Amyotrophic Lateral Sclerosis Outcome Measures and the Role of Albumin and Creatinine: A Population-Based Study

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IMPORTANCE There is an urgent need to identify reliable biomarkers of amyotrophic lateral sclerosis (ALS) progression for clinical practice and pharmacological trials.

OBJECTIVES To correlate several hematological markers evaluated at diagnosis with ALS outcome in a population-based series of patients (discovery cohort) and replicate the findings in an independent validation cohort from an ALS tertiary center.


MAIN OUTCOMES AND MEASURES The following hematological factors were investigated and correlated with survival: total leukocytes, neutrophils, lymphocytes, monocytes, glucose, creatinine, uric acid, albumin, bilirubin, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, creatine kinase, thyroid-stimulating hormones, and erythrocyte sedimentation rate; all analyses were performed separately by sex. The patient of the validation cohort also underwent bioelectrical impedance analysis for the calculation of fat-free mass.

RESULT Of the 712 patients in the examined period in Piemonte and Valle d’Aosta, 638 (89.6%) were included in the study. Only serum albumin (men: ≤4.3 vs >4.3 mg/dL, P < .001; women: ≤4.3 vs >4.3 mg/dL, P < .001) and creatinine levels (men: ≤0.82 vs >0.82 mg/dL, P = .004; women: ≤0.65 vs >0.05 mg/dL, P = .004) and lymphocyte count (men: ≤1700 vs >1700/μL, P = .04; women: ≤1700 vs >1700/μL, P = .02) were significantly associated with ALS outcome in both sexes with a dose-response effect (better survival with increasing levels). These findings were confirmed in the validation cohort. Multivariable analysis showed that serum albumin (men: hazard ratio [HR], 1.39; 95% CI, 1.05-1.80; P = .02; women: HR, 1.73; 95% CI, 1.35-2.39; P = .001) and creatinine (men: HR, 1.47; 95% CI, 1.11-1.95; P = .007; women: HR, 1.49; 95% CI, 1.07-2.05; P = .02) were independent predictors of survival in both sexes; no other hematological factor was retained in the model. In patients with ALS, serum albumin was correlated with markers of inflammatory state while serum creatinine was correlated with fat-free mass, which is a marker of muscle mass.

CONCLUSIONS AND RELEVANCE In ALS, serum albumin and creatinine are independent markers of outcome in both sexes. Creatinine reflects the muscle waste whereas albumin is connected with inflammatory state. Both creatinine and albumin are reliable markers of the severity of clinical status in patients with ALS and can be used in defining prognosis at the time of diagnosis.
Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder of adult life characterized by the involvement of upper and lower motor neurons and, in about 50% of patients, prefrontal areas. In most cases, ALS appears sporadically in the population; roughly 10% of patients have a positive family history for ALS or frontotemporal dementia.

Amyotrophic lateral sclerosis is almost invariably fatal with a median survival time of 2 to 4 years from onset and 1 to 3 years from diagnosis. The only drug that has been found to be effective in prolonging life is riluzole, which increases life expectancy by about 3 months.

Several clinical prognostic factors have been identified in ALS, namely age, site of onset, functional and respiratory status, cognitive function, noninvasive ventilation, some genetic mutations, and clinical phenotypes. In addition, various biological markers have been proposed as potentially related to a better ALS outcome including dyslipidemia, elevated levels of uric acid, and creatinine, and reduced granulocyte count. However, most of these markers have been evaluated only in small single-center series and have not been confirmed by subsequent studies.

The aim of this study was to assess the correlation of several hematological markers evaluated at diagnosis with ALS outcome in a population-based series of patients living in the Piemonte and Valle d’Aosta regions of Italy between January 1, 2007, and December 31, 2011. The study findings were then replicated in an independent validation cohort from an ALS tertiary center.

Methods

Discovery Cohort

The study design was approved by the institutional ethical committees of Azienda Ospedale Università, Città della Salute e della Scienza, and Azienda Ospedale Università Maggiore di Novara. Patients provided written informed consent.

All patients with ALS in the Piemonte and Valle d’Aosta regions of Italy (n = 712), identified through the Piemonte and Valle d’Aosta Register for ALS and diagnosed between January 1, 2007, and December 31, 2011, were eligible for enrollment in the study. All patients met the revised El Escorial diagnostic criteria for definite and probable laboratory-supported ALS. A complete clinical history was collected for each patient. Disease severity was assessed with the Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised scale (ALSFRS-R). Pulmonary function tests were performed at diagnosis and forced vital capacity (FVC) percentage of prediction was annotated. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Body weight was measured with individuals wearing only undergarments and no shoes by means of a stadiometer (precision, ±0.1 cm). Patients who could not maintain the erect position were weighed in the seated position on an electronic chair scale (Seca) while body height was determined by measuring the knee height. No differences were found between these methods. Levels of BMI were categorized according to the World Health Organization classification.

