

## Original Research Article

# Association of serum uric acid, homocystine and ferritin among amyotrophic lateral sclerosis patients

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## ABSTRACT

**Background:** Amyotrophic lateral sclerosis (ALS) disease which is also known as motor neuron disease (MND) or Lou Gehrig's disease, is causes the death of neurons controlling voluntary muscles. There may have association of serum uric acid, homocystine and ferritin with amyotrophic lateral sclerosis. But we have not enough data regarding these issues. The aim of this study was to evaluate the association of serum uric acid, homocystine and ferritin with amyotrophic lateral sclerosis.

**Methods:** It was a case-control study conducted in the department of neurology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh from January 2010 to December 2011. Finalized 76 study people were divided into two equal groups containing 38 participants in each. In group I (case group) there were 38 patients with ALS and in group II (control group) there were 38 healthy people. The correlation of annual decline of ALS Functional Rating Scale-Revised (ALS-FRS) and forced vital capacity (FVC) were analyzed. Data were collected through pre-designed questioners and processed and analyzed by using SPSS version 11.5.

**Results:** In this study the inverse correlation between serum uric acid and the annual decline of ALS-FRS in male, spearman rho correlation was -0.37 ( $p<0.01$ ) and in female it was -0.78 ( $p<0.001$ ). The inverse correlation between serum uric acid and the annual decline of FVC were in male, spearman rho correlation was -0.33 ( $p<0.05$ ) and in female it was -0.39 ( $p<0.05$ ). Inverse correlation between homocystine and the annual decline of ALS-FRS in male, spearman rho correlation was -0.42 ( $p<0.02$ ) and in female, it was -0.64 ( $p<0.001$ ). The inverse correlation between homocystine and the annual decline of FVC in male, spearman rho correlation was -0.41 ( $p<0.04$ ) and in female, spearman rho correlation was -0.37 ( $p<0.05$ ). The inverse correlation between serum ferritin and the annual decline of ALS-FRS in male, spearman rho correlation was 0.47 ( $p<0.01$ ) and in female, spearman rho correlation was 0.76 ( $p<0.001$ ). The inverse correlation between serum ferritin and the annual decline of FVC in male, spearman rho correlation was 0.49 ( $p<0.001$ ) and in female, it was 0.71 ( $p<0.001$ ).

**Conclusions:** In most of the cases we found significant correlation of serum uric acid, serum homocystine and serum ferritin with amyotrophic lateral sclerosis (ALS). So all these components would be considered as some potential indicators or bio-markers of amyotrophic lateral sclerosis (ALS).

**Keywords:** Amyotrophic lateral sclerosis (ALS), Ferritin, Homocystine, Serum uric acid

## INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease (ND), which were reported as early as 1824 by Charles Bell and others. Lord Russell Brain proposed the term motor neuron disease (MND) to incorporate these conditions into a single spectrum of disorders.<sup>1</sup> MND is a progressive degenerative disease of the motor neurons of motor cortex, brainstem and spinal cord.<sup>2</sup> The prevalence of MND is 4-6 per 100,000 in most of the parts in the world, except the Western Pacific foci.<sup>3</sup> The annual incidence rate of the disease varies from 0.5 to 2.6 per 100,000 populations.<sup>4</sup> It is now considered as the 3rd most common neurodegenerative disorder after AD and PD.<sup>5</sup> There are approximately 5000 individuals with amyotrophic lateral sclerosis at any one time in the UK. The incidence is fairly uniform throughout the world, with the exception of a few high incidence foci, for example, on the Kii peninsula of Japan and the Western Pacific Island of Guam. Incidence rates for ALS in Europe and North America range between 1.5 and 2.7 per 100,000/year, while prevalence rates range between 2.7 and 7.4 per 100,000. The disease predominantly affects middle aged and elderly individuals, with a mean age of 55 years, though younger individuals can also be affected. The mean age of onset is 63 years and male to female ratio is about 1.3 to 1.5 for sporadic MND.<sup>6</sup> The incidence of ALS increases with each decade, especially after age 40 years and it peaks at age 74, decreasing thereafter.<sup>7</sup> In a systematic review, the mean age of ALS onset was 62 years and the incidence and mortality rates of ALS have been slowly increasing over decades.<sup>7</sup> For reasons that are not understood, men are affected more commonly than women, with a male/female ratio of approximately 1.6/1. ALS is sporadic in 90% of cases, but 5-10 % of cases the disease is familial, usually with an autosomal dominant mode of the inheritance.

