A small pericardial effusion is a marker of increased mortality
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Objective  The study aimed to evaluate the prognostic importance of an incidental small pericardial effusion found on echocardiography.

Methods  We identified 10,067 consecutive patients undergoing echocardiography at 1 of 3 laboratories. Patients were excluded if they were referred for evaluation of the pericardium (n = 133), had cardiac surgery within the previous 60 days (n = 393), had a moderate or greater pericardial effusion (>1 cm if circumferential, n = 29), had no follow-up (n = 153), or had inadequate visualization of the pericardial space (n = 9). The Social Security Death Index was used to determine survival.

Results  A small pericardial effusion was noted in 534 (5.7%) of 9,350 patients. Compared to patients without a small effusion, those with an effusion were slightly older (68 ± 13 vs 67 ± 12 years, P = .02) and had a lower ejection fraction (52% vs 55%, P < .0001). Mortality at 1 year was greater for patients with a small effusion (26%) compared to those without an effusion (11%, P < .0001). After adjustment for demographics, medical history, patient location, and other echocardiographic findings, small pericardial effusion remained associated with higher mortality (hazard ratio 1.17, 95% CI 1.09-1.28, P = .0002). Of 211 with an effusion and follow-up echocardiography (mean 547 days), 136 (60%) had resolution, 63 (28%) showed no change, and 12 (5%) had an increase in size, although no patient developed a large effusion or cardiac tamponade.

Conclusion  The presence of a small asymptomatic pericardial effusion is associated with increased mortality. (Am Heart J 2011;161:152-7.)
Pericardial effusion classification

Patients were grouped into those with and without an effusion defined as the presence of an echolucent pericardial space that persisted in diastole. For those with follow-up echocardiography, the size of any effusion was graded as small (<1 cm, circumferential average), moderate (1-2 cm), or large (>2 cm).

Outcome

The primary outcome was all-cause mortality as determined by the Social Security Death Index. For those undergoing follow-up echocardiography, secondary outcomes included the progression to tamponade and resolution of the effusion.

Study variables

Patient demographic data included age and gender. Echocardiographic data included the presence of a pericardial effusion, the left ventricular ejection fraction, right atrial enlargement (defined as a length ≥5 cm during systole in the 4-chamber view), left atrial enlargement (defined as a length ≥5.5 cm during systole in the 4-chamber view), presence of tricuspid regurgitation, and presence of mitral regurgitation. Evidence for echocardiographic tamponade included any of the following: RV collapse during diastole, a >25% drop in mitral inflow velocity with respiration, or an exaggerated septal shift toward the left ventricle with respiration if associated with an inferior vena cava diameter over 2 cm.

Comorbid conditions were defined as present at baseline if documented with an International Classification of Disease, 9th Revision, Clinical Modification code in a patient encounter during the 5 years before the index date: coronary artery disease (410-414), heart failure (428), diabetes mellitus (250), malignancy (140-208), chronic obstructive pulmonary disease (490-496), liver disease (570-571), connective tissue disease (710.0, 710.1, 710.4, 714.0, 714.1, 714.2, 714.81, 725), and renal disease (582, 583, 585, 586, 588).7

Follow-up

We used the Social Security Death Index to determine survival. A random subset of 50 charts of patients who died (25 with an effusion and 25 without an effusion) were blindly reviewed by a board-certified cardiologist for cause of death (heart disease, malignancy, other). For those patients with follow-up echocardiography, we recorded any change in effusion size and the presence of tamponade. If patients had more than one follow-up echocardiogram, the most recent study was used. We reviewed the charts of patients with a pericardial effusion that was moderate or greater in size to determine the presence of a physician’s clinical diagnosis of cardiac tamponade.

Statistical analysis

JMP (SAS Institute, Cary, NC) was used for all the statistical analyses. Data are expressed as means or proportions. Comorbidity data were missing for 0.6% of patients with effusion and 0.4% without effusion. Given the small numbers, these patients were excluded from multivariate analysis. The findings were unchanged when missing comorbidities were imputed to 0. Approximately half of systolic pulmonary artery pressure data were missing, and therefore, these data were not included in the primary multivariate analysis. In a secondary analysis, the missing pulmonary artery pressure data were imputed using means.

Comparisons between proportions were evaluated by the χ² test with the Yates correction. Survival for those with and without an effusion was displayed with Kaplan-Meier survival curves. Unadjusted differences in survival were determined with the log-rank test. We used a Cox proportional hazards model to determine the association between the presence of an effusion and survival after adjustment for demographics, clinical, and other echocardiographic findings. We included covariates in the final model if they were associated with mortality at the P < .05 level. The sample size was designed to have 90% power to detect a 6% increase in 1-year mortality for those with a pericardial effusion (eg, 10% vs 16%) assuming a
5% effusion prevalence rate. Differences were considered significant at $P < .05$ (2-tailed).

