Pericardial Fluid Analysis in Diagnosis and Prognosis of Patients Undergoing Pericardiocentesis

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ABSTRACT

In this study we aim to examine the diagnostic yield of pericardial fluid biochemistry and cytology; and their prognostic significance in patients with percutaneously drained pericardial effusions, with and without malignancy. This is a single centre retrospective study of patients who underwent pericardiocentesis between 2010 and 2020. Data were extracted from electronic patient records including procedural information, underlying diagnosis and laboratory results. Patients were grouped into those with and without underlying malignancy. A Cox proportional hazards model was used to analyse association of variables with mortality. The study included 179 patients; 50% had underlying malignancy. There were no significant differences in pericardial fluid protein and LDH between the two groups. Diagnostic yield from pericardial fluid analysis was greater in the malignant group (32% Vs 11%, p=0.002); 72% of newly diagnosed malignancies had positive fluid cytology. 1-year survival was 86% and 33% in non-malignant and malignant groups respectively (p<0.001). Of 17 patients that died within the non-malignant group, idiopathic effusions were the largest group (n=6). In malignancy lower pericardial fluid protein and higher serum CRP were associated with increased risk of mortality. In conclusion pericardial fluid biochemistry has limited value in determining the aetiology of pericardial effusions; fluid cytology is the most important diagnostic test. Mortality in malignant pericardial effusions may be associated with lower pericardial fluid protein levels and a higher serum CRP. Non-malignant pericardial effusions do not have a benign prognosis and close follow-up is required.

Key words: pericardial fluid, pericardial effusion, pericardiocentesis

Pericardial effusions can be the manifestation of serious systemic pathology and the underlying diagnosis may be evident at the time of detection e.g. in the presence of active

auto-immune disease. However, the aetiology is frequently elusive and/or tamponade physiology is present requiring pericardiocentesis for diagnostic and therapeutic purposes. In developed countries malignancy is the most common sinister cause of pericardial effusions requiring pericardiocentesis, but other inflammatory and infective causes should always be sought to allow appropriate, potentially curative treatment [1–3]. When no cause is found, pericardial effusions are labelled idiopathic and frequently assumed to have a benign course [4].

Current guidelines recommend that pericardial fluid should be routinely sent for biochemical, microbiological and cytological examinations to help establish the cause [5]. Paired serum and pericardial fluid protein and lactate dehydrogenase (LDH) levels are examined to distinguish transudative from exudative effusions [5] but unlike cytology or microbiology which can conclusively expose the cause, this strategy is limited as it only narrows the differential diagnoses. Whether pericardial fluid biochemistry has a value in prognosis is not known[1,6].

The aim of this study was to examine the diagnostic yield of pericardial fluid biochemistry and cytology, and prognostic significance of pericardial fluid LDH and protein levels in patients with and without malignancy.

METHODS

This is a single centre retrospective study based at Barts Health NHS Trust (London, UK). All patients who underwent pericardiocentesis between February 2010 and July 2020 were considered. The patients were selected from an electronic database where all procedures carried out in the cardiac catheterization laboratories are prospectively recorded. Patients with iatrogenic pericardial effusions and those without available pericardial fluid LDH and

protein levels were excluded. Additional data were retrospectively collected via electronic chart review and recorded in a dedicated database (Microsoft Access). Data analysis was approved by Barts Health NHS Trust Clinical Effectiveness Unit as part as part of a local audit (ID: 11731). All authors have read and agree to the manuscript as written.

All patients underwent pericardiocentesis in a catheter laboratory at a tertiary cardiology centre. Prior to the procedure patients were clinically assessed by a physician and echocardiography was undertaken to assess effusion size and echocardiographic features of tamponade. Subcostal, apical and sub-xiphoid approaches were used depending on the anatomical distribution of the effusion. Fluoroscopic guidance (with/without additional echocardiographic imaging) was used for all procedures. Patients subsequently underwent repeat echocardiographic imaging to assess for re-accumulation, after an interval. Routine investigations to determine the underlying cause of pericardial effusion included blood tests (full blood count, creatinine, urea, electrolytes, c-reactive protein [CRP], total protein and LDH) and cross sectional imaging such as CT chest, abdomen and pelvis, in addition to echocardiography and pericardial fluid analysis. Other tests for specific causes such as TB, bacterial infection, autoimmunity were performed based on clinical suspicion.

Electronic patient records were reviewed and the following information was extracted: age, gender, procedural approach, procedural imaging mode, complications of procedure, need for repeat drain or pericardial window, size of the effusion, indication, urgency of procedure (emergency, urgent or elective cases), volume drained in the lab, pericardial drain duration, visual appearance of fluid, pre-procedural CRP, pericardial fluid protein and LDH, serum protein and LDH, pericardial fluid microbiology, pericardial fluid tuberculosis (TB) status, pericardial fluid cytology, initial diagnosis and final diagnosis was recorded. In the absence

of an alternative explanation, effusions were considered malignant if they occurred in the context of a pre-existing diagnosis or subsequent diagnosis of malignancy. An effusion was considered an exudate if effusion protein/serum protein >0.5, effusion LDH/serum LDH >0.6 or effusion LDH level >2/3 upper limit of laboratory reference range as per Light's criteria. The primary outcome was all-cause mortality at follow up and where death occurred, the date of death was recorded. The need for repeat pericardiocentesis and pericardial window procedures was also recorded.