People who develop ALS at young age are more likely to be male, less likely to have bulbar onset and more likely to have a slower disease course.<sup>8</sup> The disease usually begins with weakness and wasting of hand muscles associated with cramp-ing and fasciculation's in the arm muscles and then shoulder girdles. Less often, the symptoms begin in one leg as a foot drop soon followed by weakness of plantar flexor and other leg muscles. ALS is a relentlessly progressive, presently incurable disorder with an incidence of about 1/10000012. 50% patients die within 30 months 20% of patients survive between 5 years and 10 years 10% of patients with ALS survive for more than 10 years of symptoms.<sup>9</sup> Factors associated with reduced survival are older age at symptom onset, early respiratory muscle dysfunction, bulbar-onset disease. Independent predictors of prolonged survival are younger age at presentation, limb-onset disease, longer diagnostic delay.<sup>9</sup>

Factors contributing to the pathogenesis of ALS: genetics, excitotoxicity, oxidative stress, mitochondrial dysfunction, impaired axonal transport, neuro-filament aggregation, protein aggregation, inflammatory

dysfunction and contribution of non-neuronal cells, deficits of neurotrophic factors and dysfunction of signaling pathways and apoptosis.<sup>1</sup> Familial ALS accounts for only 5-10% of all ALS cases, remaining are sporadic. Mutations in the familial cases: Cu/Zn superoxide dismutase gene (SOD1) for about 20%, TARDBP (TDP-43) gene for about 2-5%. Two percent of sporadic case, SOD1 and TARDBP mutations also occur<sup>1</sup>. The risk factors for sporadic ALS that have been identified are increasing age, male sex and smoking.<sup>10</sup> Other agents include agricultural work, exposure to lead or mercury, athletic activity, milk ingestion, work in the textile or plastic industries, mechanical trauma and exposure to welding or soldering.<sup>11</sup>

It is said that, uric acid (UA) plays a vital role in amyotrophic lateral sclerosis (ALS). UA is produced from purines by the enzyme xanthine oxidase via the purine metabolism pathway.<sup>12</sup> Uric acids is a natural antioxidant, accounting for up to 60% of the free radical scavenging activity in human blood and can scavenge superoxide, the hydroxyl radical, and singlet oxygen.<sup>13</sup> Removal of superoxide helps to prevent its reaction with NO, blocking the formation of perox-ynitrite.<sup>14</sup> Uric acid is also very effective at preventing peroxynitrite from nitrating the tyrosine residues of proteins, thereby preventing the inactivation of cellular enzymes and modification of the cyto-skeleton.<sup>15</sup> Uric acid also has the ability to bind iron and inhibit iron-dependent ascorbate oxidation, preventing an increased production of free radicals that can further contribute to oxidative dam-age.<sup>16</sup> Uric acid acts upon astroglia and up-regulates protein levels of EAAT-1, a glutamate transporter, to protect neurons from glutamate-induced toxicity. On the other hand, homocysteine is a potential component of ALS.

A Medline literature identified all studies on hcy and ALS or motor neurons published from 1 January 1966 through 28 February 2009. Twelve studies (one in vitro, eight in vivo, and three studies on human subjects) were reviewed.<sup>17</sup> The in vitro and in vivo animal studies showed that Hcy can damage motor neurons by inducing oxidative stress and stimulating excitotoxic receptors. In initial studies on ALS higher median hcy levels compared to age- and sex-matched controls. Higher hcy levels were also correlated with a probable marker of disease expansion. Finally, an interim treatment with a high dose of methyl-cobalamin, which reduces hcy levels, active in enlightening multipart motor action in patients with ALS.<sup>17</sup> On the other hand, serum ferritin level is another potential component of amyotrophic lateral sclerosis. In a study it had been found, serum ferritin levels were significantly higher in the ALS group compared with the MSA and control groups in both males ( $p=0.001$  and  $p<0.0001$ , respectively) and females ( $p=0.034$  and  $p<0.0001$ , respectively) and serum transferrin levels were significantly lower in females of the sALS group compared with the MSA ( $p=0.016$ ) and control ( $p=0.015$ ) groups. The CSF ferritin level and the serum levels of total iron binding capacity and iron were similar among the

sALS, MSA and control groups. Survival analysis demonstrated that higher serum ferritin levels were predictors of reduced survival of sALS patients.<sup>18</sup>

The main objective of this study was to evaluate the association of serum uric acid, homocystine and ferritin with amyotrophic lateral sclerosis.

