Journal of Clinical Laboratory Analysis 22:334–336 (2008)

# Pleural Fluid Findings as Prognostic Factors for Malignant Pleural Mesothelioma

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The aim of this study was to determine the prognostic value of pleural fluid glucose, lactate dehydrogenase (LDH), albumin, total protein, and total leukocyte levels in patients with malignant pleural mesothelioma. We retrospectively analyzed 71 consecutive patients (33 men and 38 women) who were referred to the department of chest diseases in a university hospital. Pleural fluid glucose levels, the ratio of pleural fluid to serum LDH $>$ 1.0, and total leukocyte count were significant predictors for the survival in univariate analysis. However, none of these variables emerged as statistically significant from the multivariate Cox model. In conclusion, our results showed that there is an inverse correlation between the intensity of inflammation and survival. J. Clin. Lab. Anal. 22:334–336, 2008. © 2008 Wiley-Liss, Inc.

**Key words:** pleural neoplasms; prognosis; survival analysis; malignant pleural effusion

## INTRODUCTION

Malignant pleural mesothelioma (MPM) is an aggressive tumor for which there is no satisfactory treatment available to date. The identification of prognostic factors is particularly important in MPM, a malignancy whose clinical behavior and biology are poorly understood. To our knowledge, there is only one article that investigates the pleural fluid characteristics on the prognosis of MPM (1), however, this study consisted of only 26 patients. We aimed to determine the role of pleural fluid parameters on patient survival in the present article.

## MATERIALS AND METHODS

Patients referred to our institution between January 1993 and January 2006 with a histologically (90%) or cytologically confirmed diagnosis of MPM were reviewed. In our pathology department, we routinely used an immunohistochemical panel, generally composed of antibodies directed against calretinin, epithelial membrane antigen (EMA), thrombomodulin, HBME-1, CD15, B72.3, or carcinoembryonic antigen (CEA). Histological subtype was defined as epithelial, sarcomatoid, or mixed types according to the WHO classification of MPM (2). The medical records of all patients with pleural fluid analysis were included for the study. The following factors were collected by retrospective chart review: age, gender, smoking history, previous diuretic usage, side of disease, diagnostic procedure, values of pleural fluid glucose, lactate dehydrogenase (LDH), albumin, total protein with comparisons to serum levels, and pleural fluid leukocyte counts. The total fluid leukocyte count was performed with the use of a manual cell counter (THOMA cell). Biochemical measurements were made on pleural fluid sent to the central biochemistry laboratory. Radiographic, clinical, or laboratory evidence for a primary nonpleural malignancy was not found in all patients.

Survival was defined as the period between the date of thoracentesis and the date of death or last contact if the patient had not died at the time of analysis. Statistical analyses were performed using SPSS 10.0 software (SPSS, Chicago, IL). General data are presented as median $\pm$ SE. Survival (Kaplan–Meier) data are presented as median survival in months. Comparisons of survival were done using the log-rank test to evaluate equality of Kaplan–Meier survival distributions. All

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Received 3 April 2008; Accepted 16 May 2008
DOI 10.1002/jcla.20266
Published online in Wiley InterScience (www.interscience.wiley.com).

parameters were analyzed as categorical variables. The independent value of variables was assessed in multivariate analysis using the Cox proportional hazards regression model, with an estimate of hazard ratios and 95% confidence intervals. Differences were considered significant with a $P$ value $<0.05$.

## RESULTS

The mean ($\pm$SD) age of 33 males and 38 females was $59.3 \pm 12.8$ (range 25–85) years. Twenty-three patients (32%) were smokers. The disease was right-sided in 31 patients (44%); and no bilateral case was found. Sixteen patients (22.5%) had cardiovascular diseases (13 hypertension, 2 coronary artery disease, 1 both). Consequently, they use diuretics or angiotensin-converting enzyme inhibitors containing a diuretic. All effusions except one were exudates by Light criteria (3). The mean ($\pm$SD) leukocyte count was $643 \pm 860/mm^3$. The diagnosis was established by pleural fluid cytologic studies in 7 patients, closed pleural biopsy in 48 patients, thoracotomy in 10 patients, transthoracic biopsy in 4 patients, thoracoscopy in 1 patient, and skin biopsy in 1 patient.

At the time of analysis, all patients were deceased. In the entire group, pleural fluid findings and survival from time of initial thoracentesis are shown in Table 1. Kaplan–Meier test showed that only the ratio of pleural fluid to serum LDH $>1.0$, and total leukocyte count was significant predictors for survival. When the patients who used diuretics were excluded, fluid glucose levels gained a borderline significance (Table 2). However, none of these variables emerged as statistically significant from the multivariate Cox model.

