Prognostic Significance of Serum Iron, Iron-Binding Capacity, Ferritin and Bronchoalveolar Lavage Ferritin Levels in Primary Lung Cancer

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ABSTRACT

Tumor markers were investigated in order to predict the prognosis of lung cancer (LC). It was aimed to find the prognostic value of serum parameters, which may reflect iron metabolism, and of bronchoalveolar lavage (BAL) ferritin measurement in LC patients. The age, gender, tumor cell type, stage of the disease, serum ferritin levels at diagnosis, BAL ferritin, serum iron, and serum iron-binding capacities (SIBC) of the patients diagnosed with LC were recorded. A total of 37 (90.2%) male and 4 (9.8%) female patients, with a mean age of 60.6 years, were included in this study. Mean follow-up period was 11.9 months. During this period, 32 patients (78.0%) died. Levels of serum iron (p= 0.175), SIBC (p= 0.577), serum ferritin (p= 0.426) and BAL ferritin (p= 0.073) did not reveal a difference regarding tumor cell type. Although the mean BAL ferritin and SIBC levels of deceased patients were not statistically different, their mean serum iron level (42.1 ± 28.0) was lower (74.7 ± 26.3) than that of survivors (p= 0.003). Serum ferritin levels of deceased patients were higher (395.3 ± 437.7), and statistically significant compared to survivors (72.9±46.3) (p= 0.006).

A weak positive correlation (p= 0.025, r: 0.349) between serum iron levels and survival, and a weak negative correlation (p= 0.034, r: –0.332) between serum ferritin levels and survival were detected.

Although SIBC and BAL ferritin levels at diagnosis are not correlated with the survival period in patients with LC, lower serum iron and higher ferritin levels are correlated with poor prognosis.

Key Words: Lung cancer, Bronchoalveolar lavage fluid, Ferritin, Iron, Iron-binding capacity

ÖZET

Primer Akciğer Kanserinde Serum Demir, Demir Bağlama Kapasitesi, Ferritin ve Bronkoalveoler Lavaj Ferritin Düzeyinin Prognostik Değeri

Akciğer kanseri (AK)'nin prognozunu tahmin etmek için çeşitli tümör markerleri araştırılmaktadır. Demir metabolizmasını yansıtan serum parametrelerinin ve bronkoalveloer lavaj (BAL) sıvısında ferritin ölçümünün AK'li hastalarda prognostik değerinin ortaya çıkarılması amaçlandı. Histopatolojik ve radyolojik olarak AK teşhis edilen hastaların yaş, cinsiyet, tümör hücre tipi, hastalığın evresi, teşhis anında serum ferritin, BAL ferritin, serum demir ve serum demir bağlama kapasitesi (SDBK) kaydedildi. Yaş ortalamaları 60.6 yıl olan 37 (%90.2) erkek, 4 (%9.8) kadın hasta alındı. Hastaların ortalama takip süreleri 11,9 ay idi. Hastaların 32'si (%78,0) takip süresinde ex olmuştu. Tümör hücre tipine göre serum demir (p= 0.175), SDBK (p= 0.577), serum ferritin (p= 0.426), BAL ferritin (p= 0.073) düzeyleri farklılık göstermedi. Ex olan hastaların yaşayan hasta grubuna göre BAL ferritin, SDBK ortalamaları istatistiksel olarak farklı değilken, serum demir (42.1 ± 28.0) ortalaması yaşayan gruba göre (74.7 ± 26,3) düşük saptandı (p= 0.003). Serum ferritini (395.3±437.7) ise yaşayan gruba göre (72.9 ± 46.3) yüksek ve istatistiksel olarak anlamlı bulundu (p= 0.006).

Serum demiri düzeyleri ile yaşam süreleri arasında pozitif yönde, zayıf bir ilişki (p= 0.025, r: 0.349), serum ferritin düzeyleri ile yaşam süreleri arasında negatif yönde, zayıf bir ilişki (p= 0.034, r: –0.332) saptandı.

Akciğer kanserli hastalarda teşhis anında SDBK ve BAL ferritin düzeyleri yaşam süresi ile ilişkili değilken, serum demirinin düşük ve serum ferritinin yüksek olması kötü prognoz ile ilişkilidir.

