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Association of Serum Creatinine Level among Patients with Amyotrophic Lateral Sclerosis

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Abstract

Background: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative condition for which there is no single diagnostic test or biomarker. These is necessity to identify reliable biomarkers of ALS progression for clinical practise. Plasma creatinine has been described as a prognostic biomarkers for ALS patients. **Objective:** The purpose of the present study was to determine the association of serum creatinine in patients with amyotrophic lateral sclerosis. **Methodology:** This analytical cross-sectional study was conducted in the Department of Neurology at Dhaka Medical College Hospital, Dhaka, Bangladesh from January 2019 to December 2020 for a period of two years. The amyotrophic lateral sclerosis patients were enrolled in group I and age and gender matched healthy control were enrolled in group II. Clinical variables were obtained from the ALS patients and control groups including age, sex, BMI, site of onset, disease duration and other relevant information. Focused and detailed neurological examination was performed in each of the participants. Revised ALS functional rating scale (ALS-FRS) was also performed for functional assessment. Venous blood samples were collected for serum creatinine investigations. **Results:** A total number of 70 patients were enrolled for this study of which 35 cases of ALS were in group I and the rest of 35 healthy participants were in group II. The mean age was 52.8±12.73 years in group I and 53.57±6.56 years in group II. More than half (51%) patients had serum creatinine level less than 0.8 mg/dL in group I and not found in group II. The mean serum creatinine was 0.76±0.17 mg/dl in group I and 1.03±0.12 mg/dl in group II (p=0.01). The mean ALS-FRS was 26.88±4.88 in serum creatinine less than 0.60 (mg/dL), 26.83±3.81 in serum creatinine 0.61-0.79 (mg/dL), 30.38±5.3 in serum creatinine 0.80 to 1.00 (mg/dL) and 36.0±2.83 in serum creatinine more than 1.00 (mg/dL) (p<0.01). The mean serum creatinine was 0.72±0.13 (mg/dL) in limb onset, 0.73±0.15 (mg/dL) in bulbar onset and 0.95±0.08 (mg/dL) in mixed (p<0.01). **Conclusion:** Serum creatinine level is significantly lower in amyotrophic lateral sclerosis patients and low serum creatinine significantly associated with increased severity of the disease as well as pattern of onset of the disease and ALS-FRS in patients with amyotrophic lateral sclerosis. *[Journal of National Institute of Neurosciences Bangladesh, January 2025;11(1):19-27]*

Keywords: Serum creatinine; Amyotrophic Lateral Sclerosis; ALS

Introduction

Amyotrophic Lateral Sclerosis (ALS) is a rapidly progressive, invariably fatal neurological disease. It is characterized by the selective loss of upper motor neurons, which originate in the motor cortex and lower motor neurons, which connect the spinal cord and brainstem to skeletal muscles[1]. In ALS both upper and lower motor neurons are simultaneously affected and patients have combination of both upper and lower motor neuron signs. The usual presentation is wasting and weakness of limbs and/or bulbar muscles. The average age of onset is 55 to 60 years and death usually follow from respiratory failure, 2 to 3 years from symptom onset[2].

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Dissociated pattern of muscle atrophy is specific for amyotrophic lateral sclerosis and is not evident in amyotrophic lateral sclerosis and neuromuscular mimicking disorders such as Kennedy's disease or autoimmune motor neuropathy. Cortical hyperexcitability appears to underlie the development of the dissociated pattern of muscle wasting in amyotrophic lateral sclerosis[3]. In addition, a split-hand plus phenomenon, referring to preferential weakness of the APB muscle when compared to the flexor pollicis brevis, was also reported as a specific clinical feature of amyotrophic lateral sclerosis mediated by cortical hyperexcitability. More recently, split leg like preferential weakness of posterior calf muscles and split elbow like preferential weakness of the biceps brachii compared to the triceps muscle were also reported as specific clinical features of amyotrophic lateral sclerosis and related to cortical dysfunction[4].

The presentation, progression and the fatality of the amyotrophic lateral sclerosis showed remarkable variability among the patients. The reason behind it is not known. Till date there is no biomarker which could predict the severity and the progression of the disease. Several researches showed a spotlight on serum creatinine level. The serum creatinine level has been suggested as a muscle mass biomarker in amyotrophic lateral sclerosis, with level correlating inversely with the rate of disease progression[5-7].

