Prognostic impact of small pericardial effusion in acute heart failure

Tahir Bezgin, MD and Aziz Inan Celik, MD

Department of Cardiology, Gebze Fatih State Hospital, Gebze, Kocaeli, Turkey

ABSTRACT

Background: The relationship between small pericardial effusion (SPE) and outcomes has not been well studied in patients with heart failure. Therefore, we aimed to investigate the prevalence and importance of SPE in acute heart failure (AHF).

Methods: A total of 398 hospitalized patients with AHF were retrospectively reviewed. Patients' baseline demographic, clinical, echocardiographic, and laboratory characteristics were noted. SPE was defined as the presence of a pericardial effusion <10 mm. The primary outcome was one-year mortality.

Results: SPE was noted in 54 (13.6%) of the patients. Mortality at one year was greater for patients with a small effusion compared with those without SPE (44.4 vs. 11.4%, respectively; $p < 0.001$), and the one-year mortality rate for the whole group was 15.8%. Age (HR = 1.12, 95% CI 1.054−1.854, $p = 0.024$), N-terminal pro-B-type natriuretic peptide >4800 pg/ml (HR = 1.628, 95% CI 01.102−4.805, $p = 0.001$), left ventricular ejection fraction <30% (HR = 1.878, 95% CI 1.154−4.524, $p = 0.001$), and presence of SPE (HR = 1.567, 95% CI 1.122−2.991, $p = 0.005$) were independent predictors of one-year mortality on multivariate analysis.

Conclusions: The presence of SPE on admission was an independent predictor of one-year mortality in AHF.

Keywords: Heart failure; Acute; Pericardial effusion; Mortality. **[Am J Med Sci 2022;364(6):729–734.]**

INTRODUCTION

The prognosis of moderate or large pleural and pericardial effusion is associated with the etiology of the effusion in various diseases.[1,2] However, the clinical importance of trivial and hemodynamically insignificant pericardial effusion has not been well studied in different patient populations. In heart failure, the main cause of pleural effusion is increased left heart filling pressure, increased right heart filling pressure, or both, whereas pericardial effusion is generated only if the filling pressures of the right heart are increased.[3] Therefore, pericardial effusions are less common than pleural effusions in chronic heart failure (CHF).[4] However, small pericardial effusion (SPE) is not an uncommon finding for patients with acute heart failure (AHF) or chronic heart failure (CHF) in real-life clinical practice.[5] Previous studies showed that presence or development of SPE was associated with adverse events in patients with lung cancer,[6] acute ischemic stroke,[7] human immunodeficiency virus infection,[8] and pneumonia,[9] as well as in heart transplant patients[10] and patients undergoing hip fracture surgery.[11] Although the prevalence of SPE varied from 12 to 20% in patients with heart failure,[12,13] only one study has examined the association between SPE and prognosis in CHF,[14] and only one study has investigated the prognostic value of SPE in AHF.[15] Therefore, the present study aimed to examine the frequency and prognostic relevance of SPE in AHF.

METHODS

Ethics statement

The study protocol was approved by the University of Health Sciences, Derince Education and Research Hospital Ethics Committee. Consent was not required due to the retrospective nature of the study. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Study design

This was a single-center, retrospective study, including all consecutive patients with AHF hospitalized between December 2016 and March 2019. Patients aged 18 years or older who had undergone transthoracic echocardiography within the first 24 h of admission were eligible for inclusion. Patients with incomplete echocardiographic or laboratory data, patients with a history of chronic inflammatory disease or an active cancer, patients who had undergone cardiac or thoracic surgery within the last 12 months, or patients who had an acute myocardial infarction within the previous six months were excluded from the study. Patients with a pericardial effusion >10 mm and patients with inadequate echocardiographic visualization were also excluded. Demographic information, past medical history, vital signs, and electrocardiographic, echocardiographic, and laboratory data on admission were noted. Transthoracic echocardiography was performed in all patients, and the severity