Cardiac tamponade was used to describe patients with clear signs of circulatory compromise and echocardiographic features of cardiac tamponade in the presence of pericardial effusion. Impending cardiac tamponade was used to describe the presence of echocardiographic features of tamponade (swinging heart, respiratory variation >25% mitral E velocity and >40% tricuspid E velocity, diastolic right atrial or right ventricular collapse, inferior vena cava dilatation >20mm and <50% reduction of diameter in inspiration) in the absence of significant clinical signs of circulatory collapse. Emergency cases were defined as those with cardiac tamponade as described above, urgent for cases of impending tamponade and elective where neither clinical signs, nor echo features of cardiac tamponade were present.

From a diagnostic perspective a pericardial effusion was considered to malignant if this occurred in the context of a known or subsequent diagnosis of malignancy. Effusions secondary to pericarditis were defined as those occurring in the context of symptomatology of pericarditis and evidence of raised inflammatory markers without another clear underlying cause such as autoimmunity or infection. Myopericarditis was diagnosed with the addition of elevated cardiac biomarkers not explained by another underlying cause. Reactive or post/viral effusions were considered the cause when there was a clearly defined prodrome of viral

symptoms with or without supporting virological analysis. Idiopathic effusions were defined when none of these factors were present and no other cause was found with subsequent investigation and follow up.

Variables are expressed as mean ± standard deviation (SD), median (25^{th} to 75^{th} percentiles) or counts and percentages. Differences between means were compared using the Student t-test and Mann-Whitney U test for normally distributed and non-normally distributed continuous data respectively. Categorical data were compared using the Pearson Chi-squared test. A two-sided $p<0.05$ was considered statistically significant. Survival was examined using the Kaplan-Meir method. Association between biochemical characteristics and mortality was explored using Cox proportional hazards model with a multivariate analysis. Further multivariate adjustment to confirm associations was carried out using a stepwise backward multivariate model. All statistical analyses were carried out using R (version 1.3.1093).

RESULTS

During the study period 263 patients who underwent pericardiocentesis were initially identified, 27 patients were excluded with a clear iatrogenic aetiology and 57 patients were excluded as no pericardial fluid protein or LDH was measured. The study population included in the final analysis consisted of 179 patients with a median age 57.0 years (25^{th} centile: 42.4 years; 75^{th} centile: 69.3 years). Patients with malignancy had a similar age (median 60.0 years; 25^{th} centile 46.2 years; 75^{th} centile 68.1 years) to patients with non-malignant pericardial effusions (median 54.1years; 25^{th} centile 39.1 years; 75^{th} centile 71.8 years) at the time of the procedure ($p= 0.29$).

Most were urgent or emergency procedures and the primary indication was impending cardiac tamponade or cardiac tamponade, with a small subgroup of patients undergoing pericardiocentesis for diagnostic purposes or symptom relief. At the time of the procedure most effusions were large (>2cm) and were drained via the subcostal approach under fluoroscopic guidance. The volume drained during the initial procedure was similar in malignant and non-malignant groups (p= 0.76). The baseline characteristics are shown in table 1.

Malignancy was responsible in 49.7% (89/179) of patients and lung cancer was the most common malignancy accounting for nearly half (42/89) of all malignant effusions. In the non-malignant group 13.4% (24/89) had no clear cause of their effusion and were therefore classed as idiopathic. Pericarditis or myopericarditis was the most common non-malignant cause as shown in table 2.

The underlying cause of the effusion was provided by pericardial fluid analysis in 21.2% (38/179) of patients as shown in Figure 1. The yield of pericardial fluid analysis in establishing a novel diagnosis was higher in the malignant group (31.5 % Vs 11.1 %, p= 0.002). Cytology was the most conclusive diagnostic test; 36 patients were newly diagnosed with malignancy of which 72% (26/36) had positive pericardial fluid cytology; the remainder were diagnosed following cross-sectional imaging. Fifty-three patients had a diagnosis of underlying malignancy pre-procedure, 60% (32/53) of these patients had positive pericardial fluid cytology.

The pericardial fluid and serum characteristics in the malignant and non-malignant groups are shown in table 3. The majority of pericardial fluid samples were bloodstained and

characterized as exudates. Pericardial fluid protein and LDH levels were similar in both groups (p=0.99 and p=0.08 respectively). Serum LDH was higher in patients with malignancy (p=0.001) whilst serum protein levels appeared similar in both groups (p=0.05). Figures 2A and 2B show the distribution of pericardial fluid LDH and protein in the malignant and non-malignant groups. Figure 2C shows the scatter plot of pericardial fluid LDH against protein levels for each patient.

During the follow-up period (median 13 months) 80 deaths were observed with a 1-year survival of 62% (86% and 33% in the non-malignant and malignant group respectively). The overall median survival was 45.6 months. All-cause mortality and requirement for further procedures are shown in table 4. Figure 3A shows the Kaplan-Meier survival curve for all patients included in the analysis. Survival was significantly lower in the malignant group as shown in figure 3B ($p < 0.0001$). Of the 17 patients that died within the non-malignant group during the study period, idiopathic effusions made up the largest group (6/17). Other aetiologies in non-malignant deaths were parapneumonic (4/17), renal (2/17), bacterial infection (3/17) and heart failure (2/17). No patients with pericarditis/myopericarditis, reactive effusions, autoimmune disease or TB died.

Univariate analysis in the malignant group showed that a higher CRP was associated with increased mortality whilst a higher fluid protein was associated with lower mortality. Table 5 outlines the univariable Cox proportional hazards model analysing predictors of mortality in the malignant and non-malignant groups. The association of CRP and protein with survival were also confirmed on multivariate adjustment (see figure 4A and 4B). In the non-malignant group only increasing age was found to be associated with mortality in the univariate analysis but not in the backward selection multivariate model.

DISCUSSION

This study shows the limited diagnostic value of pericardial fluid biochemistry in determining the cause of the effusion. Pericardial fluid cytology combined with cross sectional imaging are the most important diagnostic tests to detect malignancy and, in this setting, a higher serum CRP and lower pericardial fluid protein level may be associated with increased mortality. Importantly, this study highlights that non-malignant pericardial effusions do not always have a benign prognosis.