## DISCUSSION

In 1988, Sahn and Good (4) demonstrated the prognostic importance of pleural fluid pH and survival in patients with malignant pleural effusions. Mean survival was only 2 months if the pleural fluid pH was $<7.30$, whereas mean survival was 10 months if the pleural fluid pH was7.30. Within a few years, other studies also demonstrated the importance of pleural fluid pH and pleural fluid glucose on the survival time (5,6). However, patients with MPM were not included in these studies. Some years later, retrospective (7) and prospective (8) studies have not found a significant effect of pleural fluid analysis on the survival of patients with malignant pleural effusion although they contain seven (7) and ten (8) patients with MPM. However, this study shows that low fluid glucose levels are significant predictors of survival time of the patients with MPM.

Pleural fluid LDH may reflect the degree of pleural inflammation similar to the fluid leukocyte count (9). We found that the ratio of pleural fluid to serum LDH $>1.0$, and total leukocyte count $>700/mm^3$ in the fluid were significant predictors for survival. Moreover, our results strongly suggest that there is an inverse correlation between the intensity of inflammation and

**TABLE 1. Prognostic Parameters as Predictors for Disease-Specific Survival (Median $\pm$ SE)**

| Variables | Status/survival (months)/number of patients | | $P$ level |
|---|---|---|---|
| PF glucose (mg/dL) | $<60/7.0 \pm 1.2/22$ | $\geq 60/8.0 \pm 1.9/41$ | 0.22 |
| PF/S LDH | $\leq 1.0/6.0 \pm 1.1/10$ | $>1.0/8.0 \pm 1.4/52$ | 0.04 |
| PF/S albumin | $\leq 0.70/7.0 \pm 0.8/30$ | $>0.70/9.0 \pm 3.6/34$ | 0.73 |
| PF/S total protein | $\leq 0.70/7.0 \pm 1.1/42$ | $>0.70/9.0 \pm 1.8/23$ | 0.34 |
| PF/S cholesterol | $\leq 0.50/6.0 \pm 1.9/14$ | $>0.50/6.0 \pm 2.9/19$ | 0.84 |
| PF/S bilirubin | $\leq 1.0/7.0 \pm 2.8/14$ | $>1.0/4.0 \pm 2.0/17$ | 0.94 |
| PF total leukocyte (per $mm^3$) | $\leq 700/6.0 \pm 1.1/13$ | $>700/18.0 \pm 8.6/6$ | 0.01 |

PF, pleural fluid; S, serum; LDH, lactate dehydrogenase.

**TABLE 2. The Results of Univariate Analyses in the Patients Who Had Not Previous Diuretic Usage**

| Variables | Status/survival (months)/number of patients | | $P$ level |
|---|---|---|---|
| PF glucose (mg/dL) | $<60/6.0 \pm 1.3/16$ | $\geq 60/9.0 \pm 2.3/34$ | 0.04 |
| PF/S LDH | $\leq 1.0/6.0 \pm 1.5/9$ | $>1.0/9.0 \pm 1.6/39$ | 0.03 |
| PF/S albumin | $\leq 0.70/7.0 \pm 1.1/20$ | $>0.70/9.0 \pm 2.3/30$ | 0.92 |
| PF/S total protein | $\leq 0.70/7.0 \pm 1.4/32$ | $>0.70/9.0 \pm 2.6/18$ | 0.47 |
| PF/S cholesterol | $\leq 0.50/8.0 \pm 1.8/13$ | $>0.50/6.0 \pm 2.4/15$ | 0.77 |
| PF/S bilirubin | $\leq 1.0/7.0 \pm 2.1/11$ | $>1.0/6.0 \pm 2.1/11$ | 0.94 |
| PF total leukocyte (per $mm^3$) | $\leq 700/6.0 \pm 1.0/11$ | $>700/20.0 \pm 3.0/4$ | 0.001 |

PF, pleural fluid; S, serum; LDH, lactate dehydrogenase.

survival. MPM presents infrequently periodical diseases such as recurrent laryngeal nerve paralysis, recurrent pneumothorax, or recurrent pleurisy (10). This periodicity suggests a dynamic competition between host and tumor for the appearance/disappearance of the disease. Our study also showed that the mean total leukocyte count in the fluid was only 643/mm$^3$, although it has been reported that most exudates have a total leukocyte count more than 1,000/mm$^3$ (11). This finding indicates a weak inflammatory reaction against to the tumor. In future, the stimulation of antitumor immune response may be helpful in the treatment of this serious malignancy.

## ACKNOWLEDGMENTS

We thank the physicians of the Department of Chest Diseases of Cumhuriyet University Hospital for their follow-up of patients. No portion of this work was supported by a foundation.

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