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Title

Non-Malignant Pleural Effusions (NMPE): a prospective study of 356 consecutive unselected patients.

For CHEST Journal

Background

Pleural effusions secondary to a non-malignant aetiology can represent significant morbidity and mortality. These non-malignant pleural effusions (NMPE) are common, with congestive heart failure (CHF) representing the leading cause. Despite this, there is limited data on mortality risk and the factors which influence them.

Methods

We recruited 782 consecutive patients presenting to a pleural service, between 03/2008 and 03/2015, with an undiagnosed pleural effusion. Further analysis was conducted on the 356 patients with NMPE. Pleural biochemistry, cytology, thoracic USS and chest radiograph were performed. Echocardiogram, CT scans, radiology-guided biopsy and medical thoracoscopy were undertaken as clinically indicated. Patients were followed-up for a minimum duration of 12 months with final diagnosis decided by independent review by 2 respiratory consultants.

Results

Of the 782 patients, 356(46%) were diagnosed with a NMPE. These patients had a mean age of 68(SD17) with 69% of patients male. Cardiac, renal and liver failure patients had 1-year mortality rates of 50%, 46% and 25% respectively. Bilateral effusions (HR 3.55 CI 2.22-5.68) and transudative effusions (HR 2.78 CI 1.81-4.28) were associated with a worse prognosis in patients with NMPE, with a 57% and 43% 1-year mortality respectively.

Conclusions

This is the largest prospectively collected series in patients with NMPE, demonstrating that those secondary to organ dysfunction have an extremely high 1-year mortality. In addition, the presence of bilateral and transudative effusions are an indicator of increased mortality. Clinicians should be aware of these poor prognostic features and guide management accordingly.

Introduction

1.5 million people develop pleural effusions each year in the United States[1] with an estimated 1.1 to 1.3 million caused by a non-malignant aetiology[1,2]. Non-malignant pleural effusions (NMPE) are caused by either systemic factors, such as heart, liver or renal failure or local factors such as infection, pulmonary embolism, inflammatory pleuritis or thoracic surgery. Despite congestive heart failure (CHF) representing the leading cause of pleural effusions[3] there is very limited data on the mortality rates in NMPE. The evidence that is available suggests a poor prognosis, with one case series demonstrating a median survival of 1 year in effusions secondary to CHF [4].

The aim of this study was to determine the mortality rates in NMPE by undertaking a prospective observational trial that would evaluate baseline factors associated with increased mortality.

Materials and Methods:

We identified 782 consecutive patients in a prospective observational cohort study, presenting with a new undiagnosed pleural effusion, to a single UK institute, between 03/2008 and 03/2015. Patients were recruited as both inpatients and outpatients.

Pleural and serum biochemistry, pleural cytology, thoracic ultrasound (USS) and a chest radiograph were performed on all patients. Echocardiogram, computerised tomography (CT) scans, radiological-guided biopsy and medical thoracoscopy were undertaken as clinically indicated. Patients were followed-up for a minimum duration of 12 months

or until death, with the final diagnosis decided by independent review by two respiratory consultants. Where more than one aetiology was felt to be responsible, the principal contributing factor was listed first. There was a high level (0.94 p<0.001) of inter-observer agreement, as calculated by kappa statistics. Patients were classified into diagnostic categories for analysis: malignant; CHF; liver failure; renal failure; pleural infection (empyema, complicated parapneumonic effusion, simple parapneumonic effusion, TB pleuritis); benign asbestos pleural effusion & diffuse pleural thickening (DPT); coronary artery bypass graft (CABG), pulmonary embolism, and other (including chylothorax, rheumatic, trauma and drug-induced). Effusions were defined as malignant if either the primary or secondary diagnoses included a malignant cause.

Effusions were classified either as transudative or exudative by Lights criteria[5] and either bilateral or unilateral based on PA chest radiograph appearance. The effusions were categorised by cytology as either blood, macrophage, neutrophilic or lymphocytic predominant (>50%), mixed if no clear predominance in cytology and eosinophilic if >10% eosinophils. Eastern Cooperative Oncology Group Performance score (ECOG-PS)[6] was recorded for 77.6% of patients.