Determining the aetiology of a pericardial effusion is challenging. The 2015 ESC guidelines on the diagnosis and management of pericardial disease recommend that paired pericardial fluid and serum protein and LDH levels are assessed to determine if the pericardial fluid is an exudate or a transudate [5]. However, our understanding of the normal biochemical composition of pericardial fluid is limited and there are no recognised reference ranges[7]. Light's criteria are often applied, but this practice is questionable as the criteria were developed for pleural fluid assessment and a recent study of physiological pericardial fluid found that most samples were classified as an exudate due to high physiological fluid protein and LDH [7,8]. Even though some studies have reported a higher fluid LDH content in malignant effusions, LDH levels lack the ability to accurately discriminate malignant and non-malignant effusions [6,8,9]. This study adds to the evidence highlighting the diagnostic limitations of pericardial fluid biochemistry, as the majority of both malignant and non-malignant effusions were exudates according to Light's criteria, without significant differences in fluid protein and LDH between the two groups. For diagnostic purposes imaging techniques such as cardiac magnetic resonance T1 mapping may be a useful alternative, non-invasive assessment tool to characterize pericardial effusions [10].

Cytological examination of pericardial fluid was the most important diagnostic test and provided a new diagnosis of malignancy in a large number of our patients. With adequate volumes of fluid (> 60 mL), cytology has a specificity nearing 100% and sensitivity of up to 90% [3,11–13]. Microbiological and TB culture are also helpful in identifying infective effusions, which although rarer, are important to identify to ensure appropriate therapy. Despite investigations, a significant subgroup of patients were labelled as having an idiopathic effusion indicating an unmet clinical need for improved diagnosis.

Malignant pericardial effusions are associated with poorer outcomes with a median survival generally reported as less than 6-12 months [2,6,14–18], but there are limited data on the association between pericardial fluid biochemistry and outcomes. Positive cytology for malignant cells, indicating a significant metastatic burden, has variously been associated with poor prognosis in previous studies [14,16,17]. To our knowledge the association between pericardial fluid protein or LDH and outcomes has not been previously examined. This study found that a lower pericardial fluid protein was associated with increased mortality in patients with malignant effusions. A similar association has been reported in pleural effusions related to non-small cell lung cancer but this relationship has not been consistently replicated [19–21] and the underlying biological mechanism is unclear. Higher serum CRP was associated with increased mortality in the malignant pericardial effusion group in keeping with studies of cancer patients who were included regardless of the presence of a pericardial effusion [22]. Prognostication based on pericardial fluid composition in patients with malignancy remains poorly understood and may be more accurately determined by a more global assessment of cancer spread in individual patients.

Underlying malignancy was present in nearly half of the patients in this cohort consistent with previous studies which reported a prevalence between 25% to 65% [1,2,6,18,23,24]. This variability can be explained by population demographics and different selection criteria (e.g. the current study excluded iatrogenic effusions thus increasing the prevalence of malignant effusions). Lung cancer is the most common malignancy, followed by haematological and breast malignancies [17]. Some malignancies may be specifically associated with pericardial involvement due to specific oncogenic mutations e.g. anaplastic lymphoma kinase in non-small cell lung cancer [25]. Radiotherapy used in lung, breast and haematological malignancies may also contribute to this pattern by causing radiation induced pericarditis[26].

Non-malignant pericardial effusions are associated with a range of underlying conditions. Idiopathic effusions are often assumed to be secondary to a viral infection (post-viral/reactive) with a benign prognosis [4]. However, of those that died in the non-malignant group, idiopathic effusions made up the largest cohort. It is possible that some of the patients with idiopathic effusions had significant underlying pathology which was not uncovered by initial investigations e.g pericardial effusion as the first manifestation of malignancy [27]. Some patients with idiopathic effusions may also have succumbed to an unrelated condition. The clinical implication of this finding is that patients with idiopathic effusions should be closely followed up and additional investigations should be considered. There is a need for a prospective study to confirm these findings and further establish cause of mortality in this group.

In non-malignant effusions half of patients with heart failure related effusions died, presumably because the presence of significant pericardial effusions requiring drainage represents those with more advanced disease. Renal patients fared somewhat better than heart

failure because of the availability of dialysis [28]. High mortality was observed in bacterial infection and parapneumonic effusions, which is reflected in the literature, with purulent pericardial disease holding significant mortality despite treatment [29]. Patients autoimmune disease and TB had a good prognosis which can be attributed to the availability of highly effective therapy.

Recurrence following pericardiocentesis can be a problem in both malignant and non-malignant effusions. Malignancy increases the risk of recurrence, with a reported prevalence of 9 – 33% [6,14,15,24,30]. In this cohort there was a trend towards increased repeat pericardiocentesis in the malignant group which was not statistically significant; rates of pericardial window were similar. Extended catheter drainage appears to significantly reduce this risk but there are no strict criteria on the optimal duration of drainage [14,17,30].

This study is based on a relatively small cohort of patients from a tertiary cardiology centre with the potential to introduce selection bias. There were no cases of traumatic and aortic dissection patients as at centre these patients are treated by cardiothoracic/trauma surgery. The use of T1 imaging at our centre to assess pericardial effusions [10] potentially reduced the number of patients with heart failure related pericardial effusions included in the study. Data regarding pericardial effusion onset and distribution (circumferential vs loculated) was not available and therefore not included in this study. In addition the results of pericardial fluid tumour markers and immunohistology analysis were not included in our database, however these assessments are more important for determining tumour subtypes and to guide oncological therapy rather than prognosis which was our primary focus here. It is important to note that in the malignant group a proportion of patients had negative cytology. As the sensitivity of pericardial fluid cytology can be limited, particularly if insufficient fluid is sent

for analysis, the authors felt that these patients were best included in the malignant group for analysis as they had an active malignancy and no clear alternate diagnosis for the cause of effusion.

