

Etiology and Long-Term Outcome of Patients Undergoing Pericardiocentesis

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Background—Pericardial effusions can be caused by a variety of disorders. The frequency of the underlying diseases varies with patient population; therefore, previously reported series are not necessarily representative of other populations. Our purpose was to examine the etiology of pericardial effusions and the survival of patients requiring pericardiocentesis at a tertiary center.

Methods and Results—We performed a retrospective observational study of 269 consecutive patients who underwent percutaneous pericardiocentesis at our university hospital between 2006 and 2016 and had prospective follow-up for up to 10 years. The most frequent etiologies were idiopathic (26%), malignancy (25%), and iatrogenicity (20%), whereas bacterial causes were very rare. The most frequent malignancies originated from the lung (53%) or breast (18%). A new cancer was diagnosed with malignant pericardial effusion as the presenting complaint for 9% of patients, whereas the pericardium was the first metastatic site of a known malignancy in 4% of patients. Survival was significantly poorer in malignancy-related versus non-malignancy-related effusions ($P<0.001$) and in cytology-positive versus cytology-negative effusions in the overall cohort ($P<0.001$). Among cancer-only patients, however, there was no significant difference in long-term survival between cytology-positive and -negative effusions.

Conclusions—In this contemporary tertiary-center cohort, pericardial effusions often represent the primary instance of a new malignancy, underscoring the importance of cytological analyses of noniatrogenic effusions in patients without known cancer, as survival is significantly worse. In cancer patients, however, the presence of pericardial malignant cytology does not appear to affect outcome significantly. (*J Am Heart Assoc.* 2017;6:e007598. DOI: 10.1161/JAHA.117.007598.)

Key Words: pericardial disease • pericardial effusion • pericardiocentesis

Pericardial effusion requiring pericardiocentesis can be caused by a wide variety of malignant or nonmalignant causes. Known etiologies include infections, neoplasia, iatrogenicity, congestive heart failure, and metabolic causes (hypothyroidism, uremia), as well as pericardial injury (eg, following myocardial infarct, thoracotomy, or trauma), radiation, connective tissue diseases, and trauma.^{1,2} Nevertheless, a substantial number of effusions are idiopathic.³ Data on the frequency of different etiologies and, more specifically, on primary or metastasized malignancies remain scarce and vary widely among the few studied populations.^{4–10} In the past 2 decades, only 5 sizeable

prospective series on the etiology of pericardial effusions have been reported. Two of those series included distinct populations in which tuberculosis and human immunodeficiency virus (HIV) are common, and thus the participants are not necessarily representative of other cohorts.^{11–15}

Excluding malignancy or confirming pericardial involvement in patients previously diagnosed with cancer not only has important consequences for the management of patients presenting with a pericardial effusion but also affects their outcome.¹ The diagnosis or exclusion of pericardial involvement in malignancy is, to a large extent, established by pericardial cytology obtained via pericardiocentesis. The aim of this study was to examine the etiology of pericardial effusions requiring a percutaneous intervention, either because of hemodynamic compromise or for a diagnostic workup, to determine how often fluid cytology is requested in unsuspected as well as known cancer patients and to analyze the impact of these findings on patient outcome.

Methods

The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the

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Clinical Perspective

What Is New?

- Malignancy-associated effusion, representing the most frequent etiology among tertiary care patients undergoing pericardiocentesis and often the primary instance of cancer, is associated with a significantly worse survival than nonmalignant effusion, but the presence of malignant pericardial cells does not significantly affect outcome among cancer patients.

What Are the Clinical Implications?

- It is advisable to perform pericardial fluid cytological analyses in patients without known malignancy in the absence of a clear-cut alternative clinical diagnosis, whereas the relevance of such testing is less clear among cancer patients.

results; they will be provided on request to the corresponding author.

