72.7)	<0.001

Data are number (%).

Table 5. Laboratory parameters of the pericardial fluid

Variable	Groups		p
	Survivors (n=73)	Nonsurvivors (n=83)	
Leukocyte count (x 10^3/l)	1640 [20 – 58990]	1130 [10.0 – 37210]	0.278
Erythrocyte count (x 10^6/l)	130 [0.0 – 22580]	420 [0.0 – 5530]	0.264
	13 [0.0 – 289]	12 [0.0 – 290]	0.779
Monocyte count (x 10^3/l)	260 [0.0 – 15180]	75.0 [0.0 – 4090]	0.025
Neutrophil count (x 10^3/l)	985 [0.0 – 14240]	1160 [0.0 – 28760]	0.714
Eosinophil count (x 10^3/l)	10.0 [0.0 – 60.0]	30.0 [0.0 – 1615]	0.087
Basophil count (x 10^3/l)	0.0 [0.0 – 10.0]	10.0 [0.0 – 1930]	0.086
Total protein (mg/dl)	5.3 [1.8 – 6.7]	5.0 [1.4 – 9.8]	0.163
Albumin (mg/dl)	3.0 [0.8 – 3.9]	2.8 [0.9 – 3.8]	0.004
Glucose (mg/dl)	94 [17.0 – 320]	93 [5.0 – 224]	0.227
LDH (IU/l)	418 [56 – 5264]	533 [60.0 – 6777]	0.667
Pericardial fluid/ serum total protein	0.8 [0.3 – 1.1]	0.8 [0.2 – 1.4]	0.567
Pericardial fluid/ serum LDH	2.0 [0.3 – 15.5]	1.6 [0.1 – 28.7]	0.657
Δ (Serum – pericardial fluid) albumin (mg/dl)	0.5 [-0.3 – 2.4]	0.5 [-0.3 – 2.7]	0.836
Δ (Serum – pericardial fluid) albumin (%)	138 [-65.2 – 1499]	109 [-69 – 2133]	0.739*
General appearance ‡			
Transudate	5 (7.4)	6 (7.3)	0.999
Exudate	63 (92.6)	76 (92.7)	
Microbiological analysis ‡			
Sterile	60 (98.4)	62 (98.4)	0.743
Mycobacterium Tuberculosis	0 (0.0)	1 (1.6)	-
Candida albicans	1 (1.6)	0 (0.0)	-
Histopathological analysis ‡			
Benign	54 (94.7)	46 (74.2)	0.005
Malignant	3 (5.3)	16 (25.8)	-

Data are number (%) or median [minimum – maximum].
LDH, Lactate dehydrogenase.

Table 6. Univariate and multivariate Cox proportional hazard regression model for predicting mortality in patients with pericardial effusion

Factor	Univariate model	p	Multivariate model	p
	HR (95% CI)		HR (95% CI)	
Age (yr)	1.02 (1.00-1.04)	0.015	1.03 (1.01-1.05)	0.010
Diabetes mellitus (present vs. absent)	0.50 (0.24-1.05)	0.066	0.74 (0.34-1.61)	0.451
Chronic renal failure (present vs. absent)	1.85 (0.92-3.72)	0.085	1.33 (0.52-3.38)	0.548
Rheumatological diseases (present vs. absent)	0.18 (0.02-1.28)	0.086	0.32 (0.04-2.41)	0.272
Etiology (others vs. malignancy)	0.18 (0.11-0.29)	0.001	0.15 (0.08-0.27)	<0.001
High creatinine (>1.25 vs. ≤1.25)	1.64 (0.99-2.73)	0.056	1.48 (0.69-3.17)	0.314
Hypoalbuminemia (<3.5 vs. ≥3.5)	2.50 (1.49-4.19)	0.001	1.67 (0.97-2.89)	0.066
Neutrophil/lymphocyte ratio (≤4.49 vs. >4.49)	1.05 (1.02-1.09)	0.001	1.04 (1.00-1.08)	0.072

HR, hazard ratio; CI, confidence interval

Comparison of the systemic immune-inflammation index revealed no significant difference between the groups (p=0.282). Other laboratory parameters and their comparisons are summarized in Table 2. The grouping based on the categories for selected laboratory parameters revealed significant differences (Table 4). The nonsurvivors frequently had higher creatinine levels and hypoalbuminemia than the survivors (p=0.020 and p<0.001, respectively).

There were significant differences in the laboratory parameters of the pericardial fluid of the surviving and that of the nonsurviving patients (Table 5). The median monocyte count and albumin values were significantly higher in the survivors than in the nonsurvivors (p=0.025 and p=0.004, respectively). There were significantly more patients with malignant pericardial effusion in the nonsurvivor group (p=0.005). Other comparisons were similar in the groups (p>0.05).