CONCLUSIONS

This study shows that pericardial fluid biochemistry is of limited value in determining the cause of a pericardial effusion. Pericardial fluid cytology is the most important diagnostic test and adequate volumes of fluid should be sent for cytological analysis. We demonstrate for the first time that mortality in malignant pericardial effusions may be associated with lower pericardial fluid protein levels and a higher serum CRP. Non-malignant pericardial effusions do not have a benign prognosis and patients with idiopathic effusion should have additional investigations and close follow-up. Novel diagnostic tests for pericardial diseases need to be developed.

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Table 1: Baseline clinical characteristics			
	All patients	**Malignant**	**Non-malignant**
Patients	179 (100%)	89 (50%)	90 (50%)
Male	98 (55%)	52 (58%)	46 (51%)
Volume drained (mL)	*760 (560 - 1000)*	750 (600 – 1000)	800 (500 – 1000)
Drain duration (hrs)	*20 (0-39)*	17 (0-26)	23 (7 – 48)
Age (years) at time of procedure			
18-39	40 (22%)	16 (18%)	24 (27%)
40-54	39 (22%)	18 (20%)	21 (23%)
55-69	55 (31%)	36 (40%)	19 (21%)
≥70	45 (25%)	19 (21%)	26 (29%)
Urgency			
Emergency	49 (27%)	27 (30%)	22 (24%)
Urgent	118 (66%)	58 (65%)	60 (67%)
Elective	12 (7%)	4 (5%)	8 (9%)
Size of effusion n (%)			
Small	0	0	0
Moderate	18 (10%)	9 (10%)	9 (10%)
Large	158 (88%)	79 (89%)	79 (88%)
Not stated	3 (2%)	1 (1%)	2 (2%)
Indication n (%)			
Tamponade	49 (27%)	27 (30%)	22 (24%)
Impending tamponade	102 (57%)	54 (61%)	48 (53%)
Symptoms/Diagnosis	28 (16%)	8 (9%)	20 (22%)
Access n= (%)			
Subcostal	*162 (91%)*	80 (90%)	82 (91%)
Apical	*14 (8%)*	6 (7%)	8 (9%)

Parasternal	*1 (1%)*	1 (1%)	0
Unknown	*2 (1%)*	2 (2%)	0
Imaging n= (%)			
Fluoroscopic only	*37 (21%)*	17 (19%)	20 (22%)
TTE	*26 (15%)*	12 (14%)	14 (16%)
Both	*116 (64%)*	60 (67%)	56 (62%)

Variables are expressed as mean ± standard deviation (SD), median (25^{th} to 75^{th} centile) or counts and percentages as appropriate.

TTE: transthoracic echocardiogram

Table 2: Causes of pericardial effusions			
Malignancy n=89	**n (%)**	**Non-malignant n=90**	**n (%)**
Lung	42 (24%)	Idiopathic	24 (13%)
Haematological	14 (8%)	Pericarditis/myopericarditis	15 (8%)
Breast	10 (6%)	Reactive/Post-viral	11 (6%)
Unknown primary	8 (5%)	Parapneumonic	11 (6%)
Gastrointestinal	7 (4%)	Renal failure	8 (5%)
Gynaecological	3 (2%)	Bacterial infection	7 (4%)
Sarcoma	2 (1%)	Tuberculosis	6 (3%)
Thymic	2 (1%)	Heart failure	4 (2%)
Germ cell	1 (1%)	Autoimmune disease	4 (2%)

Table 3: Pericardial fluid and serum biochemical characteristics			
	All patients	**Malignant**	**Non-malignant**
Pericardial Fluid			
Exudate	172 (96%)	85 (96%)	87 (97%)
Bloodstained	134 (75%)	70 (79%)	64 (71%)
Serous	38 (21%)	17 (19%)	21 (23%)
Turbid	8 (5%)	3 (3%)	5 (6%)
Chylous	1 (1%)	0 (0)	1 (1%)
Cytology positive	58 (32%)	58 (65%)	0
Microbiology positive	6 (3%)	2 (2%)	4 (4%)
TB positive	3 (2%)	0	3 (3%)
LDH (U/L)	1160 (463-2030)	1427 (540-2812)	1068 (435-1800)
Protein (g/L)	51.4 (+/- 11.2)	51.6 (+/- 11.9)	51.5 (+/- 10.7)
Serum			
CRP (mg/L)	67.5 (25.5 – 119.3)	65.0 (27.0 – 105.0)	69.0 (29.5 – 140.5)
LDH (U/L)	496 (324 – 792)	622 (471 – 1160)	417 (310 – 559)
Protein (g/L)	63.9 (+/- 8.6)	62.6 (+/- 8.3)	65.2 (+/- 8.7)
Pericardial fluid to serum ratios			
LDH	1.9 (1.0 – 4.0)	1.7 (0.9 – 3.4)	2.6 (1.0 – 4.1)
Protein	0.8 (+/- 0.2)	0.8 (+/- 0.2)	0.8 (+/- 0.2)
Median protein ratio (IQ range)	0.8 (0.7 – 0.9)	0.8 (0.7 – 0.9)	0.8 (0.7 – 0.9)

Variables are expressed as mean ± standard deviation (SD), median (25^{th} to 75^{th} centile) or counts and percentages as appropriate.