In addition, the decline rate for ALSFRS-R score and its 4 subscores (bulbar, fine motor, gross motor, and respiratory) was calculated as the mean monthly number of points lost from symptom onset to the time of diagnosis. The FVC and BMI decline were also calculated.

Patients underwent hematological examinations as part of the diagnostic workup. Blood sampling was performed after overnight fasting. The following hematological tests were considered for this study: total leukocytes, neutrophils, lymphocytes, monocytes, glucose, creatinine, uric acid, albumin, bilirubin, total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, creatine kinase, and erythrocyte sedimentation rate (ESR). Five male patients who had a creatinine level in the range from 1.3 to 1.8 mg/dL (to convert to micromoles per liter, multiply by 76.25), indicating a reduction of renal function, were excluded from the study.

A total of 565 patients also underwent an extensive genetic assessment using standard procedures. Thirty-seven patients (6.6%) carried a C9ORF72 GGGGCC repeat expansion, 17 (3.0%) carried SOD1 missense mutations, 6 patients (1.2%) carried TARDBP missense mutations, 1 patient carried an FUS and 1 patient carried an OPTN missense mutation, and 16 patients (2.8%) carried polyQ repeat expansions (≥31) in the ATXN2 gene.

Validation Cohort

This cohort consisted of 122 patients with ALS at different stages of the disease consecutively seen at an ALS tertiary center between 2007 and 2009. Patients underwent all the same evaluations of the discovery cohort plus fat-free mass (FFM; in kilograms), determined by bioelectrical impedance analysis using a single-frequency tetrapolar technique with an electrical current of 800 mA at 50 kHz (STA-BIA; Akern) according to a method validated for ALS.

Statistical Methods

Comparisons between means were made with the t-test or analysis of variance, comparison between categorical variables was made with the χ² test, and the equality of variances was confirmed with the Levene test. Correlations were calculated with the Pearson coefficient; because multiple comparisons were performed, P values were Bonferroni-adjusted (Table 1 and Table 2).

Survival was calculated from diagnosis to death, tracheostomy, or censoring date (December 31, 2013) using the Kaplan-Meier method and compared with the log-rank test. No patient was lost to follow-up. For survival analysis, each hematological factor was dichotomized according to its median value. Multivariable analysis was performed with the Cox proportional hazards model (stepwise backward) with a retention criterion of P < .10. Two separate models were used for men and women; the variables included in the model are listed in Table 2. A level of P < .05 was considered significant for multivariable analyses. To assess the prognostic performance of serum albumin, creatinine, and other significant prognostic factors, receiver operating characteristic (ROC) analysis was performed with the area under the curve.
factors, we calculated test specificity, sensitivity, positive predictive value, and negative predictive value using 1-year mortality after diagnosis as reference. The number needed to treat was also calculated. All tests were 2-tailed. Statistical analyses were carried out using a version 20.0 statistical package (SPSS).

Results

Discovery Cohort

Of the 712 patients in the examined period, 638 (89.6%) were included in the study, 352 men and 286 women. The remaining 74 patients were not included because of incomplete hematological data. Patients’ mean (SD) age at onset was 66.3 (10.7) years (range, 25.3-91.5 years) and mean (SD) ALSFRS-R score was 37.4 (7.5; range, 5-47). Patients included and not included in the study did not differ in regards to demographic or clinical variables (Table 1).

The results of hematological analyses are reported in eTable 1 in the Supplement. The levels of all hematological parameters except for lymphocytes and albumin significantly differed between sexes. All values were normally distributed within each sex.

Next, we analyzed the influence of hematological factors on patients’ survival. The overall median survival from diagnosis of the whole cohort was 1.7 years (interquartile range, 0.8-3.3 years). The results of univariate analyses for each hematological factor are reported in eTable 2 in the Supplement. Only serum albumin and creatinine levels and lymphocyte count were significantly related to ALS outcome in both sexes (Figure 1); patients’ survival increased with higher levels of serum albumin and creatinine and higher lymphocyte count. Among the other hematological factors, higher levels of total cholesterol and LDL cholesterol in men as well as lower LDL cholesterol to HDL cholesterol ratio and higher serum thyrotropin levels in women were significantly related to longer survival. To identify a dose-response effect, serum albumin and creatinine were also assessed according to their quartiles; both factors remained highly significant in both sexes, with a better survival with increasing levels (eFigures 1 and 2 and eTable 3 in the Supplement). The presence of genetic mutations did not modify the results (data not shown).