Serum creatinine is a product of non-enzymatic catabolism of creatinine phosphate in muscles, produced at a constant rate by the body (each day, 1.0% to 2.0% of muscle creatine is converted to creatinine) and is transported from muscle through the circulation to the kidneys[8]. Its level depends on muscle mass; men tend to have higher level than women because they generally have a greater muscle mass. In contrast to serum creatinine kinase, creatinine levels are not modified by physical activity[9]. Some study showed that serum creatinine has also been found to be a predictive factor of survival in patients with spinal muscular atrophy and progressive bulbar palsy[10]. Serum creatinine level found lower in patient with limb onset than in those with bulbar onset. An early decrease of creatinine level associated with a short disease duration[11].

Some studies reported that creatinine levels are low in amyotrophic lateral sclerosis patients[12] and baseline serum levels of creatinine were correlated with annual decline of ALSFRS-R score in one study. Creatinine at diagnosis may also be a strong factor of disease duration[7]. The amyotrophic lateral sclerosis functional rating scale-revised (ALSFRS-R) has become the standard to evaluate amyotrophic lateral sclerosis disease progression. Association of serum creatinine with amyotrophic lateral sclerosis in Bangladeshi population is largely unknown. The aim of the study was to determine the association of serum creatinine with the disease severity and the progression of the amyotrophic lateral sclerosis.

Methodology

Study Settings and Population: This analytical cross-sectional study was conducted in the Department of Neurology at Dhaka Medical College, Dhaka, Bangladesh from January 2019 to December 2020 for a period of two years. The adult patients more than or equal to 18 years of age who fulfilled the revised El Escorial diagnostic criteria of ALS for both gender admitted in the neurology department were included in the study as case and individuals with age and gender matched healthy volunteers, as control.

Study Procedure: The data regarding the epidemiology, clinical profiles, laboratory values, electrodiagnostic findings of 35 patients of ALS were enrolled after fulfilling the criteria. Control groups were included outpatient healthy individuals with no neurodegenerative disease, aneamia, malignancy and no inflammatory disease, coming from the same geographical origin, and matched with ALS patients for age and gender. For the purpose of the analysis, ALS patients were considered as group I and healthy participants were considered as group II. An ALS group consisting of 35 patients and another group consisting of equal number of healthy volunteers matched with age and gender. The final diagnosis of Amyotrophic lateral sclerosis was made according to revised EL Escorial Criteria of World Federation of Neurology on the basis of clinical and EMG findings excluding the other differential diagnosis of ALS. For each patient, clinical data including information on diagnosis, gender, age, site of onset, age of onset, and disease duration was obtained. The site of onset was defined as either bulbar or limb onset. Bulbar onset was defined as symptoms first occurring at the bulbar level with dysphagia, dysphonia, or dysarthria. Limb onset was defined as symptoms first occurring in the limbs. The age of onset was determined as the time at which motor weakness was first noted by the patient and disease duration of ALS as the time since onset (first symptoms). Detailed neurological examination was performed in all participants. ALSFRS-R (ALS functional rating scale-revised) score was measured in all the amyotrophic lateral sclerosis patients. EMG for ALS

patients was done in study place. The serum creatinine was measured in ALS patients and controls.

Statistical Analysis: Differences were considered significant at $p < 0.05$ in two tailed test. Analyses were performed with the SPSS version 22.0 software Each question was coded with a number and all alternative responses for each question was registered to enable a statistic analysis, The data was systematically described, summarized, and presented through descriptive statistics. Continuous variables were expressed as means± standard deviations (SD) for the normally distributed data and for other as median (IQR). While categorical variables were described as frequency and percentage. To compare the baseline characteristic between the case and the control chi square test/fisher's exact test as appropriate was used for categorical data and Student's t test or one way ANOVA for the continuous data as appropriate. A binary logistic regression model was formulated to determine the odd ratio with 95.0% CI. For the continuous variable whereas Chi-square test was also considered to express association between categorical variable. P value less than 0.05 was considered as level statistical significance and $p<0.001$ was considered highly significant.