TB: tuberculosis; LDH: lactate dehydrogenase; U/L: units per liter; g/L: grams per liter; CRP: c-reactive protein; mg/L: milligrams per liter; IQ: interquartile

Table 4: Outcomes			
	All patients	**Malignant**	**Non-malignant**
Repeat pericardiocentesis	12 (7%)	9 (10%)	3 (3%)
Pericardial window	36 (20%)	19 (21%)	17 (19%)
Alive at follow up	99 (55%)	26 (29%)	73 (81%)
Death	80 (45%)	63 (71%)	17 (19%)

Table 5: Predictors of mortality – exploratory univariable analysis								
	Malignant				Non-malignant			
Variable	**Hazard ratio**	**Lower 95% CI**	**Upper 95% CI**	**P value**	**Hazard ratio**	**Lower 95% CI**	**Upper 95% CI**	**P value**
Age	1.013	0.998	1.03	0.098	1.035	1.007	1.064	0.0136*
Male sex	1.296	0.778	2.157	0.319	1.37	0.521	3.607	0.522
Fluid LDH (U/L)	1	1	1	0.468	1	0.999	1	0.898
Fluid protein (g/L)	0.969	0.947	0.992	0.009*	0.983	0.935	1.033	0.494
Fluid:serum LDH ratio	0.961	0.878	1.053	0.396	1.024	0.708	1.481	0.901
Fluid:serum protein ratio	0.240	0.049	1.164	0.077	1.234	0.015	102.8	0.926
Bloodstained effusion	1.219	0.660	2.253	0.525	0.873	0.321	2.371	0.789
Lights criteria positive	0.716	0.259	1.976	0.52	0.418	0.055	3.189	0.4
CRP (mg/L)	1.004	1.001	1.007	0.012*	1.0001	0.995	1.005	0.963
Fluid cytology positive	1.160	0.661	2.035	0.605	-	-	-	-
Pre-procedure known malignancy	1.268	0.753	2.136	0.372	-	-	-	-

*significant ($p<0.05$)

CI: confidence interval; LDH: lactate dehydrogenase; U/L: units per liter; g/L: grams per liter; CRP: c-reactive protein; mg/L: milligrams per liter.

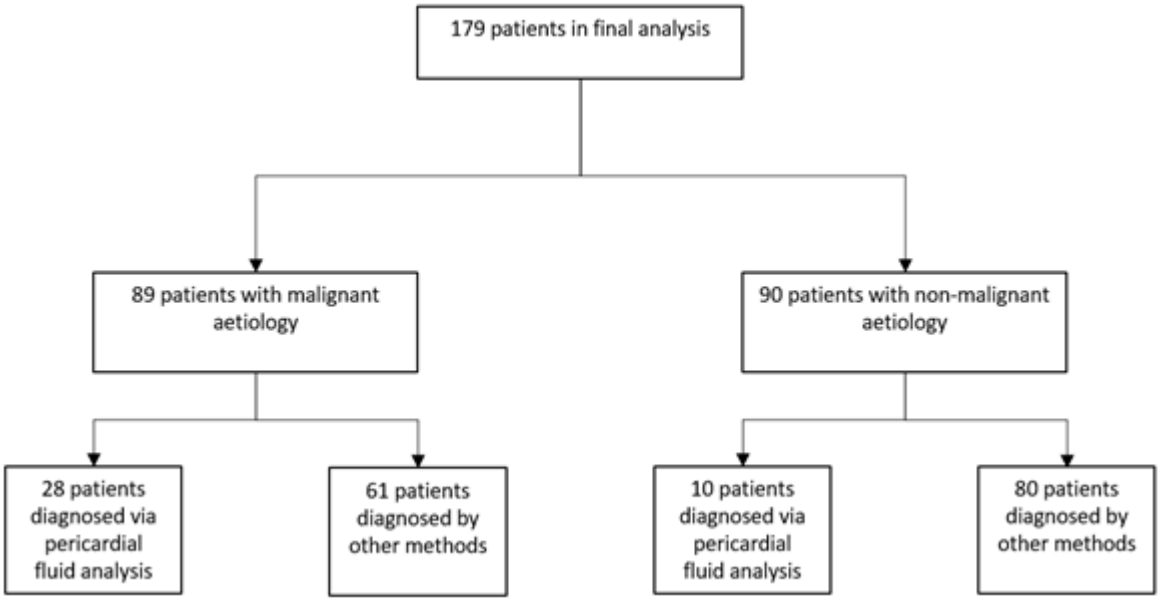

Figure 1. Diagnostic value of pericardial fluid analysis. Flow diagram exhibiting the mode of diagnosis for underlying aetiology of pericardial effusions in malignant and non-malignant groups. Significantly more patients in the malignant group received a diagnosis via pericardial fluid analysis ($p = 0.002$).