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**Results**

**Patient characteristics**

Of 9,350 patients, there were 534 (5.7%) with a small pericardial effusion. Table I summarizes the baseline demographic and clinical characteristics of these patients. Compared to patients without an effusion, those with an effusion were slightly older, more likely to be hospitalized, and have a history of heart failure, diabetes mellitus, renal disease, and neoplasm. Patients with an effusion had a lower ejection fraction (Table II), and were more likely to have atrial enlargement, and moderate or greater mitral or tricuspid regurgitation.

The prevalence of an effusion for different subgroups of patients by diagnosis is shown in Figure 1. An effusion was significantly more common in patients with a history of heart failure, prior malignancy, liver disease, diabetes, but not ischemic heart disease.

Survival

During a mean 2.3 ± 1.9 years of follow-up, 2125 (23%) patients died. Mortality was greater for patients with a small effusion (26% at 1 year) compared to those without an effusion (11% at 1 year, $P < .0001$). The survival difference was evident within the first 100 days of diagnosis (Figure 2) and persisted throughout follow-up.

The increased mortality with an effusion at 1 year was observed for patients in most subgroups examined (Table III) including inpatients and outpatients, and those with prior malignancy, liver disease, and diabetes. A nonsignificant trend toward increased mortality with a pericardial effusion was observed for patients with a
Prior history of heart failure and ischemic heart disease (Table III).

In a secondary analysis, we limited the patients to those not hospitalized with preserved left ventricular function (≥50%), normal right and left atrial size, and mild or less mitral and tricuspid regurgitation. This cohort, where an effusion was likely an incidental finding, had a very low 1-year mortality if there was no effusion (3%, 67/2168) but had a much higher 1-year mortality if an effusion was present (11%, 7/62, P = .0004).

After adjusting for demographics, medical history, patient location, and other echocardiographic findings, a small pericardial effusion remained associated with worse mortality (hazard ratio 1.17, 95% CI 1.09-1.28, P = .0002) (Figure 3). When pulmonary artery pressure was added to the model (imputed for half the patients), the pericardial effusion hazard ratio for mortality was similar (1.14, 95% CI 1.05-1.23).

Among a random sample of 50 deaths (25 with and 25 without effusion) that were reviewed, the cause of death

<table>
<thead>
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<th>Characteristic</th>
<th>Pericardial effusion</th>
<th>No pericardial effusion</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n)</td>
<td>26% (112/432)</td>
<td>11% (772/6798)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Inpatients (n)</td>
<td>39% (89/229)</td>
<td>28% (473/1693)</td>
<td>.001</td>
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<td>Outpatients (n)</td>
<td>10% (16/159)</td>
<td>5.6% (240/4269)</td>
<td>.03</td>
</tr>
<tr>
<td>Heart failure (n)</td>
<td>33% (15/45)</td>
<td>29% (86/301)</td>
<td>.51</td>
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<tr>
<td>Ischemic heart disease (n)</td>
<td>20% (13/64)</td>
<td>12% (118/833)</td>
<td>.07</td>
</tr>
<tr>
<td>Diabetes mellitus (n)</td>
<td>23% (13/56)</td>
<td>12% (64/523)</td>
<td>.003</td>
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<td>Liver disease (n)</td>
<td>86% (6/7)</td>
<td>46% (23/50)</td>
<td>.04</td>
</tr>
<tr>
<td>Neoplasm (n)</td>
<td>46% (29/63)</td>
<td>23% (162/533)</td>
<td>.0002</td>
</tr>
</tbody>
</table>

Figure 3

The hazard ratio for mortality with a small pericardial effusion is shown for different levels of risk adjustment. The survival association is partially attenuated with adjustment for location (more inpatients had effusions than outpatients). However, additional adjustment did not substantially reduce the association between an effusion and survival, which remained statistically significant (95% CI did not include 1.0). Inpatient status refers to location of the patient (inpatient or outpatient) at the time of the echocardiogram. Variables associated with survival (P < .05) and included in the final model include age, inpatient status, moderate or greater tricuspid regurgitation, left ventricular ejection fraction, liver disease renal disease, ischemic heart disease, and neoplasm.
for those with a pericardial effusion was heart disease in 9 (36%), cancer in 7 (28%), other cause in 9 (36%) compared to heart disease in 7 (28%), cancer in 8 (32%), and other cause in 10 (40%) of those without an effusion (P = .83).

Follow-up
There were 211 patients (40%) with an effusion who underwent follow-up echocardiography. The mean follow-up time was 547 days (range 1-2,311 days). From these patients, 136 (64%) had resolution of effusion, 63 (30%) showed no change, and 12 (5.7%) had an increase in the size of the effusion. Of these 12 patients, none developed a large effusion, an echocardiographic or clinical diagnosis of cardiac tamponade, or underwent pericardiocentesis.

