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Multiple aetiology in unilateral pleural effusions: A prospective observational study

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RF, AM & NZE collected patient data and performed sample analysis.
JH collected patient data and recorded consultant diagnoses.
IR & ASJ performed and analysed echocardiograms and electrocardiograms
NM conceived the design of the study, recorded consultant diagnoses, prepared the manuscript and is the guarantor.

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ABSTRACT

RATIONALE: Evaluation of a pleural effusion has historically focussed on establishing a single aetiology. Pleural fluid may accumulate through multiple pathophysiological processes. The prevalence of multiple aetiology in pleural effusions has not been established. The identification of contributing processes may improve clinical outcomes.

OBJECTIVE: The objective of this prospectively collected case series was to establish the prevalence and nature of multiple aetiology in unilateral pleural effusions.

METHODS: Consecutive patients presenting with an undiagnosed unilateral pleural effusion were recruited at a tertiary pleural centre. Patients underwent a comprehensive structured clinical work up and were followed up for a minimum of 12 months after which one or more diagnoses was recorded independently by two experienced clinicians.

MEASUREMENTS AND MAIN RESULTS: 130 patients were recruited to the study over a 24 month period and 126 patients completed follow up. 88 patients (70%) had a single cause for their pleural effusion and 38 (30%) had multiple causes. Serum NT-pro BNP ≥ 1500 pg/ml was predictive of multiple aetiology, the most common cause of which was congestive heart failure. NT-pro BNP had a sensitivity and specificity of 79% and 88% respectively for establishing heart failure as a primary or contributory cause. 13 patients with a malignant pleural effusion had an NT-pro BNP ≥ 1500 pg/ml.

CONCLUSIONS: This study is the first to establish the prevalence of multiple aetiology in patients with unilateral pleural effusions. 38 patients (30%) had multiple causes for their effusion. The identification of multiple pathology may be important in determining optimum treatment and improving patients' symptoms.

TRIAL REGISTRATION: Central Bristol research ethics committee (Reference: 08/H0102/11)

Introduction

Historically, the diagnostic evaluation of pleural effusions has been structured around identifying a single aetiology. The binary classification system of Light's criteria divides effusions into transudates and exudates and presupposes a single disease process leading to fluid accumulation (1). A number of potential mechanisms which may lead to accumulation of pleural fluid in disease are described: increased permeability of the pleural membrane, increased pulmonary microvascular pressure, decreased intrapleural pressure, decreased plasma oncotic pressure and an obstruction or reduction in lymphatic flow (2). Given these different mechanisms, it may follow that the accumulation of pleural fluid, to a degree which causes symptoms, may well be a multifactorial process. The fact that Light's criteria (1) has been shown to be neither completely sensitive (3, 4) nor specific for heart failure and that malignant pleural effusions may be misclassified as transudates (5) may be explained, in some instances, by multiple aetiologies driving fluid accumulation. This may present opportunities for tailored treatment in patients with contributing pathological processes.

The presence of five different disease processes giving rise to a pleural effusion sequentially in a single patient has been described (6). Although an extreme example, this case report illustrates the importance of considering alternative mechanisms of fluid accumulation both over time and simultaneously, and how this may affect formulation of an optimal management strategy.

No previous prospectively study has set out to define the prevalence of multiple pathologies contributing to pleural effusions. This study recruited consecutive patients presenting with undiagnosed unilateral pleural effusions to a single centre with the aim of establishing this.

The utility of N-Terminal pro Brain natriuretic peptide (NT-pro BNP) has been assessed in patients with pleural effusions (7-9), though this has typically been in patients with a high pre-test probability of heart failure or bilateral effusions (8, 10-12). We have therefore evaluated NT-pro BNP in a group of patients with undiagnosed unilateral pleural effusions and established its role in predicting multiple aetiology. As serum and pleural fluid NT-pro BNP levels are closely correlated, serum NT-pro BNP alone was measured (11).

We hypothesised that, in patients presenting with a symptomatic unilateral pleural effusion, a robust and structured follow-up will establish the prevalence of multiple aetiology. The study also aimed to establish any factors predicting the presence of multiple aetiology.

