PLEURA
January-December 2015: 1-5

DOI: 10.1177/2373997515600657
plr.sagepub.com
SAGE

Pleural Effusion Size as Prognostic Marker in Patients With Malignant Pleural Effusion: A Retrospective Cohort Study

Felicia Montero-Arias, MD[1], Rodrigo Cartin-Ceba, MD[2], Jose Rojas-Solano, MD[1], Luis Ugalde-Gamboa, MD[1], and Allan Ramos-Esquivel, MD, MSc[3]

Abstract

Background: Inconsistent results have been reported regarding mortality predictors of malignant pleural effusion (MPE). **Objective:** We aim to describe prognostic features of MPE in patients evaluated over 5 years in a referral center. **Methods:** All consecutive MPEs (confirmed by pleural cytology or biopsy) from January 2009 to July 2014 were included in this retrospective cohort study. Clinical data were collected from medical registries. Overall survival (OS) rate was calculated with Kaplan-Meier method and compared by the log-rank test. Hazard ratios (HRs) were calculated by the Cox proportional regression model. **Results:** A total of 110 patients were identified. Mean OS was 8.3 months (range: 25-426 days). No difference in OS was noted based on tumor type. Patients with MPE <50% had a significant better survival than those with malignant pleural effusion ≥50% (median OS: 15.7 vs 5.7 months; HR: 1.71; 95% confidence interval [CI]: 1.06-2.78; $P = .0026$). After adjusting for confounding variables, MPE size was independently associated with mortality (HR: 1.78; 95% CI: 1.11-2.91; $P < .001$). No association between glucose or pH in pleural fluid and OS was noted. **Conclusion:** Our study showed that MPE size, as determined by chest X-ray, is significantly associated with mortality.

Keywords

malignant pleural effusion, pleural biopsy, pleural cytology

Introduction

Malignant pleural effusion (MPE) develops when tumor cells directly infiltrate the pleura and denoted a reduced life expectancy for patients with cancer.[1] Malignant pleural effusion represents advanced malignant disease, with median survival ranging from 3 to 12 months depending on the type of the underlying malignancy.[2] For these patients, some palliative treatment options can be offered based on tumor type, functional status, pleural apposition, and expected survival.[3,4] Nevertheless, a better identification of patients with the worst outcomes is mandatory in order to guide their medical management. Multiple studies have attempted to define mortality predictors for MPE based on clinical characteristics and biochemical parameters; however, the results have been inconsistent.[1,5-7] Therefore, we aim to describe clinical, biochemical, and radiological prognostic features of MPE in consecutive patients evaluated over 5 years in our referral center.

Materials and Methods

We retrospectively reviewed a cohort of consecutive patients with MPE who were treated in our referral center (Hospital Mexico, San José, Costa Rica). We identified cases from an institutional database from January 2009 to July 2014. Inclusion criteria included age more than 18 years and confirmed MPE by pleural cytology or biopsy. We excluded

[1] Division of Pulmonology, Hospital Mexico, San José, Costa Rica
[2] Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, USA
[3] Department of Medical Oncology, Hospital San Juan de Dios, San José, Costa Rica

Corresponding Author:
Allan Ramos-Esquivel, Department of Medical Oncology, Hospital San Juan de Dios. Apdo. 1000-SJO, San José, Costa Rica.
Email: allan.ramos@ucr.ac.cr; allanramoscr@gmail.com

Table 1. Clinical Characteristics of the Study Population.

Characteristic	n (%)
Male gender	38 (34.5)
Mean age, years	61 ± 15
Previous history of malignancy (recurrence)	59 (53.6)
Breast	34 (30.9)
Lung	12 (10.9)
Lymphoma	3 (2.7)
Genitourinary tract	7 (6.4)
Gastrointestinal tract	3 (2.7)
Symptoms	
Dyspnea	93 (84.5)
Chest pain	49 (44.5)
Weight loss in the last 3 months	26 (23.6)
Karnofsky Performance Status < 70%	13 (11.8)
Treatment after diagnosis	
Systemic treatment	37 (33.9)
Thoracocentesis	60 (55.1)
Indwelling catheter	53 (48.6)
Pleurodesis	29 (26.6)
CT findings	
Lung infiltrates (mass or nodules)	95 (66.4)
Pleural nodules	7 (6.4)
Mediastinal adenopathy	32 (29.1)
Pericardial effusion	8 (7.3)
Primary tumor	
Lung	40 (36.4)
Breast	34 (30.9)
Genitourinary tract	15 (13.6)
Gynecological	
Ovary	8 (7.3)
Endometrial	4 (3.6)
Cervix	3 (2.7)
Lymphoma	7 (6.4)
Gastrointestinal tract	
Colon	4 (3.6)
Gastric	2 (1.8)
Others	
Malignant histiocytoma	1 (0.9)
Mixed germ cell tumor	1 (0.9)
Thymoma	2 (1.8)
Unknown primary	4 (3.6)
Biochemical	
Glucose, mg/dL	108 ± 54
Lactate dehydrogenase, U/L	515 ± 258
Proteins, g/dL	4.6 ± 1.2
pH, Units	7.41 ± 0.2

