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MYOSTATIN AS A POTENTIAL DIAGNOSTIC BIOMARKER IN ELDERLY PATIENTS WITH SARCOPENIA

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Abstract:

Background: Sarcopenia is a condition characterized by loss of muscle mass, strength, and function in elders. Myostatin is a myokine, and a potent negative regulator of muscle growth. The purpose of this research is to assess the accuracy of serum myostatin as a predictor of Sarcopenia in elders and the effect on their daily life activities. The study involved 64 elderly patients aged 65 years and older; Group (I):32 sarcopenic patients, and Group (II):32 healthy controls of comparable age and gender. Participants with chronic renal, hepatic, or cardiac decompensation, DM, women on hormonal replacement therapy were excluded. Full history was taken from all participants along with thorough examination, anthropometric measurements, routine investigations, serum myostatin using ELISA, and SF-36 to assess quality of life. Sarcopenia was diagnosed using EWGSOP-2 criteria. **Results:** Sarcopenic patients had significantly lower ASMI, hand grip strength, and physical performance values ($p<0.001$). Serum Myostatin was significantly higher in sarcopenic patients compared to controls (32.73 ± 5.0 vs. 26.49 ± 6.44 IU/dl) ($p<0.001$). SF-36 scores were significantly lower in patients with Sarcopenia compared to controls (74.19 ± 5.04 vs 84.84 ± 3.33). Serum myostatin and SF-36 scores were negatively correlated in both studied groups ($r= -0.345$; $p<0.001$).Serum myostatin level more than 29 (IU/dl) has sensitivity of (87.5%) and specificity of (75%) in discriminating sarcopenic patients from healthy elders. **Conclusion:** serum myostatin is a possible blood-based biomarker for Sarcopenia prediction as well as quality of life assessment in such population. Further researches with more sample sizes are required to confirm our outcomes.

Key words: Sarcopenia; Myostatin; quality of life; SF-36; elders;

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Introduction

Sarcopenia is a geriatric condition identified by progressive loss of the mass and function of the muscles results in physical disability, inadequate life quality and increase mortality [(1)]. The definition of Sarcopenia relies upon 2010 European Working Group on Sarcopenia in Older People (EWGSOP) criteria [(2)]. Sarcopenia can be divided into primary and secondary Sarcopenia. Primary

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Sarcopenia is idiopathic, may be due to hormonal disturbances, geriatric anorexia, dysfunctional mitochondria, and malfunctioning neuromuscular junctions [3]. Secondary Sarcopenia is not due to aging process. It may be secondary to malignancy, diabetes mellitus, or severe organ dysfunction. The type of Sarcopenia should be addressed to know how to deal with this condition [4]. The varied prevalence of Sarcopenia depends on ethnicity, the studied population, and diagnostic criteria used [3]. The reported prevalence of Sarcopenia was 1–30% in a community dwelling elders, 14–33% in a nursing homes, up to 60% in hospitalized patients [5], and from 0.8 to 26% in the outpatient settings [6]. Ten years earlier, the prevalence of Sarcopenia was 5–10% in elders older than 65 years [7]. According to WHO records, 40–50% of octogenarians aged 80 years and more have Sarcopenia [8]. Risk factors for Sarcopenia include; aging, gender, degree of physical activity, gait instability, frailty, multiple comorbid conditions, low body mass, malnutrition, smoking, and somnolence [9]. Early dealing with Sarcopenia in elders could decrease hospitalization rates and reduce health care expenses [3]. The muscle quality in Sarcopenia can be determined by a variety of radiological modalities, such as dual energy X-ray absorptiometry (DEXA) scan, bioelectrical impedance assessment (BIA), computed tomography (CT), magnetic resonance imaging (MRI), or muscle ultrasound (US) [10]. Muscle strength can be determined by hand grip test, and knee flexion and extension [11]. Evaluation of muscle function via performing the followings tests; Stand-up, stand-up walking, and long-distance walking [11]. These three aspects can determine the presence of Sarcopenia [10].

Myostatin, is a myokine, belongs to transforming growth factor-β superfamily that is synthesized and released by myocytes and can retard the growth and development of skeletal muscle by autocrine or paracrine signalling [12]. Myostatin signalling is an example of muscular transduction pathways, which control the balance between synthesis and degradation of protein within the muscles leading either to hypertrophy or atrophy [13]. Stopping growth of the skeletal muscle is induced by binding of Myostatin to the myostatin receptor, activin type IIB receptor (ActR2B) that leads to phosphorylation of Smad2 and Smad3. Activated Smad 2, and Smad3 results in formation of Smad4 that regulates gene transcription [14], and inhibit the IGF-1/Akt/ mammalian target of rapamycin (mTOR) pathway which is responsible for protein synthesis [14].Current research supports this Smad-mediated pathway as the pathway through which myostatin acts to suppress protein synthesis and potentially other metabolic effects.