Anahtar Kelimeler: Akciğer kanseri, Bronkoalveoler lavaj sıvısı, Ferritin, Demir, Demir bağlama kapasitesi

INTRODUCTION

Ferritin is an important, hydrosoluble, iron-storage protein. Highest concentrations in the human body are found in the liver, spleen and bone marrow. However, ferritin was detected in all types of human cells including erythrocytes, leukocytes and thrombocytes (1,2). It was verified that ferritin concentrations increased in lower respiratory tracts of smokers, and chronic bronchitis, cystic fibrosis, pneumonia and lung transplant patients. Increases of intracellular ferritin levels were suggested to be a response to the higher iron load in these diseases. Extracellular ferritin can synthesize iron using oxygen and nitrogen products. High concentrations of extracellular ferritin might cause an oxidative damage in patients with the mentioned conditions. Alveolar cells may be exposed to hypoxia and nitric oxide in many respiratory diseases and the effect of such exposures on ferritin synthesis can make alveolar cells sensitive to oxidant damage catalyzed by iron (3).

Serum ferritin rapidly increases during acute infection or inflammation while serum iron rapidly decreases. Hepatoma, lung cancer (LC), pancreatic cancer and metastatic breast cancer are solid tumors which ferritin concentration increases most (2). Nevertheless, the sensitivity of serum ferritin in early cancer diagnosis does not exceed 40%. Moreover, its specificity is also low since there are many diseases that affect iron metabolism (4-7).

The possible factors that might cause the increase of serum ferritin levels in malignancies can be illustrated as follows:

1. Malignancy might cause anemia and iron accumulation in the reticuloendothelial system cells just like inflammation,

2. Ferritin levels might be elevated since tissue necrosis would lead to direct release of cytosolic ferritin (this might also be a consequence of chemotherapy or radiotherapy),

3. Experimental studies revealed that ferritin is cleared from blood circulation by liver parenchymal cells. Disruption of liver function due to the disease would lead to a decrease in clearance rate and an increase in serum ferritin level.

4. Ferritin synthesis in malignant cells can exhibit quantitative and qualitative abnormalities (2).

Bronchoalveolar lavage (BAL) is used in various lung diseases to investigate cells and other system elements representing inflammatory and immune systems of the lower respiratory tract epithelium. Although BAL alone cannot provide enough information for a definite diagnosis in many cases, cell

profiles of BAL may give important clues when combined with other clinical data. When BAL is performed with 100 ml of physiological saline on a normal adult, 40-60 ml of fluid containing 5-10 x 10^6 cells and 1-10 mg proteins is obtained (8).

In this study, the correlation between survival and serum iron level, serum iron-binding capacity (SIBC), serum ferritin level, and BAL ferritin level was investigated, and the prognostic value of these parameters was examined.

MATERIALS AND METHODS

Patient Groups

Patients without a BAL contraindication among those who underwent bronchoscopy with a LC prediagnosis in inpatient or outpatient clinics were included in the study. Informed consents were obtained. Patients with forced expiratory volume per one second under 1000 ml, uncooperative, or having moderate or serious asthma, oxygen resistant hypoxemia, hypercarbia, severe cardiac arrhythmia, persistent hemorrhagic diathesis, myocardial infarction in the last six weeks or endobronchial hemorrhage were excluded from the study (8). The age, gender, tumor cell type, stage of the disease (9), serum ferritin levels at diagnosis, BAL ferritin, serum iron, and SIBC of patients radiologically and histopathologically diagnosed with LC were recorded.

Bronchoscopy and BAL

Pre-medication with 10 mg diazepam (intramuscular) was performed 45 minutes before bronchoscopy. Anesthesia was conducted with injection of 5 ml Lidocaine 2% into the upper respiratory tract. Patients, placed in supine position, were trans-orally operated with fiber-optic Olympus BF1T-30 bronchoscope. BAL was performed according to chest radiography and thoracic computed tomography findings in patients prediagnosed with LC. Those with a peripheral mass lesion and no endobronchial lesion on bronchocopy underwent BAL through the relevant segment. Those with a central mass lesion and an endobronchial lesion on bronchoscopy underwent BAL through the same party middle lobe bronchus/lingula or lower lobe segments, providing that the lobe was unaffected by the disease. The tip of the fiberoptic bronchoscope was wedged into a bronchial segment. Saline heated up to 37°C was administered at a rate of 5 ml/sec through the catheter placed in the aspiration channel of the bronchoscope. Re-aspiration was performed with injector. For BAL, 100 ml saline was administered to all patients, and at least 60% was withdrawn. The material was transported to the laboratory within the injectors.