Abbreviation: CT, computed tomography.

cases with missing data on any of the variables we consider in the hypothesized models. The study was reviewed and approved by the institutional review board (CLOBI Hospital México 2012-22), and all patients gave informed consent to the work. Clinical data, radiological features, and biochemical analyses were collected from medical records. Analyzed variables included age; gender; presence of previous malignancy; symptoms including dyspnea, chest pain, or self-reported weight loss during the last 3 months; performance status (determined by Karnofsky scale); pleural fluid analyses including glucose, lactate dehydrogenase (LDH), and pH; cytological and histological studies as well as the effusion size determined by the radiologist on charge based on conventional chest X-ray (<25%, 25%-50%, 50%-75%, and >75% of the compromised lung).

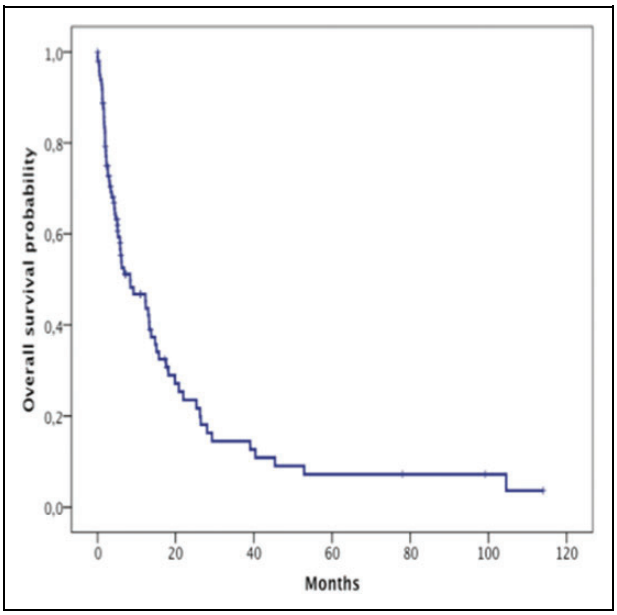

Figure 1. Overall survival probability (Kaplan-Meier Method) of the studied population.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation. Categorical variables are presented as percentages. Survival time was determined from the day of MPE diagnosis to the day of death. Cases were censored at August 2014 or death. Overall survival (OS) rate was calculated with the Kaplan-Meier method and compared by the log-rank test. Hazard ratios (HRs) were calculated by the Cox proportional hazard regression model. We preselected potential prognostic variables based on previous studies.[2,8] Statistical significance was established at $P < .05$. Calculations were performed in statistical software SPSS for MAC 20.0 (Chicago, Illinois).

Results

During follow-up time, we identified 110 patients with MPE. The diagnosis was confirmed by positive cytology in 70 patients and by biopsy in 40 patients. Table 1 summarizes the clinical characteristics of the entire cohort. Median follow-up time was 33.3 months and median overall survival (OS) was 8.3 months (range: 25-426 days; Figure 1). Using the Kaplan-Meier method, no difference in OS based on tumor type was noted ($P = .812$). Median OS for breast cancer was 395 days (95% confidence interval [CI]: 213-576), for lung cancer 249 days (95% CI: 140-357), and for the other types of malignancy 151 days (95% CI: 61-240).

Patients with MPE < 50% had a significant better survival than those with MPE > 50%, with a median OS of 15.7 months compared to 5.7 months (HR: 1.71; 95% CI: 1.06-2.78; $P = .002$; Figure 2).

No predictive prognostic value on mortality was identified by quartile distribution of age, pH, or glucose level in pleural fluid. Patients with pH $\leq$ 7.30 and glucose $\leq$60 mg/dL were compared with those who had pH > 7.30 and glucose > 60 mg/dL, and no significant survival differences were found ($P = .45$ and $P = .56$, respectively). All cases with MPE showed a predominantly lymphocytic cell count differential. The size of pleural effusion was the only variable associated with mortality in the multivariate analysis (Table 2).