To evaluate the ability in predicting 1-year mortality, we calculated the sensitivity, specificity, positive predictive value, and negative predictive value of serum creatinine and albumin, ALSFRS-R score, FVC, and age (eTable 4 in the Supplement). In both sexes, serum albumin showed sensitivity and specificity similar to FVC, which is the prognostic factor with higher values, while creatinine had values similar to age and ALSFRS-R total score.

Multivariable analysis confirmed that albumin and creatinine levels were independent predictors of survival in both sexes; no other hematological factors were retained in the model (Table 2). As expected, other strong predictors of outcome were patients’ age, FVC, ALSFRS-R bulbar score (both sexes), ALSFRS-R respiratory score (men), and ALSFRS-R total score (women). Similar results were obtained when we included the rate of decline of ALSFRS-R score in the multivariable analysis instead of its value at the time of diagnosis (data not shown).

Next, the correlation between hematologic factors and patients’ clinical status at diagnosis was explored (eTable 5 in the Supplement). Creatinine was significantly correlated with the ALSFRS-R total score (Figure 2A), its gross motor, fine motor, and respiratory subscores in both sexes, and with FVC (Figure 2B) and BMI, only in men. A significant correlation was found between albumin and ALSFRS-R total score (Figure 2C), all ALSFRS-R subscores, and FVC (Figure 2D) in both sexes.

To better clarify mechanisms underlying the prognostic role of albumin and creatinine, we performed another exploratory analysis assessing whether they were correlated with markers of inflammatory state. In both sexes, serum albumin levels significantly decreased with the increase of total leucocytes, neutrophils, monocytes, and ESR while creatinine levels were not influenced by any marker of inflammatory state (eTable 6 in the Supplement).

Validation Cohort

To confirm our findings, we considered an independent clinical cohort of patients with ALS. This cohort included 122 patients (54 men, 68 women), with a mean (SD) age at onset of 59.8 (11.0) years (range, 32.7-83.6 years), disease duration of 2.5 (2.1) years (range, 0.5-10.8 years), and ALSFRS-R score of 25.8 (10.0; range, 3-45). Albumin levels were similar in men (mean [SD], 4.0 mg/dL [0.4 mg/dL]) and women (mean [SD], 4.0 mg/dL [0.3 mg/dL]) (to convert to grams per liter, multiply by 10), while serum creatinine levels were higher in men (0.67 mg/dL [0.21 mg/dL]) than in women (0.54 mg/dL [0.19 mg/dL]) (P<.001).
Mean (SD) BMI was 23.3 (4.7; range, 14.0-43.1) in men and 22.6 (4.7; range, 11.5-34.6) in women (P = .36). Mean (SD) FFM was 47.6 (9.6; range, 14.5-69) in men and 35.7 (7.6; range, 2.3-51.4) in women (P < .001). Body mass index and FFM were highly correlated with each other (men, r = 0.623, P < .001; women, r = 0.516, P < .001). Serum creatinine levels were correlated with FFM (men: r = 0.336, P = .02; women: r = 0.261, P = .04) (eFigure 3 in the Supplement) but not with BMI (men: r = 0.191, P = .18; women: r = 0.067, P = .60). Serum albumin was not correlated with BMI (men: r = 0.111, P = .43; women: r = 0.166, P = .18) or with FFM (men: r = 0.231, P = .10; women: r = 0.215; P = .08). In this cohort, serum albumin and creatinine correlated significantly with survival in both sexes (eFigures 4 and 5 in the Supplement).

Discussion

In our population-based series of patients diagnosed as having ALS in the regions of Piemonte and Valle d’Aosta from 2007 to 2011, we found that serum albumin and creatinine measured at time of diagnosis were markers of outcome in both sexes, even after correction for known prognostic factors. No other examined hematological factors were significantly related to survival at multivariable analysis. Moreover, a dose-response effect was found for albumin and creatinine in both sexes. These findings were confirmed in an independent validation cohort from a tertiary ALS center.

