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SEMIQUANTITATIVE ASSESSMENT OF SURGICAL LUNG BIOPSY: PREDICTIVE VALUE AND IMPACT ON SURVIVAL OF PATIENTS WITH DIFFUSE PULMONARY INFILTRATE

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Canzian M, Soeiro A de M, Taga MF de L, Farhat C, Barbas CSV, Capelozzi VL. Semiquantitative assessment of surgical lung biopsy: predictive value and impact on survival of patients with diffuse pulmonary infiltrate. Clinics. 2007; 62(1):23-30.

PURPOSE: Surgical lung biopsy has been studied in distinct populations, mostly going beyond clinical issues to impinge upon routine histopathological diagnostic information in diffuse infiltrates; however, detailed tissue analyses have rarely been performed. The present study was designed to investigate the prognostic contribution provided by detailed tissue analysis in diffuse infiltrates.
METHODS: Medical records and surgical lung biopsies from the period of 1982 to 2003 of 63 patients older than 18 years with diffuse infiltrates were retrospectively examined. Lung parenchyma was histologically divided into 4 anatomical compartments: interstitium, airways, vessels, and alveolar spaces. Histological changes throughout these anatomical compartments were then evaluated according to their acute or chronic evolutional character. A semiquantitative scoring system was applied to histologic findings to evaluate the intensity and extent of the pathological process. We applied logistic regression to predict the risk of death associated with acute and chronic histological changes and to estimate the odds ratios for each of the independent variables in the model.
RESULTS: Impact on survival was found for male gender (P = 0.03), presence of diffuse alveolar damage (P = 0.001), and chronic histological changes (P = 0.0004) on biopsy. Thus, being male was associated with a slightly lower risk (O.R. = 0.18; P=0.03) of dying than being female. Death risk was increased 17 times in the presence of acute histological changes such as diffuse alveolar damage and 2.5 times in the presence of chronic histological changes.
CONCLUSION: Detailed analysis of histological specimens can provide more than a nosological diagnosis: this approach can provide valuable information concerning prognosis.

KEYWORDS: Surgical lung biopsy. Diffuse pulmonary infiltrate. Histopathological score. Diffuse alveolar damage. Prognosis.

INTRODUCTION

Diffuse pulmonary disease of uncertain etiology represents a diagnostic and therapeutic challenge in the general population. Most of the causes of pulmonary infiltrates can be diagnosed by noninvasive or minimally invasive means, such as transbronchial or transthoracic needle biopsies. However, when these efforts fail to provide a diagnosis or when a patient does not respond to appropriate therapy, a surgical lung biopsy may be required to assist in treatment efforts. This biopsy produces a histologic diagnosis in almost every case, but considerable controversy exists regarding whether the information provided justifies its routine use. Thus, similarly to the approach used from previously reported tumor recurrence studies[1–5] and aiming for the effectiveness of treatment, there is great interest in identifying, as soon as possible, morphological parameters of sur-

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gical lung biopsies associated with the shortening of the patient's life.

Because semiquantitative approaches have been thought to be important in evaluating the intensity and extent of pathologic processes,[6–9] a scoring system has been considered to be potentially useful with surgical lung biopsies specimen markers.[10,11] Several parenchymal alterations related to necrosis, degeneration, hyperplasia, neoplasia, inflammation/remodeling (fibrin and hyaline membranes deposition, polymorphonuclear and mononuclear cell infiltration, granulation tissue, granuloma, fibrocellular proliferation), and circulatory changes (edema, hemorrhage, congestion, thrombosis) have shown promise as useful markers.

Scoring systems have also been found to be significantly associated with survival,[8,12] but there has been uncertainty about how best to design a scoring system. Hence, this project was undertaken to validate the importance of a scoring system and to explore the semiquantitative relationship between score and outcome; we also explored the relationship between the result of a scoring system and other epidemiological factors.