Preparation of Materials and Measurements

Blood was collected from the patients into 10 ml empty tubes on the bronchoscopy day in order to measure serum iron, serum ferritin, and SIBC. Blood samples were examined after a 10-minute centrifugation. Serum ferritin was evaluated in Advia Centavur (Bayer) hormone analyzer by using direct chemiluminometric technology (two-side sandwich immunoassay). Iron and SIBC were evaluated in Olympus AU-640 auto-analyzer with the colorimetric method. BAL fluid ferritin level was evaluated in Advia Centavur (Bayer) hormone analyzer by using direct chemiluminometric technology (two-side sandwich immunoassay).

Follow-up

Patients were referred to chemotherapy, radiotherapy, surgical treatment or supportive treatment after being diagnosed with LC, and then followed-up. At the end of a mean follow-up period of 11.9 months, the outcomes were recorded.

Statistical Analysis

Data was analyzed using the program Statistical Package for the Social Sciences (SPSS), version 12.0 for Windows. Definitive statistics were presented as mean, median, standard deviation, minimum, maximum and percentage. Significances between groups were compared using the Fisher test for qualitative data, and Student's t-test, Mann-Whitney U test, and Kruskal-Wallis test for quantitative data. Disease-free survival rates were assessed with the Kaplan-Meier method. Risk factors affecting the survival rates were determined through Cox regression analysis.

RESULTS

A total of 37 (90.2%) male and 4 (9.8%) female LC patients, with a mean age of 60.6±10.0 (41-79) years were included in the study (Table 1).

Smokers represented 92.7% (38) of all patients, who consumed about 47 packs/year. Only 3 (7.3%) patients had never smoked before. After LC diagnosis, 14 patients only received supportive treatment, 21 patients received chemotherapy, 10 patients received radical radiotherapy, 6 patients received surgical resection, 6 patients received palliative radiotherapy, and 3 patients received secondary chemotherapy.

The mean follow-up period was 11.9 (SD= 8.9) months. There were 32 (78.0%) death records during this period, 78.4% of which were male and 75% were female patients (p= 1.000). Mean ages were 61.6 ± 9.8 years for deceased patients and 57.2 ± 10.4 years for survivors. The mean survival period of the 32 patients who died was 8.1 ± 5.7 (0.5-21) months, being 25.6 ± 2.1 (24-30) months for the 9 survivors ($p < 0.001$). The mean survival period for all patients was 11.9 ± 8.9 (0.5-30) months (Figure 1).

Survival period was 5.3 ± 6.6 (1.5-17) months for small cell (SC) LC patients, and 12.9 ± 8.9 (0.5-30) months for non-small cell (NSC) LC patients (p= 0.033) (Figure 2).

Survival period was 22.5 months for stage 1A, 27.5 months for stage 1B, 17.0 months for stage 2B, 14.0 months for stage 3A, 6.4 months for stage 3B, and 9.9 months for stage 4.

The mean levels of serum iron (p= 0.175), SIBC (p= 0.577), serum ferritin (p= 0.426), and BAL fer-

Table 1. General characteristics of patients and survival

	Survivor	Exitus	Total
Gender (p=1.000)			
Male	8 (21.6%)	29 (78.4%)	37 (90.2%)
Female	1 (25.0%)	3 (75.0%)	4 (9.8%)
Tumor cell subtype			
SCLC	0 (0.0%)	5 (100.0%)	5 (12.2%)
Squamous	2 (40.0%)	3 (60.0%)	5 (12.2%)
Adenocarcinoma	3 (37.5%)	5 (62.5%)	8 (19.5%)
NSCLC	4 (17.4%)	19 (82.6%)	23 (56.1%)
Tumor cell type (p= 0.568)			
SCLC	0 (0.0%)	5 (15.6%)	5 (12.2%)
NSCLC	9 (100.0%)	27 (84.4%)	36 (87.8%)
Stage			
1A	1 (50.0%)	1 (50.0%)	2 (4.9%)
1B	2 (100.0%)	0 (0.0%)	2 (4.9%)
2B	1 (33.3%)	2 (66.7%)	3 (7.3%)
3A	2 (28.6%)	5 (71.4%)	7 (17.1%)
3B	0 (0.0%)	8 (100.0%)	8 (19.5%)
4	3 (15.8%)	16 (84.2%)	19 (46.3%)
Total	9 (22.0%)	32 (78.0%)	41 (100%)