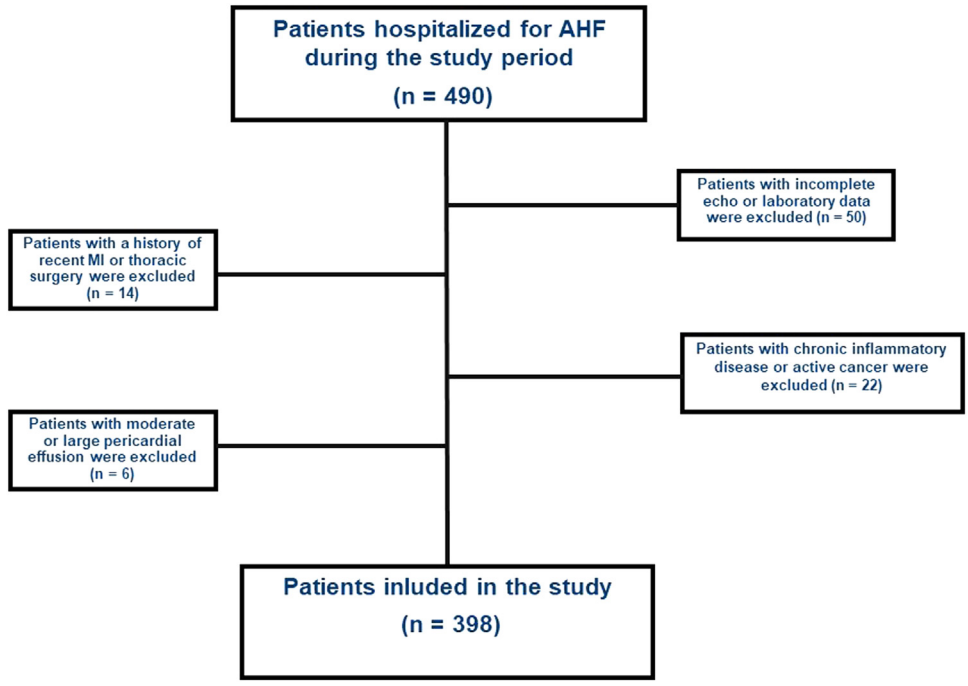

FIGURE 1. Flowchart of study population selection. *Abbreviations*: AHF, acute heart failure;,MI, myocardial infarction.

of valvular heart disease was defined according to the current guidelines.[16] The pericardial effusion was defined as SPE when the maximum pericardial space at end-diastole was <10 mm. Patients with moderate or greater pericardial effusion (>10 mm) were excluded from the study. The primary etiology of AHF was classified as ischemic heart failure, idiopathic dilated cardiomyopathy, hypertensive heart failure, and other reasons. The other reasons were primary valvular heart diseases, alcoholic cardiomyopathy, peripartum cardiomyopathy, infectious cardiomyopathy, diabetic cardiomyopathy, and drug-induced cardiomyopathy. Data for patients' survival status were collected by phone call or from an electronic database at the end of the first year. The primary outcome was all-cause mortality at 12 months.

Statistical analysis

Data were analyzed using SPSS for Windows version 20.0 (IBM, Armonk, NY, USA). The impact of parameters on prognosis was evaluated using univariate and multivariable Cox proportional hazards analyses. Age, N-terminal pro-B-type natriuretic peptide (NT-proBNP), left ventricular ejection fraction, comorbid diseases, and presence of SPE were forced in models to adjust the multivariate analysis. Receiver operating characteristic (ROC) curves for independent parameters were drawn, and the areas under the curves were calculated. For a specific parameter, the cutoff level that resulted in the highest sensitivity and specificity was an optimal cutoff value for prognostication. Kaplan-Meier methods were used to estimate rates of death after AHF. For all analyses, $p < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

A total of 490 patients were hospitalized with a primary diagnosis of AHF during the study period. However, 92 of the patients were excluded from the study for various reasons (Fig. 1). Therefore, the final study population consisted of 398 patients (mean age 73.4 ± 8.7 years, 51.5% male). The most common cause of AHF was ischemic cardiomyopathy (43.5%), and the most common comorbid disease was hypertension (72.1%) in our study population. The mean left ventricular ejection fraction was 38.1 ± 15.2%, and 105 (26.4%) of the patients had preserved left ventricular ejection fraction at presentation.