We performed a retrospective observational study of all patients undergoing percutaneous pericardiocentesis from January 2006 to August 2016 at Leuven University Hospital. Data were collected by accessing patient electronic medical records, using a comprehensive automated search of both digital clinical and procedural pathway labels of *tamponade*, *pericardial effusion*, and/or *pericardiocentesis*. Follow-up was performed by reviewing digital medical records and identifying the date of death. The study was approved by Leuven University Hospital's institutional Committee on Medical Ethics and included a waiver of the requirement for participant informed consent. The local urban region consists of 100 000 people and is ethnically homogeneously white. Recent data from 2014 indicate that 14% of inhabitants have a non-Belgian nationality, 7.6% of whom originated from a non-European country. The following patient variables were collected: age (at the time of pericardiocentesis), date of procedure, date of death or dropout from follow-up, sex, medical history, laboratory values, effusion size, fluid sample characteristics, and clinical diagnosis.

Collected laboratory values included prothrombin time, serum albumin, total protein, serum creatinine, blood urea nitrogen, and thyroid stimulating hormone. Serological testing was not uniformly performed but was reported if applicable. Bacterial cultures included peripheral blood and pericardial fluid samples.

Effusion size was determined by reviewing prepuncture echocardiogram reports, using the most extensive diastolic measurement. Small size was defined as <10 mm, medium was >10 and <20 mm, and large was >20 mm. Analyzed fluid characteristics included macroscopic aspect, biochemistry,

cytology, and microbiology. Volume of drained fluid during or after the procedure could not be accurately determined because of nonuniform reporting. Survival rates were obtained by reviewing the standardized electronic medical records for the date of death or by identifying the last follow-up visit.

The etiology of pericardial effusion was classified using the following criteria. The effusion was labeled as malignant when pericardial fluid cytology included atypical or overtly malignant cells. We categorized these cases by primary presentation: *newly diagnosed malignancy*, *first metastasis of a known malignancy*, or *known metastasized malignancy*. We also separately identified patients with negative pericardial fluid cytology but known malignancy. The infectious group included patients with a positive history of viral infection and signs of inflammation (eg, precordial pain) after exclusion of other etiologies. Specific viruses were not identified because of the standard institutional policy not to pursue viral etiologies by either serology or polymerase chain reaction in pericarditis or pericardial effusion unless strictly indicated. Bacterial effusion, however, was defined only by positive pericardial fluid culture. Iatrogenic pericardial effusion included patients who underwent an invasive medical or surgical procedure before pericardial effusion (eg, coronary intervention, pacemaker or implantable cardioverter-defibrillator implementation, thoracic surgery). Postpericardial injury syndrome included patients who had acute coronary syndrome or who underwent thoracic surgery during the preceding months in whom we found no other etiology. Uremic pericarditis was diagnosed when blood urea nitrogen was >60 mg/dL or dialysis dependency existed in the absence of other identifiable causes. Radiation therapy-related pericardial effusion was diagnosed in patients with a history of thoracic radiotherapy in whom other causes were excluded. Thyroid-related pericardial effusion was diagnosed in patients with elevated thyroid-stimulating hormone and decreased tetra- or tri-iodothyronine. Patients were categorized with effusion due to congestive heart failure in cases with clinical symptoms and reduced left ventricle ejection fraction (<50%) in the absence of other identifiable etiologies. The final group included patients with idiopathic pericardial effusion, for whom no clear explanation or evidence was found for any etiology using standard, routine clinical care.

Statistical Analyses

IBM SPSS Statistics version 23 and Wizard Pro (v1.9) were used for all analyses. Continuous variables are presented as mean±SD. Curves for long-term survival were obtained using the Kaplan–Meier method, comparisons were calculated using the log-rank test, and hazard ratios (HRs) and the 95% confidence intervals (CIs) were calculated using an unadjusted Cox proportional hazards model.

Results

We prospectively registered 286 individual pericardiocentesis entries in our electronic patient record database, excluding recurrences. After review, 17 cases (5.9%) were omitted from the present retrospective analyses because of a small pericardial effusion for which, ultimately, no pericardiocentesis was attempted. A total of 269 patients, of whom 119 (44.2%) were female, underwent a primary pericardiocentesis as the initial approach. Ages ranged from 0 to 94 years with a mean of 62 years (± 15.9 years). In most cases (237, 88.1%), hemodynamic instability (ie, cardiac tamponade) formed the main indication for the pericardiocentesis. In 32 patients (11.9%), drainage was performed for a clinically asymptomatic effusion. A small effusion was present in 5 patients (1.9%), a medium effusion was present in 51 (19.1%), and a large effusion was present in 194 (72.1%). The extent of the effusion was not recorded for 15 patients (5.6%), mainly those with an acute tamponade during a coronary intervention. There were 149 samples (55.4%) with a bloody aspect, 62 (23.0%) serous samples, 53 (13.7%) serosanguineous samples, and 5 (1.9%) in which the appearance of the fluid could not be retrieved from the records. Among patients with atypical cells in their pericardial fluid sample, 38 (55.9%) had a bloody sample, 14 (20.6%) had a serous sample, and 16 (23.5%) had a serosanguineous sample.