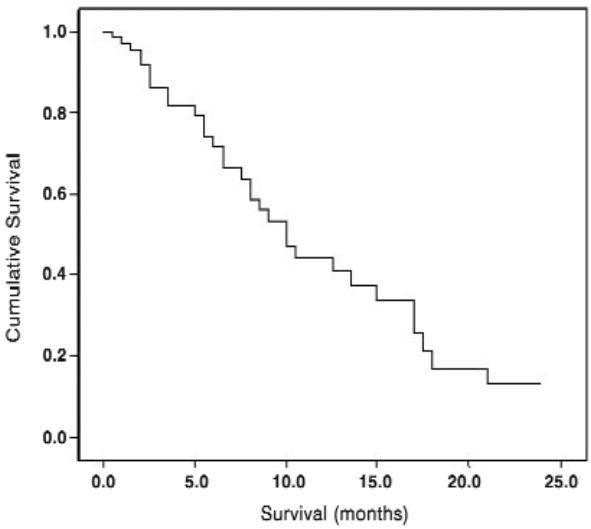

Figure 1. General survival

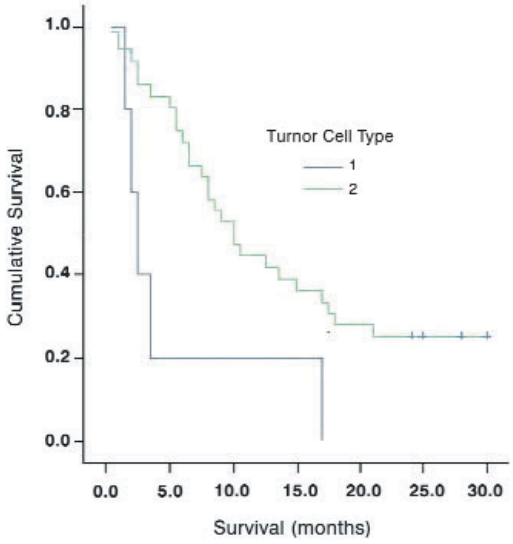

Figure 2. Survival with regard to tumor cell type (1=SCLC, 2=NSCLC).

ritin (p= 0.073) did not differ between tumor-type groups. Although the mean BAL ferritin and the mean SIBC of deceased patients were not statistically different compared to survivors, their mean serum iron (mean= 42.1 ± 28.0) was lower (mean=74.7 ± 26.3, p= 0.003) (Table 2-3).

Serum ferritin levels were higher (mean= 395.3 ± 437.7), and statistically significant compared to survivors (mean= 72.9 ± 46.3, p= 0.006). A weak positive correlation (p= 0.025, r:0.349) between serum iron levels and survival, and a weak negative correlation (p= 0.034, r:–0.332) between serum ferritin levels and survival were detected (Figure 3-4).

The models generated for factors negatively affecting survival are illustrated below:

In Model 1, considering age, gender, low serum iron level (< 50 mg/dl), high serum ferritin level (>220 ng/ml), SCLC, and tumor stages 3A, 3B, and 4 as risk factors, revealed that SCLC negatively affects survival 8.6 fold (p= 0.001, 95% CI:2.515-29.218), and that tumor stages 3A, 3B, and 4 negatively affect survival 4.6 fold (p= 0.036, 95% CI:1.106-19.337) (Table 4).

In Model 2, considering age, gender, low serum iron level (< 50 mg/dl), high serum ferritin level (>220 ng/ml), BAL ferritin levels, SCLC, and tumor stages 3A, 3B, and 4 as risk factors, revealed that SCLC negatively affects survival 8.7 fold (p= 0.001, 95% CI: 2.345-32.09), and that tumor stages 3A, 3B, and 4 negatively affect survival 4.6 fold (p= 0.036, 95% CI: 1.102-19.345) (Table 5).