METHODS

Patient selection

We examined the medical records of all patients who underwent surgical lung biopsy at our institution from 1982 to 2003 for age, sex, total hospitalization time, days from admission to the biopsy procedure, outcome, main clinical diagnosis, underlying disease, respiratory failure proven through clinical and or gasometric data (respiratory rate over 28 breaths per minute and/or $PaO_2 < 60$ mm Hg and/or $SpO_2 < 90\%$, while breathing room air). From this group were selected those patients older than 18 years showing diffuse infiltrates on chest roentgenogram and whose hospitalization was not exclusively motivated by the biopsy procedure.

Over the period examined, 1657 surgical lung biopsies were performed at our institution; 63 patients (3.8%) met our study criteria. Thirty-two patients (51%) were men and 31 (49%) were women, with a mean age of 49 years (range, 18 to 92 years). Arterial blood samples for gas analysis taken during inspiration of room air in the 24 hours preceding SLB were obtained for 51 patients (81%), and 41 of them showed signs of acute respiratory failure. Table 1 lists the preexisting medical conditions in the study population. Thirty-three patients (52%) were immunocompromised, and 48 (76%) had at least 1 underlying disease. The mean time from admission to SLB was 18 days (range, 0 to 61). The mean interval from SLB to hospital discharge or death was 18 days (range, 1 to 143), and the mean total hospitalization time was 39 days (range, 4 to 184). The overall death rate was 49%, and death rate for immunocompromised patients and for patients presenting respiratory failure or underlying diseases was 61%. Death occurred in 69% of patients presenting diffuse alveolar damage. Other details about the patients are summarized in Table 1.

Pathology review of surgical lung biopsy specimens

Samples were uniform and obtained generally in 2 different compromised regions; the entire sample was submitted to histological examination, generally on 2 different slides. The specimens were fixed in 10% phosphate-buffered formaldehyde solution and embedded in paraffin. Serial sections were cut (5 mm), deparaffinized, and processed according to routine tissue processing. Staining with hematoxylin and eosin was done for histological examination in all cases. In cases exhibiting proteinaceous intraalveolar exudates, granulomas, or microabscesses, the following stains were used: silver stains and PAS for *Pneumocystis* and fungi, Ziehl-Neelsen for mycobacterium, and Gram stains for bacteria, respectively.

The biopsies were considered representative when the histological sections comprised at least 1 bronchovascular axis in continuity with septal interstitium, alveolar spaces, and peripheral interstitium. The lung parenchyma was then histologically divided into 4 anatomical compartments of reference: a) interstitium (septal, peripheral, and axial); b) airways (terminal and respiratory bronchioles); c) vessels (arteries, veins, and lymphatics); and d) alveolar spaces (including alveolar ducts) (Figure 1).

Histological changes throughout the 4 anatomical compartments were then evaluated for temporal evolution into 2 groups as follows: 1) acute (necrosis, degeneration, edema, hemorrhage, congestion, thrombosis, fibrin deposition, hyaline membranes, and polymorphonuclear cells), and 2) chronic (hyperplasia, neoplasia, mononuclear cells, granulation tissue, granuloma, and fibrocellular proliferation) (Figures 2A to 2I and 3A to 3F).

Semiquantitative assessment of histological compartments and histological changes

The severity of the acute and chronic histological changes in terms of the extent, intensity, and distribution were heterogeneous along the anatomic compartments. Therefore, the severity of these various acute and chronic histological changes was rated semiquantitatively accord-