We also found that lower albumin and creatinine levels were strongly related to worse clinical function at diagnosis (ALSFRS-R score and FVC). Albumin levels were correlated with indices of inflammatory state and not with nutritional parameters. In the validation series, serum creatinine levels (but not albumin levels) were related to patients’ FFM, indicating that serum creatinine is a proxy of muscle mass. Sensitivity and specificity values in predicting 1-year mortality indicated that serum albumin and creatinine have properties similar to the best established prognostic factors of ALS such as FVC, ALSFRS-R score, and age. For all these factors, sensitivity was higher than specificity, indicating that they reliably predict a survival of less than 1 year.

Albumin is a plasma-nonglycosylated protein with various functions including transportation of several substances such as fatty acids, bilirubin, and regulation of colloidal osmotic pressure and has strong antioxidant properties. Albumin is synthesized by the liver and its metabolism is influenced by nutritional intake and inflammatory disorders. It has been reported that albumin is a prognostic marker in geriatric long-term care facility residents, individuals undergoing surgical interventions, patients with kidney disorders, internal medicine patients, and patients diagnosed as having cancer. It is unclear whether in these conditions albumin levels are a marker of patients’ nutritional status or chronic inflammatory state, which decreases the hepatic synthesis of albumin through the production of proinflammatory cytokines.

### Table 2. Discovery Cohort Multivariable Model in Men and Women*

<table>
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<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
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<tr>
<td><strong>Men</strong></td>
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<td>60-69</td>
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<td>70-79</td>
<td>3.08 (1.69-5.61)</td>
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<td>≥80</td>
<td>4.57 (2.08-10.0)</td>
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<td>FVC</td>
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<tr>
<td>≥85</td>
<td>1 [Reference]</td>
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<tr>
<td>≤85</td>
<td>1.91 (1.33-2.73)</td>
<td>&lt;.001</td>
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<tr>
<td>ALSFRS-R bulbar score</td>
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<tr>
<td>12</td>
<td>1 [Reference]</td>
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<tr>
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<td>1.63 (1.23-2.15)</td>
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<tr>
<td>ALSFRS-R respiratory score</td>
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<tr>
<td>12</td>
<td>1 [Reference]</td>
<td>.004</td>
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<tr>
<td>&lt;12</td>
<td>1.53 (1.15-2.05)</td>
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<td>Creatinine, mg/dL</td>
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<tr>
<td>Albumin, g/dL</td>
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<td>1 [Reference]</td>
<td>.02</td>
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<tr>
<td>≤4.3</td>
<td>1.39 (1.05-1.90)</td>
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<td><strong>Women</strong></td>
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<td>Age, y</td>
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<td>FVC</td>
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<td>≥0.85</td>
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<td>1.77 (1.25-2.49)</td>
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<td>ALSFRS R bulbar score</td>
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<td>Creatinine, mg/dL</td>
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<td>≥0.65</td>
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<tr>
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<td>1.49 (1.07-2.05)</td>
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<tr>
<td>Albumin, mg/dL</td>
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<tr>
<td>≥4.3</td>
<td>1 [Reference]</td>
<td>.001</td>
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<tr>
<td>≤4.3</td>
<td>1.73 (1.25-2.39)</td>
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<td>ALSFRS-R total score</td>
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<td>≥19</td>
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<tr>
<td>≤19</td>
<td>1.40 (1.01-1.94)</td>
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Abbreviations: ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale−Revised; FVC, forced vital capacity.

* Hematological factors were included in the Cox model, stratified according to their median value. Enteral nutrition and noninvasive ventilation were included as time-dependent variables. A second model was performed replacing ALSFRS-R total score and its subscores with their decline rates (data not shown).
In 2 studies, serum albumin decreased in patients with ALS compared with healthy control participants. However, to our knowledge, this is the first study demonstrating that albumin levels, evaluated at the time of diagnosis, are a strong and independent marker of ALS outcome and strictly correlated with patients’ clinical status. The lack of correlation of serum albumin with BMI in both cohorts indicates that in ALS, albumin levels are poorly influenced by nutritional status. On the other hand, the significant correlation of serum albumin with leukocytes, granulocytes, and ESR indicates that the lowering of albumin levels in patients with ALS is probably caused by their inflammatory state. In both our cohorts, the increase
of leukocytes and granulocytes was significantly related to a low ALSFRS-R respiratory subscore and reduced FVC, suggesting that respiratory failure could be one of the causes of inflammatory state in ALS.

In a previous study, chronic inflammatory state was identified in 80 patients with ALS in whom wide-range C-reactive protein, ESR, and fibrinogen levels were significantly higher than in matched control participants; these parameters showed a significant correlation with ALSFRS-R scores, which persisted on sequential examinations. In line with this observation, ALSFRS-R score was correlated with ESR and neutrophils count.