Table 2. Laboratory parameters regarding patients' outcome

	Number	Serum Iron (mg/dl)	Serum Iron Binding Capacity (mg/dl)	Serum Ferritin (ng/ml)	BAL Ferritin (ng/ml)
Survivor	9	74.6	241.3	72.9	40.4
Exitus	32	42.1	219.2	395.3	63.2
Whole group	41	49.2	224.0	324.5	58.2
Mann-Whitney-U test		0.003	0.231	0.005	0.987

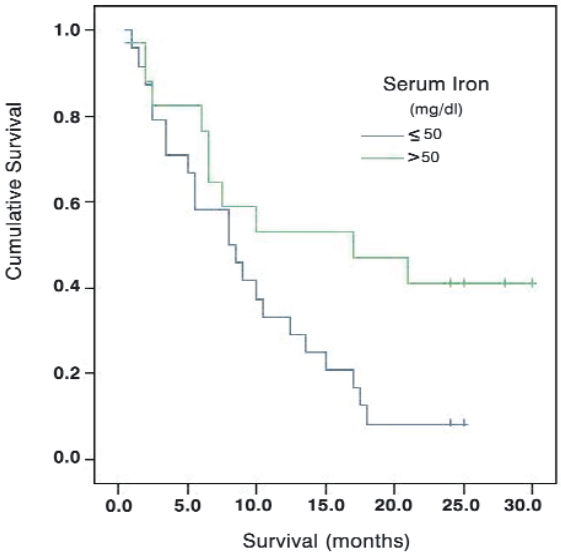

Figure 3. Survival with regard to serum iron level.

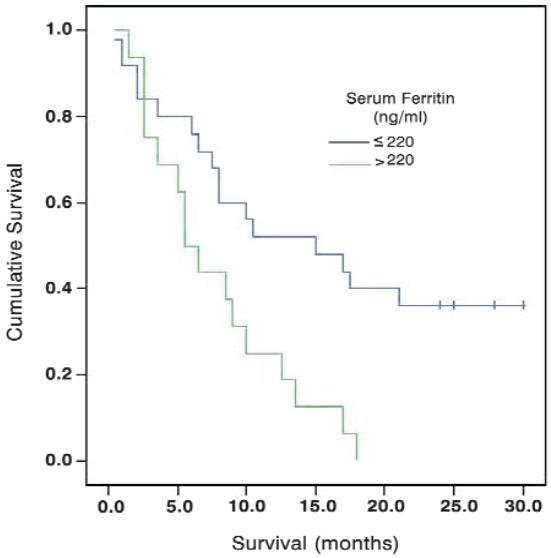

Figure 4. Survival with regard to serum ferritin.

In Model 3, considering age, gender, low serum iron level (< 50 mg/dl), BAL ferritin levels, SCLC, and tumor stages 3A, 3B, and 4 as risk factors revealed that SCLC negatively affects survival 8.7 fold (p= 0.001, 95% CI: 2.345-32.09), and that tumor stages 3A, 3B, and 4 negatively affect survival 4.6 fold (p= 0.036, 95% CI: 1.102-19.345) (Table 6).

In all of the generated Cox regression models, factors negatively affecting survival rates were similar. In none of the models the negative effects of low serum iron and high ferritin and BAL ferritin were present if the tumor type was SCLC and tumor stage was 3A, 3B or 4.

DISCUSSION

Although SIBC and BAL ferritin levels at diagnosis are not correlated with the survival period in patients with LC, lower serum iron and higher ferritin levels are correlated with poor prognosis.

Many studies investigate serum concentrations of ferritin. However, its possible diagnostic value as a tumor marker and biological function in the tumoral tissue and BAL fluid has rarely been discussed in the literature (10).

In patients with malignancy, serum ferritin levels are affected by both the amount of iron storage and

Table 3. Patients' outcome regarding serum parameters

	Number	Exitus	Survivor	Log Rank
Serum Iron (≤50 mg/dl)	24	22	2	
Serum Iron (>50 mg/dl)	17	10	7	0.031
Serum ferritin (>220 ng/ml)	16	16	0	
Serum ferritin (≤220 ng/ml)	25	16	9	0.004
Total	41	32	9	

Table 4. Model 1: Age, Gender (Male), Serum Iron (≤50 mg/dl), Serum Ferritin (> 220 ng/ml), Tumor Type (SCLC), Tumor Stage (3A, 3B, 4) Multiple Regression Model.