Survival data was calculated from date of study entry to date of death. Surviving patients were censored on 07/2016.

The study protocol was approved by local ethical approval, South-West Bristol Research Ethics Committee (Ref 08/H0102/11), in accordance with the Declaration of Helsinki. Study participants gave written informed consent.

Statistics Analysis

Descriptive statistics were used to summarise patient characteristics and clinical data. Means (±SD) were calculated for age and percentage values for subgroups. Multivariate proportional hazard ratios were calculated using Cox regression analysis for 6 and 12 month mortality for presence of bilateral pleural effusion (compared to unilateral), transudative effusions (compared to exudative), and the following aetiologies (compared to malignant pleural effusion cohort): CHF, liver failure, pleural infection, renal failure, BAPE/DPT, CABG, PE, and other. Kaplan-Meier plots for survival probabilities were created for overall mortality and stratified for aetiologies, bilateral vs unilateral effusions and transudative for exudative effusions. All statistical analyses were performed using IBM SPSS statistics version 23.0 (SPSS Inc. Chicago, IL)

Results

Data was obtained for a total of 782 patients, with 774 included in analysis. Eight participants were excluded for multiple reasons, including no diagnosis reached at 12 months and withdrawal of consent. Further analysis was conducted on the 356 (46%) patients with NMPE (see Figure 1)

The baseline characteristics for NMPE cohort are presented in table 1, with characteristics by aetiology presented in table 2. The majority of NMPE were exudative (73%), unilateral (88%) with pleural infection being the commonest aetiology (40.6 %). Nearly a quarter (23.6%) of the NMPEs were felt to have more than one identifiable cause.

Mortality rates and multivariate predictors of mortality in NMPE cohort are displayed in table 3, with hazards ratio of bilateral effusion compared to unilateral, transudative effusion compared to exudates and aetiology compared to malignancy. There were high 1-year mortality rates in patients with congestive heart (50%), renal (46%) and liver failure (25%). Thirty day mortality was low, at 9% for CHF and no deaths in the liver and renal failure cohort. Malignant pleural effusions had the highest mortality at 49% and 70% at 6 and 12 months respectively. In patients with NMPE, bilateral and transudative effusions were associated with a significantly worse prognosis with HR 3.55(2.22-5.68) and 2.78(1.81-4.28) when compared to unilateral and exudative effusions respectively. A serosanguinous effusion was associated with a significantly increased risk of death (HR 2.8, CI 1.1-6.8, p-value 0.027) when compared to eosinophilic effusions.

Discussion

Non-malignant pleural effusions are not a benign process, and represent a significant mortality risk. This paper demonstrates that patients with effusions secondary to organ failure (heart, liver, and kidney) are at significantly higher risk than those related to a local disease process, whether that be infection or inflammation. Correspondingly, the transudative, bilateral effusions that often accompany organ failure are independently associated with a worse prognosis. This supports the findings of an earlier paper demonstrating high mortality rates in CHF, liver and renal failure[4]. These mortality rates are not dissimilar to that seen in some malignant disease. Effusions refractory to medical therapy and repeated aspiration may require more definitive management strategies. This may involve disease specific procedures, including transjugular intrahepatic portosystemic shunt (TIPS) procedure or liver transplantation in liver disease, or pleural interventions including pleurodesis or indwelling pleural catheter placement.

CHF is the commonest cause of pleural effusions, with as many as 87% of patients with decompensated heart failure requiring diuresis having pleural effusions[7]. The documented 1-year mortality risk for patients with CHF is broad, ranging from 11-30% [8-14], with multiple studies examining the risk factors associated with mortality [10,15-19] (echocardiogram criteria, NYHA score, age, male gender, blood pressure, CRP, renal dysfunction and biomarkers[15] to name a few). There has been little work performed investigating whether the presence of an effusion effects prognosis, with the studies that have examined this either looking at incidental effusions found on transthoracic echocardiogram[20] or small effusion that didn't required thoracentesis[21]. The one year-mortality rate for patients with an effusion secondary to heart failure in our cohort was found to be 50%, similar to the 1- year mortality rate (46%) of patients with acute decompensated heart failure admitted to intensive and coronary care units[22] and significantly more than the 1 year mortality for outpatients with NYHA class IV CHF (28%)[8]