Of the patients undergoing a primary percutaneous pericardial puncture, 23 (8.6%) had a second pericardiocentesis. In addition, 7 (2.6%) had a subsequent thoracotomy, 3 (1.1%) had a sternotomy, 4 (1.5%) had a video-assisted thoracoscopy, 22 (8.2%) had subxiphoidal pericardial window, and 1 (0.4%) had a subxiphoidal approach followed by a video-assisted thoracoscopy. The procedures were all performed for persisting clinical significant effusion, not to obtain a more definitive diagnosis. Most pericardiocenteses were performed without complications. In 2 patients (0.7%), the right heart was “punctured,” which resulted in an increased tamponade; in 7 patients (2.6%), a pneumothorax was documented on subsequent chest x-ray or hospitalization records; 1 patient (0.4%) had pneumomediastinum; 4 (1.5%) had pneumopericardium; 2 (0.7%) had a punctured peritoneal cavity; and 2 patients (0.7%) developed atrial fibrillation during or shortly after the procedure.

A cytological analysis was ordered in 208 cases (77.3%), and atypical cells suggestive of malignancy were found in 68 (25.3%). Among the 80 patients with known malignancy, atypical cells were found in 45 (56.3%). Fluid culture was performed in 206 cases (76.6%). The different final etiologies are listed in Table 1. The most common final etiologies were idiopathic (26.4%), malignancy (25.3%), iatrogenicity (20.8%), infection (7.4%), heart failure (3.7%), cardiac injury (3.7%), uremia (3.7%), or systemic diseases (2.6%: systemic sclerosis

Table 1. Etiology of Pericardial Effusion

Diagnosis	Patients (N=269)	
	n	%
Idiopathic	71	26.4
Malignancy	68	25.3
Iatrogenicity	56	20.8
Coronary	10	3.7
TAVI/PTAV	6	2.2
ICD/PM	11	4.1
Surgery	20	7.4
EP/ablation	3	1.1
Anticoagulation	4	1.5
Pleural puncture	1	0.4
DVC	1	0.4
Infection	20	7.4
Viral	9	3.3
Bacterial	10	3.7
HIV	1	0.4
Heart failure	10	3.7
After cardiac injury	10	3.7
Uremic	8	3.0
Systemic disease	7	2.6
Medication	5	1.9
Constrictive pericarditis	3	1.1
MOF	3	1.1
Radiotherapy	2	0.7
Myocardial infarction	2	0.7
Aortic dissection	2	0.7
Transplant	1	0.4
Traumatic	1	0.4

DVC indicates deep veinous catheter; EF, electrophysiology; HIV, human immunodeficiency virus; ICD/PM, implantable cardioverter-defibrillator/pacemaker; MOF, multi-organ failure TAVI/PTAV, transcatheter aortic valve implantation/ percutaneous transluminal aortic valvuloplasty.

[n=2] and CREST syndrome, systemic lupus, rheumatoid arthritis, juvenile arthritis, nondifferentiated systemic disease [each n=1]). Only 4 patients from the idiopathic group did not undergo cytological testing. Fourteen patients with positive (percutaneous) cytology also had a biopsy (n=3) and/or subsequent surgical sample obtained: There were 4 true positives, 1 false negative, 8 true negatives, and 1 false positive.