Table 1 - Epidemiological data of the 63 patients studied

Case	Sex	Age	Total Hospitalization Time (days)	Underlying disease	Presence of immunosuppression factor	Outcome
1	m	56	20	No	No	Dead
2	m	48	32	No	No	Dead
3	m	76	60	Renal and heart failure	No	Survived
4	f	19	47	BMT (aplastic anemia)	Yes	Dead
5	m	67	44	No	No	Survived
6	m	55	17	Rheumatologic disease NOS	No	Dead
7	f	52	27	Heart failure	No	Survived
8	m	48	55	Crohn's disease+ renal failure	No	Dead
9	m	66	42	Rheumatoid arthritis	No	Dead
10	f	37	44	SLE	No	Dead
11	m	34	16	AIDS	Yes	Dead
12	m	45	18	CML	Yes	Dead
13	m	52	20	No	No	Survived
14	f	21	38	Non-Hodgkin's lymphoma	Yes	Survived
15	f	30	37	No	No	Survived
16	f	63	9	Carcinomatosis	Yes	Dead
17	m	37	48	No	No	Dead
18	f	51	22	Gastroesophageal reflux	No	Survived
19	m	52	38	Liver cirrhosis	No	Survived
20	f	46	26	Adenocarcinoma NOS	No	Dead
21	f	34	4	CML	Yes	Dead
22	f	49	19	Carcinomatosis	Yes	Survived
23	m	23	21	Burns	No	Dead
24	m	58	13	Adenocarcinoma NOS	Yes	Dead
25	m	77	45	COPD	Yes	Dead
26	m	36	20	BMT	Yes	Dead
27	m	78	17	No	Yes	Survived
28	f	54	9	SLE	No	Dead
29	f	51	184	Wegener's granumatosis	No	Dead
30	m	57	33	Ischemic myocardiopathy	No	Dead
31	f	21	42	SLE	No	Survived
32	f	74	16	Congestive myocardiopathy	No	Dead
33	m	55	91	Congestive myocardiopathy	No	Dead
34	m	65	69	Sarcoidosis	No	Dead
35	f	46	15	Wegener's granumatosis	No	Survived
36	f	52	76	No	Yes	Survived
37	f	92	24	Ischemic myocardiopathy	No	Survived
38	f	26	27	BMT (CML)	Yes	Dead
39	f	53	98	Rheumatoid arthritis	No	Dead
40	m	70	47	Non-Hodgkin's lymphoma	Yes	Dead
41	f	30	65	Colitis NOS	No	Survived
42	f	82	22	Neoplasia NOS	Yes	Survived
43	f	50	91	SLE	Yes	Survived
44	m	57	38	Gastroesophageal reflux+DM 2	No	Survived
45	m	65	37	Ischemic myocardiopathy+DM 2	No	Dead
46	m	47	37	ALL	Yes	Dead
47	m	32	16	ALL	Yes	Dead
48	f	68	37	Hypertension	No	Survived
49	m	53	26	Heart transplantation	Yes	Dead
50	m	22	89	ALL	Yes	Survived
51	m	18	7	BMT (ALL)	Yes	Survived
52	f	76	36	Ischemic myocardiopathy	No	Dead
53	f	55	17	Carcinomatosis	Yes	Dead
54	f	25	47	No	No	Survived
55	f	38	42	No	No	Dead
56	m	37	84	CML	Yes	Dead
57	f	36	10	Ischemic myocardiopathy	No	Survived
58	f	36	14	Carcinomatosis	Yes	Survived
59	m	73	34	No	No	Survived
60	f	52	36	No	No	Survived
61	m	31	49	SLE	No	Dead
62	m	28	48	Aplastic anemia	Yes	Dead
63	f	73	37	No	No	Survived

AIDS: acquired immunodeficiency syndrome; ALL: acute lymphocytic leukemia; BMT: bone marrow transplantation; CML: chronic myelocytic leukemia; CPOD: chronic obstructive lung disease; DM: diabetes mellitus; NOS: no other specification; SLE: systemic lupus erythematous.

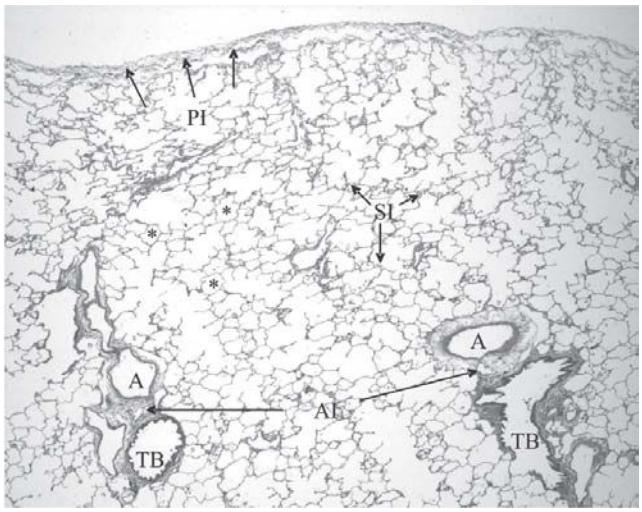

Figure 1 - (HE, 25X): Normal lung histology showing the 4 compartments studied: interstitium, alveolar spaces, airways and vessels. "PI": peripheral interstitium; "SI": septal interstitium; "AI": axial interstitium; "*": alveolar spaces; "TB": terminal bronchioles; "A": pre-acinar arterioles