Ethical Consideration: All procedures of the present study were carried out in accordance with the principles for human investigations (i.e., Helsinki Declaration 2013) and also with the ethical guidelines of the Institutional research ethics. Formal ethics approval was granted by the local ethics committee (Ref: IRB/NINS/…..). Participants in the study were informed about the procedure and purpose of the study and confidentiality of information provided. All participants consented willingly to be a part of the study during the data collection periods. All data were collected anonymously and were analyzed using the coding system.

Results

In this study, among 70 study subjects more than one third 15(43.0%) patients belonged to age 51 to 60 years in group I and 18(51.0%) in group II. The mean age was 52.8±12.73 years in group I and 53.57±6.56 years in group II. Almost three fourth (74.0%) patients were male in group I and 25(71.0%) in group II. It was also observed that more than half (52.0%) patients had BMI 18.5 to 22.9 kg/m2 normal in group I and 20(57%) controls had BMI 23 to 29.9 kg/m2 overweight in group II. The mean BMI was 18.86±1.99 kg/m2 in group I and 22.98±1.87 kg/m2 in group II. The difference was statistically significant ($p<0.05$) between two groups (Table 1).

Table 1: Distribution of the Study Subjects by Demographic Profiles (n=70)

Variables	Group I	Group II	P value
Age Group			
• ≤50 Years	11(31.0%)	10(29.0%)	
• 51 to 60 Years	15(43.0%)	18(51.0%)	0.71
• 61 to 70 Years	8(23.0%)	7(20.0%)	
• More than 70 Years	1(3.0%	0(0.0%)	
Total	**35(100.0%)**	**35(100.0%)**	
Mean (SD)	52.8±12.73	53.57±6.56	0.71
Range	18 to 73	40 to 66	
Gender			
• Male	26(74.0%)	25(71.0%)	0.79
• Female	9(26.0%)	10(29.0%)	
BMI (kg/m^2)			
Under nutrition	15(43.0%)	0(0.0%)	0.001
Normal	18(52.0%)	20(57.0%)	
Overweight	2(6.0%)	15(43.0%)	
Mean±SD	18.86±1.99	22.98±1.87	
Range	15.44-25.73	20.06-30.83	

Under nutrition=Less Than 18.5; Normal=18.5 to 22.9; Overweight=23 to 29.9

Serum creatinine values of study subjects revealed that more than one third (43.0%) subjects had serum creatinine 0.80-1.00 mg/dl in group I and 14(40.0%) in group II. The mean serum creatinine was 0.76±0.17 mg/dl in group I and 1.03±0.12 mg/dl in group II. The difference was statistically significant (p=0.01) between two groups (Table 2).

Table 2: Distribution of the Study Subjects by Serum Creatinine (n=70)

Serum creatinine	Group I	Group II	P value
<0.60 mg/dL	0(0.0%)	6(17.0%)	
0.61 to 0.79 mg/dL	0(0.0%)	12(34.0%)	0.01
0.80 to 1.00 mg/dL	14(40.0%)	15(43.0%)	
1.01 to 1.50 mg/dL	21(61.0%)	2(9.0%)	
Mean±SD	1.03±0.12	0.76±0.17	0.01
Range	0.82 - 1.3	0.55 - 1.26	

The mean ALS-FRS was 26.8±5.63 in BMI less than 18.5(kg/m2), 29.56±3.91 in BMI 18.5-22.9 (kg/m2) and 35±5.66 in BMI 23-29.9 (kg/m2). The mean serum creatinine was 0.74±0.16 (mg/dl) in BMI <18.5(kg/m2), 0.9±0.2 (mg/dL) in BMI 18.5-22.9 (kg/m2) and 1.03±0.13 (mg/dl) in BMI 23-29.9 (kg/m2). The difference was statistically significant ($P<0.05$) between two groups (Table 3).

Table 3: Serum Creatinine Levels and ALS-FRS Scores in ALS Patients according to BMI values (Mean±SD)

	BMI (kg/m^2)			P value
	<18.5 (n=15)	18.5-22.9 (n=18)	23-29.9 (n=02)	
ALS –FRS	26.8±5.63	29.56±3.91	35±5.66	0.001
Range (min-max)	18-40	22-38	31-39	
Serum creatinine (mg/dl)	0.74±0.16	0.9±0.2	1.03±0.13	0.001
Range (min-max)	0.55-0.99	0.55-1.26	0.80-1.26	

Association between serum creatinine levels with pattern of onset of ALS had been shown That the mean serum creatinine was 0.72±0.13 (mg/dl) in limb onset, 0.73±0.15 (mg/dl) in bulbar onset and 0.95±0.08 (mg/dl) in mixed. The difference was statistically significant ($p<0.05$) between two groups (Table 4).

