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Predictors of Clinical Use of Pleurodesis and/or Indwelling Pleural Catheter Therapy for Malignant Pleural Effusion

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BACKGROUND: The clinical course of patients with malignant pleural effusions (MPEs) varies. The decision to undertake "definitive therapy" (pleurodesis, indwelling pleural catheter [IPC], or both) for MPEs is decided on a case-by-case basis. Identifying factors that predict definitive therapy may help guide early initiation of treatment. The aim of the study was to identify clinical, laboratory, and radiologic predictors associated with clinicians' prescription of definitive therapy for patients with MPE.

METHODS: A multicenter, observational study was conducted over 55 months involving tertiary centers in Perth, Western Australia, Australia, and Lleida, Spain. Demographic, clinical, radiologic, biochemical, and histologic data and the treatments received were recorded. Logistic regression was performed to determine the variables useful for predicting definitive therapy.

RESULTS: Data of 540 patients (365 from Perth and 184 from Lleida) were analyzed; 537 fulfilled the criteria of an MPE. Definitive therapy was used in 288 patients (53.6%): 199 received a pleurodesis and 89 an IPC. Univariate analysis of the combined cohort revealed that definitive therapy was more likely if the effusion has low pH, either as a continuous variable (OR, 30.30; $P < .01$) or with a pH cutoff of < 7.2 (OR, 2.09; $P = .03$); was large ($> 50\%$ of hemithorax) (OR, 2.75; $P < .01$); or was associated with mesothelioma (OR, 1.83; $P < .01$). Following multivariate analysis, low pleural pH (OR, 37.04; $P < .01$), large effusions (OR, 3.31; $P < .01$), and increasing age (OR 1.02, $P = .01$) were associated with the use of definitive therapy.

CONCLUSIONS: Patients with MPE with an effusion of low pleural fluid pH and large size on radiographs at first presentation are more likely to be treated with pleurodesis and/or IPC.

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ABBREVIATIONS: IPC = indwelling pleural catheter; MPE = malignant pleural effusion

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Malignant pleural effusions (MPEs) are common and affect as many as 15% of patients with cancer.[1] MPEs cause considerable symptoms, especially breathlessness, and morbidity. Many patients require inpatient and/or outpatient pleural procedures for fluid evacuation for symptom relief, with significant associated health-care costs.

The rate of recurrence of MPE is very variable, with some patients never requiring any fluid removal, to those needing frequent (even daily) drainages.[2] For patients whose effusion recurs slowly or whose life expectancy is limited, simple thoracentesis is recommended. However, "definitive therapy" is recommended for those who would otherwise require frequent pleural drainages to control their symptoms.

Pleurodesis (usually using talc) and placement of a tunneled indwelling pleural catheter (IPC) are the most commonly used definitive therapy for MPE.[3-7] The principles of both treatments are the same: to minimize pleural interventions and the associated costs, discomfort, and risks of procedural complications in patients with MPE who often have a limited lifespan. Pleurodesis is the conventional method to obliterate the pleural cavity and prevent fluid accumulation. IPCs facilitate fluid drainage and provide symptom control in an ambulatory setting. Both pleurodesis and IPCs offer comparable improvement in symptom and quality-of-life measurements when used as first-line management of MPE.[3,4] Nonetheless, pleurodesis and IPCs carry their own costs and risks, and should only be used in patients whose effusions recur and cause symptoms.

At the time of diagnosis, identifying which of the patients with MPE will need definitive therapy and distinguishing them from those in whom observation and/or simple thoracentesis would suffice is notoriously difficult. Delay in definitive therapy can expose the patient with recurrent MPEs to prolonged symptoms, extra drainage interventions, and cumulative procedural complication risks. On the other hand, a blanket strategy of early definitive therapy at diagnosis for all patients with MPE will mean subjecting many to unnecessary interventions.

No studies have specifically examined predictors of need for definitive therapy at the time of diagnosis to guide clinical care. As such, physicians often treat patients on a case-by-case basis. In this study, we interrogated databases of patients with MPE to identify those offered definitive therapy by their attending clinicians. We aim to identify predictors that are associated with the eventual need of definitive therapy. This can potentially allow early selection of suitable patients and avoid repeated pleural procedures. Examining the identified predictors may also provide insight into the biology of the clinical course of MPE.

Materials and Methods

Data from the MPE databases at Sir Charles Gairdner Hospital (which also include patients from Fremantle and Royal Perth Hospitals, Perth, Western Australia, Australia) and at University Hospital Arnau de Villanova (Lleida, Spain) were interrogated. Respective local ethics committees have approved longitudinal studies on the clinical outcomes of MPE; all patients gave informed consent. Data of patients presenting with an MPE were prospectively collected.

Clinical, pathologic, radiologic, and biochemical variables of interest in predicting the need for intervention in patients with MPE were determined a priori (Table 1). These data were recorded in each local database at the time of diagnosis of MPE from August 2009 to July 2013 in Western Australia and between December 2007 and April 2012 for the Spain cohort. Size of effusion was graded on the initial preprocedure chest radiograph using a previously described system[5]: grade 0 referred to no radiographic evidence of pleural fluid; grade 1 = blunting of the costophrenic angle; grade 2 to 5 referred to fluid occupying $<$ 25%, 25% to 50%, 51% to 75%, and $>$ 75% of the hemithorax, respectively.

Patients were diagnosed as having an MPE if they had (1) histologic or cytologic confirmation or both of malignant cells from pleural tissue biopsy or pleural fluid cytology or (2) an exudative pleural effusion by Light's criteria[6] in the setting of histocytologically proven extrapleural malignancy with no obvious alternative diagnosis of their effusion. The latter mainly referred to individuals who were too frail for or declined further invasive testing.

Patients were followed until death (n = 426, 78.9%) or for a minimum of 6 months. Pleural interventions were recorded prospectively.

Comorbidity was recorded. Pleural effusion was considered loculated if there was evidence of septations on ultrasonography or if drainage was incomplete and the remaining fluid did not collect as expected according to gravity on postprocedure radiography. Nonexpandable lung referred to radiographic evidence that the lung had not fully reexpanded following evacuation of the pleural effusion. Renal failure was defined as an estimated glomerular filtration rate of $<$ 50 mL/min. Significant ischemic heart disease was defined by prior myocardial infarction, coronary artery intervention (balloon angioplasty, stent placement, and/or bypass surgery), or both. Left ventricular failure was defined by echocardiographic findings of moderate or severe left ventricular failure. Patient's home location was classed as metropolitan if they lived within a defined metropolitan area according to the local government definition. COPD and asthma were defined according to the World Health Organization (WHO) definition of these diseases, and patients had to be currently receiving inhaled or other therapy for these conditions.

Predefined variables from the data of Western Australia and Lleida were analyzed separately using univariate and multivariate logistic regression. Then, a combined analysis of all variables with data that were $>$ 90% complete and the pleural pH was performed. Pleural pH was included despite being only 74% complete because of its very strong statistical significance in all the univariate analyses compared with the other variables as well as its clinical and biologic importance. Univariate and multivariate binary logistic regressions were conducted on the combined cohort. Two multivariate analyses were performed; the first included pleural pH as a continuous variable and the second used a pH cutoff of 7.2. Variables that were significant at a 5% significance level were retained in the final models. Adjusted ORs and 95% CIs were calculated for the final models. Data were analyzed using R: a language and environment for statistical computing.[7]