The effect of age on the quantity and function of myostatin remains uncertain. A preliminary study found that blood myostatin levels rise with age, with the greatest levels observed in physically feeble older women, and a negative correlation between its levels and muscle mass was detected. However,

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subsequent studies did not detect an association between neither serum myostatin levels nor skeletal muscle myostatin mRNA and age [15].

The causal role of Myostatin in pathogenesis of Sarcopenia is not fully determined. In experimental elder animals, inhibition of myostatin results in significant increase in muscle mass and improvement in its function. More researches are required to determine the optimal means to safely inhibit myostatin activity to improve muscle quality. This novel treatment represents hope for all elderly people who suffer from Sarcopenia [16].

The aim of the present work is to evaluate the accuracy of serum myostatin as a predictor of Sarcopenia in elders and to study the correlation between this biomarker and the quality of life in such patients

Methods:

The current case-control trial was carried out on 64 elders aged 65 years and older of both genders divided into 2 groups; group (I): 32 elderly cases diagnosed with Sarcopenia based on EWGSOP-2 definition, and group (II): 32 of age & gender matched subjects served as a control group. Participants were recruited from the geriatric outpatient clinic and inpatient ward. The aim, purpose, and procedures of the study were explained to all participants and a verbal consent was obtained. The study proposal was accepted by the relevant ethical committee. Participants suffered these disorders were excluded from the study; chronic renal or hepatic decompensation, chronic heart failure, Diabetes mellitus, and Postmenopausal women on hormonal replacement therapy.

A through history was taken from all participants or their care giver along with complete general systematic clinical examination. Routine investigations included; complete blood count (CBC), blood urea, serum uric acid, serum creatinine, creatinine clearance, complete urine analysis, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum albumin, Serum aspartate & alanine aminotransferases (AST & ALT), serum gamma-glutamyl transferase (GGT), serum bilirubin, prothrombin time, fasting blood sugar, glycosylated haemoglobin, thyroid stimulating hormone (TSH), and free thyroxin level (Free T4). Serum myostatin levels was evaluated in all participants' sera using an enzyme-linked immunosorbent test (ELISA).

Anthropometric measurements [17] were conducted to participants and included; Weight in kilograms: It was calculated using a digital weighing scale. The scale was calibrated and checked daily. The scale was positioned on a concrete and level surface. Participants instructed to wear light clothes, *Height in centimetres*: It was measured using a vertical scale fixed to the wall. Patients were bare-feeted and they were inquired to position on the flat floor in front of the scale with parallel feet, gluteus, heels, shoulders and head touching the scale. The head

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was kept in a comfortable erect position, with the bottom border of the orbits in the same horizontal plane as the external auditory meatus. Additionally, the arms were hung at the sides in a manner that was natural. A rigid cardboard headgear has been dropped in a gentle manner, allowing it to make contact with the hair as well as the top of the head. Body Mass Index was assessed by dividing person's weight (Kg), by the square of height (m); BMI below 18.5: under-weight; between 18.5 and 24.9: average weight; between 25 and 29.9: overweight; 30 or greater: obese. Waist in centimetres was measured above the iliac crest by flexible tape, in a horizontal plane at the end of normal expiration with measuring tape. Patients were asked to abdominal muscles relaxed, stand erectly, arms at the side & feet together.

Based on EWGSOP-2 definition; Sarcopenia was diagnosed at a cut-off measure of 7.0 kg/m2 for males and 5.5 kilograms/m2 for women in terms of appendicular skeletal muscle mass index (ASMI). The cut-off points for handgrip strength are below 27 kg for both genders. The threshold for decrease physical performance was beneath 0.8 m/s for both males and females [18].

The assessment of skeletal muscle mass was performed utilizing direct segmental 8-point multi-frequency bioelectrical impedance analysis (InBody220, InBody Co. Ltd. Seoul, Korea). Appendicular skeletal muscle mass (ASM) refers to the combined muscular mass of the four limbs. The appendicular skeletal muscle mass index (ASMI) is obtained by dividing the appendicular skeletal muscle mass (Kg) by the height's square (m).Handgrip strength was assessed bilaterally using a grip dynamometer, with three measurements taken for each hand. The highest recorded result was selected for analysis [19]. A walking speed in excess of 4.57 m was utilized to estimate physical performance [20]. The Short Form 36 Health Survey Questionnaire (SF-36) was utilized to assess the QoL in individuals with Sarcopenia [21]. (Supplementary material)

Statistical analysis of the data:

We employed IBM SPSS software package version 20.0 to analyse the information collected that was fed into the computer. (New York: IBM Corp., Armonk) Numbers & percentages were employed to describe the qualitative data. The Shapiro-Wilk test ensured that the data followed a normal distribution. Standard deviation, median, interquartile range (IQR), range (minimum in addition maximum), & mean were used to characterize quantitative data. The outcomes were considered significant at the 5% level.

