Mortality among patients with pleural effusion undergoing thoracentesis

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ABSTRACT   Of the 1.5 million people diagnosed with pleural effusion in the USA annually, ∼178 000 undergo thoracentesis. While it is known that malignant pleural effusion portends a poor prognosis, mortality of patients with nonmalignant effusions has not been well studied.

This prospective cohort study evaluated 308 patients undergoing thoracentesis. Chart review was performed to obtain baseline characteristics. The aetiology of the effusions was determined using standardised criteria. Mortality was determined at 30 days and 1 year.

247 unilateral and 61 bilateral thoracenteses were performed. Malignant effusion had the highest 30-day (37%) and 1-year (77%) mortality. There was substantial patient 30-day and 1-year mortality with effusions due to multiple benign aetiologies (29% and 55%), congestive heart failure (22% and 53%), and renal failure (14% and 57%, respectively). Patients with bilateral, relative to unilateral, pleural effusion were associated with higher risk of death at 30 days and 1 year (17% *versus* 47% (hazard ratio (HR) 2.58, 95% CI 1.44–4.63) and 36% *versus* 69% (HR 2.32, 95% CI 1.55–3.48), respectively).

Patients undergoing thoracentesis for pleural effusion have high short- and long-term mortality. Patients with malignant effusion had the highest mortality followed by multiple benign aetiologies, congestive heart failure and renal failure. Bilateral pleural effusion is distinctly associated with high mortality.

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Introduction

Pleural effusions are diagnosed annually in >1.5 million people in the USA [1] and are caused by various medical conditions. The most common causes of pleural effusion are, in descending order, congestive heart failure (CHF), pleural infection and malignancy [2]. CHF alone is responsible for about one-third of all cases in the USA each year [1]. Although malignant pleural effusions are associated with high mortality, there is little in the literature regarding mortality of patients with nonmalignant pleural effusion.

Bilateral pleural effusions are common, accounting for 15% of the cases in non-critically ill patients, and up to 55% of those in the intensive care population. The aetiology of bilateral pleural effusion includes CHF, coronary artery bypass graft, fluid overload, liver and renal failure, and malignancy [3, 4]. To our knowledge, the association between bilateral pleural effusion and mortality has not been previously reported.

In this study, we determined 30-day and 1-year mortality for patients with pleural effusions of differing aetiologies. We also compared the mortality rates between patients with unilateral and bilateral pleural effusion.

Methods

This prospective observational cohort study was performed at Yale–New Haven Hospital (YNHH), New Haven, CT, USA, a tertiary care academic hospital with >1000 beds, and approved by the Institutional Review Board (IRB) of YNHH. All patients who underwent thoracentesis between December 2010 and December 2011 by the interventional pulmonary service were approached for enrolment. In addition to informed consent for the procedure, IRB-approved informed consent for the study was obtained from each participant. The interventional pulmonary service at YNHH performs the majority of the thoracenteses on both in- and outpatients, with a minority performed by interventional radiology, surgical services and others. Chart review and patient interviews were performed to identify baseline patient characteristics and demographics, including medical comorbidities.

All thoracenteses were performed using ultrasound guidance (S-ICU; SonoSite, Bothell, WA, USA) in a sterile fashion using the Safe-T-Centesis kit (Cardinal Health, Dublin, OH, USA). Fluid was aspirated manually and routinely sent for analysis including cell count with differential count, total protein, lactate dehydrogenase, glucose, pH, cultures (bacterial, fungal and acid-fast bacilli) and cytology. Flow cytometry was requested if lymphoma was a reasonable concern. Light's criteria were used to classify each effusion as transudate or exudate [5]. When bilateral effusions were present, concurrent bilateral thoracenteses were always performed [3].

Table 1 provides the definitions used to categorise the aetiology of the pleural effusion. Patients were classified as having a certain aetiology if they met one of the characteristics listed in a category. Mortality was determined at 30 days and 1 year using chart review.