Hepatic hydrothorax is a complication of liver cirrhosis in which hydrostatic imbalances result in fluid accumulation within the pleural space[23] and occurs in 6-10% of patient with advanced liver cirrhosis[24]. The initial management is a low-salt diet and diuretics, although 20% of patients are refractory to this[25], and may require a transjugular intrahepatic portosystemic shunt (TIPS) procedure or liver transplantation. In our cohort hepatic hydrothorax was a predictor of significant mortality, with a quarter of patients dying within a year. This is higher than patients with chronic alcoholic liver disease (16.4%)[26] and equivalent to a high MELD (Model For End-Stage Liver Disease) score of 20-29[26] that would be an indication for liver transplant.

A fifth of patients on long-term haemodialysis will have a pleural effusion [27], usually as a result of hypervolaemia, though heart failure, parapneumonic effusion and uraemic pleuritis may be responsible [27]. 1.6-10% of patients on peritoneal dialysis (PD) will also develop a PD-related effusion[28], which can occur from pleuro-peritoneal communication via a porous diaphragm[28,29]. A study looking at mortality in patients with effusion secondary to PD demonstrated a wide range between the different cohorts, with the worse outcomes amongst those with fluid overload, with a median survival of around a year[30]. The renal cohort in our study had a high 1-year mortality rate (46%) which is triple the one-year mortality (15.6%) of patients on dialysis [31]. The increased hazard ratio associated with renal failure do not, however, reach significance, presumably due to low numbers in the cohort.

Infections of the pleural space are common and associated with high mortality[32]. In our cohort, the 1-year mortality (19%) was similar to documented mortality rates for pleural infection [32-34]. The mortality rate in patients with pleural effusions secondary to pulmonary embolism or post CABG were slightly higher than would be expected[35,36], however the numbers involved were low (5 and 6 patients, respectively) and the associated increased hazard ratios do not reach statistical significance. Therefore we cannot conclude whether the presence of an effusion is an adverse prognostic feature in these conditions.

In this study, the presence of a transudate or bilateral effusions were independently associated with increased hazard ratios and higher mortality rates, with 43% and 18% 1-year mortality in transudative and exudative effusions respectively and a 57% and 20% 1-year mortality rates in bilateral vs unilateral effusion. This supports the findings that pleural effusions secondary to organ (heart, renal and liver) dysfunction, as opposed to an exudative effusion secondary to localised inflammation is an indicator of poorer prognosis.

To our knowledge this is the largest prospective study to date examining the mortality rates in NMPE. It included approximately equal inpatient and outpatient numbers and involved patients managed by a range of specialities. All patients presenting with an undiagnosed pleural effusion were eligible aside from those excluded if they could not give informed consent, declined to participate in the trial or were pregnant or lactating. The findings are consistent with a previous study demonstrating high mortality rates in patients with CHF and bilateral effusions[4].

A limitation of this study is that it was performed at a single centre. All these patients required pleural aspiration, either for diagnostic or therapeutic purposes. A diagnostic aspirate would not usually be indicated for an effusion with a high pre-test probability of cardiac aetiology and a low probability for an alternate cause. Hence it is likely that the CHF effusions aspirated were either refractory to medical management or there was level of concern in the treating physician that warranted an invasive investigation. This is the likely explanation for pleural infection representing the commonest cause of NMPE in our cohort, as opposed to CHF worldwide[3]. We cannot comment on the mortality rate amongst patients that did not require a pleural procedure, and it is likely that requiring an aspiration in NMPE is an indicator of disease severity in itself.

Conclusion

This is the largest prospectively collected series in patients with NMPE to date, demonstrating that pleural effusions secondary to organ dysfunction, in particularly cardiac, have an extremely high 1-year mortality and the presence of an effusion requiring aspiration is a marker of severe disease and poor prognosis. In addition, the presence of bilateral and transudative effusions are an indicator of increased mortality. Clinicians and patients should be aware of this poor prognostic features and guide management accordingly.

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