Methods

Study Design and Patients

This study prospectively recruited consecutive patients presenting to North Bristol NHS Trust (UK) with a new undiagnosed unilateral pleural effusion. Recruitment began in April 2008 and the final patient completed follow up in March 2013. Patients were followed up for a minimum of 12 months, though some patients required longer follow-up with interval imaging for two years or more before a diagnosis was definitively reached. The study was approved by the Central Bristol research ethics committee (Reference 08/H0102/11), and all participants gave written informed consent for study participation.

Procedures

All patients underwent a comprehensive clinical assessment including a full medical history and clinical examination with prospective data collection. World health organisation performance status was recorded. Pleural effusions were classified by laterality and size

based on the chest x-ray at the time of presentation: [small (≤1/3 hemithorax), moderate (> 1/3 and ≤ 1/2 hemithorax) and large (> 1/2 hemithorax)]. Diagnostic thoracentesis was undertaken with ultrasound guidance in all patients. Blood tests were performed including a full blood count, urea and electrolytes, liver function tests, C reactive protein, total protein, lactate dehydrogenase and an NT-pro BNP. Pleural fluid analysis included a total protein, lactate dehydrogenase, glucose, microscopy and culture and cytological analysis with a differential cell count. Chest radiographs, computed tomography, electrocardiograms and echocardiograms were also carried out. NT-pro BNP levels were measured using a point of care sandwich enzyme-linked immunosorbent assay test kit (Cobas h232 – Roche Diagnostics, Germany) according to the manufacturer's instructions. The test has intra-assay variation of <8% and measured range of 60-3000 pg/ml. The cut off (1500 pg/ml) was used as has been recommended in earlier studies (9).

Computed tomography (CT) scan reports were categorised on the likelihood of malignant disease as: benign/inflammatory, suspicious for malignancy, probable malignancy or definite malignancy. Pleural biopsies were performed when clinically necessary, either when the diagnosis was not clear, or if malignancy was suspected.

After a minimum of 12 months had elapsed from time of recruitment, a comprehensive case note review was undertaken with review of available results by two independent experienced consultant chest physicians (NAM, JEH). All clinical details were available, with the exception of serum NT-pro BNP levels, to which reviewing consultants were blinded. One primary diagnosis and up to two contributory diagnoses were recorded. Required clinical criteria for specific diagnoses are listed in Appendix 1. In case of disagreement a consensus was established through both consultants reappraising relevant investigations

and clinical details. Where multiple diagnoses were thought to have contributed to the effusion, these were ranked as primary and secondary causes by their degree of contribution to the effusion based on clinical details, pleural fluid analysis and their temporal relationship with the effusion. In cases of uncertainty the cause thought to have led to the patient's initial presentation was assigned the primary cause. A consensus decision was made when necessary.

Statistical analysis

Non-normally distributed data were expressed as medians with interquartile ranges. Frequency data were expressed as number of patients with percentage of total in parentheses. The sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) were calculated for Light's criteria in identifying an exudative cause for the pleural effusion and for NT-pro BNP in establishing a primary diagnosis of congestive heart failure (CHF) and a contribution of CHF to the effusion. All pleural effusions other than those due to CHF, hepatic hydrothorax or renal failure were considered to have an exudative cause.

Chi-squared test was used to compare the occurrence of multiple aetiologies between transudates and exudates, between different primary aetiologies and between lung cancer and mesothelioma. Chi-squared test was also used to examine the relationship between the side of effusion, its aetiology and categorisation by Light's criteria. NT-pro BNP levels were compared between groups of patients with a single or multiple cause for their effusion using the Mann-Whitney test. The association of NT-pro BNP level with single or multiple aetiology was tested for the whole group and for all patients excluding those with a primary diagnosis of CHF. Statistical analysis was performed with Stata 13.1.

Results

176 patients were screened for study entry. Figure 1 illustrates the reasons potential participants were excluded. 130 patients were recruited to the study, 4 patients were lost to follow up and 126 patients were followed up for 12 months or until death and included in the final analysis. Patient characteristics and the primary diagnosis are shown in Table 1. The classification of patients' pleural effusions by Light's criteria, the predominant cell type and CT features are summarised in Table 2. The primary diagnosis of the cause for the pleural effusion was consistent between reporting consultants (kappa=0.95).