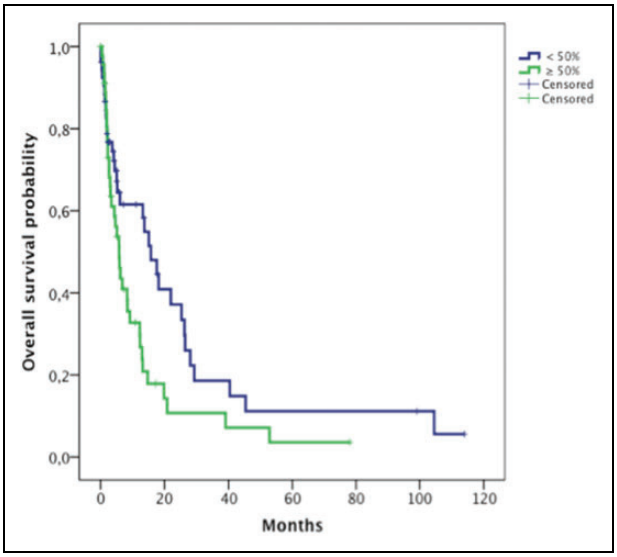

Figure 2. Overall survival probability according to malignant pleural effusion size (HR: 1.71 [95% CI: 1.06-2.78]; log-rank test $P = .026$). HR indicates hazard ratio; CI, confidence interval.

Table 2. Multivariate Analysis of Potential Prognostic Mortality Factors.

Variable	Hazard Ratio	95% Confidence Interval	*P* Value
Age, years	1.04	0.99-1.01	.14
25% increase in pleural effusion size	1.78	1.11-2.91	.01[a]
Pleural fluid glucose, mg/dL	0.98	0.96-1.01	.13
Pleural fluid pH, Units	1.29	0.09-16.93	.85
KPS < 70%	1.21	0.88-1.55	.42
Systemic treatment after diagnosis	0.87	0.79-1.33	.32

Abbreviation: KPS, Karnofsky Performance Status.
[a]Statistically significant

Discussion

Determinants of OS in patients with MPE are useful to stratify them according to their prognosis and guide their palliative management. In this study, we demonstrated that MPE size, as determined by chest X-ray, is an independent prognostic variable for mortality in patients with this condition. This cheap and very available technique can identify patients with the poorest prognosis and thus minimize unnecessary procedures in their final stages of life. It has been demonstrated that patients with a poor prognosis may prefer a therapeutic pleural aspiration to pleurodesis in order to relieve their symptoms.[8]

A number of studies have reported risk factors for survival in patients with MPE. Unfortunately, some of these results are inconsistent and few of them have been carried out in developing countries where the access to some diagnostic methods and procedures are sometimes unreachable. Furthermore, ethnic and epidemiological factors can vary from industrialized countries where the majority of trials have been implemented.

Some authors have reported contrasting results about the relationship between massive pleural metastatic involvement and mortality. For example, Rodriguez-Panadero and colleagues[9] investigated the correlation between OS and the extent of tumor spread by direct pleural visualization by thoracoscopy, but no correlation with pleural effusion size was reported. On the other hand, the report of Jiménez and colleagues showed a direct association between massive MPE and mortality.[10] Our findings are in accordance with this latter report, since we found an increased risk of mortality for each quartile increase in MPE size. Thus, massive and nonmassive MPEs are independently associated with poor survival after adjusting for confounding variables.

In contrast with previous studies,[6,9-12] we did not find any significant association between biochemical parameters in pleural fluid (ie, low glucose, high LDH, and low pH) and overall mortality. These discrepancies can be attributable to sample handling or as a consequence of a different composition of the cohorts. For example, the study of Ozyurtkan and colleagues[13] contained almost one-quarter of patients with mesothelioma, and the report of Rodriguez-Panadero and Lopez-Mejias[9] included 17% of patients with this diagnosis, as opposed to our cohort, which did not include any patient with this malignant condition. Besides, the relationship between pH and survival has a marginal prognostic value for estimating mortality in patients with MPE,[14] and its association with poor outcomes is currently under debate. The same is true for pleural fluid glucose, which has been inconsistently related to OS in previous trials.[15]

Our population was mainly composed of patients with lung and breast cancer (67.3%), as similarly reported by previous series.[1,3-10] Although we didn't find any statistical difference in survival based on tumor type, we observed a shortest OS in patients with lung cancer compared to those with breast cancer. Some authors have shown this same difference in survival according to tumor type.[16] Nevertheless, median OS for women with breast cancer was better in our

cohort than in the study of Clive and colleagues[17] (395 vs 192 days) as well as in patients with lung cancer (249 vs 74 days).

There are several limitations to our study including the retrospective design and the small number of patients. Besides, the unicenter study design limits its external validity. Nevertheless, giving the heterogeneity of data regarding this subject, we consider our findings valuable in order to better identify predictors of OS in this particular scenario. Further studies are necessary to guide clinicians for treatment of these patients.