Discussion
Although the outcome of patients with large and clinically significant pericardial effusions has been described, the clinical significance of a small incidental pericardial effusion is unclear. This lack of knowledge is due in part to a paucity of information regarding the natural history of a small pericardial effusion. In contrast, the prognosis for patients with large effusions has been shown to vary from poor to those with malignant effusions to good for those with malignant effusions determined to be idiopathic. Thus, the clinician is often unsure of the implications of an incidental effusion, particularly if it is small in size.

While pericardiocentesis may provide a diagnosis, the procedure is not without risk and is often associated with recurrence rates up to 40% when used for treatment. Thus, pericardiocentesis is usually reserved for effusions that are hemodynamically significant. While small incidental effusions rarely present with tamponade, the rate and predictors of progression to tamponade are unknown. Such information on natural history is important for determining the appropriate frequency of follow-up studies.

While we found that progression of an incidental small pericardial effusion was rare including no development of tamponade, we also noted that these small effusions were associated with shortened survival. Patients with effusions had more comorbidities than patients without effusions and had more structural heart disease on echocardiography that is known to be associated with increased mortality. However, after we adjusted for observable characteristics, the presence of a small pericardial effusion remained significantly associated with an increased risk of death. Furthermore, the negative survival impact of a pericardial effusion was seen across multiple subgroups of patients.

Although few studies have examined the association of survival and small pericardial effusions, our findings are consistent with data previously reported for patients infected with the HIV. That study from the early 1990s that included 231 patients at various stages of HIV disease found that the presence of any effusion (most were small in size) was associated with a 6-month mortality of 64% compared with 7% for those without an effusion. The difference remained significant after adjustment for CD4 count and albumin level. Similar to our study, no infectious or malignant cause was documented and the development of tamponade was rare.

One plausible explanation for this effusion-mortality association is that a pericardial effusion is associated with the severity of the underlying disease. We hypothesize that a small pericardial effusion is a marker for systemic processes that lead to extra vascular fluid accumulation. Individuals with inflammatory disease such as rheumatic disease were shown to have pericardial involvement manifested as an effusion at a rate of 2% to 10% among patients with rheumatoid arthritis, 6% to 50% in patients with systemic lupus erythematosus, and 60% to 80% in systemic sclerosis.

We have previously suggested that capillary leak syndrome may be responsible for the increased incidence of small pericardial effusions. The capillary leak syndrome includes generalized serous fluid extravasation that usually involved pleural, peritoneal, and pericardial surfaces. In another unrelated study, other inflammatory markers such as interleukin 6, interleukin 8, and interferon γ were found to be associated with the presence of an idiopathic pericardial effusion. Therefore, cytokines may also play a major role in the pathogenesis of idiopathic small pericardial effusion regardless of the underlying condition.

Clinical implications
There are several clinical implications of our findings. First, for clinicians confronted with an incidental finding of a small pericardial effusion, concern over subsequent development of cardiac tamponade should be minimal. Thus, routine follow-up echocardiography is not warranted unless there are other clinical factors suggesting the continued presence of a pericardial effusion. This is consistent with an American College of Cardiology/American Heart Association/American Society of Echocardiography joint statement that does not recommend routine follow-up echocardiography for patients with an asymptomatic small pericardial effusion.

Although the presence of a small effusion should not lead to any specific therapy, it should prompt the clinician to consider progressive chronic and inflammatory diseases as the etiology. The increased risk of death associated with a small pericardial effusion may be used along with other clinical characteristics when estimating a patient’s prognosis.
Limitations

Our study was limited to those undergoing echocardiography. Thus, our study is not applicable to a healthy population that would not be referred for echocardiography. However, it is directly applicable for the provider that receives an echocardiography report with an incidental finding of a pericardial effusion. Given the small size of the effusions, pericardiocentesis was not performed and most effusions resolved spontaneously. Therefore, the etiologies of the pericardial effusions are unknown. Follow-up echocardiography was at the discretion of the provider; however, progression of the effusion was rare in those with follow-up studies. It is likely that if there was 100% follow-up, the rate of resolution would have been higher. Most of the study patients were male (95%), and therefore the association of pericardial effusion and survival in women is less clear. Finally, we used all-cause mortality because cause of death was not available for all patients.

In summary, we found that small incidental pericardial effusions were not uncommon for patients undergoing echocardiography. Progression to a large effusion was rare and no patient was ever diagnosed with cardiac tamponade. However, the presence of a small pericardial effusion was associated with worse survival even after adjustment for patient characteristics suggesting that it is a marker of underlying disease.

Disclosures

Teferi Y. Mitiku has no conflicts of interest to disclose. Paul A. Heidenreich has no conflicts of interest to disclose.

References