The underlying malignancies are specified in Table 2. The most common malignancies were lung (52.9%), breast (17.6%), pleural mesothelioma (5.9%), ovarian (5.9%), and esophageal (2.9%). The most frequent lung tumor was adenocarcinoma (30 cases). There were no cases of

Table 2. Etiology of Malignant Effusions

Diagnosis	Frequency (n=65)	Malignancy (%)	Total (%)
Lung	36	52.9	13.4
Adenocarcinoma	30
Squamous carcinoma	0
Small cell carcinoma	3
Unspecified	3
Breast	12	17.6	4.5
Pleural mesothelioma	4	5.9	1.5
Ovary	4	5.9	1.5
Esophageal	2	2.9	0.7
Cervical	1	1.5	0.4
Gastric	1	1.5	0.4
Parotid	1	1.5	0.4
Thymic	1	1.5	0.4
Rectal	1	1.5	0.4
Intima sarcoma	1	1.5	0.4
Pleural (unspecified)	1	1.5	0.4
Leukemia (unspecified)	1	1.5	0.4
Ear, nose, and throat	1	1.5	0.4
Non-Hodgkin lymphoma	1	1.5	0.4

squamous cell lung carcinoma. Eighty patients (29.7%) had a known malignancy before pericardiocentesis, and 64 of those already had known (extrapericardial) metastases. In 24 patients (8.9%), the pericardial effusion was the first presentation of a previously undiagnosed malignancy (12.7% of patients without previously known cancer). In addition, a positive pericardial cytology was the first metastatic site of a known malignancy in 10 patients, constituting 12.5% (10/80) of all patients with known cancer or 62.5% (10/16) of patients with a known but nonmetastasized malignancy. A substantial proportion of pericardiocentesis patients without a final definite explanation for their effusion (ie, the idiopathic patients) had underlying diseases, often a malignancy. In the idiopathic group, 25 of 71 patients (35.2%) had a known malignancy with extrapericardial metastasis and 6 of 71 (8.5%) had known malignancy without known metastasis; none had detectable atypical or malignant cells on cytology of the pericardial fluid (Table 3). Among the remaining idiopathic patients, 32 (45%) did not have any other diagnosis.

The most frequent iatrogenic causes leading to a percutaneous pericardiocentesis were cardiothoracic surgery (7.4%), pacemaker or implantable cardioverter-defibrillator placement (4.1%), and percutaneous coronary intervention (3.7%). In the infectious group, we identified only 10 cases of culture-confirmed bacterial pericarditis, 9 cases of (assumed)

Table 3. Characteristics of the “Idiopathic” Group

Possible Etiology or Concomitant Disease	Patients (n=71)	
	n	%
Absence of any other diagnosis	32	45.1
Lung squamous cell carcinoma	7	9.9
Lung adenocarcinoma	4	5.6
Gastric carcinoma	4	5.6
Infectious	4	5.6
Small cell lung carcinoma	3	4.2
Breast carcinoma	3	4.2
Pleural mesothelioma	2	2.8
Thymic carcinoma	2	2.8
Bone marrow transplant	2	2.8
Adenocarcinoma unknown primary	1	1.4
Tonsil carcinoma	1	1.4
Esophageal carcinoma	1	1.4
Renal cell carcinoma	1	1.4
Pancreatic carcinoma	1	1.4
Cervical carcinoma	1	1.4
Uterus leiomyosarcoma	1	1.4
Rheumatoid arthritis	1	1.4
Late-onset posttrauma	1	1.4
Total	71	100

viral pericarditis, and 1 case of HIV. There were no confirmed cases of fungal pericarditis. The most common bacterial pathogen was *Staphylococcus aureus* (3 cases). In addition, there was 1 case of each of the following pathogens: *Escherichia coli*, *Staphylococcus epidermidis*, *Klebsiella pneumoniae*, *Streptococcus anginosus*, *Staphylococcus capitis*, *Staphylococcus auricularis* and *Mycobacterium* genus.