Fifty-four of the patients (13.6%) had SPE on admission. Comparison of patients with and without SPE is presented in Table 1. There were no significant differences between the two groups in terms of age, gender, smoking, etiology of heart failure, prevalence of diabetes, hypertension, chronic renal or liver disease, and malignancy. However, patients with an effusion were more likely to have coronary artery disease and atrial fibrillation and had lower albumin, higher creatinine, higher NT-proBNP, and higher high-sensitivity C-reactive protein (hsCRP) levels on admission compared with patients without effusion. The left ventricular ejection fraction was similar in the two groups.

TABLE 1. Comparison of patients with and without small pericardial effusion.

	SPE (+) (*n* = 54)	SPE (-) (*n* = 344)	*P* value
Gender (male)	29 (53.7)	176 (51.2)	0.875
Age (years)	73.2 ± 10.4	73.7 ± 12.5	0.232
Etiology			
Ischemic	25 (46.3)	148 (43.0)	0.105
Hypertensive	15 (27.8)	78 (22.7)	
Idiopathic dilated cardiomyopathy	10 (18.5)	50 (14.5)	
Other	10 (18.5)	72 (20.9)	
Comorbidities			
Atrial fibrillation	20 (37.1)	99 (28.8)	0.035
Smoking	9 (16.7)	45 (13.0)	0.847
Diabetes mellitus	14 (25.9)	85 (24.7)	0.527
Hypertension	40 (74.1)	247 (71.8)	0.951
Chronic renal failure	4 (7.4)	16 (4.7)	0.098
Chronic liver disease	2 (3.7)	8 (2.3)	0.711
Malignancy	4 (7.4)	18 (5.2)	0.621
Coronary artery disease	32 (59.3)	175 (50.9)	0.012
Laboratory results			
NT-proBNP (pg/ml)	4241 (1799–12,371)	3678 (1491–11,629)	0.002
Hemoglobin (g/dL)	13.1 ± 2.4	13.2 ± 2.2	0.613
Albumin (g/dL)	3.58 ± 0.35	3.70 ± 0.39	0.041
Creatinine (mg/dL)	1.39 ± 1.23	1.32 ± 1.12	0.042
hsCRP (mg/dl)	1.52 (0.44–6.72)	0.86 (0.38–3.34)	<0.001
Echocardiography			
≥Moderate mitral regurgitation	25 (46.3)	80 (23.3)	<0.001
≥Moderate tricuspid regurgitation	30 (55.6)	150 (43.6)	0.036
Pulmonary systolic pressure (mmHg)	34.6 ± 8.3	30.8 ± 4,3	0.025
Left ventricle ejection fraction (%)	37.8 ± 14.9	38.5 ± 14.6	0.082
Mortality	24 (44.4)	39 (11.4)	0.001

Values are given as mean ± SD or number (percentage)
Abbreviations: SPE, small pericardial effusion; NT-proBNP, N-terminal pro B-type natriuretic peptide; hsCRP, high-sensitivity C-reactive protein.

One-year mortality

The one-year mortality rate was 15.8%. Results of univariate comparison of baseline clinical, demographic, and laboratory parameters between the two groups (deceased and survivors) are listed in Table 2. Patients who died were older and more often had coronary artery disease, diabetes, or chronic renal failure. There were no differences in medications at discharge between the two groups. Deceased patients had higher levels of creatinine, hsCRP, and NT-proBNP but lower levels of albumin at presentation. Prevalence of the ischemic etiology was more common in deceased patients, whereas the hypertensive etiology was more common in the survivors. Non-survivors had a lower left ventricular ejection fraction and were more likely to have mitral regurgitation at presentation. Mortality at one year was higher in patients with SPE compared with those without pericardial effusion (44.4 vs. 11.4%, respectively; $p < 0.001$) (Fig. 2).

Predictors of one-year mortality

In univariate analysis, age, diabetes mellitus, coronary artery disease, chronic renal failure, ischemic etiology of AHF, NT-proBNP, creatinine, hsCRP, left ventricular ejection fraction, mitral regurgitation, and presence of SPE were associated with higher one-year mortality rates. However, age (HR = 1.12, 95% CI 1.054−1.854, $p = 0.024$), NT-proBNP >4800 pg/ml (HR = 1.628, 95% CI 01.102−4.805, $p = 0.001$), left ventricle ejection fraction <30% (HR = 1.878, 95% CI 1.154−4.524, $p = 0.001$), and presence of SPE (HR = 1.567, 95% CI 1.122−2.991, $p = 0.005$) were independent predictors of one-year mortality on multivariate analysis (Table 3).