Multiple aetiology

88 patients (70%) had one identified cause for their pleural effusion, 35 patients (28%) had two causes and 3 patients (2%) had three causes. In the 38 patients with more than one cause there were 41 secondary or tertiary causes of which the most common was CHF (n=21, 51%), followed by pleural infection (n=8, 20%) and pleural malignancy (n=7, 17%). Other contributing causes, including benign asbestos pleural effusion (BAPE) (n=3), pulmonary embolism (PE) (n=1) and renal failure (n=1), accounted for the remainder.

Figure 2 demonstrates the number of patients in each primary diagnostic category with a multiple cause for their effusion and whether that was due to CHF or another secondary cause. Notable patterns were CHF as a contributory cause in patients with malignant pleural disease (8/58 – 14%), CHF as a contributory cause in patients with both BAPE (3/11, 27%) and idiopathic pleuritis (2/8, 25%) and the prevalence of both malignancy (2/11, 18%) and CHF (2/11, 18%) in patients with a primary diagnosis of pleural infection.

Malignancy

Of 58 patients with a primary diagnosis of malignancy, the most common sites were lung and mesothelioma as shown in Table 3. Rates of cytological diagnoses were lower in patients with mesothelioma than with other causes of pleural malignancy (11% vs 38%; p=0.04). Multiple aetiology was significantly more common in patients with lung cancer compared with those with mesothelioma (41% vs 6%; p=0.01).

Laterality

Patients with a primary diagnosis of heart failure had a right sided effusion in 76% of cases (16/21) compared with 59% (62/105) in those patients with an alternative primary diagnosis. The apparent tendency of patients with heart failure to be more likely to have a right sided effusion was not statistically significant (p=0.14). No relationship was detected between the side of pleural effusion and the effusion being classified as a transudate by Light's criteria (p=0.24) or there being multiple causes of the pleural effusion (p=0.54).

Light's Criteria

Light's Criteria had a sensitivity of 97.9%, specificity 73.9%, PPV 94.1% and NPV 89.5% for the correct identification of an exudative cause for the pleural effusion. The distribution of transudates and exudates amongst diagnostic groups is shown in Figure 3. The category 'Other' includes patients with a PE, an effusion following coronary artery bypass grafting, transudative effusions due to hepatic hydrothorax or renal impairment and effusions due to connective tissue disease or medication. Light's criteria was unavailable in six patients due to missing pleural fluid or serum levels, including two patients with purulent fluid pleural fluid for whom levels were not measurable. Six patients with a primary diagnosis of CHF were erroneously classified as an exudate by Light's criteria. Two patients were misclassified

as a transudate by Light's criteria, one had a benign asbestos pleural effusion and the other a pulmonary embolism, both of these patients had an elevated NT-pro BNP.

NT-pro BNP Results

In order to establish the value of NT-pro BNP, physicians assigning diagnoses were blinded to NT-pro BNP results. Using a threshold of 1500 pg/ml, NT-pro BNP measurement had a sensitivity of 76.2%, a specificity of 74.3%, a PPV of 37.2% and an NPV of 94.0% in establishing a primary diagnosis of CHF. In terms of establishing CHF as a primary or a contributory cause the sensitivity was 78.6%, specificity 88.1%, PPV 76.7% and NPV 89.2%. 13 patients with an NT-pro BNP ≥1500 had a malignant pleural effusion, and therefore it is clear that an elevated NT-pro BNP cannot reliably be used to exclude a malignant aetiology for a pleural effusion.

CT Features

A CT demonstrating definite malignant features had a 44.6% sensitivity and 100% specificity for the identification of patients with pleural malignancy (PPV 100%, NPV 59.6%). A CT demonstrating probable or definite malignant features had a sensitivity of 64.6% and specificity 92.5% (PPV 91.3%, NPV 68.1%).

Predicting multiple aetiology

NT-pro BNP levels were higher in patients with multiple aetiology (Median 1964 pg/ml, IQR 935-3000) than in those with a single cause for their pleural effusion (263, 88-1057; $p<0.001$). This finding remained significant ($p<0.001$) when patients with a primary diagnosis of CHF were excluded. However, the prediction of a multiple aetiology with NT-pro BNP related to the identification of those patients with CHF as a secondary or tertiary cause of

their pleural effusion. The proportion of patients with transudates and exudates by Lights' criteria was not significantly different in patients with single (13% transudates) or multiple aetiology (23% transudates; p=0.176).