Median follow-up was 26.1 months, with a maximum follow-up duration of 132 months. The Kaplan–Meier survival curve for the whole pericardiocentesis cohort is presented in Figure 1A and 1B. We observed a significant difference in survival among malignancy-free pericardial effusion, newly diagnosed malignancy (HR: 5.40; 95% CI, 3.53–8.26), and known malignancy (both with or without new pericardial metastasis; HR: 3.01; 95% CI, 1.66–5.45; $P<0.001$; Figure 2A). In the complete cohort, survival was significantly worse in patients with pericardial malignancy versus patients with no pericardial malignancy (HR: 3.31; 95% CI, 2.37–4.61; $P<0.001$; Figure 2B). Unsurprisingly, among idiopathic patients, there was also a significant difference in outcome between malignancy-free pericardial effusion versus malignancy-associated but idiopathic pericardial effusion (HR: 16.4; 95% CI, 6.12–43.9; $P<0.001$). There was no significant

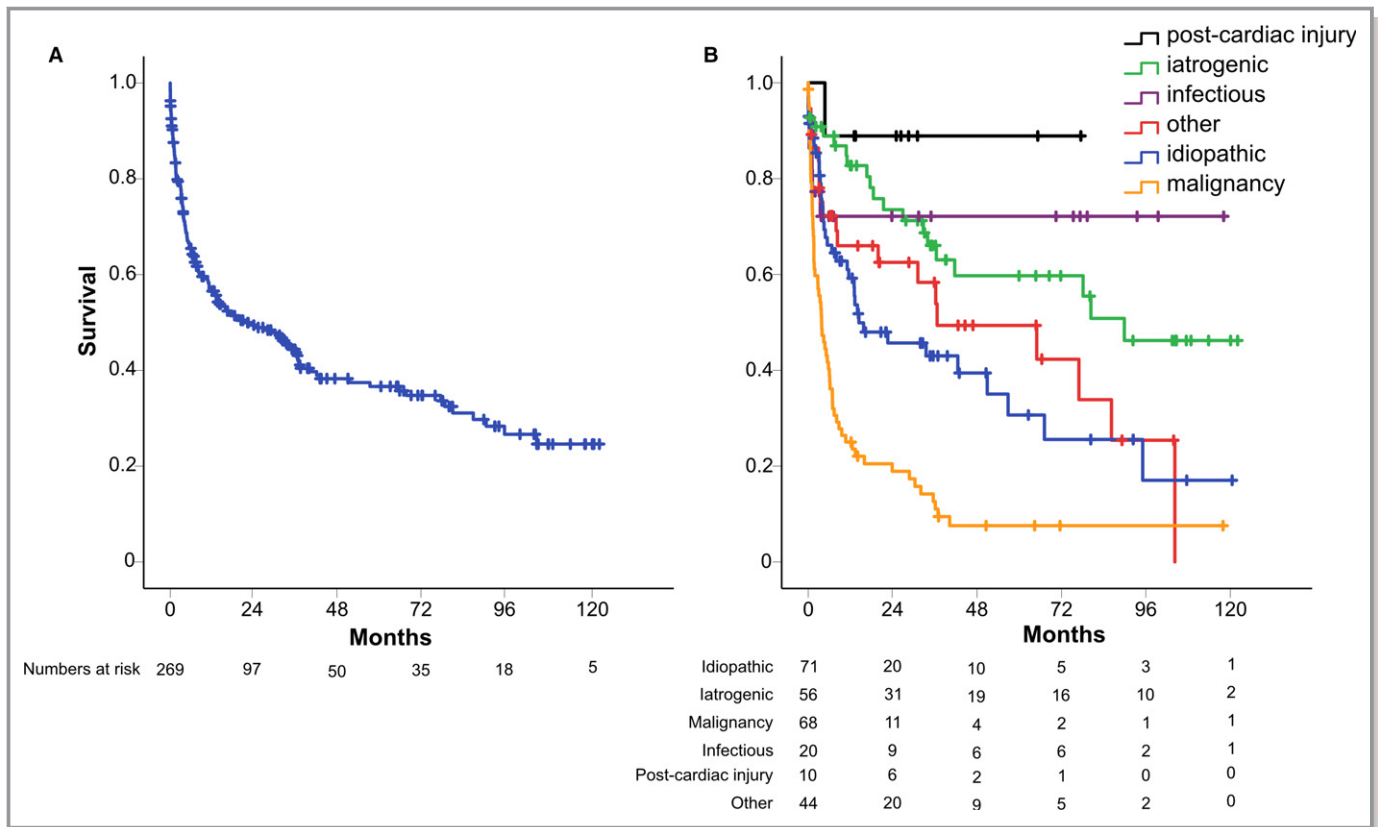


Figure 1. Kaplan–Meier survival curves for the overall cohort (A) and by etiology (B). The idiopathic group includes all patients without an identifiable cause, including cancer patients with cytology-negative pericardial fluid.