DISCUSSION

Our study showed that SPE was present in 13.6% of the patients with AHF, and the presence of SPE on admission was associated with a greater risk of one-year mortality in AHF. However, the prevalence and significance of SPE have not been well studied in various cardiovascular conditions. Fröhlich and colleagues analyzed the data of 897 patients with CHF to identify the prognostic value of hemodynamically irrelevant pericardial effusion for one-year mortality.[14] They found that 73 (8.1%) of the patients had SPE, and it was independently associated with increased mortality at one year.[14] Similar to our findings, they also found that patients with SPE had higher C-reactive protein and NT-proBNP levels at

TABLE 2. Patient characteristics by vital status at 12 months.

	Alive (*n* = 335)	Deceased (*n* = 63)	*P* value
Gender (male)	172 (51.3)	33 (52.4)	0.165
Age (years)	72.4 ± 8.9	76.8 ± 8.5	<0.001
Etiology			
Ischemic	140 (41.8)	33 (52.4)	0.003
Hypertensive	85 (25.4)	8 (12.7)	
Idiopathic dilated cardiomyopathy	50 (14.9)	10 (15.9)	
Other	61 (18.2)	21 (33.3)	
Comorbidities			
Atrial fibrillation	105 (31.3)	14 (22.2)	0.089
Smoking	44 (13.1)	10 (15.9)	0.447
Diabetes mellitus	80 (23.9)	19 (30.2)	0.045
Hypertension	250 (74.6)	37 (58.7)	0.001
Chronic renal failure	13 (3.8)	7 (11.1)	0.036
Chronic liver disease	7 (2.1)	3 (4.8)	0.166
Malignancy	17 (5.1)	5 (7.9)	0.411
Coronary artery disease	165 (49.3)	43 (68.3)	0.002
Medication at discharge			
ACEI or ARB	260 (77.6)	49 (77.8)	0.865
Loop diuretics	314 (93.7)	60 (95.2)	0.362
Thiazides	44 (13.1)	7 (11.1)	0.102
Beta blockers	290 (86.6)	55 (87.3)	0.754
MRA	230 (68.6)	42 (66.7)	0.512
Laboratory results			
NT-proBNP (pg/ml)	2564 (1491–8697)	5247 (1854–12,391)	<0.001
Hemoglobin (g/dL)	13.2 ± 2.3	13.2 ± 2.4	0.748
Albumin (g/dL)	3.77 ± 0.46	3.74 ± 0.41	0.102
Creatinine (mg/dL)	1.32 ± 1.21	1.42 ± 1.32	0.002
hsCRP (mg/dl)	0.75 (0.38–5.31)	1.12 (0.51–6.72)	0.001
Echocardiography			
≥ Moderate mitral regurgitation	81 (24.2)	24 (38.1)	0.025
≥ Moderate tricuspid regurgitation	150 (44.8)	30 (47.6)	0.965
Pulmonary systolic pressure (mmHg)	31.6 ± 9.3	34.8 ± 10.2	0.085
Left ventricle ejection fraction (%)	38.6 ± 13.9	35.5 ± 11.6	0.001
Small pericardial effusion	30 (8.9)	24 (38.1)	<0.001

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker, MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro B-type natriuretic peptide; hsCRP, high-sensitivity C-reactive protein.

presentation. Santas et al. included 1827 patients with AHF to find the association between pericardial effusion and the risk of one-year mortality.[15] The prevalence of mild, moderate, and severe pericardial effusion was 11.6%, 1.9%, and 0.9%, respectively, in the study cohort. In multivariate analysis, patients with moderate and severe effusion were at increased risk for mortality compared with those without pericardial effusion. However, AHF patients with SPE showed similar mortality risk with no pericardial effusion.[15] In contrast to the findings of Santas et al., all-cause mortality at one year was greater for patients with SPE compared with those without an effusion (44.4% *vs*. 11.4%, $p = 0.001$) in our study. The main difference in our study was the lower mean left ventricular ejection fraction (38.1%) compared with Santas and colleagues' study (49.6%).