Table 4: Association between Serum Creatinine Levels with Pattern of Onset of ALS (n=35)

Pattern of onset of ALS	n	BMI (kg/m^2) Mean±SD	Range (min-max)	P value
Limb onset (A)	25	0.72±0.13	0.55-1.26	
Bulbar onset (B)	3	0.73±0.15	0.59-0.99	
Mixed (C)	7	0.95±0.08	0.61-1.26	
A vs B vs C				0.01^s
A vs B				0.91^{ns}
A vs C				0.01^s
B vs C				0.01^s

Association between serum creatinine levels and ALS-FRS was shown in figure IV.

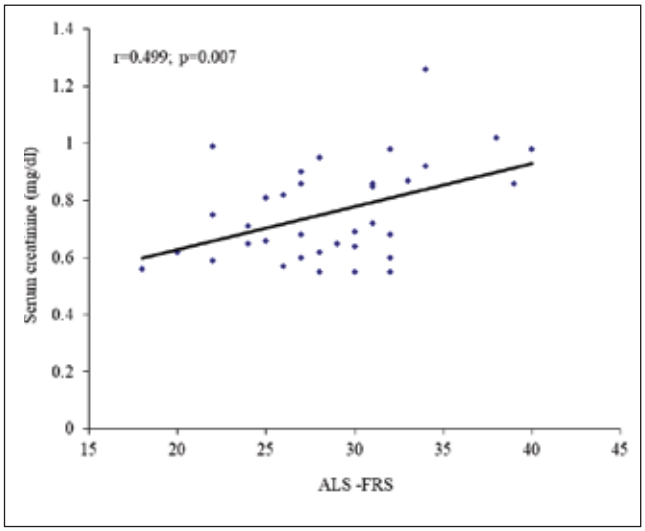

Figure I: Scatter diagram showing positive significant Pearson's correlation (r=0.499; p=0.007) between ALS –FRS and serum creatinine.

Discussion

This case-control study was conducted in the Neurology department of Dhaka Medical College Hospital, Dhaka, included 35 patients with amyotrophic lateral sclerosis as case (Group I) and 35 individuals with no neurodegenerative disorders as control (Group II). This study documented that the presence of decreased serum creatinine in patients with amyotrophic lateral sclerosis compared to age and gender matched controls at a single center in Bangladesh. The mean serum creatinine was 0.76±0.[17] mg/dl in group I and 1.03±0.12 mg/dl in group II. The difference was statistically significant (p=0.01) between two groups. This finding supported the previous studies. Japanese group found decreased serum creatinine levels in SALS patients and decreased serum creatinine was correlated with the annual decline rate of ALS-FRS[12-13]. An Italian group also found that decreased serum creatinine levels were more prevalent among SALS patients[14].

In the current study it was observed that 43% patients belonged to age 51 to 60 years in group I and 51.0% in group II. The mean age was 52.8±12.73 years in group I and 53.57±6.56 years in group II. The difference was statistically not significant (p=0.71) between two groups. Zheng et al[15] study observed that the mean age was 53.85±4.98 years in amyotrophic lateral sclerosis and 51.26±4.13 years in controls which support with the present study. Similarly, in another study Chen et al[12] found the mean age was 53.29±11.72 years in SALS patients and 53.35±11.59 years in controls. The difference was statistically not significant (p>0.05) between two groups, which are comparable with the current study. On the other hand, Patin et al[11] found the mean age was 64.65 ± 11.56 years, which is higher with the present study. Higher mean age also observed by Ikeda et al[13] and Nadjar et al[16]. The higher mean age and age range obtained by the above authors may be due to geographical variations, racial, ethnic differences, and genetic causes may have significant influence on their study subjects.

In this present study, it was observed that 74.0% patients were male in group I and 71.0% in group II. The difference was statistically not significant (P>0.05) between two groups. Similarly male predominant was also observed by Saha et al[17], Zheng et al[15], Patin et al[11] and Chen et al[12], which are closely resembled with the present study, which support with the present study.