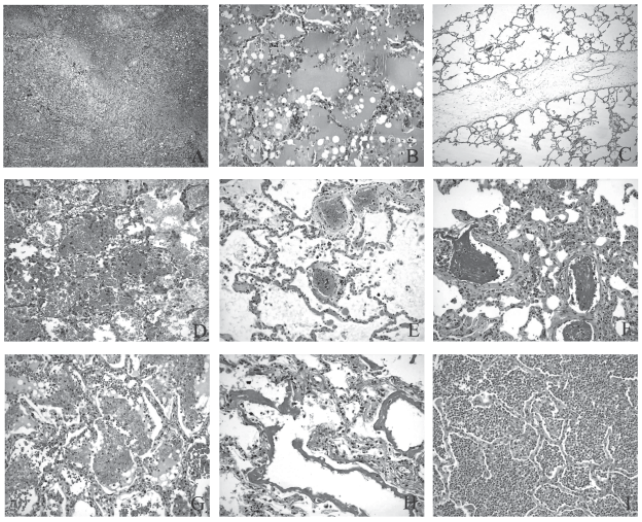

Figure 2 - A (HE, 100X): parenchymal necrosis; B (HE, 200X): alveolar edema; C (HE, 100X): peripheral interstitium edema; D (HE, 200X): alveolar hemorrhage; E (HE, 200X): microvascular congestion; F (HE, 200X): acute vascular thrombosis; G (HE, 200X): alveolar fibrin deposition; H (HE, 200X): hialine membranes; I (HE, 200X): neutrophilic filling of alveolar spaces

ing to the amount and severity of disease by the following histological score:

0: absence of histological changes;
1: parenchymal alterations in 1 to 25% of the tissue examined;
2: parenchymal alterations in 26 to 50% of the tissue examined;
3: parenchymal alterations in 51 to 75% of the tissue examined;
4: parenchymal alterations in 76% to 100% of the tissue examined.

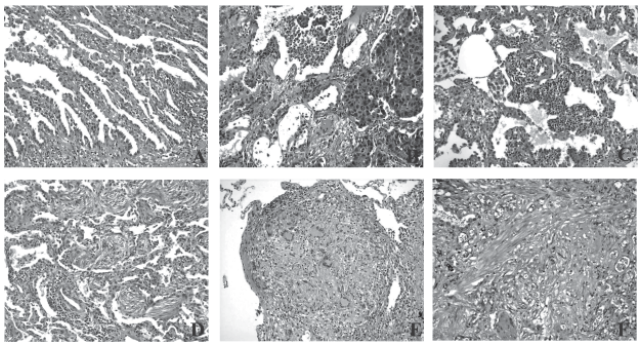

Figure 3 - A (HE, 200X): pneumocytes hyperplasia; B (HE, 200X): neoplastic parenchymal infiltration; C (HE, 200X): mononuclear cell interstitial infiltrate; D (HE, 200X): granulation tissue filling alveolar spaces; E (HE, 200X): granuloma; F (HE, 200X): fibrosis (fibrocellular proliferation)

The sum of the scores for acute and chronic changes, respectively, represented continuous variables that we designated as acute and chronic indices.