## METHODS

This was a case-control study was conducted in the department of neurology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh during the period from January 2010 to December 2011. Finalized 76 study people were divided into two equal groups containing 38 participants in each. In group I (case group) there were 38 patients with ALS and in group II (control group) there were 38 healthy people. The correlation of annual decline of ALS Functional Rating Scale-Revised (ALS-FRS) and forced vital capacity (FVC) were analyzed.

Convenient non-probability type of technique was followed to collect sample. According to the inclusion criteria for the case group, patients of definite ALS with upper motor neuron (UMN) signs and lower motor neuron (LMN) signs in three regions, cases of probable ALS with UMN signs and LMN signs in two regions with at least some UMN signs rostral to LMN signs and cases of possible ALS with UMN signs and LMN signs in one region (together), or UMN signs in two or more regions and UMN and LMN signs in two regions with no UMN signs rostral to LMN signs. Besides these, in inclusion evidence of LMN degeneration by clinical, electrophysiological or neuropathological and UMN degeneration by clinical examinations were considered.

Except this in inclusion process, the absence of electrophysiological and pathological evidence of other diseases that might explain the signs of LMN and/or UMN degeneration and neuroimaging evidence of other diseases processes that might explain the observed clinical and electrophysiological signs were considered with full care. On the other hand, according to the exclusion criteria of the study, patients with known other iron overloading conditions (congenital hemolytic anemia, chronic iron user, haemochromatosis), patients having a history of acute inflammation, malignant diseases like acute leukaemia and/or active Hodgkin's diseases, MND patients having iron deficiency anemia, patients with known chronic anemia and cases with abnormal TC, DC, ESR and CRP reports were excluded for case group.

On the other hand, according to the inclusion and exclusion criteria for the control group apparently healthy subjects of similar age and sex free from history of acute inflammation and abnormal TC, DC, ESR and CRP reports the participants were finalized for control group. This intervention was approved by the ethical committee of BSMMU.

Proper written consents were taken from all the participants before starting the main intervention. A pre-designed questioner was used to collect the data from the participants. Data were processed and analyzed using software SPSS version 11.5. For all analytical tests, the level of significance was set at 0.05 and  $p < 0.05$  was considered significant.

## RESULTS

In this study, in analyzing the ages of the participants of both the groups we found, the mean ( $\pm SD$ ) age of case group participants was  $37.1 \pm 12.9$  years whereas it was  $39.2 \pm 13.5$  years in control group participants. In case group male were 28 and female were 10 in number whereas in control group male were 29 and female were 9 in number. Besides these, the mean ( $\pm SD$ ) BMI ( $kg/m^2$ ) was  $20.69 \pm 2.73$  in case group and  $20.11 \pm 2.23$  in control group. In case group smoker was 26.30% whereas it was 21.10% in control group. On the other hand, the mean ( $\pm SD$ ) Symptom duration (in months), ALS-FRS (functional rating scale) and FVC (forced vital capacity) % were  $8.67 (\pm 12.47)$ ,  $40.3 (\pm 3.9)$  and  $94.3 (\pm 19.0)$ .

In case group the mean ( $\pm SD$ ) uric acid ( $mg/dL$ ) levels are  $3.8 (1.3)$  in male and  $2.9 (1.2)$  in female. On the other hand, in control group, in male it was  $6.7 (1.4)$  and in female it was  $5.9 (1.5)$ . Moreover, in case group the mean ( $\pm SD$ ) Homocystine ( $nmol/L$ ) levels were  $62.3 (9.3)$  in male and  $59.7 (8.7)$  in female. On the other hand, in control group, in male it was  $13.7 (2.5)$  and in female it was  $13.1 (2.4)$ . Besides these, in case group the mean ( $\pm SD$ ) ferritin ( $ng/mL$ ) levels were  $16.8 (4.3)$  in male and  $15.9 (5.1)$  in female. On the other hand, in control group, in male it was  $252.3 (56.7)$  and in female it was  $201.5 (41.4)$ . In this study in analyzing the inverse correlation between serum uric acid and the annual decline of ALS-FRS we found, in male patients (blue line) the spearman rho correlation was  $-0.37$  ( $p < 0.01$ ) and in female patients (red line) the spearman rho correlation was  $-0.78$  ( $p < 0.001$ ).