The existing diagnostic criteria for definite, probable and possible amyotrophic lateral sclerosis require at

least one upper motor neuron (UMN) sign[18]. In this present study, it was observed that 60.0% patients of amyotrophic lateral sclerosis had definite followed by 31.0% had probable and 9.0% had possible. Number of definite, probable and possible amyotrophic lateral sclerosis increased with the addition of the findings of the electrophysiological studies to clinical criteria as per El Escorial criteria with clinical examination alone[17]. Traynor et al[19] study observed that 30.0% definite, 31.0% probable and 35.0% possible amyotrophic lateral sclerosis and in another study Beghi et al[20] reported that 30.0% definite, 35.0% probable amyotrophic lateral sclerosis and 38.0% had possible amyotrophic lateral sclerosis. In this study number of definite amyotrophic lateral sclerosis was higher and possible amyotrophic lateral sclerosis were lower, both statistically significant, after addition of EMG findings with that of clinical examination. This was because of the fact that EMG can detect LMN features in regions without clinical features of LMN.

In this current study, it was observed that 46.0% patients belonged to age of onset 51 to 60 years. The mean age of onset was 52.57±12.67 years with ranged from 18 to 74 years. Huisman et al[21] study found the mean age of onset in clinic populations is about 58 years and in population studies about 64 years[22] but it can affect people of any age reported by Mehta et al[23] which is comparable with the present study.

In this present study, it was observed that 71.0% patients had limb onset followed by 20.0% had mixed and 9.0% had bulbar onset. Saha et al[17] study observed that 57.0% patients had upper limb onset, followed by 33.0% and 9.0% cases; that had lower limb onset and bulbar onset respectively. Ikeda et al[13] study found that limb onset had 89.0% cases and bulbar onset had 11.0% cases. Almost similar findings were also observed by Veyrat-Durebex et al[24] and Nadjar et al[16].

In this current study, it was observed that the mean disease duration was 8.17±4.98 months with ranged from 1 to 25 months. In another study Ikeda et al[13] study showed the mean symptom duration was 23.7±21.3 months in amyotrophic lateral sclerosis patients, which differ with the present study. This may be due to enrollment criteria in the present study. The Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS) is an instrument for evaluating the functional status of patients with Amyotrophic Lateral Sclerosis. It can be used to monitor functional change in a patient over time[21]. In this current study, it was observed that the mean revised amyotrophic lateral sclerosis functional rating scale score was 28.69 ±5.1 with ranged from 18 to 40. Veyrat-Durebex et al[24] obtained in their study that as expected, body weight loss at diagnosis, progression rate, and ALSFRS-R slope during the first year following diagnosis were associated with disease duration.

In this current study, it was observed that 43.0% subjects had serum creatinine 0.80 to 1.00 mg/dl in group I and 40.0% in group II. The mean serum creatinine was 0.76±0.17 mg/dl in group I and 1.03±0.12 mg/dl in group II. The difference was statistically significant (P<0.05) between two groups.

Chen et al[12] study showed serum creatinine levels significantly lower in SALS patients than in controls (p<0.001), that were 0.70±0.22 mg/dl and 0.95±0.18 mg/dl in SALS and control group respectively after adjusted for age and gender. Sporadic amyotrophic lateral sclerosis patients with different site of onset have similar serum creatinine levels, but underweight patients presented lower levels of serum creatinine. The investigators considered the disease status of amyotrophic lateral sclerosis as the dependent variable and serum creatinine levels as a categorical variable. The unadjusted odds ratio for the highest versus the lowest quartile of creatinine levels was 0.043 (95% CI 0.025–0.075), the subjects with the second, the third and highest quartiles of creatinine levels had a significantly lower presence of ALS compared with those with the lowest quartile (p<0.051).

Chen et al[12] study showed that baseline serum creatinine levels may be related with disease severity of amyotrophic lateral sclerosis. ALS-FRS-R is the most relevant index to assess disability in patients with ALS. Longitudinal[13] study had demonstrated that annual decline rate of serum creatinine levels was correlated with decline rate of ALS-FRS and baseline serum levels of creatinine was inversely correlated with rate of progression of amyotrophic lateral sclerosis.