Statistical Analysis

Logistic regression analysis was used to attain the best separation of survivors and nonsurvivors, discriminating between the two categories of patients according to clinical and histological variables. Evaluation of the predictive ability was determined by the percentage of patients correctly placed into the proper categories by the classification rules developed. In logistic regression, the probability of an event occurring is directly estimated. For more than 1 dependent variable, the model can be written:

$$\text{Prob (event)} = e^z / 1 + e^z$$

where Z is the linear combination of β_0 (constant) and β_1 to β_7, the estimated coefficients of the independent variables (X_1 to X_7), and *e* is the base of the natural logarithms, (2.718, approximately), as shown below:

$$Z = \beta_0 + \beta_1 X_1 + \beta_2 X_2 \ldots \beta_7 X_7$$

We considered results with *P* values less than 5% to be statistically significant. All analysis was done with SPSS for Windows 10.0 statistical software.

RESULTS

The total mean score for acute histological changes was 2.11 (range, 0.02 to 0.56), and for chronic histological changes it was 4.09 (range, 0.14 to 0.76) (Table 2). The acute or chronic compromise of axial interstitium and airways characterized respectively acute and chronic bronchi-

olitis (Figure 4A). Similarly, the acute or chronic compromise of septal and peripheral interstitium, alveolar spaces, and vessels comprised the histologic pattern of chronic interstitial pneumonia (Figure 4B), diffuse alveolar damage (Figure 4C), and vasculitis (Figure 4D), respectively (Table 2). Table 3 shows the predictive ability for survival of the clinical and histological variables evaluated using the logistic regression model. Statistically significant impact on survival was found for male gender (P = 0.03), diffuse alveolar damage (P = 0.001), and chronic histological changes (P = 0.0004). Thus, being male was associated with a lower risk (O.R. = 0.18; P=0.03) of dying than being female. Presence of acute histological changes, such as diffuse alveolar damage at biopsy, increased the risk of death 17.5 times, whereas the presence of chronic histological changes increased risk of death related 2.5 times. Although not statistically significant, patients with immunosuppression, arterial hypertension, and chronic cardiac

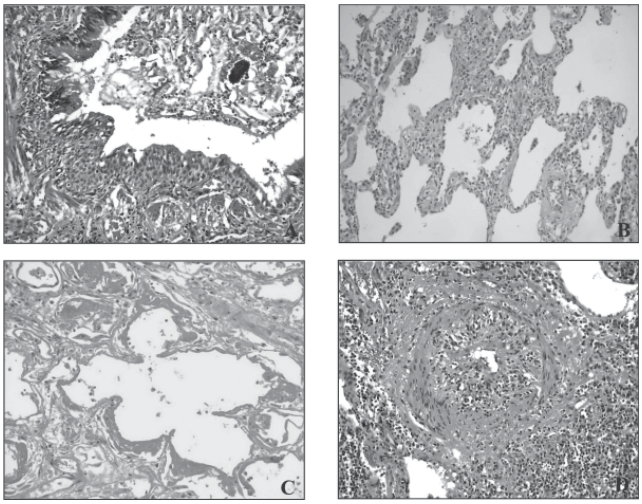

Figure 4 - Prototypical histopathological changes: A (HE, 200X): chronic bronchiolitis with squamous metaplasia; B (HE, 200X): non-specific interstitial pneumonia (cellular pattern); C (HE, 200X): diffuse alveolar damage; D (HE, 200X): chronic vasculitis

Table 2 - Mean, maximum, and minimum values of the acute and chronic histological score obtained by semiquantitative assessment

Histological compartments	Temporal evolution	N	Score			Histological changes
			Mean	Minimum	Maximum	
Septal interstitium	acute	63	0.19	0	1.25	Diffuse alveolar damage
	chronic	63	0.55	0	1.38	
Alveolar spaces	acute	63	0.56	0	1.20	
	chronic	63	0.36	0	1.13	Chronic interstitial pneumonia
Peripheral interstitium	acute	63	0.31	0	1.67	
	chronic	63	0.76	0	2.50	
Axial interstitium	acute	63	0.08	0	0.60	Acute bronchiolitis
	chronic	63	0.45	0	1.75	
Terminal bronchioles	acute	63	0.38	0	1.00	
	chronic	63	0.14	0	0.67	Chronic bronchiolitis
Respiratory bronchioles	acute	63	0.37	0	1.00	
	chronic	63	0.26	0	1.00	
Pre-acinar arterioles	acute	63	0.12	0	0.43	Acute vasculitis
	chronic	63	0.44	0	1.25	
Post-acinar arterioles	acute	63	0.08	0	0.67	
	chronic	63	0.40	0	1.33	Chronic vasculitis
Veins and lymphatics	acute	63	0.02	0	0.50	
	chronic	63	0.73	0	2.25	