Statistical analysis

The demographics and occurrence of common comorbidities were described. Unadjusted 30-day and 1-year mortalities were calculated and diagrammed for subgroups according to the following hierarchy: laterality (bilateral *versus* unilateral) and malignancy (yes *versus* no). Nonmalignant effusion was further classified by type of effusion (exudate *versus* transudate and mismatch, or dissimilar between sides, for some bilateral). Multivariable proportional hazards Cox models evaluated associations between short-term (30-day) and long-term (1-year) mortality, and the following explanatory variables. 1) Age in years. 2) Male sex (referent to female). 3) Nonwhite race. 4) Number of comorbidities. 5) Bilateral thoracentesis (referent to unilateral). 6) Indicators for each of the following aetiologies (referent to malignancy): CHF, infectious disease, liver failure, renal failure, multiple benign aetiologies and paramalignancy. Kaplan–Meier plots of adjusted survival probabilities were created for 30-day and 1-year mortality, and stratified for bilateral *versus* unilateral thoracentesis. All analyses were performed using SAS v9.3 (SAS Institute, Cary, NC, USA), and p<0.05 (two-tailed) was used to denote statistical significance.

Results

A total of 320 patients over the study period were enrolled and 308 patients were included in the analysis. 12 participants were excluded for multiple reasons including incomplete clinical data or insufficient pleural fluid for thoracentesis after enrolment in the study. Baseline patient characteristics are presented in table 2. The majority of thoracenteses were performed on inpatients and patients with a history of cancer or a cardiac condition (53% and 80%, respectively). A total of 247 unilateral and 61 bilateral thoracenteses were performed. Overall mortality across all groups was 21% (65 out of 308 patients) at 30 days and 51% (158 out of of 308 patients) at 1 year, with no procedure-related deaths.

TABLE 1 Categories of pleural effusion aetiologies and their corresponding definitions

Congestive heart failure
 Echocardiogram within 1 month or at the time of the procedure documenting one or more of:
  Decreased systolic ejection fraction ($\leqslant$45%) and pulmonary oedema on CXR;
  Diastolic dysfunction and pulmonary oedema on CXR;
  Moderate-to-severe aortic stenosis (valve area<1 cm), aortic regurgitation, mitral stenosis or
   mitral regurgitation and pulmonary oedema on CXR;
  Restrictive and/or constrictive pericardial disease and pulmonary oedema on CXR
  Severe pulmonary hypertension;
 Or:
  Cardiac arrhythmia on ECG and pulmonary oedema on CXR
Renal failure
 Documented nephrotic range proteinuria; or
 Creatinine >1.5 mg·dL^{-1}; or
 Ongoing renal replacement therapy
Liver failure
 Documented cirrhosis with ascites; or
 Acute, fulminant liver failure
Pneumonia/infection
 Ipsilateral infiltrate on CXR and >500 WBCs per mL in fluid or positive fluid culture
Multiple benign aetiologies
 Documentation of more than one of the above aetiologies without one predominant aetiology
Malignant
 Positive pleural fluid cytology or flow cytometry
Paramalignant
 Negative cytology in patient with known cancer localised in the ipsilateral chest and no other potential
  cause for pleural effusion

CXR: chest radiography; WBC: white blood cell.

Figure 1 depicts the pleural effusion characteristics and corresponding unadjusted mortality at 30 days and 1 year. Malignant pleural effusion was identified in 27% of patients. The percentage of patients with malignancy as their aetiology was similar in patients with unilateral and bilateral effusion. The pleural fluid type of nonmalignant effusion differed by whether it was bilateral; most unilateral nonmalignant

TABLE 2 Baseline characteristics and demographics (n=308)

Age years	67.6±14.4
Male	155 (50.3)
Nonwhite race	48 (16.1)
Inpatient	258 (83.8)
Number of comorbidities	4.5±1.9
Arthritis	163 (53.3)
Diabetes	86 (27.9)
GI conditions[#]	148 (48.4)
Mental issues[¶]	187 (60.7)
Liver failure/cirrhosis	38 (12.3)
Renal failure	67 (21.8)
Obesity	59 (19.3)
Autoimmune disease	76 (24.8)
Cancer	162 (52.6)
Neurologic disease[+]	52 (16.8)
Pulmonary disease[§]	81 (26.3)
Sleep apnoea	25 (8.1)
Heart condition[f]	247 (80.2)