On the other hand, the in analyzing the inverse correlation between serum uric acid and the annual decline of FVC we found, in male patients (blue line) the spearman rho correlation was  $-0.33$  ( $p < 0.05$ ) and in female patients (red line) the spearman rho correlation it was  $-0.39$  ( $p < 0.05$ ).

In this study in analyzing the inverse correlation between serum homocystine and the annual decline of ALS-FRS we found, in male patients (blue line) the spearman rho correlation was  $-0.42$  ( $p < 0.02$ ) and in female patients (red line) the spearman rho correlation was  $-0.64$  ( $p < 0.001$ ).

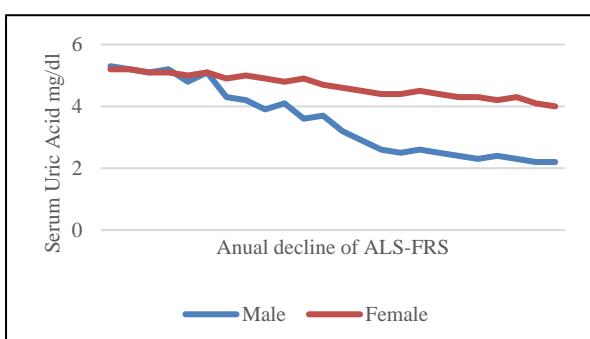
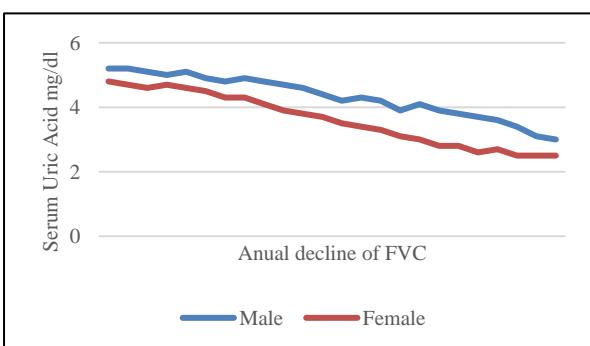
On the other hand, the in analyzing the inverse correlation between homocystine and the annual decline of FVC we found, in male patients (blue line) the spearman rho correlation was  $-0.41$  ( $p < 0.04$ ) and in female patients (red line) the spearman rho correlation it was  $-0.37$  ( $p < 0.05$ ).

**Table 1: Clinical background of participants (N=76).**

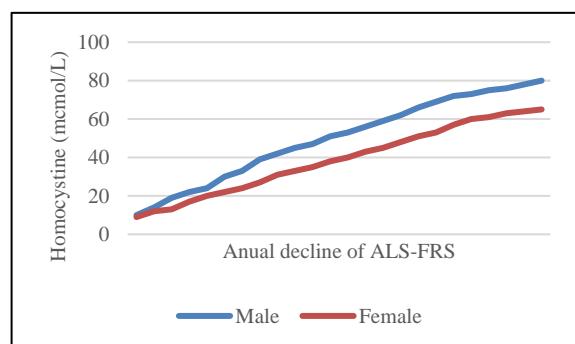
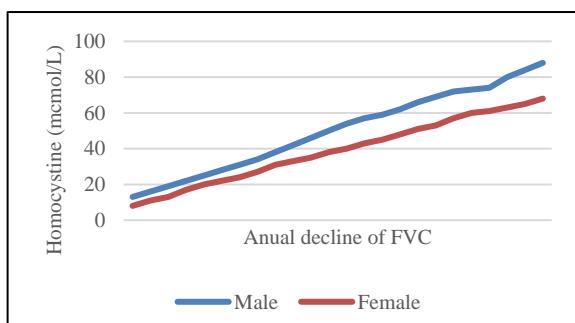
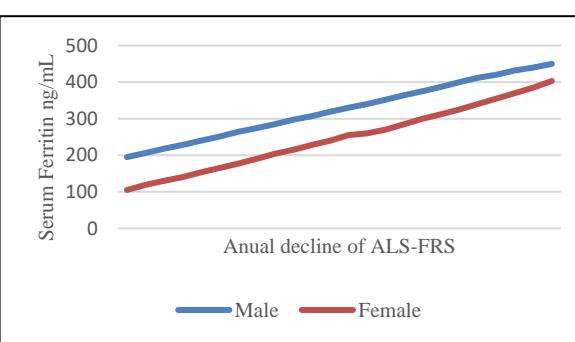
Components	Case	Control
<b>Men/women</b>	28/10	29/9
<b>Mean (<math>\pm</math>SD) age in year</b>	37.1 $\pm$ 12.9	39.2 $\pm$ 13.5
<b>BMI kg/m<sup>2</sup></b>	20.69 $\pm$ 2.73	20.11 $\pm$ 2.23
<b>Smoker (%)</b>	26.30%	21.10%
<b>Symptom duration (months)</b>	8.67 $\pm$ 12.47	
<b>ALS-FRS</b>	40.3 (3.9)	
<b>FVC %</b>	94.3 (19.0)	