Discussion

This prospective study of 126 patients with unilateral effusions is the first to establish the prevalence of multiple aetiology. In patients undergoing robust follow up, multiple aetiologies were present in 30% of patients. NT-pro BNP levels were significantly higher in the group of patients with multiple causes for their pleural effusion, compared with those patients with a single cause.

Some disease processes may, in isolation, not give rise to a symptomatic effusion but when they co-exist with a second process, might result in a significant effusion. The presence of other contributing processes may help explain the variable presence of pleural effusion in conditions such as mesothelioma or benign asbestos pleural disease and the unpredictable speed of accumulation of a pleural effusion in patients with the same condition.

Our data has demonstrated Light's criteria to have an impressive sensitivity (98%) and PPV (94%) for the identification of an exudative cause for the pleural effusion. Only two patients were misclassified as transudates by Light's criteria, one patient with a PE and another with a benign asbestos pleural effusion. Light's criteria was less effective in the identification of a transudative cause for the effusion, with six patients out of 21 (29%) with CHF classified in error as an exudate. This misclassification rate is similar to that described

previously (4). Of patients with CHF, only two of the six patients with exudates were on diuretic treatment at the time of thoracentesis compared with 8 out of 14 patients with transudates, suggesting that in our study, diuretic therapy was not an important predictor of elevated pleural fluid protein levels as has been previously suggested (13). The albumin gradient has been shown to be potentially more specific than Light's criteria in patients receiving diuretic therapy (14). Unfortunately albumin gradient was not calculable within this study, as though serum albumin levels were available, pleural fluid albumin levels were not.

Of the 58 patients with a diagnosis of malignancy 12 (21%) had a multiple aetiology contributing to their pleural effusion. Lung cancer patients were significantly more likely to have a multiple aetiology compared with patients with mesothelioma. The reasons for this are unclear, but the difference may reflect a difference in rates of pre-existing comorbidity. Alternatively, this could be hypothesised to be due to differences in the process of fluid accumulation between patients with lung cancer and metastatic disease to the pleura and those with mesothelioma.

CT features appeared to have poor sensitivity for the diagnosis of pleural malignancy within our study population. Five patients with pleural malignancy (7.7%) had CT features classified as indicating benign disease only, and a further 18 patients (27.7%) with pleural malignancy had a CT with some suspicious features, but were not classified as probable or definite malignancy. This finding should highlight the caution required in using radiology in isolation for diagnosis, and the need for interval imaging and close clinical follow-up in cases where there is doubt regarding the diagnosis. CT findings were, by contrast, a specific marker of malignancy. Three patients with BAPE and one patient with idiopathic pleuritis

had CT findings classified as indicative of probable malignant disease but all patients with definite features of malignancy on CT were ultimately diagnosed with pleural malignancy.

This study is the first to prospectively evaluate the utility of NT-pro BNP in undiagnosed unilateral pleural effusions. In a meta-analysis of 10 previous studies, pleural fluid NT-pro BNP is reported to have a sensitivity of 94% and specificity of 94% (15). In some clinical settings, such as critical care, caution is advised in view of false positive results (16). Serum and pleural fluid NT-pro BNP levels are closely correlated (11), and therefore measurement of serum levels alone is thought to be sufficient (17). In our study the ability of serum NT-pro BNP to establish a primary diagnosis of heart failure (sensitivity 76%, specificity 74%), or any contribution from heart failure in the aetiology of the pleural effusions (sensitivity 79%, specificity 88%) were significantly less impressive than those seen in previous studies. This difference is likely to be explained by the fact that our study recruited patients with undiagnosed unilateral effusions in whom the pre-test probability of heart failure was lower and there was diagnostic uncertainty at the time of enrolment. Additionally, the vast majority of previous studies examining NT-pro BNP have used pre-selected patient cohorts with strong evidence of CHF and clear-cut causes of effusions in control groups, excluding those with diagnostic uncertainty (15).

This study would suggest that the previously stated assertion that “NT-pro BNP levels higher than 1500 pg/ml are virtually diagnostic of heart failure” (11) needs to be viewed with caution. Our finding of 13 patients with malignant pleural effusions and an NT-pro BNP ≥ 1500 pg/ml highlights the potential danger of using NT-pro BNP in this way. Though this group may well have a degree of heart failure and respond to diuretics and the optimisation of cardiac treatment, it cannot be assumed that this group do not have an additional

pathological process requiring careful evaluation. In our view it is clear that the identification of one cause for a pleural effusion should not prevent more detailed diagnostic evaluation for alternative additional processes where this is thought to be clinically necessary.