Data are presented as mean±SD or n (%). Missing data: race (n=10); arthritis (n=2); gastrointestinal (GI) conditions (n=2); obesity (n=2); autoimmune disease (n=2). [#]: digestive problems (such as gastro-oesophageal reflux disease, Crohn's disease, ulcerative colitis or irritable bowel syndrome); [¶]: anxiety, depression or memory problems; [+]: stroke, ministroke or seizure; [§]: asthma, chronic obstructive pulmonary disease or interstitial lung disease; [f]: myocardial infarction, angina, coronary disease, arrhythmia, hypertension, hyperlipidaemia, congestive heart failure or a pacemaker.
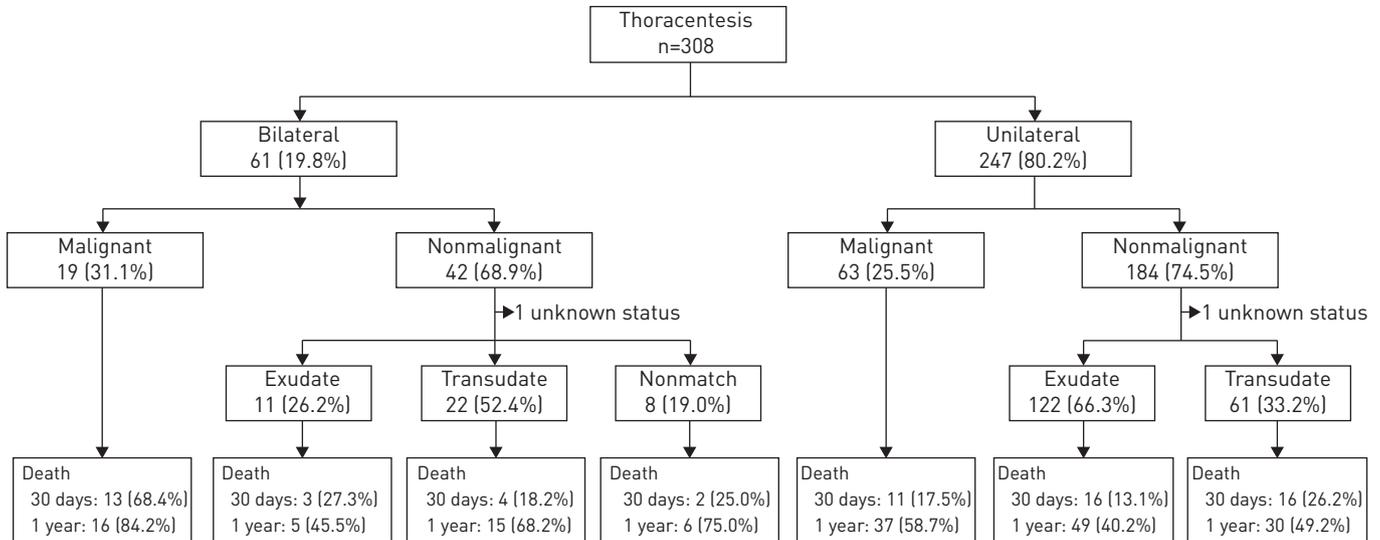
FIGURE 1 Pleural effusion characteristics and corresponding unadjusted mortality at 30 days and 1 year.

cases were exudates whereas most bilateral nonmalignant cases were transudates. As calculated from figure 1, 30-day and 1-year mortality of patients with unilateral effusion was 17% and 47%, compared with 36% and 69% in patients with bilateral effusion. Relative to patients with unilateral effusion, unadjusted mortality of patients with bilateral effusion was higher at 30-days ($p=0.0003$) and at 1-year ($p=0.0001$).

Figure 2 depicts mortality based on the aetiology of the pleural effusion at 30 days and 1 year. Patients with malignant and paramalignant pleural effusion had the highest 30-day (37% and 28%, respectively) and 1-year mortality (77% and 75%, respectively). Patients whose effusions were attributed to multiple benign aetiologies also had high mortality at 30 days and 1 year (29% and 55%, respectively), as did patients with pleural effusion singularly due to CHF (22% and 53%, respectively). Patients with infection, including parapneumonic effusion and empyema, also exhibited substantive 30-day and 1-year mortality (11% and 26%, respectively).
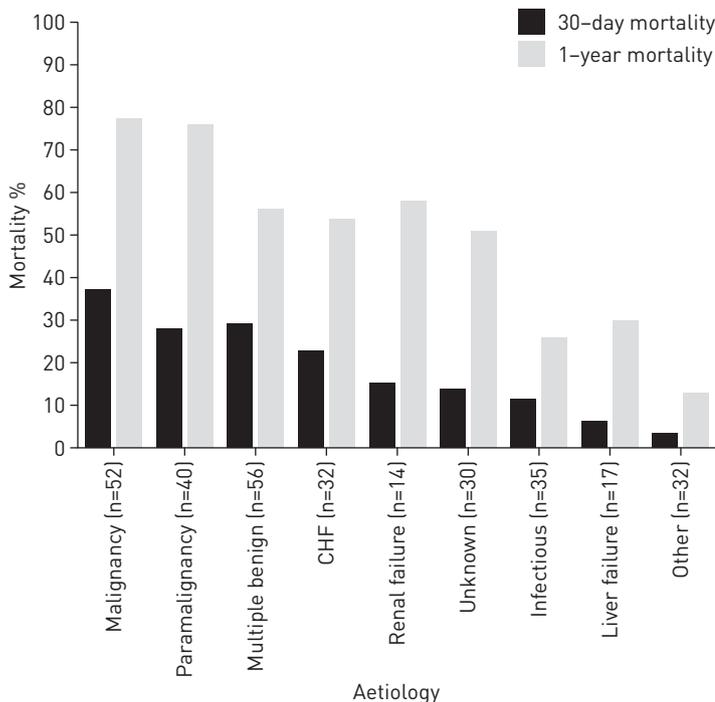