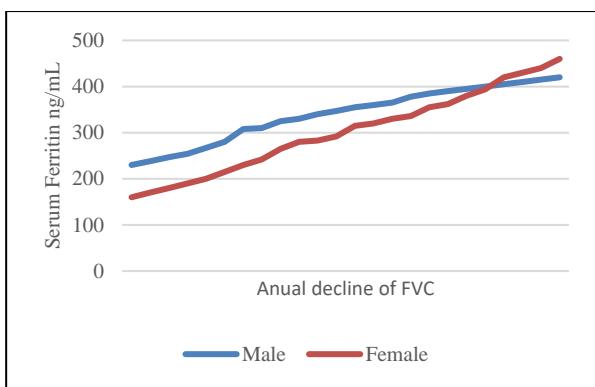
**Table 2: Uric acid, homocystine and ferritin levels in participants (N=76).**

Components	Case		Control	
	Mean ( $\pm$ SD)	Mean ( $\pm$ SD)	Male	Female
<b>Uric acid (mg/dL)</b>	3.8 (1.3)	2.9 (1.2)	6.7 (1.4)	5.9 (1.5)
<b>Homocystine (mcmol/L)</b>	62.3 (9.3)	59.7 (8.7)	13.7 (2.5)	13.1 (2.4)
<b>Ferritin ng/mL</b>	16.8 (4.3)	15.9 (5.1)	252.3 (56.7)	201.5 (41.4)

**Figure 1: The inverse correlation between serum uric acid and the annual decline of ALS-FRS among participants.****Figure 2: The inverse correlation between serum uric acid and the annual decline of FVC among participants.**

In this study in analyzing the inverse correlation between serum ferritin and the annual decline of ALS-FRS we found, in male patients (blue line) the spearman rho correlation was 0.47 ( $p<0.01$ ) and in female patients (red line) the spearman rho correlation was 0.76 ( $p<0.001$ ). On the other hand, the in analyzing the inverse correlation between serum ferritin and the annual decline of FVC we found, in male patients (blue line) the spearman rho correlation was 0.49 ( $p<0.001$ ) and in female patients (red line) the spearman rho correlation it was 0.71 ( $p<0.001$ ).

**Figure 3: The inverse correlation between serum homocystine and the annual decline of ALS-FRS among participants.****Figure 4: The inverse correlation between serum homocystine and the annual decline of FVC among participants.****Figure 5: The inverse correlation between serum ferritin and the annual decline of ALS-FRS among participants.**



**Figure 6: The inverse correlation between serum ferritin and the annual decline of FVC among participants.**

## DISCUSSION

The study was carried out in the department of neurology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from January 2010 to December 2011 for the duration of two years. A total of 76 participants were allocated into two groups. In case group there were 38 patients (28 males and 10 female) with ALS and in control group there were 38 (29 males and 9 female) healthy persons. The main objective of this study was to evaluate the association of serum uric acid, homocystine and ferritin with amyotrophic lateral sclerosis.

The study subjects in both case and control groups were predominantly workers/ housewife (65%) followed by day laborer (26%), few students and service holders. A large proportion of patients in both groups were non-smoker (73.7% of cases and 78.9% of controls). Approximately 11% of patients in case group and 5.3% patients in control group were ex-smoker.