difference in survival between the following groups: lung and nonlung malignancy ($P=0.791$), pericardial versus no pericardial malignancy in all cancer patients (HR: 0.85; 95% CI, 0.55–1.31; $P=0.451$; Figure 2C), and known cancer patients (HR: 1.09; 95% CI, 0.69–1.74; $P=0.704$; Figure 2D). In addition, there was no significant outcome difference between (pericardial) cytology-positive and -negative cancer patients ($P=0.661$). There was no significant survival difference between men and women ($P=0.170$), both in the whole cohort and among cancer patients. However, after exclusion of breast cancer patients, men had significantly worse outcomes than women in the whole cohort (HR: 1.43; 95% CI, 1.02–2.01; $P=0.038$) and among cancer patients only (HR: 1.59; 95% CI, 1.01–2.51; $P=0.048$).

Discussion

A significant pericardial effusion often requires a percutaneous drainage, not only to relieve the hemodynamic compromise but also to determine or (dis)prove the putative cause of the effusion. This can be relevant not only for patients without a known underlying disease but also for patients with a condition known to be prone to develop pericarditis or pericardial effusions.⁶ Indeed,

establishing an etiology, especially pericardial malignancy, metastasis, or bacterial causes, can be crucial for immediate management as well as the long-term prognoses of these patients. Nevertheless, few contemporary data exist on the frequency of the varying conditions leading to pericardial effusions. In addition, the significant impact of these causes on outcome is often underestimated. We reported on the outcome and etiology, per standard care, of pericardial effusion requiring percutaneous pericardiocentesis in 269 consecutive patients over the span of a decade, making this study one of the largest to date. We found that in about half of the patients with known malignancy, abnormal pericardial cytology was observed, whereas for two thirds of the patients with previously nonmetastasized cancer, the effusion constituted their first metastatic site. Vice versa, one out of eight patients without a history of cancer was newly diagnosed with malignancy after pericardiocentesis. Importantly, patients with malignant pericardial effusion had significantly worse long-term prognoses compared with patients with another or no definite diagnosis. Still, outcome appeared to be poor for all cancer patients undergoing pericardiocentesis, regardless of pericardial cytology. Finally, bacterial pericardial effusion appeared to be rare in our population.