Median follow-up time in non-survivors was 274.5 [4.0–3507.0] years, while median follow-up time in survivors was 1490.0 [109.0–3209.0]. In-hospital mortality was seen in only 8 patients. No patient died during the procedure.

The univariate Cox proportional hazard regression model revealed that age, etiology, hypoalbuminemia, and neutrophil/lymphocyte ratio were the significant risk factors for mortality in patients with pericardial effusion (Table 6). Nevertheless, age (HR=1.03, 95% CI: 1.01–1.05, p=0.010) and etiology (HR=0.15, 95% CI: 0.08–0.27, p<0.001) were the independent risk factors. As the age of the patients increased, the risk of mortality also increased, with an HR of 1.03. Patients with etiologies other than malignancy had a lower mortality risk with an HR of 0.15.

Discussion

The present study found that, other than etiology, the increasing age of patients with moderate-to-large pericardial effusions was a significant factor in determining the prognosis. Regarding etiology, the neutrophil/lymphocyte ratio, urea, eosinophil, lymphocyte, basophil, albumin, CA125, CA19–9, and albumin in the pericardial fluid plus malign pathology have roles in prognosis.

Data on the prognosis of pericardial effusion patients are limited, as there have been no randomized studies on pericardiocentesis. Thus, the prognosis of pericardial effusion has been determined by the underlying etiology and by the extent of fluid accumulation [4]. Clinical parameters are not always sufficient for predicting the prognosis, and additional information is required. However, there are no biochemical parameters in the recommended guidelines that can be clearly used to predict prognosis. Thus, determining and using additional laboratory and clinical parameters will more effectively predict the prognosis of pericardiocentesis patients. The present study found that the neutrophil/lymphocyte ratio and albumin, which are easily accessible, inexpensive, and reproducible, plus albumin in pericardial fluid, as well as malign pathology, play roles in this prognosis.

Although the epidemiology of diseases is constantly changing, viral pericarditis is the most common cause of pericardial effusion in the developed world. Among the patients with moderate-to-large pericardial effusion included in the current study, pericarditis, malignancy, and idiopathy were the most common etiologies. Viral pericarditis was the most common cause, with a rate of 32.7%. Malignancies were reported in patients with pericardial effusion at rates ranging from 12 to 23% [5]. In the present study, this rate was 29.5%. This higher rate was expected because malignancy often causes large effusion, and patients with mild conditions were not included in the study.

Traditionally accepted criteria for characterizing pericardial effusion in transudates and exudates have been the Light Criteria for Pleural Effusion [6]. The Light Criteria uses 0.5 and 0.6 as normal cut-off values for the pleural fluid protein/serum and the pleural fluid lactate dehydrogenase (LDH)/serum ratios, respectively. However, Buoro et al. reported that the normal range of protein and LDH was different in the pericardial space. This often results in incorrect exudate identification, especially in non-inflammatory pericardial effusions [7], and it shows that the Light criteria should not be applied in pericardial

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effusion. In the present study, whether the fluid was transudate or exudate according to the Light Criteria did not affect the prognosis.

It can be tricky and time-consuming to determine the underlying cause of pericardial effusion. To our knowledge, no study has been conducted on any laboratory parameter to predict mortality in patients presenting with pericardial effusion. CRP is used in the follow-up of pericardial effusion, since a 2021 retrospective study found that serum CRP predicted in-hospital mortality [8]. However, no significant correlation was detected between serum CRP level and prognosis in the present study.

The neutrophil/lymphocyte ratio is a simple biomarker of inflammation that can be measured during routine hematology assays, and an increased neutrophil/lymphocyte ratio has been identified as a biomarker of systemic inflammation and cardiovascular diseases [9–12]. This ratio was shown to be an important risk factor in predicting mortality by the univariate Cox analysis in the present study. A neutrophil/lymphocyte ratio >4.49 predicted mortality with a sensitivity of 78.6% and a specificity of 51.8%. Also, serum and pericardial fluid albumin values are essential for predicting mortality. Other indicators of inflammation (e.g., sedimentation, systemic immune-inflammation index) were not associated with the prognosis, except for a poor prognosis in patients with malignancy, as similar to the literature data.

The present study is limited by its retrospective design and inclusion of all-cause mortality. Also, only patients with moderate-large effusions who required pericardiocentesis were included in the study.

Conclusion

Although the etiology is a significant risk factor among patients with pericardial effusion, it is only one crucial factor affecting mortality along with increasing age. The serum neutrophil/lymphocyte ratio, urea, eosinophil, lymphocyte, basophil, albumin, CA-125, CA19–9 values, and albumin in pericardial fluid, plus malign pathology, all have important roles in the prognosis of patients with pericardial effusions requiring pericardiocentesis.

Ethics Committee Approval

Ethical committee approval was received from Aydın Adnan Menderes University Clinical Research Ethics Committee (Date: 01.03.2023; No: 2022–219).

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No conflicts of interest are reported.

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