In our study we have excluded inflammation, infection, iron overloading condition and found that out of 38 ALS patients 36.8% (n=14) had higher serum Ferritin level and 28.9% (n=11) has higher serum iron level. Out of 14 ALS patients with high serum Ferritin 10 were male and 4 were female (in 10 male ALS patient's serum ferritin level was >300pgm/L and in 4 female ALS patients' serum ferritin level was >120pgm/L). Out of 11 ALS patients with higher iron level 8 are male and 3 are female (in all cases total serum iron level was >150pgm/dL). Our study also found that the proportion of patients below 40 years of age was a bit higher and this may be due to most our patients are illiterate and they have no idea about their age. But in a previous study,<sup>19</sup> in Neuromuscular Clinic at the Massachusetts General Hospital (MGH) about 321 patients of ALS over ten years' period between January 1994 and December 2003 and found serum ferritin levels elevated in ALS patients and the majority of participants were male (59%) and the mean age was 56.3 years (mean 1: SD =13.0). further analysis in a small subgroup of 30 individuals with ALS and 30 healthy controls. The mean serum Ferritin level in the ALS population significantly

higher (ANOVA: male p=0.037, female p=0.032). The present case-control study was targeted to find out the association of serum uric acid level with Amyotrophic lateral sclerosis. For the research in total 38 patients (ALS cases) were selected of all age group along with control group. They were interviewed by specific questionnaire to find out the association. The mean age of the cases was  $37.1 \pm 12.9$  years. The mean age of onset of ALS varies from 50 to 65 years.<sup>20</sup> In this study mean age of ALS was found low in comparison to other studies. Out of 38 cases 28 were male and only 10 were female. BMI is considered as a potential component in such studies. The respondents were measured by the BMI (categorized in body build), where majority of them had was healthy level of BMI (cases 22 and control 26). But it is observed that underweight (BMI) is more likely in ALS cases.<sup>1</sup> In this study the involvement of anatomical sites at onset were identified by interviewing the cases. Among the cases majority had the onset of ALS by spinal involvement and some bulbar onset were prominent. According to the study result about 24% of cases, muscles of the bulbar region are affected first. In approximately 25% of patients, weakness begins in bulbar-innervated muscles (bulbar-onset ALS).<sup>21</sup> In our study, the mean duration of illness presented to us was  $8.67 \pm 12.47$  months. Among them 19 cases were more than 12 months' duration. Following the ALS functional rating scale score interpreted by Carmel Armon in Medscape wed page, ALS cases were categorized to mild (>40), moderate (39-30), severe (<30) and advanced (<20). One case was in advanced state and 6 were in severe state, others (30) were in mild to moderate state of the disease among the ALS cases. Respondents with smoking history group showed more likely to develop ALS than the respondents with no smoking history. The association between smoking and ALS status showed statistically significant ( $p \leq 0.05$ ). Smoking is possibly associated with ALS. A 2009 review concluded that smoking was an established risk factor for ALS.

According to the research of Armon C Twenty-eight titles were identified, but only 7 articles met inclusion criteria. Of these, 1 provided class II evidence, and 1 class III evidence: both showed increased risk of ALS with smoking. The class II study showed a dose-response effect, and risk decreasing with number of years since quitting smoking.<sup>1</sup> In this study, variable analysis revealed that the mean of uric acid in ALS cases is lower than in control group. Where the P value is <0.001 which explains uric acid level declines significantly in ALS. Various studies support these findings except few. Association analysis of ALS functional rating scale with uric acid level revealed that UA is significantly related with ALS functional rating scale ( $p$  value <0.05). That indicates decrease in uric acid level with the decline of ALS-FR scale (severity).

On the other hand, uric acid declines with the duration of the disease onset. Various studies showed consistently with the above result. Study variable analysis revealed that the mean of uric acid in female is significantly lower than male ALS cases ( $p$  value is <0.001). Where mean of UA

in female are 3.55. Similar report was found in another study.<sup>22</sup> For this, disease progression rate is higher among female ALS due to their lower serum UA level than male. In our study we have found no significant difference of mean of UA between bulbar and spinal onset ALS which is in contrast to the result of a study done in Italy.<sup>23</sup> The current study design does not allow us to conclude the causal relationship between low uric acid level and ALS. But decreased serum levels of UA in ALS patients compared to control might be the outcome of an oxidative stress-related process in the CNS, meaning that this decrease is resulting from the direct reaction between UA and oxidizing agents with the metabolism of UA.<sup>24</sup>

## CONCLUSION

In most of the cases we found significant correlation of serum uric acid, serum homocystine and serum ferritin with amyotrophic lateral sclerosis (ALS). So all these components would be considered as some potential indicators or bio-markers of amyotrophic lateral sclerosis (ALS). These findings of this study may be helpful in further studies and in treatment arena. But as it was a single centered study with a small sized sample. So the findings may not reflect the exact scenario of the whole nation. For more specific information, we would like to recommend for conducting similar more studies with some larger sized sample.

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*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Ethics Committee*

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