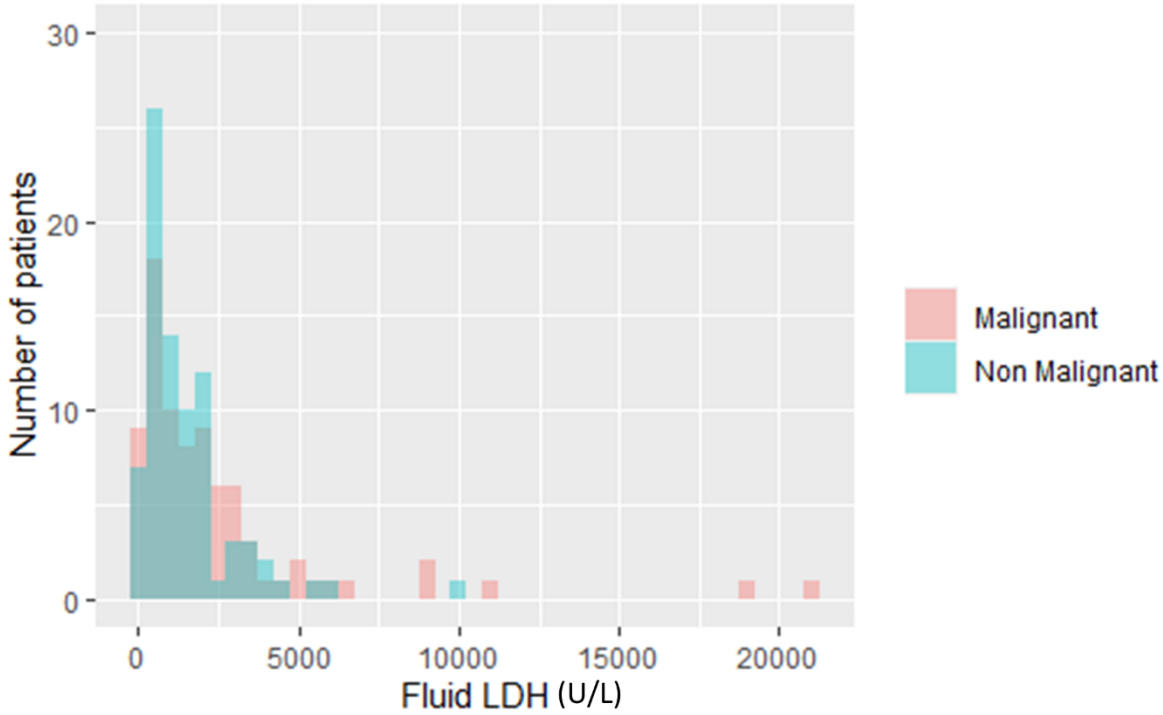

Figure 2A: Pericardial fluid LDH levels. Histogram of pericardial fluid LDH levels in malignant and non-malignant groups. There was no significant difference in pericardial fluid LDH between the two groups (p = 0.082). Fluid LDH was measured in 81/89 in the malignant group and 82/90 in the non-malignant group. (LDH: lactate dehydrogenase).

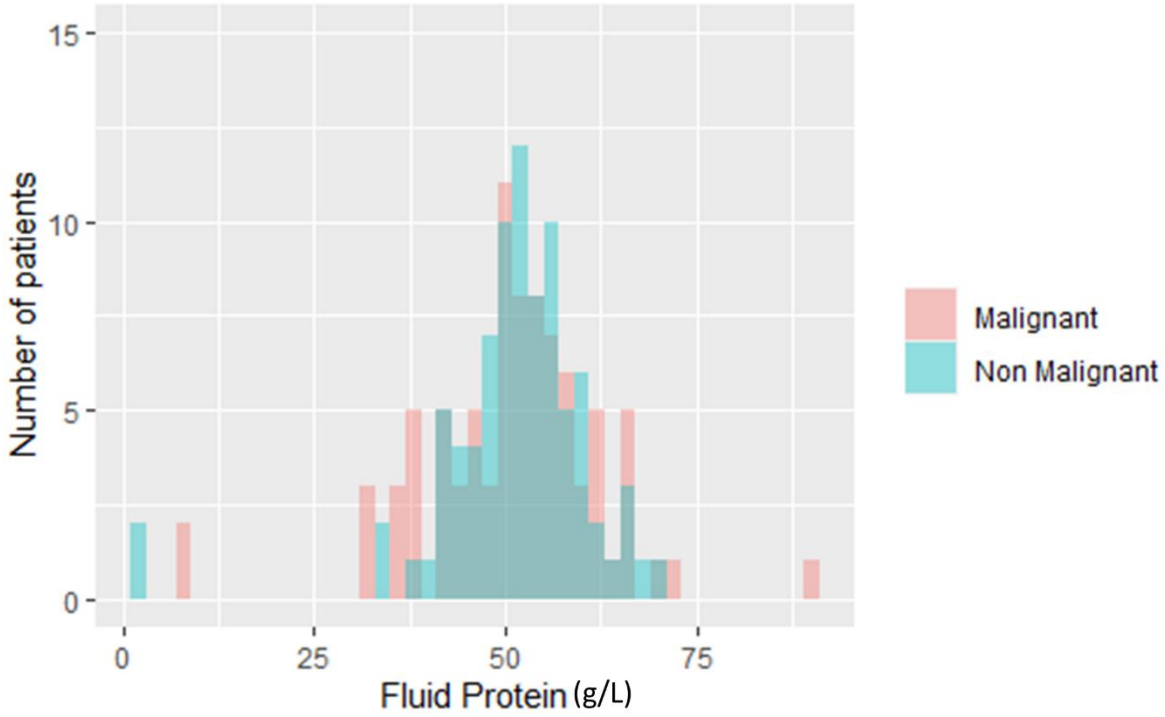

Figure 2B. Pericardial fluid protein levels. Histogram of pericardial fluid protein levels in malignant and non-malignant groups. There was no significant difference in pericardial fluid protein between the two groups (p = 0.992) Fluid protein was measured in 86/89 of patients in the malignant group and 85/90 patients in the non-malignant group.