Conclusion

To the best of our knowledge, our study provides the first documentation that MPE size as determined by chest X-ray is independently associated with survival. Thereby, chest X-ray can be used as a predicting tool in patients with MPE, particularly in developing countries where the pleural ultrasound or computed tomography scan is not readily available.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Chernow B, Sanh SA. Carcinomatous involvement of the pleura. *Am J Med*. 1997;63(5):695-702.
2. Shaw P, Agarwal R. Pleurodesis for malignant pleural effusions. *Cochrane Database Syst Rev*. 2004;(1):CD002916.
3. Roberts ME, Neville E, Berrisford RG, Antunes G, Ali NJ, BTS Pleural Disease Guideline Group. Management of a malignant pleural effusion: British Thoracic Society Pleural Disease Guideline 2010. *Thorax*. 2010;65(suppl 2):ii32-ii40.
4. Thomas R, Francis R, Davies HE, Lee YC. Interventional therapies for malignant pleural effusions: the present and the future. *Respirology*. 2014;19(6):809-822.
5. Anevalvis S, Kouliatsis G, Sotiriou I, et al. Progostic factors in patients presenting with pleural effusion revealing malignancy. *Respiration*. 2014;87(4):311-316.
6. Bielsa S, Salud A, Martinez M, et al. Prognostic significance of pleural fluid data in patients with malignant effusion. *Eur J Intern Med*. 2008;19(5):334-339.
7. Pilling JE, Dusmet M, Ladas G, Peter G. Prognostic factors for survival after surgical palliation of malignant pleural effusion. *J Thorac Oncol*. 2010;5(10):1544-1550.
8. Davies HE, Mishra EK, Kahan BC, et al. Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial. *JAMA*. 2012;307(22): 2382-2389.
9. Rodriguez-Panadero F, Lopez-Mejias J. Survival time of patients with pleural metastatic carcinoma predicted by glucose pH studies. *Chest*. 1989;95(2):320-324.
10. Jiménez D, Díaz G, Gil D, Cicero A, et al. Etiology and prognostic significance of massive pleural effusions. *Respir Med*. 2005;99(9):1183-1187.
11. Rodriguez-Panadero F, Lopez-Mejias J. Low glucose and pH levels in malignant pleural effusions: diagnostic significance and prognostic value in respect to pleurodesis. *Am Rev Respir Dis*. 1989;139(3):663-667.
12. Heffner JE, Nietert PJ, Barbieri C. Pleural fluid pH as a predictor of survival in patients with malignant pleural effusion. *Chest*. 2000;117(1):79-86.
13. Ozyurtkan MO, Balci AE, Cakmak M. Predictors of mortality within three months in the patients with malignant pleural effusion. *Eur J Intern Med*. 2010;21(1):30-34.
14. Heffner JE, Heffner JN, Brown LK. Multilevel and continuous pleural fluid pH likelihood ratios for evaluating malignant pleural effusions. *Chest*. 2003;123(6):1887-1894.
15. Burrows CM, Mathews WC, Colt HG. Predicting survival in patients with recurrent symptomatic malignant pleural effusions: an assessment of the prognostic values of physiologic, morphologic, and quality of life measures of extent of disease. *Chest*. 2000;117(1):73-78.
16. Abrao FC, de Abreu IR, Fogarolli M, et al. Prognostic factors of 30-day mortality after palliative procedures in patients with malignant pleural effusion[published online March 11, 2015]. *Ann Surg Oncol*. 2015. doi:10.1245/s10434-015-4491-6.
17. Clive AO, Kahan BC, Hooper CE, et al. Predicting survival in malignant pleural effusion: development and validation of the LENT prognostic score. *Thorax*. 2014;69(12):1098-1104.

Author Biographies

Felicia Montero-Arias obtained her specialization in Internal Medicine and Pulmonary Medicine from the University of Costa Rica and received a post-graduate training in Pulmonary Medicine at Mayo Clinic, USA.

Rodrigo Cartin-Ceba obtained his medical degree from the University of Costa Rica, subsequently trained in Internal Medicine at Baylor College of Medicine and then finalized a fellowship in Pulmonary and Critical Care Medicine at Mayo Clinic where he currently works as a pulmonologist and intensivist.

José Rojas-Solano is specialist in Internal Medicine and Pulmonary Medicine from the University of Costa Rica (2003-2009). Received a postgraduate training in Interventional Pulmonology at Thoraxklinik Heidelberg, Germany (2009-2010) and did a visiting research fellowship at Vanderbilt University Medical Center, USA (2008).

Luis Ugalde-Gamboa obtained his pneumologist specialization from the University of Costa Rica and received a postgraduate training in Bronchoscopy at the University of Heidelberg, Germany.

Allan Ramos-Esquivel is a Medical Oncologist and Internal Medicine Specialist from the University of Costa Rica. He obtained a Master of Sciences degree in Health Sciences, specialization in Clinical Epidemiology, from the Erasmus University and National Institute of Health Sciences (NIHES) in Rotterdam, The Netherlands. He currently works as Professor of the Pharmacology Department at the University of Costa Rica.