The median age in this study was 75 years and in view of the significant comorbidity of this age-group the incidence of multiple causes for pleural effusions may be higher than in other healthcare settings representing a younger population. Though patients' diagnoses were established by two independent experienced clinicians, the work up of these patients may extend beyond that used in other clinical environments. As a result, the prevalence of multiple aetiology reported here may be higher than that seen in other populations with a less comprehensive work up. Additionally, as all patients were recruited from a single tertiary centre, the proportion of diagnoses may not be representative of those seen elsewhere. Specifically, the study may over-represent patients with mesothelioma, and low cytological diagnostic rates may reflect the patients referred to this centre following initial evaluation prior to referral. The validation of clinical diagnoses could have been made more robust with more thorough investigation, such as pleural biopsy in all patients, but this was not possible in this study, as in many patients such an approach would not be clinically justified.

This study has not established whether clinical outcomes may be improved by the identification of a contributing processes, though clearly for some patients with a contributory cause such as pleural infection, malignancy or thromboembolic disease there would be a clear rationale for changing management. It is less clear whether the

identification and treatment of, for example CHF in a patient with pleural malignancy, will improve patient symptoms or clinical outcome.

Serum NT-pro BNP levels have been shown to be independently associated with poor prognosis in patients with malignant pleural effusions (18). It has not been established whether this poorer prognosis is modified with the optimisation of cardiac treatment but this may be an area for investigation in future interventional studies. As well as potentially improving prognosis, the treatment of heart failure in patients with other aetiologies to their pleural effusion may attenuate the accumulation of pleural fluid, reduce the frequency of pleural aspirations or potentially improve the chances of successful pleurodesis.

The possibility of multiple pathologies contributing to pleural effusions should prompt a robust diagnostic work up where indicated, which extends beyond the identification of one explanation for the effusion. NT-pro BNP levels may prove of value in the identification of patients with CHF as a contributing process leading to development of a symptomatic pleural effusion. Further interventional studies may help evaluate whether the identification and treatment of secondary aetiologies, particularly heart failure, may help improve patient outcomes in this comorbid patient population.

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Figure Legends

Figure 1: Study flow diagram

A demonstration of the numbers of patients screened for and included in the study providing reasons for non-inclusion where necessary.

Figure 2: Frequency of multiple aetiology by Primary diagnosis

A bar chart illustrating the numbers of patients in each of the major diagnostic groups and the proportion of patients with a contributing secondary cause for their pleural effusion and whether that contributing cause was heart failure or another cause.

Footnote:

CHF – Congestive heart failure

BAPE - Benign asbestos pleural effusion

Figure 3: Light's criteria classification by primary aetiology

An illustration of the number of patients categorised as a transudate or exudate by Light's criteria depending on the primary diagnostic category established after follow up.

Footnote:

CHF – Congestive heart failure

BAPE - Benign asbestos pleural effusion

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338 **Table 1: Patient Demographics**

Patient Characteristics	Result
Age (years) – median (Interquartile range)	75 (67-79)
Sex - no. (%)	
Male	83 (66%)
Female	43 (34%)
Side of Effusion - no. (%)	
Left	48 (38%)
Right	78 (62%)
Size of Effusion – no. (%)	
Small	26 (21%)
Moderate	70 (56%)
Large	30 (24%)
Inpatient or Outpatient – no. (%)	
Outpatient	87 (69%)
Inpatient	39 (31%)
World Health Organisation Performance Status	
0	13 (12%)
1	53 (48%)
2	31 (28%)
3	11 (10%)
4	3 (3%)
Primary Diagnosis	
Pleural Malignancy	58 (46%)
Congestive Heart Failure	21 (17%)
Pleural Infection	11 (9%)
Benign Asbestos Pleural Effusion	11 (9%)
Idiopathic pleuritis	8 (6%)
Other (Haemothorax, Drug reaction or Trapped lung)	4 (3%)
Pulmonary Embolism	4 (3%)
Non-cardiac Transudate	3 (2%)
Coronary Artery Bypass Graft	2 (2%)
Rheumatoid Effusion	2 (2%)
Undiagnosed	2 (2%)