Patin et al[11] mentioned in their study that a large annual decrease in ALSFRS-R score was associated with a large reduction of creatinine (p<0.05). Lawton et al[25] studies have reported that creatinine levels are low in amyotrophic lateral sclerosis patients and baseline serum levels of creatinine were correlated with annual decline of ALSFRS-R score. Creatinine at diagnosis may also be a strong prognostic factor of disease duration[7]. In Patin et al[11] study found early and long-term variations of creatinine levels were associated with disease duration and annual decline of ALSFRS-R, respectively.

Van Eijk et al[26] found that plasma creatinine had strong longitudinal correlations with the ALSFRS-R (0.43 (0.39–0.46), muscle strength (0.55 (0.51–0.58) and overall mortality (HR 0.88 (0.86–0.91) ($p<0.05$). Chio et al[27] and Lunetta et al[28] studies had shown that the baseline measurement of plasma creatinine is a strong predictor of survival. The reported HRs vary between studies varied from 1.2 to 1.5, but consistently show an increased risk of death if levels of plasma creatinine are low. Heterogeneity in rates of decline is inevitable in amyotrophic lateral sclerosis due to its divergent prognosis. However, patient variability in rate of decline of the ALSFRS-R could be due to the internal construction of the ALSFRS-R score: as patients with the same score may not represent the same severity of amyotrophic lateral sclerosis, this may influence the rate of decline[25]. The findings of above authors are comparable with the present study.

In this present study, it was observed that the mean ALS-FRS was 26.8±5.63 in BMI less than 18.5(kg/m^2), 29.56±3.91 in BMI 18.5 to 22.9 (kg/m^2) and 35±5.66 in BMI 23 to 30.9 (kg/m^2). The mean ALS-FRS was significantly increased with BMI increased.

In this current study, it was observed that the mean serum creatinine was 0.74±0.16 (mg/dl) in BMI less than 18.5(kg/m^2), 0.9±0.2 (mg/dL) in BMI 18.5 to 22.9 (kg/m^2) and 1.03±0.13 (mg/dL) in BMI 23 to 30.9 (kg/m^2). The mean serum creatinine was significantly increased with BMI increased.

Chen et al[12] reported that patients with low serum creatinine levels are more likely to have severe motor impairment and low body mass index (BMI) values. This study demonstrates that higher levels of serum creatinine are less likely to be associated with the presence of amyotrophic lateral sclerosis in Chinese populations. Low serum creatinine levels may be related to severe motor impairment in SALS patients. The authors hypothesized that baseline BMI may be useful to predict disease severity of amyotrophic lateral sclerosis. This concept is supported by previous studies that the baseline BMI was an independent prognostic indicator of amyotrophic lateral sclerosis[25]. Furthermore, Shimizu et al[29] study showed that faster reduction of BMI at the initial stage predicted shorter survival length in Japanese amyotrophic lateral sclerosis patients. Thus, the nutrition status is important in evaluating the disease severity and progression of amyotrophic lateral sclerosis, and worse nutritional status (at time of diagnosis) was associated with a higher mortality[22]. Alteration of nutritional status is multi-factorial, including dysphagia, chewing difficulties, difficulty in moving the extremities[22,25].

In this present study, it was observed that the mean BMI was 18.21±1.59 (kg/m^2) in serum creatinine <0.60 (mg/dl), 18.33±1.32 (kg/m^2) in serum creatinine 0.61-0.79 (mg/dl), 21.2±2.5 (kg/m^2) in serum creatinine 0.80-1.00 (mg/dl) and 22.88±2.35 (kg/m^2) in serum creatinine >1.00 (mg/dl). The mean BMI was significantly increased with elevated serum creatinine level.

Similarly, Chen et al[12] study found that patients with lower BMI values were likely to have lower serum creatinine levels and lower ALS-FRS-R scores ($p<0.05$). Patients with low serum creatinine levels (<0.82) are more likely to have severe motor impairment and low BMI values than those with high levels of serum creatinine, suggesting a possible role of creatinine in the pathogenesis of amyotrophic lateral sclerosis. However, serum creatinine level was not associated with the survival of Chinese ALS patients. Their study found that serum creatinine levels of amyotrophic lateral sclerosis patients were significantly lower than that of healthy control. This finding was consistent with the results of previous studies[7,11], but these studies did not take BMI into consideration, while BMI could have an impact on serum creatinine levels.