FIGURE 2 Percent mortality based on the aetiology of the pleural effusion at 30 days and 1 year. The number of pleural effusions with the corresponding aetiology is shown. CHF: congestive heart failure.

Figure 3 contrasts the Kaplan–Meier survival curves of patients with unilateral and bilateral pleural effusion at 30 days and 1 year. In both time periods, the presence of bilateral pleural effusion was associated with significantly lower survival probability.

Table 3 presents associations between the following explanatory variables and short term (30-day) and long-term (1-year) mortality: age, sex, race, number of comorbidities, aetiology (relative to malignancy) and bilateral (relative to unilateral). Number of comorbidities was the only covariate significantly associated with mortality at both 30-days and 1-year (hazard ratio (HR) 1.21 (95% CI 1.05–1.39, p=0.009) and HR 1.19 (95% CI 1.09–1.30, p=0.0002), respectively). Even after adjustment for these covariates, the presence of bilateral effusion, relative to unilateral effusion, was significantly associated with higher 30-day and 1-year mortality (HR 2.58 (95% CI 1.44–4.63, p=0.002) and HR 2.32 (95% CI 1.55–3.48, p<0.001), respectively).

Discussion

Encountered frequently by chest physicians and other medical subspecialists, pleural effusion is a significant cause of dyspnoea and patient suffering. Therapeutic thoracentesis may provide symptomatic relief, and care directed at the underlying aetiology often determines whether the effusion recurs. This study is the first to evaluate both short- and long-term mortality in patients who have undergone thoracentesis, and whose pleural effusion is attributed to a variety of aetiologies.

The short-term mortality in patients undergoing thoracentesis for pleural effusion is high, with >20% of patients dying within 30 days. In the USA, the Centers for Medicare and Medicaid Services and the Hospital Quality Alliance began publically reporting 30-day mortality measures for acute myocardial infarction and CHF in 2007, and for pneumonia in 2008. Hospitals may be penalised for high readmission and mortality rates, and rewarded for significant improvements in such measures. It stands to reason that patients with cardiac disease and pneumonia develop pleural effusion, and that a heightened awareness of pleural effusion's role in these diseases may influence treatment decisions. Recognising that pleural effusion is associated with high mortality may prompt more aggressive treatment of the disease process driving its manifestation.

Unilateral versus bilateral effusion

The study is novel in evaluating mortality associated with bilateral effusions. We demonstrated a significant positive association with mortality at both 30 days and 1 year in patients with bilateral *versus* unilateral pleural effusion. Because each group had similar percentages of malignant effusions, that single aetiology does not fully account for the difference. A large study of patients with community-acquired pneumonia demonstrated that patients with bilateral pleural effusion had significantly higher 30-day mortality than those with unilateral (26% *versus* 5.9%, respectively) [6]. We believe this is not attributable to the bilateral nature of the intervention, but rather, an indication of seriously advanced disease.