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340 **Table 2: Pleural Fluid and CT Characteristics**

Variable	Result (%)
Light's Criteria – no. (%)	
Exudate	101 (80%)
Transudate	19 (15%)
Unavailable	6 (5%)
Predominant cell type – no. (%)	
Mesothelial cells	36 (29%)
Lymphocytes	34 (27%)
Eosinophils	8 (6%)
Neutrophils	7 (6%)
Other (Malignant cells, paucicellular, predominantly blood)	39 (31%)
Unavailable	2 (2%)
CT Features	
Benign appearances/Inflammatory	31 (24.6%)
Suspicious for malignancy	41 (32.5%)
Probable malignancy	17 (13.5%)
Definitely malignant	29 (23.0%)
Unavailable	8 (6.4%)

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343 **Table 3: Cytology and radiology results and rates of multiple aetiology in patients**

344 **diagnosed with malignancy**

	Total (%)	Diagnostic cytology (%)	CT probable or definite malignancy (%)	Multiple aetiology (%)
Lung	17 (29%)	5 (29%)	17 (100%)	7 (41%)
Mesothelioma	18 (31%)	2 (11%)	8 (44%)	1 (6%)
Breast	5 (9%)	3 (60%)	5 (100%)	0 (0%)
Gastrointestinal	4 (7%)	3 (75%)	3 (75%)	2 (50%)
Renal	4 (7%)	0 (0%)	4 (100%)	0 (0%)
Haematological	2 (3%)	1 (50%)	0 (0%)	1 (50%)
Ovarian	2 (3%)	2 (100%)	1 (50%)	0 (0%)
Other	6 (10%)	1 (17%)	3 (50%)	1 (17%)

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Figure 1

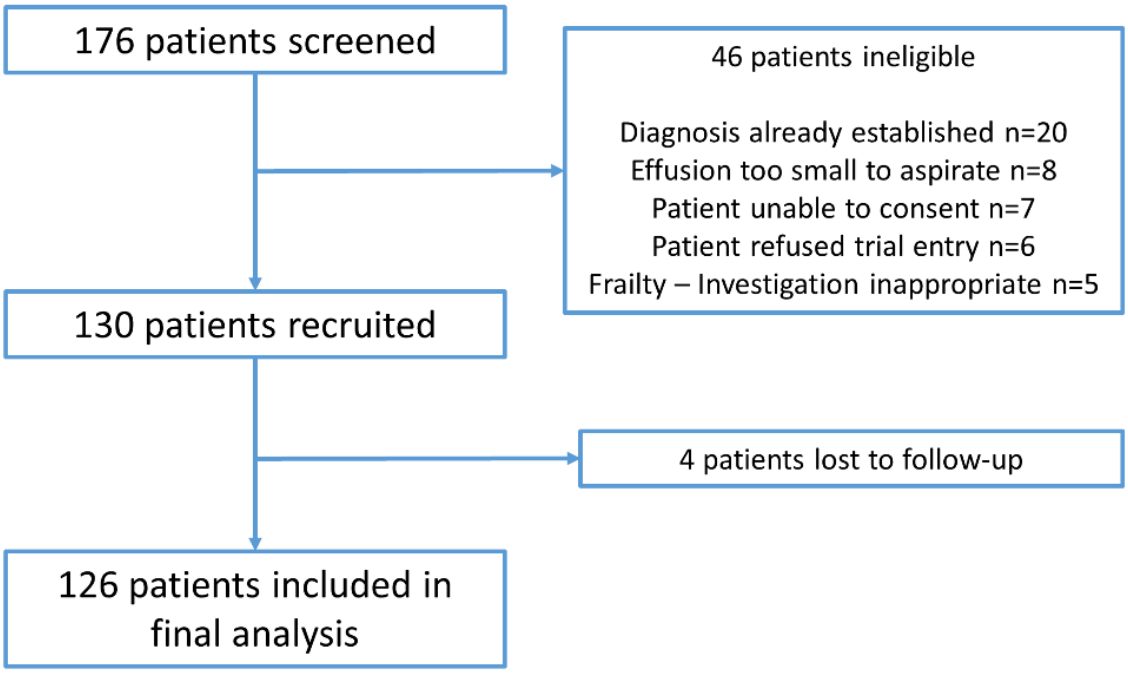

176 patients screened
46 patients ineligible
Diagnosis already established n=20
Effusion too small to aspirate n=8
Patient unable to consent n=7
Patient refused trial entry n=6
Frailty – Investigation inappropriate n=5
130 patients recruited
4 patients lost to follow-up
126 patients included in final analysis