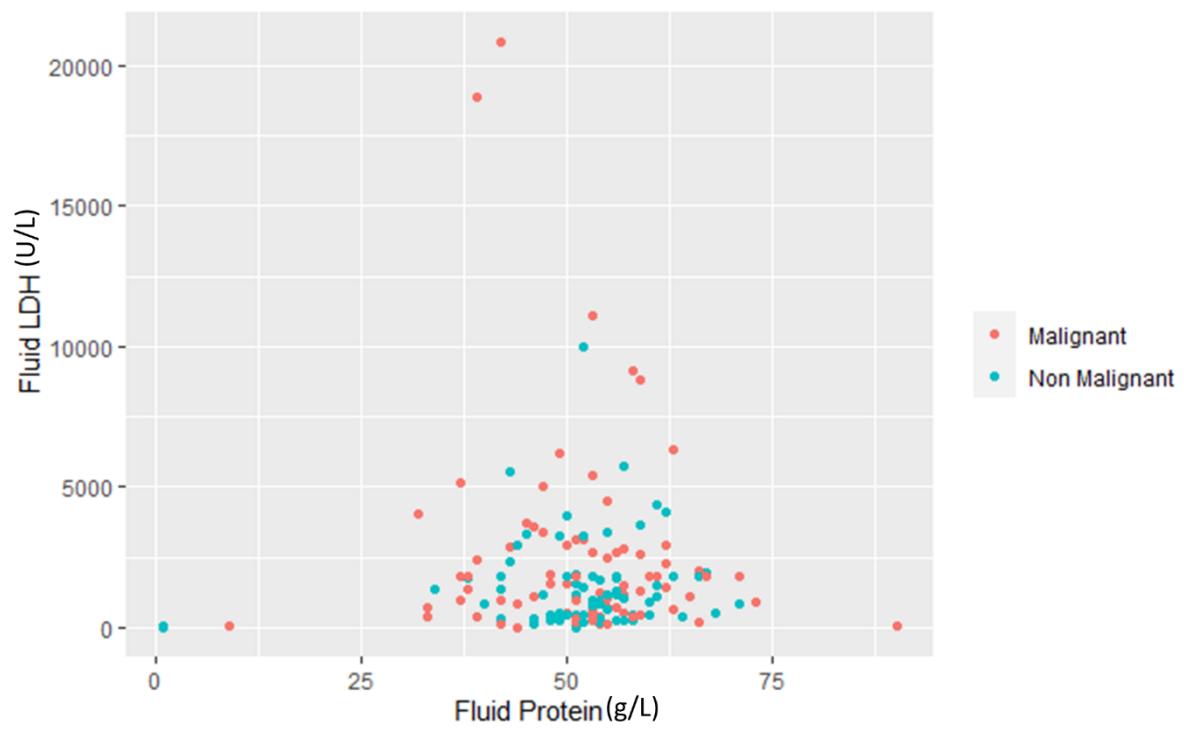

Figure 2C: Pericardial fluid protein and LDH levels in malignant and non-malignant groups. Scatter plot of pericardial fluid protein and LDH levels in malignant and non-malignant groups. (LDH: lactate dehydrogenase).

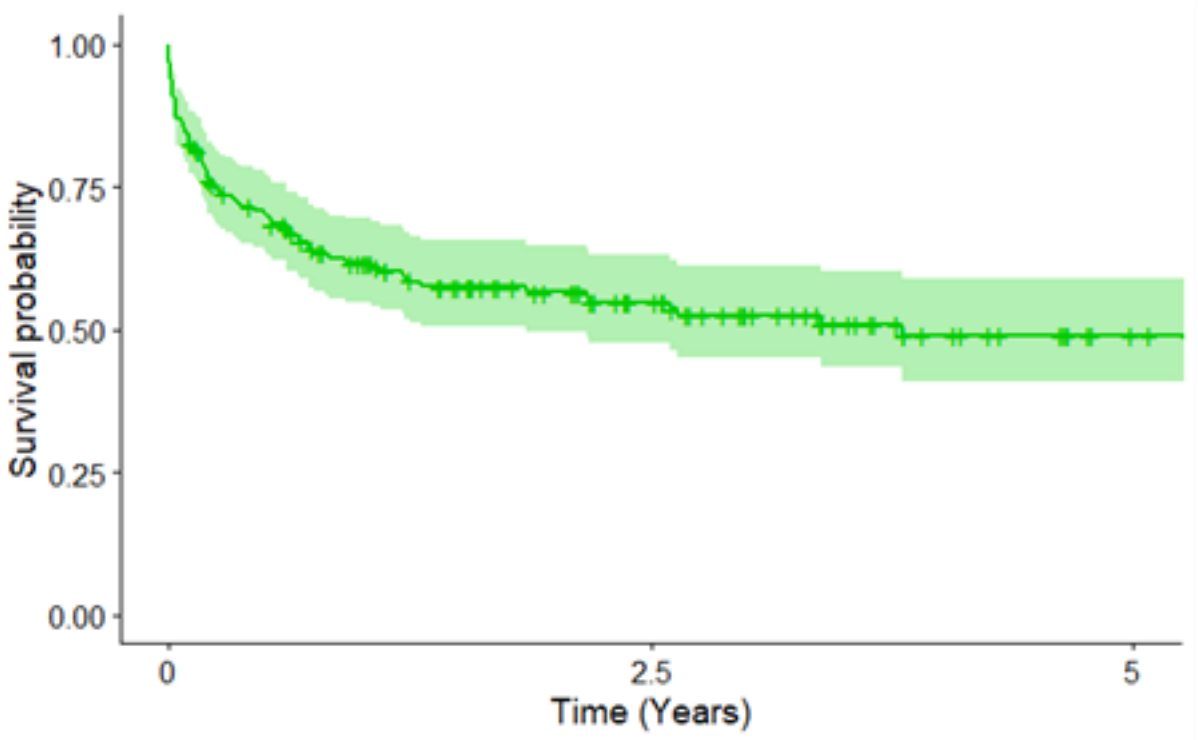

Figure 3A: Kaplan-Meier 5-year survival curve (all patients).