Table 3 - Evaluation of the risk of death using the scoring system on surgical lung biopsies by the multiple logistic regression model (chi-square = 32.9; $P < 0.001$)

Variable	β	SE	Wald	P	Exp(B)	95% CI for Exp(B)	
						Lower	Upper
Gender	-1.68	0.78	4.61	0.031	0.18	0.039	0.86
Diffuse alveolar damage	2.83	0.86	10.78	0.001	17.05	3.13	92.74
Chronic histological score	0.86	0.25	11.41	0.000	2.36	1.43	3.89
Systemic arterial hypertension	2.34	1.27	3.35	0.067	10.39	0.84	127.32
Cardiac chronic failure	0.41	2.37	0.03	0.862	1.50	0.01	159.53
Diabetes mellitus	-1.24	1.86	0.44	0.506	0.28	0.01	11.26
Immunosuppression	0.88	0.73	1.48	0.22	2.43	0.58	10.19
Constant	0.82	36.79	0.00	0.982			

β: coefficient of model; SE: Standard error; Wald: Wald statistics; P: probability of the null hypothesis; Exp (B): odds ratio; CI: confidence interval.

failure presented an apparently greater risk of death. When this model was evaluated on the original data used for its development, 26 of 32 (81.3%) patients were correctly classified as nonsurvivors, and 25 of 31 (80.7%) patients as survivors. Overall, 81% of the cases were correctly classified.

DISCUSSION

Diffuse infiltrates are usually a diagnostic challenge; they are also the most severe pulmonary nosologic pattern when compared to focal and nodular ones.[13] At the timing of writing, the role of surgical lung biopsies in the management of diffuse pulmonary infiltrates remains obscure. Although such biopsies reveal some clinical homogeneity, diffuse pulmonary infiltrates can originate from different etiologies such as infectious pneumonias, organizing pneumonia, acute eosinophilic pneumonia, and pulmonary capillaritis, which thus require different treatment strategies.[14]

Several studies have been published concerning different aspects of surgical lung biopsies in distinct populations with diffuse infiltrates.[15,16] Clinical implications of these biopsies have been greatly exploited, mostly concerning their contribution to the determination of prognosis through therapeutic changes, but also because such surgical biopsied can be carried out with relatively low morbidity and frequently promote changes in treatment.[17–20]

Clearly, most of the studies concerning surgical lung biopsies take into account only diagnostic information provided by routine histological analysis, usually regarded as the gold standard for clinical hypotheses in diffuse infiltrates,[21] in addition to clinical data. Histopathological data from surgical lung biopsies have rarely been exploited in detail.[22] The likely reason why such biopsies frequently fail to provide information in routine use is that histopathological details have not so far been adequately correlated with either routine clinical or pathological analyses. Frequently, clinical or radiological findings reflect such minimal tissue changes that they can be result in misdiagnosis. The question of interest is whether additional, more technologically enhanced information gathered from surgical lung biopsies or from clinical records can help us to better predict a patient's outcome. Lung pathology undoubtedly comprises a series of complex stereotyped reactions, which make differential diagnosis using only qualitative approaches difficult. However, semiquantitative assessment is thought to be useful because it facilitates the creation of mathematical models to predict outcome. In a variety of conditions, especially diffuse pulmonary parenchymal diseases, a scoring system for quantitative assessment has been associated with guidance or evaluation of therapy response and prognosis.[6–8] Thus, for all these reasons, we should not be surprised to learn that detailed pulmonary analysis of the different histological compartments, where alterations are classified in accordance with their acute or chronic character and semiquantified through a system of scores, can provide a significant prognostic contribution.