			95% Confidence Interval	
	p	Hazard Risk	Lower Limit	Upper Limit
Gender (male)	0.884	1.100	0.304	3.978
Age (year)	0.600	1.012	0.967	1.061
Serum Iron (≤50 mg/dl))	0.351	1.553	0.616	3.915
Serum Ferritin (>220 ng/ml))	0.223	1.708	0.722	4.040
Tumor Type (SCLC)	0.001	8.573	2.515	29.218
Tumor Stage (3A, 3B, 4)	0.036	4.625	1.106	19.337

the increase due to the tumor. While levels above 300 μg/l are considered as a moderate increase in normal cases, levels above 700-800 μg/l are considered as extreme increase (11,12). Kakari et al. observed a significantly higher serum ferritin level in patients with late-stage SCLC compared to limited stage (13).

In a recent report, we revealed that serum ferritin, iron, iron binding capacity and BAL ferritin measures do not help in differentiating LC from benign pulmonary diseases (14).

In 197 disease series of Milman et al., a negative correlation between serum ferritin levels and LC prognoses was identified as well as a significant decrease in survival rates of patients with serum ferritin levels above 300 μg/l (15). In this study, there was a relationship between low serum iron level, high serum ferritin level and poor prognosis, independently from the disease stage and tumor cell type. Considering threshold levels for serum iron of 50 mg/dl and serum ferritin of 220 ng/ml would be helpful in estimating the patients' prognoses.

Table 5. Model 2: Age, Gender (Male), Serum Iron (≤ 50 mg/dl), Serum Ferritin (> 220 ng/ml), Tumor Type (SCLC), Tumor Stage (Stage 3A, 3B, 4), BAL Ferritin (ng/ml) Multiple Regression Model

			95% Confidence Interval	
	p	Hazard Ratio	Lower Limit	Upper Limit
Gender (Male)	0.881	1.104	0.303	4.017
Age (year)	0.600	1.012	0.967	1.061
Serum Iron (≤50 mg/dl))	0.357	1.561	0.605	4.028
Serum Ferritin (>220 ng/ml))	0.224	1.707	0.721	4.039
Tumor Type (SCLC)	0.001	8.667	2.345	32.029
Tumor Stage (3A, 3B, 4)	0.036	4.616	1.102	19.345
BAL ferritin (ng/ml)	0.962	1.000	0.996	1.004

Table 6. Model 3: Age, Gender (Male), Serum Iron (≤ 50 mg/dl), BAL Ferritin (ng/ml), Tumor Type (SCLC), Tumor Stage (Stage 3A, 3B, 4), Multiple Regression Model

			95% Confidence Interval	
	p	**Hazard Risk**	**Lower Limit**	**Upper Limit**
Gender (Male)	0.743	1.242	0.339	4.549
Age (year)	0.313	1.023	0.979	1.069
Serum Iron (≤ 50 mg/dl)	0.130	1.955	0.821	4.652
BAL Ferritin (ng/ml)	0.931	1.000	0.996	1.004
Tumor Type (SCLC)	0.002	8.763	2.262	33.952
Tumor Stage (3A, 3B, 4)	0.021	5.300	1.281	21.933

Fracchia et al. detected a BAL ferritin level of 603 ± 548 ng/ml in 22 patients with peripheral LC and concluded that BAL ferritin level is a valuable tumor marker in LC. However, they did not report a survival analysis. Another finding of this study was the high standard deviation rates in both serum and BAL ferritin levels. This is associated with the fact that ferritin levels in body fluids are varying over a wide range, which may be correlated to some factors: (1) Variations in tumor histology, grade, and stage, biological differences related to individual host-response, (2) Difficulties in methods (in reaching the target) of visual diagnostic tools such as bronchoscopy, (3) Technical abilities of operators (16-18).

The correlation between LC and BAL ferritin level is not very clear. In order to specifically differentiate benignant and malignant lung diseases, it is not only necessary to investigate serum and BAL ferritin, carcinoembryonic antigens and/or other markers in combination, but also to reveal the accuracy of the compartmentalization theory and the role of smoking and inflammation.

Although there are literature reports investigating BAL ferritin level as a marker in LC, this study is the first one searching a correlation between BAL ferritin and survival. No correlation was detected between BAL ferritin level and primary LC prognosis.

In conclusion, low serum iron and high serum ferritin levels at diagnosis are indicating short survival in patients with LC, independently from the tumor type. Measuring these parameters at the time of LC diagnosis will be a guide to both follow-up and individual treatment planning.

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