Pleural effusion in malignancy

It is well known that dissemination of malignant cells into the pleural space is a marker of advanced malignancy. Survival of patients with malignant pleural effusion differs by the type of primary tumour, with the shortest survival being associated with lung cancer [7]. Numerous studies, including this one, demonstrate that malignant pleural effusion is associated with poor outcomes [8–11]. In this study, malignant and paramalignant effusion had similar mortality outcomes at both 30 days and 1 year, justifying our classification of paramalignant as those that are cytologically negative but most likely
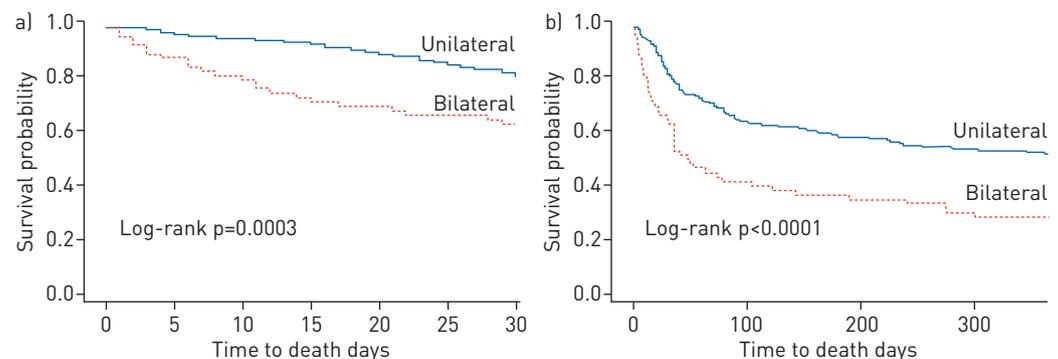
FIGURE 3 Kaplan–Meier survival plots for a) short- and b) long-term mortality (bilateral versus unilateral pleural effusion).

TABLE 3 Adjusted associations between characteristics of thoracentesis/pleural effusion and mortality among patients undergoing thoracentesis

Characteristic	30-day mortality		1-year mortality	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Thoracentesis#				
Bilateral	2.58 (1.44–4.63)	0.002	2.32 (1.55–3.48)	<0.001
Aetiology¶				
CHF	0.33 (0.13–0.85)	0.021	0.28 (0.15–0.54)	0.001
Infectious disease	0.20 (0.09–0.45)	<0.001	0.20 (0.12–0.33)	<0.001
Liver disease	0.09 (0.01–0.71)	0.022	0.17 (0.07–0.45)	0.003
Multiple benign aetiologies	0.43 (0.20–0.90)	0.024	0.36 (0.21–0.61)	<0.001
Paramalignant	0.59 (0.28–1.25)	0.164	0.87 (0.54–1.40)	0.568
Renal disease	0.24 (0.05–1.07)	0.061	0.37 (0.17–0.81)	0.013
Covariates				
Age in years	0.99 (0.97–1.01)	0.430	1.01 (0.97–1.02)	0.361
Male sex	0.96 (0.58–1.60)	0.877	1.07 (0.77–1.40)	0.686
Nonwhite race	0.63 (0.28–1.42)	0.262	0.98 (0.61–1.58)	0.937
Number of comorbidities	1.21 (1.05–1.39)	0.009	1.19 (1.09–1.30)	<0.001

CHF: congestive heart failure. #: referent to unilateral; ¶: referent to malignant.

secondary to cancer. In our study, the highest mortality associated with pleural effusion was observed in patients with underlying malignancy. One-third of these patients died within 30 days of thoracentesis and two-thirds within 1 year. Patients with bilateral malignant pleural effusion are unique and have high 30 day mortality. These patients, in particular, may be better suited to symptom management *via* therapeutic thoracentesis than more invasive procedures, such as pleurodesis [7]. For these patients, palliation and consideration of hospice care may be more appropriate.

Pleural effusion in CHF
In the USA, annual overall mortality for patients with CHF ranges from 10% to 16% [12, 13]. The patients in this study with pleural effusion due to CHF had short-term and annual mortality that was nearly triple that reported in other studies. Our results align with recent data reporting annual mortality of 33% in patients hospitalised with acute decompensation of chronic heart failure [14]. Data were recently published indicating that pleural effusion in acute decompensated CHF does not correlate with increased mortality at 6 months [15]. Notably, in that study, the majority of the pleural effusion cases were mild, identified only by chest radiography, and did not necessitate thoracentesis. We believe that pleural effusion due to CHF should be viewed as further evidence of acute decompensation and, in order to prevent readmission and death, advocate more aggressive therapy.