Serum creatinine is a product of nonenzymatic catabolism of creatine phosphate in muscles, produced at a fairly constant rate by the body (each day, 1%-2% of muscle creatine is converted to creatinine), and is transported from muscle through the circulation to the kidneys. Its levels depend on muscle mass; men tend to have a higher level than women because they generally have a greater muscle mass. In contrast to serum creatine kinase, creatinine levels are not modified by physical activity.

It has been shown that creatinine levels are correlated with lean body mass in healthy individuals and in adults and children with various diseases. Serum creatinine has also been found to be a predictive factor of survival in patients with spinal and bulbar muscular atrophy.

In both our cohorts, creatinine levels, which were independently related to ALS outcome, showed a significant correlation with ALSFRS-R score and with BMI, which are predictors of ALS prognosis. However, in our discovery cohort, which included patients enrolled at time of diagnosis, BMI was not a prognostic factor. On the other hand, in our validation cohort, serum creatinine was more strictly correlated with FFM than BMI. Fat-free mass consists of all tissues that are not body...
fat and therefore is more representative of the loss of muscle mass in ALS.\textsuperscript{41}

We did not find any other hematological factor to be independently related to ALS outcome at multivariable analysis. One of the most studied hematological factors in ALS with contrasting results is lipid status.\textsuperscript{5,6,8,29,42-44} A pivotal study\textsuperscript{5} found that higher LDL cholesterol to HDL cholesterol ratio was correlated with a better ALS prognosis. Conversely, in our discovery cohort, a lower LDL cholesterol to HDL cholesterol ratio was significantly related to better survival in women but was not retained in the multivariable analysis. Two studies have shown that both patients with ALS and their family members have a beneficial vascular risk profile (ie, a lower frequency of cardiovascular disorders) and that LDL cholesterol to HDL cholesterol ratio is not a significant prognostic factor when adjusted for known confounders.\textsuperscript{44,45} In addition, cholesterol levels have been found to be inversely related to respiratory function, suggesting the increased use of cholesterol as an energetic nutrient in respiratory failure\textsuperscript{42}; this finding is confirmed in eTable 5 in the Supplement.

The protective role of high levels of serum uric acid in neurodegenerative disorders is another area that has been explored following the demonstration that uric acid can have natural antioxidant properties in humans.\textsuperscript{46-47} There are indications that high levels of serum uric acid are related to a better prognosis in Parkinson disease,\textsuperscript{48,49} Huntington disease,\textsuperscript{50} multiple system atrophy,\textsuperscript{51} and mild cognitive impairment.\textsuperscript{52} In 2 small series, uric acid levels were found to be lower in patients with ALS than in control participants and were correlated with ALSFRS-R score decline rate\textsuperscript{7} or disease duration.\textsuperscript{53} In other studies, serum uric acid was independently correlated with the decline of ALSFRS-R score and of FVC in both sexes\textsuperscript{8} or only in male patients.\textsuperscript{43} In both our series, serum uric acid was not prognostic of ALS outcome and showed no correlation with clinical status in either sex.

A strength of our discovery cohort is that it is highly representative of the general ALS population. Our cohort includes roughly 90% of the patients who were diagnosed as having ALS in the study period in Piemonte and Valle d’Aosta regions. Captured cases did not differ for any significant demographic or clinical parameters from noncaptured patients. Our validation cohort consisted of a consecutive series of patients at different clinical stages from a tertiary center, recruited for a study on lean body mass; these patients had longer disease duration and more severe disease than those of the discovery cohort; and as predicted from our findings, in the discovery cohort, patients had lower serum albumin and creatinine levels, suggesting the progressive decrease of these hematological factors during the course of the disease.

**Conclusions**

In this study, we have shown that serum creatinine measured at diagnosis is an independent marker of ALS outcome because it reflects the state of muscle mass of the individual and is correlated with both the functional decline measured with ALSFRS-R score and FFM. Albumin levels are also independently related to ALS outcome, likely representing a marker of the inflammatory state rather than a marker of nutritional status. None of the other hematological factors examined were predictive of ALS outcome.

Both creatinine and albumin are reliable and easily detectable blood markers of the severity of motor dysfunction in ALS and could be used in defining patients’ prognosis at the time of diagnosis. Longitudinal studies on the variations of serum albumin and creatinine levels and their relationships to clinical status will help determine whether and how these hematological factors vary during the progression of the disease.
REFERENCES