Figure 2

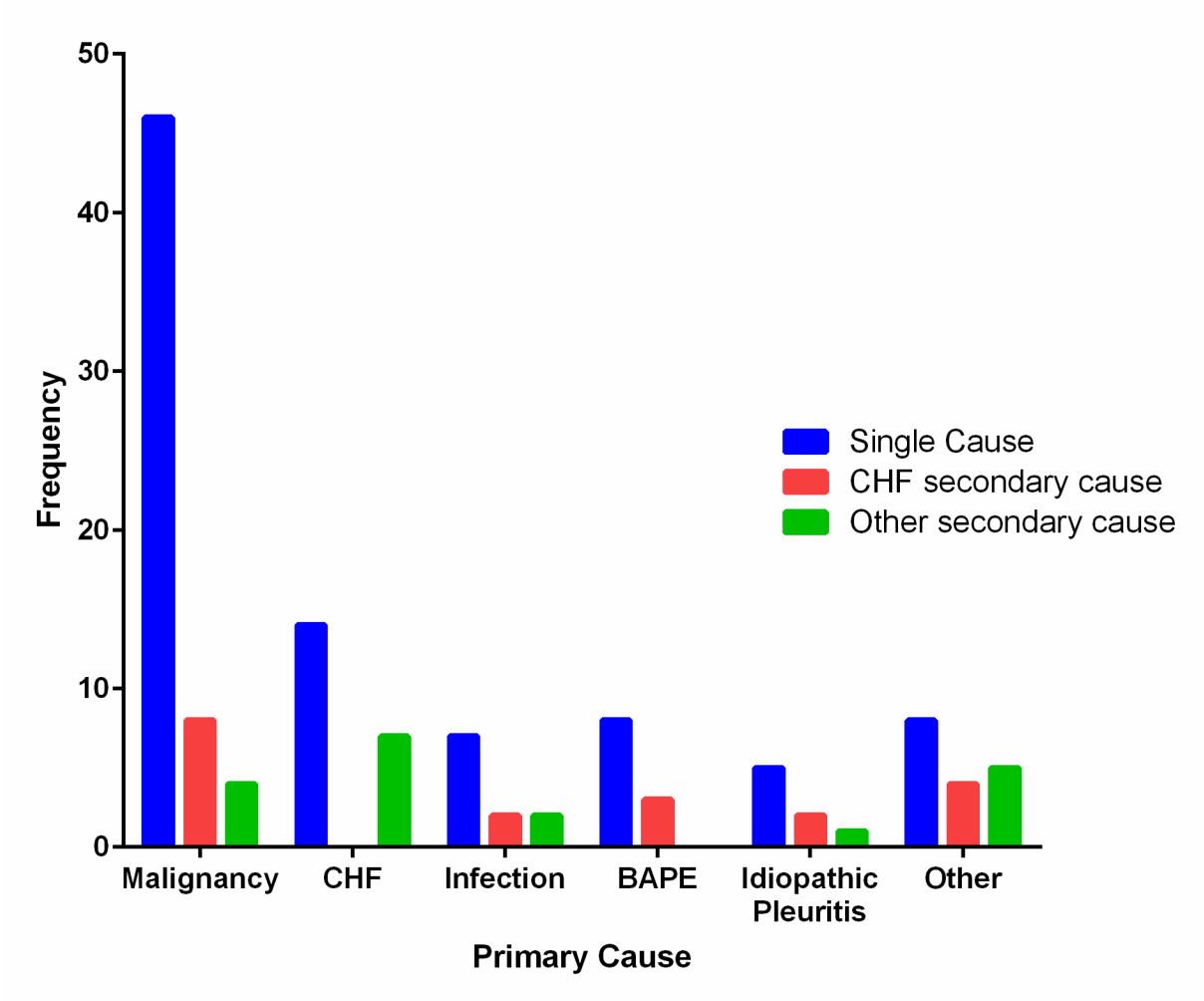
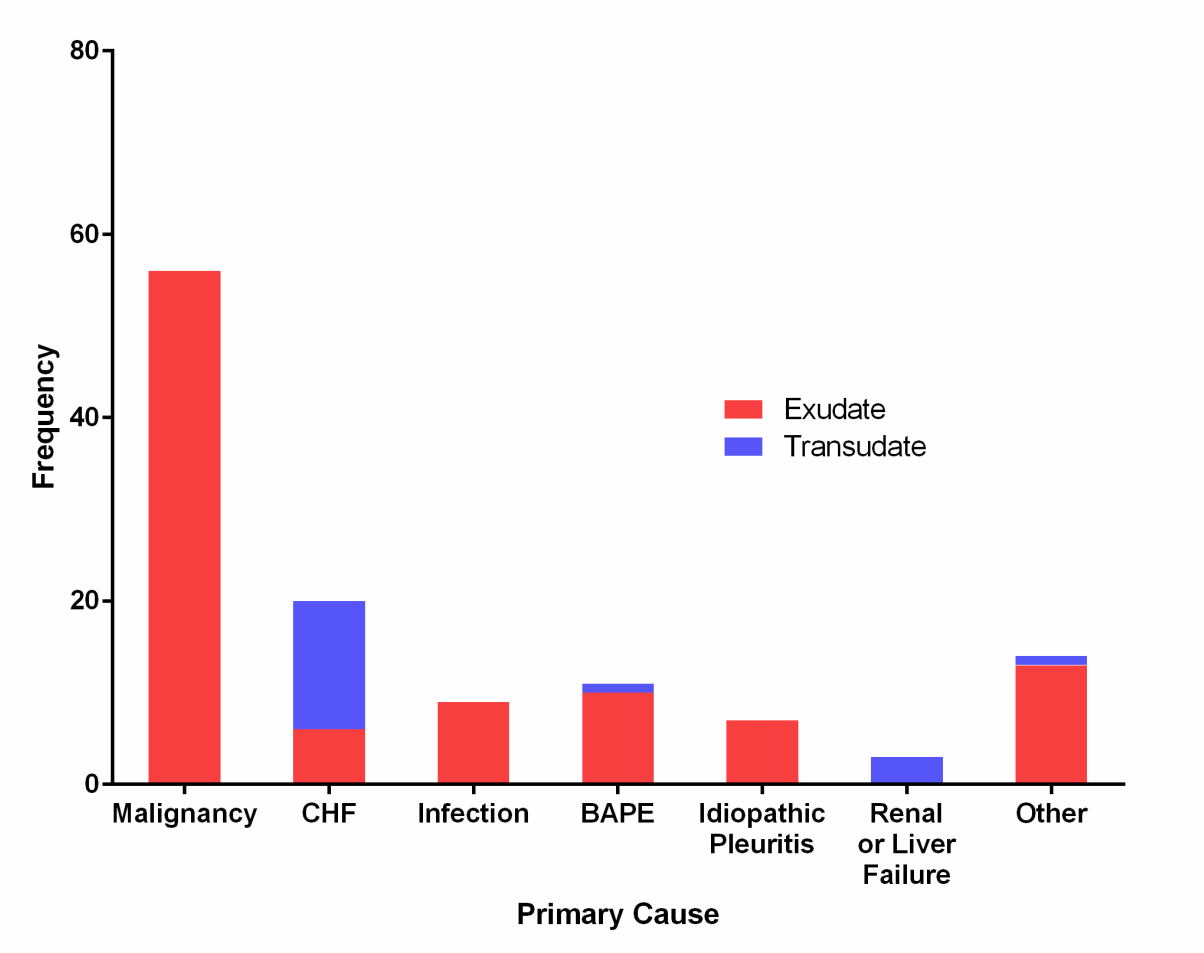

50
40
30
20
10
0
Frequency
Single Cause
CHF secondary cause
Other secondary cause
Malignancy
CHF
Infection
BAPE
Idiopathic Pleuritis
Other
Primary Cause

Figure 3


80
60
40
20
0
Frequency
Exudate
Transudate
Malignancy
CHF
Infection
BAPE
Idiopathic Pleuritis
Renal or Liver Failure
Other
Primary Cause