In this current study, it was observed that the mean ALS -FRS was 26.88±4.88 in serum creatinine <0.60 (mg/dl), 26.83±3.81 in serum creatinine 0.61-0.79 (mg/dl), 30.38±5.3 in serum creatinine 0.80-1.00 (mg/dl) and 36.0±2.83 in serum creatinine >1.00 (mg/dL). The mean ALS –FRS was significantly increased with elevated serum creatinine level. This study also shown there was significant difference across the quartiles. Chen et al[12] study divided amyotrophic lateral sclerosis patients into quartiles for serum creatinine level. There were significant differences in ALS-FRS-R and BMI ($P<0.05$) across the quartiles. Patients with lower serum creatinine levels (<0.80mg/dl) tend to have more severe disease and lower BMI values. Furthermore, underweight (BMI <18.5 kg/m^2) patients presented decreased levels of serum creatinine and lower ALS-FRS-R scores.

In this present study, it was observed that the mean serum creatinine was 0.72±0.13 (mg/dl) in limb onset, 0.73±0.15 (mg/dL) in bulbar onset and 0.95±0.08 (mg/dl) in mixed. The mean creatinine levels significantly were lower in patients with limb onset

followed by bulbar onset and mixed. Patin et al[11] study observed that Creatinine levels were lower in patients with limb onset than in those with bulbar onset, where the mean Creatinine levels were 0.85±0.03 mg/dl and 0.94±0.05 mg/l ($p<0.05$) respectively, even after inclusion of gender in a multivariate analysis ($p<0.05$).
Chen et al[12] study examine the relationship between serum creatinine level and site of onset and found no significant difference for site of onset, after adjustment for gender and age. In their study, serum creatinine levels were similar in ALS patients with different site of onset. The investigators consider it likely that serum creatinine levels may be related to site of onset, because the malnutrition due to impaired swallowing can typically occur in cases with bulbar onset. However, the results of their study showed that ALS patients with different site of onset have similar creatinine levels in serum. Klivenyi et al[30] studies showed that dietary supplementation with creatine-the precursor of creatinine, could preserve motor neurons and prolong survival in a mouse model of ALS. However, human clinical trials failed to replicate this effect[31-32]. Both high and low levels of creatinine have no significant survival advantage.
This study aimed to show the serum creatinine level as a biomarker of disease severity, so there must figure out the relationship between serum creatinine level and BMI as well its influence on disease severity at first then the correlation between serum creatinine levels decline of ALS-FRS-R scores. This study demonstrated that ALS patients have significantly lower serum creatinine levels than well matched controls. Underweight patients presented lower levels of serum creatinine. Patients with low serum creatinine levels are more likely to have severe motor impairment evidenced by their reduced ALS FRS scale and low body mass index (BMI) values. Higher levels of serum creatinine are less likely to be associated with the presence of severe ALS in study populations. Low serum creatinine levels may be related to severe motor impairment in ALS patients.

Conclusion

Plasma creatinine is an inexpensive and easily accessible biomarker that exhibits less variability between patients with ALS over time and is predictive for the patient's functional status, muscle strength and mortality risk. This study was undertaken to evaluate the association of serum creatinine in patients with amyotrophic lateral sclerosis. Most of the patients were in 6th decade, male predominant and came from rural area. BMI was significantly lower in patients with amyotrophic lateral sclerosis. Definite was the more frequent clinical presentation of ALS and 6th decade was the more common age of onset, Limb onset and serum creatinine was significantly lower in amyotrophic lateral sclerosis patients. Serum creatinine level significantly associated with ALS –FRS, pattern of onset and BMI in patients with amyotrophic lateral sclerosis.

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Contribution to authors: Rassel MA, Sina H, Shapla TJ conceived and designed the study, analyzed the data, interpreted the results, and wrote up the draft manuscript. Shapla TJ, Mahmud MR, Ahmed KG involved in the manuscript review and editing. Rassel MA, Sina H, Rony RR conceived and manuscript writing. All authors read and approved the final manuscript.

Data Availability
Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate
Ethical approval for the study was obtained from the Institutional Review Board. As this was a prospective study the written informed consent was obtained from all study participants. All methods were performed in accordance with the relevant guidelines and regulations.

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