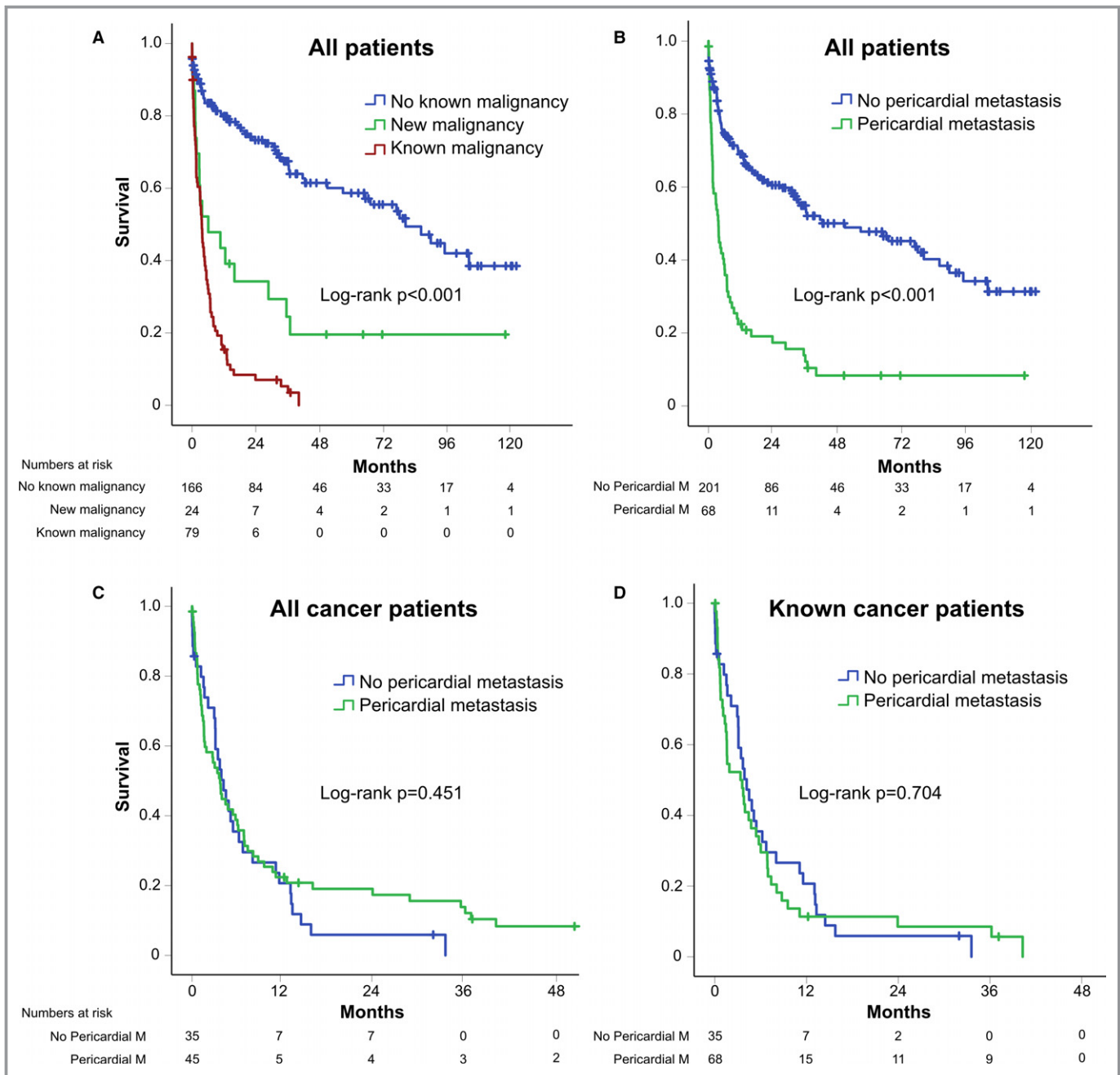


Figure 2. Kaplan–Meier survival curves by malignancy status (A) and by pericardial malignancy (B) for the overall cohort. Kaplan–Meier survival curves by pericardial metastasis (M) for the overall cohort (C) and among patients with known cancer at the time of pericardiocentesis (D).

In the present patient cohort, the underlying diagnosis of effusion was established based on pericardial fluid characteristics obtained by pericardiocentesis, using routine tests including cytology, microbiology, serology, and biochemistry, as per clinical indication. The sensitivity of pericardial fluid cytology ranges from 66.7% to 92%. This value depends heavily on the gold standard used per study (eg, follow-up, pericardial biopsy, postmortem autopsy) but nevertheless is considered a valid and useful diagnostic tool.^{9,16–18} Variation

also exists between series on what should be classified as a definite malignant effusion; some authors consider cytology-negative fluid as constituting a malignant effusion if the patient has a known malignancy. In contrast with these analyses, we chose to limit malignant effusion to those with a proven positive cytology, as determined by a pathologist, and to classify cytology-negative patients as idiopathic in the absence of another plausible cause, even when they had an underlying cancer. For this reason, and despite the context of

a large tertiary care cohort, our number of malignant effusions is slightly lower than in other reports. Consequently, about 1 in 4 patients ultimately was categorized as having no definite underlying cause of effusion (ie, the idiopathic group); however, almost half had a known malignancy and could not be distinguished from cytology-positive patients in terms of long-term outcome. If we take this into account, our data are consistent with previous studies in the sense that neoplasia was the most common cause of pericardial effusion, and lung and breast cancers were the most frequent primary sites. Incidentally, because we were unable to differentiate between a chemotherapy-related effusion and false-negative cytology, we cannot exclude the possibility that at least some of the cytology-negative effusions in known cancer patients were secondary to their chemotherapy.