Infectious pleural effusion
Pleural effusion in the setting of pulmonary infection is common, occurring in up to 9% of patients with pneumonia, and is a poor prognostic sign, particularly if the effusion is moderate to large in size, bilateral and/or associated with empyema [6, 16–18]. In our study, patients with infection contributing to their effusion had similar mortality as prior studies, with 30-day and 1-year mortality of 11% and 26%, respectively. The treatment of complicated pleural space infection with tissue plasminogen activator and DNase improves outcome [19]. Appropriate management of these cases includes early identification of empyema *via* thoracentesis, treatment with appropriate antibiotics, chest tube drainage and surgery when indicated.

Pleural effusion in renal failure
A small number of patients in this study had pleural effusion due to renal failure, which is most often due to hypervolaemia but can also be secondary to exudative uraemic pleuritis [20]. Sometimes they also occur *via* communication between the peritoneum and thorax through the diaphragm in peritoneal dialysis patients [21]. Mortality associated with effusion due to kidney disease has not been well studied. A small study of patients undergoing peritoneal dialysis demonstrated that patients with exudative pleural effusion, probably from uraemic pleuritis, had high mortality (60% at 3 years) [22]. In our small cohort of 14 patients with renal failure as the single cause of their effusion, their 30-day and 1-year mortality was 14% and 57%, respectively.

Pleural effusion associated with multiple benign aetiologies

No other study has characterised patients with pleural effusion due to multiple benign aetiologies and their mortality. Their high mortality is probably multifactorial. Common benign conditions contributing to development of pleural effusion include cardiorenal and hepatorenal disease. Underlying malnutrition and hypoalbuminaemia associated with these multiorgan disease states probably contribute to increased mortality. Pleural effusion in these patient populations may be a marker of their illness severity. In the setting of multiple benign aetiologies, these results provide evidence that multiorgan dysfunction is worse than single-organ failure.

Study strengths and limitations

Although this study is a well-characterised cohort of medical patients undergoing thoracentesis, it has general applicability to the broader inpatient medical population. The patient sample size is, to our knowledge, the largest published to date that evaluates mortality by aetiology of pleural effusion. It is also the first study to report the association between bilateral pleural effusion and mortality.

Limitations of this study include that it was performed at a single academic institution and the majority of patients had diseases with effusion secondary to their medical aetiology. Because the majority of thoracenteses in our hospital are performed by dedicated proceduralists, patients who had their procedures performed by other providers were not enrolled. Because this cohort is limited to patients who underwent thoracentesis, we cannot say anything about mortality in patients with pleural effusion who did not undergo thoracentesis. A recent paper attempted to address this question retrospectively by identifying all patients who had pleural effusion per chest imaging at time of hospital admission [23]. That study determined 30-day and 1-year mortality of patients who had thoracentesis performed *versus* those who did not. 30-day mortality trended lower in the thoracentesis subgroup (9% *versus* 16%) and trended higher at 1 year (36% *versus* 31%). However, neither of these trends was statistically significant as this was a small, underpowered retrospective study. Mortality rates were, on a whole, lower in this study compared to the current study, also probably a reflection of the small sample size of 11 patients who underwent thoracentesis over a 1-month period.

Pleural effusion serves as a marker of disease and is influenced by many factors. In CHF, for example, multiple variables are involved that subsequently influence its course, including medication regimens, patient compliance, ventricular assist devices, copresence of coronary artery disease and ischaemia, and arrhythmia. Similar variability is encountered in patients with renal failure, infection and malignancy. Importantly, this study does not evaluate the influence on mortality of different treatment regimens to control effusion. In this sense, the pleural disease serves more as a marker of severe disease, but does not guide a specific way to decrease mortality. Rather, given the degree of mortality seen in patients with pleural effusions, the requirement of undergoing a thoracentesis for diagnostic or therapeutic purposes should indicate that the patient's underlying disease process is advanced and that maximal therapy aimed at treating the underlying aetiology is paramount.

Conclusions

Patients who undergo thoracentesis as a treatment for pleural effusion are encountered across all aspects of medicine. In addition to malignant effusion, paramalignant effusion, effusion due to multiple benign aetiologies and bilateral effusion all have considerable 30-day and 1-year mortality. Malignant effusion had the highest 30-day (37%) and 1-year (77%) mortality, followed by effusions due to multiple benign aetiologies (29% and 55%), CHF (22% and 53%) and renal failure (14% and 57%). Patients with bilateral pleural effusions had a significantly higher risk of death than patients with unilateral effusions at both time-points. Caregivers encountering patients with pleural effusion should be aware of their heightened mortality risks and aggressive management of the underlying aetiology is warranted.

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