In addition to presenting a scoring system, our purpose included the correlation of histopathological findings of data concerning survival and epidemiological parameters. Descriptive analyses helped in selecting useful information for which statistical significance was verified through multiple logistic regression.

Most of our diagnoses included airway diseases in the same proportion as interstitial lung diseases; other studies found a higher percentage of idiopathic pulmonary fibrosis.[13,16,23–25]

We found a negative influence of diffuse alveolar damage and respiratory failure, mainly for men and with underlying disease ($P > 0.05$). It is widely known that the presence of underlying disease has a deleterious influence on the outcome of a pneumopathy and that diffuse alveolar damage is related to critical clinical pictures. Nevertheless, our study provided important quantitative information concerning these parameters, showing a 17 fold increase in risk of death in the presence of diffuse alveolar damage. Perhaps, according to the objective of this study, the most important evidence was the association of the chronic histological changes with survival. In fact, a direct association was found between low risk of dying and higher values of chronic histological changes. Our results confirm the prognostic importance of histopathological evaluation of surgical lung biopsies. This is possibly the first study concerning such biopsies with emphasis on detailed histological findings. Although further studies are required, our results suggest that quantitative assessment accomplished through a scoring system provides more prognostic information than does the routine clinical and pathological approach.

In conclusion, the detailed histological analysis of surgical lung biopsy specimens can provide more than nosological diagnosis; this approach can bring valuable information concerning prognosis. Additional study in a randomized and prospective trial could confirm this conclusion. We also believe that it is important to validate our semiquantitative assessment using a scoring system, as well as to extend it to other histological types of diffuse pulmonary disease, by studying the scoring system in additional patients.

RESUMO

Canzian M, Soeiro A de M, Taga MF de L, Farhat C, Barbas CSV, Capelozzi VL. Avaliação semiquantitativa da biópsia pulmonar cirúrgica: valor preditivo e impacto na sobrevida de pacientes com infiltrado pulmonar difuso. Clinics. 2007;62(1):23-30.

PROPOSIÇÃO: A biópsia pulmonar cirúrgica tem sido estudada em populações distintas, geralmente abordando aspectos histopatológicos puramente diagnósticos em infiltrados pulmonares difusos, além de dados clínicos. Contudo, análises teciduais detalhadas em tais casos têm sido pouco exploradas. O presente estudo foi delineado com o intuito de se investigar a contribuição prognóstica fornecida pela análise histológica detalhada em infiltrados difusos.

MÉTODOS: Foram examinados retrospectivamente os prontuários e biópsias pulmonares cirúrgicas de 63 pacientes maiores de 18 anos, com infiltrados difusos, de 1982 a 2003. O parênquima pulmonar foi dividido em 4 compartimentos histológicos: interstício, vias aéreas, vasos e espaços alveolares. Alterações histológicas de cada compartimento histológico foram então avaliadas de acordo com seu caráter evolutivo agudo ou crônico. Um escore semiquantitativo foi aplicado a achados histopatológicos com o intuito de se avaliar a intensidade e a extensão do processo patológico. Aplicamos regressão logística para predizer o risco de morte para alterações histológicas agudas e crônicas e para estimar a razão de probabilidades para cada uma das variáveis independentes do modelo.

RESULTADOS: O impacto sobre a sobrevida foi observado para o gênero masculino (p=0.03), para a presença de dano alveolar difuso (p=0.001) e para alterações histológicas crônicas (p=0.0004) em biópsias. Assim, homens apresentariam menor chance (O.R. = 0.18; P=0.03) de morrer do que mulheres. O risco de morte foi 17 vezes maior na presença de alterações histológicas agudas como dano alveolar difuso e 2,5 vezes na presença de alterações histológicas crônicas.

CONCLUSÃO: A análise detalhada de espécimes histológicos pode proporcionar maiores e mais valiosas informações de valor prognóstico do que o simples diagnóstico nosológico.

UNITERMOS: Biópsia pulmonar cirúrgica. Infiltrado pulmonar difuso. Escore histopatológico. Dano alveolar difuso. Prognóstico.

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