Another important finding of our study was that mortality was lower among those with a hypertensive etiology than among those with other causes. Similar to our

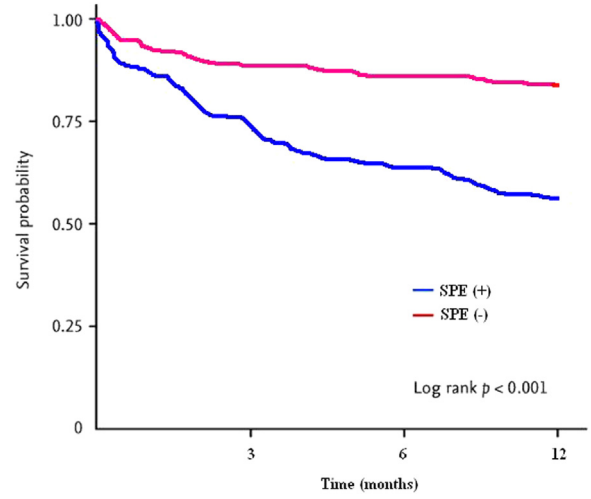

FIGURE 2. Kaplan-Meier curves for all-cause one-year mortality in acute heart failure patients with or without small pericardial effusion (SPE).

TABLE 3. Multivariate analysis for the prediction of all-cause mortality at 12 months.

	OR	95% CI	P
Age (per 10 y)	1.125	1.054–1.854	0.024
Ischemic etiology	1.086	0.985–1.412	0.205
Coronary artery disease (presence vs absent)	1.074	0.741–3.377	0.903
Hypertension (presence vs absent)	0.875	0.758–1.115	0.125
Chronic renal disease (presence vs absent)	1.102	0.848–1.432	0.334
NT-proBNP > 4800pg/ml	1.628	1.102–4.805	0.001
High-sensitivity C-reactive protein	1.086	0.913–1.412	0.504
Left ventricle ejection fraction <30%	1.878	1.154–4.524	0.001
≥ Moderate mitral regurgitation	1.110	0.921–1.412	0.223
Small pericardial effusion (presence vs absence)	1.567	1.122–2.991	0.005

Abbreviation: NT-proBNP, N-terminal pro B-type natriuretic peptide.

data, Pecini et al. found that heart failure attributed to hypertensive heart disease had a significantly better prognosis than that attributed to ischemic heart disease, valvular heart disease, dilated cardiomyopathy, or unknown/mixed etiology.[17]

The pathophysiology of pericardial effusion is unclear in AHF, but increased right heart pressures causing congestion and increased systemic inflammatory response could have an impact on the accumulation of fluid in the pericardial space. The reasons for the increased mortality in patients with SPE are also unclear, but higher burden of comorbid diseases such as atrial fibrillation and coronary artery disease and more severe mitral and tricuspid valve regurgitation are all thought to play a role.

STUDY LIMITATIONS

Due to the retrospective design of the study, serial changes in SPE could not be assessed by serial echocardiography. Other limitations of this study include the single-center study design, the lack of invasive hemodynamic data, and chest X-ray findings.

Definitive causes of SPE could not be identified due to lack of pericardial fluid analysis. However, because pericardiocentesis is reserved for hemodynamically significant or large effusions, it cannot be performed in patients with SPE. This was a single-center study, and only hospitalized patients were included. Therefore, our results cannot be directly applied to all patients with AHF. Prospective studies are needed to elucidate the prognostic value of SPE in AHF.

CONCLUSIONS

We found that 13.6% of the AHF patients had SPE at presentation, and SPE was an independent predictor of mortality at one year.

DECLARATION OF COMPETING INTEREST

The authors declare that there is no conflict of interest.

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This research received no grant from any funding agency in the public, commercial or not-for-profit sectors.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjms.2022.06.028.

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Correspondence: Tahir Bezgin, MD, Osman Yılmaz Mah., İstanbul Cad. No:127, Gebze- Kocaeli, Turkey (E-mails: bezgintahir3@yahoo.com, azizinanmd@hotmail.com).