Unsurprisingly, a malignant pericardial effusion was linked to a poor prognosis. The survival of our patients appears to be similar to other series.¹⁶ The finding of a pericardial metastasis clearly is a negative prognostic factor if the patient has no previously known malignancy, but the presence of pericardial metastases had little impact on the overall survival of patients with known malignancies. In fact, patients with a known malignancy had significant worse survival than patients with a new diagnosis of malignancy based on the pericardial fluid cytology. A likely explanation is that known cancer patients had a more advanced disease stage than those in whom the pericardial effusion was the first manifestation of malignancy.

Performing a cytological analysis is important to establish a diagnosis of tumoral involvement of the pericardium,¹⁹ with significant implications for prognosis and treatment of the underlying disease.²⁰ We found positive cytology in a quarter of total patients and in more than half of cancer patients, which is somewhat higher than in other studies.²¹ In addition, >10% of patients had a new diagnosis of cancer or had a first metastatic site, which is slightly more than other series.²² However, cytological analysis of pericardial fluid was not always requested in our series, reflecting standard clinical practice. Cytology is not always necessary if the etiology is clear from the outset, for example, in case of definite iatrogenic causes during coronary interventions. In our idiopathic group, only 4 cases had no cytological analysis. Two of those involved patients who presented with a bacterial infection that was thought to be the origin of the effusion, yet pericardial fluid cultures remained negative. Another patient had end-stage pleural mesothelioma and died shortly after the pericardiocentesis, thus the cytology result was deemed not to have therapeutic implications. The fourth case was a late-onset pleural and pericardial effusion requiring pericardiocentesis in an adolescent patient after a polytraumatic road traffic injury.²³ On aggregate, cytological analysis was requested for nearly all patients for whom it was deemed

necessary. Because of the high incidence of newly diagnosed malignancies in patients presenting with pericardial tamponade, our results suggest that it may be advisable to always request cytological analysis in the absence of a clear-cut clinical diagnosis such as iatrogenic effusion.

Iatrogenic effusions, mostly intervention-based or following cardiothoracic surgery, were relatively common in our cohort, probably also reflecting a contemporary tertiary care setting in which advanced interventional procedures and complex surgeries are performed. Of note, the survival curve of iatrogenic patients does not seem to reach a plateau after the acute phase, perhaps in part due to the presence of significant coronary disease as a survival-limiting factor. In contrast, there were only a handful of infectious cases in our cohort. The lack of HIV- and tuberculosis-related pericardial effusions can be traced to our mostly white urban population. Series reporting higher incidence of HIV and tuberculosis often took place in less developed countries or in multiracial communities.^{13,14,16} Among the infectious effusions in our cohort, we predominantly found Gram-positive cocci. In addition, serological tests were requested rarely and are discouraged by the policy of our microbiology laboratory. Therefore, and in the context of small numbers, it is impossible to draw conclusions about the typical organisms that cause pericardial effusion requiring pericardiocentesis in this type of tertiary care cohort.

Some limitations of our study need to be highlighted. The study is retrospective, and certain variables such as effusion volume, serological tests, or clinical characteristics were not systematically recorded and thus could not always be obtained. Because our hospital is a national reference center and high-volume academic teaching hospital, our patient population might not necessarily be representative of regional nonacademic hospitals. In addition, referral patients were limited because cardiac tamponade patients present acutely. Although the number of patients enrolled was large compared with other reports, the total number was still relatively small, and that made it impossible to establish significant differences among certain subgroups.

In summary, apart from iatrogenic pericardial effusion, malignancy causes or is related to a large number of the pericardial effusions in our population, with the most frequent primary sites being lung and breast, whereas HIV- and tuberculosis-related effusions are virtually absent. Malignancy-associated effusions were associated with significantly worse survival, but the presence of malignant pericardial cells did not significantly affect outcome among cancer patients. Given the relatively high rate of new diagnoses of malignancy in patients undergoing pericardiocentesis and the clear consequences for treatment and survival, it might be advisable to always request cytological analysis of pericardial fluid in the absence of a clear-cut alternative clinical diagnosis,

conforming to the recent European Society of Cardiology guidelines.²⁴

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Disclosures

None.

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