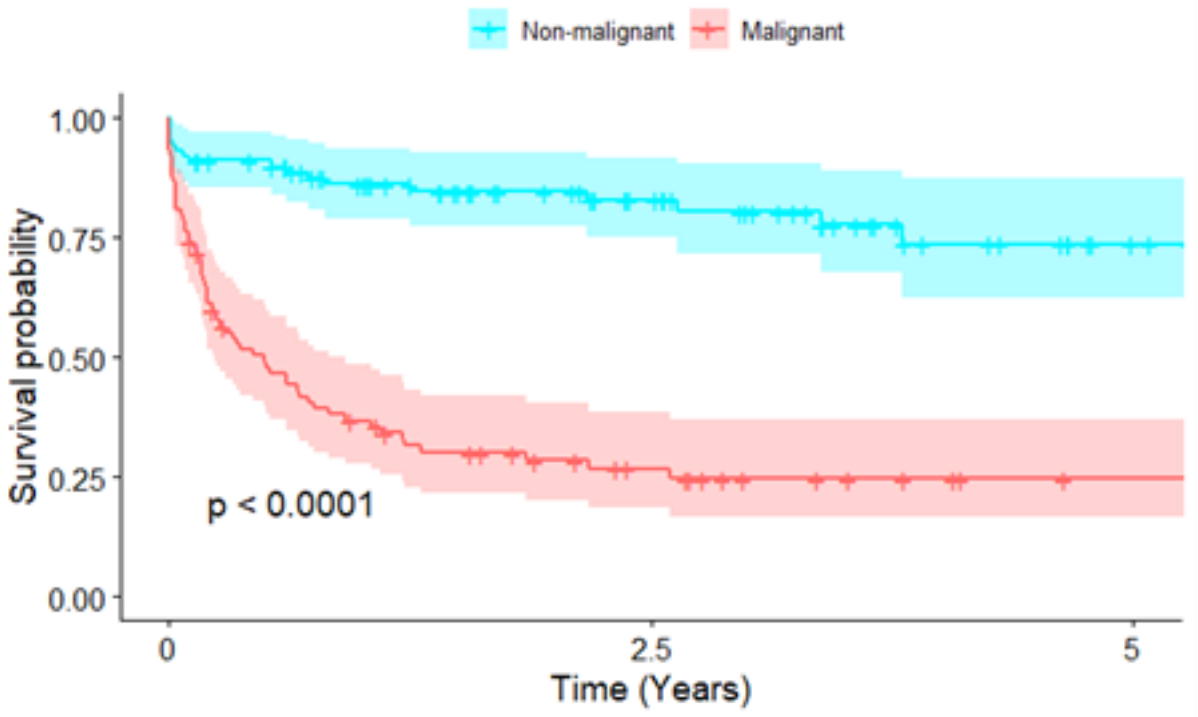

Figure 3B: Kaplan-Meier 5-year survival curve (malignant vs non-malignant)

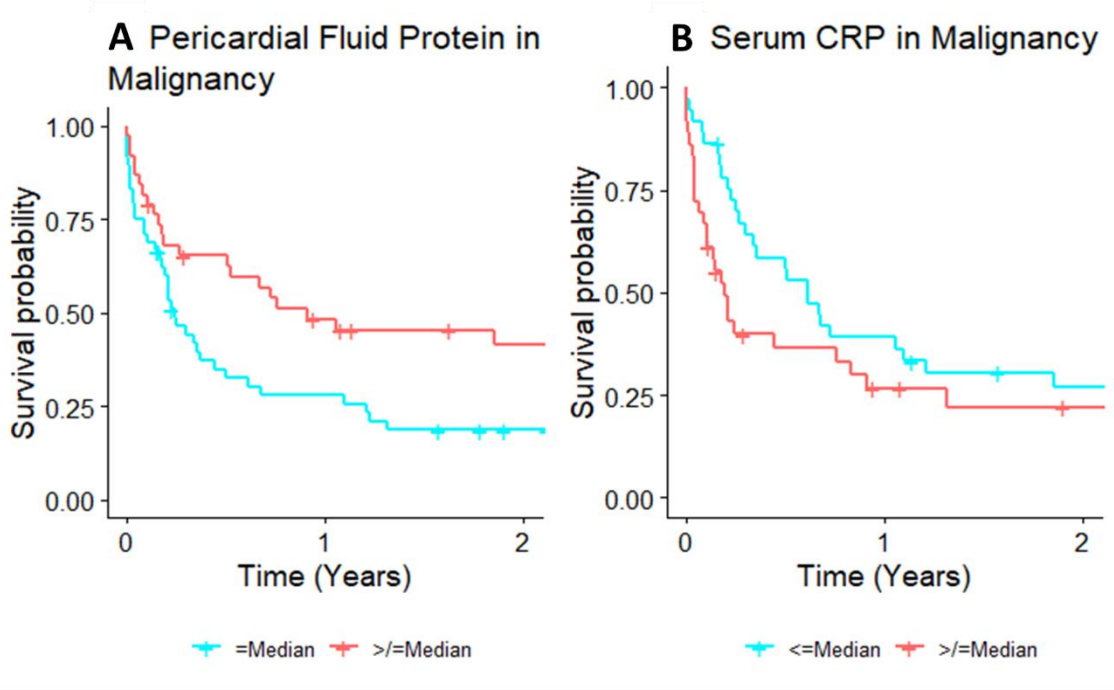

Figure 4: Association of pericardial fluid protein and serum CRP with survival in malignancy. Split-median 2-year Kaplan-Meier curve demonstrating the association of pericardial fluid protein and serum CRP with survival in malignancy. Lower pericardial fluid protein and higher serum CRP was associated with increased mortality. Median protein = 53 g/L. Median CRP = 65 mg/L. (CRP: c-reactive protein).