The used tests were; Chi-square test to contrast various groups using category variables; Student t-test to differentiate between two groups that were researched using regularly distributed quantitative variables; Mann Whitney test to compare two groups that were evaluated for quantitative characteristics that

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had aberrant distributions, and Receiver operating characteristic curve (ROC) where a sensitivity (TP) vs 1-specificity (FP) plotted against X axis at various cut off settings. The test's diagnostic performance is indicated by the area under the Receiver operating characteristic curve. An area of above fifty percent indicates satisfactory performance, whereas an area of close to 100% indicates optimal results for the test. It is also possible to compare the results of different tests using the ROC curve.

Results:

The current case-control trial was conducted on 64 elderly patients aged 65 years and older. Subjects from outpatient clinics or admitted to the hospital participated in the study. Participants were divided inti two groups; group I (Sarcopenic group) represents 32 patients; 17 men (53.1%) & 15 women (46.9%), and group II (control group) represents 32 participants; 16 men (50.0%), and 16 ladies (50.0%). Both groups did not differ significantly (p=0.802).

Group I participants had a mean age of 67.28 ± 2.23 years, while in group II was 67.16 ± 2.63 years. There was no statistical change amongst both groups (p=0.838).

Table 1 represents the anthropometric measurements of the studied groups; only the body weight showed statistical significant difference between both groups where sarcopenic patients had lower body weights (p<0.001), both groups did not differ significantly regarding other anthropometric measurements.

Table (1): The anthropometric measures of the studied groups:

Anthropometric measures	Group I (Sarcopenic group) (n=32)	Group II (Control group) (n=32)	t	P
Body weight (kg)				
Min. – Max.	63.0 – 86.0	68.0 – 88.0		
Mean ± SD.	73.44 ± 5.88	78.72 ± 5.16	3.820	<0.001*
Median (IQR)	72.50 (70.0–77.50)	79.0 (76.0–81.50)		
Height (cm)				
Min. – Max.	154.0 – 186.0	154.0 – 190.0		
Mean ± SD.	167.16 ± 9.47	166.50 ± 9.91	0.271	0.787
Median (IQR)	169.0 (158.50–174.50)	168.50 (157.0–175.0)		
Hip circumference (cm)				
Min. – Max.	94.0 – 110.0	94.0 – 110.0		
Mean ± SD.	100.44 ± 4.83	101.19 ± 4.78	0.625	0.535
Median (IQR)	99.50 (96.0–103.50)	101.0 (97.0–104.0)		
Waist circumference (cm)				
Min. – Max.	78.0 – 107.50	78.50 – 106.50		
Mean ± SD.	91.23 ± 7.70	91.38 ± 9.0	0.067	0.947
Median (IQR)	92.50 (85.25–97.0)	91.50 (82.50–99.0)		

IQR: Inter quartile range, **SD:** Standard deviation**, t:** Student t-test, **p:** p value for comparing between the two studied groups, **kg.:** kilogram, **Cm:** centimetre, *: Statistically significant at p ≤ 0.05

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Table 2 represents EWGSOP-2 of the studied groups. The mean appendicular skeletal muscle index (ASMI) in group I was 5.82 ± 0.67 kg/m^2 and was 7.10 ± 0.95 kg/m^2 in group II. Group I had significantly lower values (p<0.001). The Hand grip strength's mean in group I was 19.09 ± 5.78 kg., while it was 24.66 ± 4.86 kg in group II. Again Group I had significantly lower values (p<0.001). The Physical performance mean in group I was 0.78 ± 0.12 m/s., while it was 1.05 ± 0.15 m/s in group II. Group II had significantly higher values (p<0.001).

Table (2): Comparison between both studied groups as regards EWGSOP-2:

EWGSOP-2	Group I (Sarcopenic group) (n=32)	Group II (Control group) (n=32)	U	P
ASMI (kg/m2)				
Min. – Max.	5.0 – 6.90	5.80 – 8.60		
Mean ± SD.	5.82 ± 0.67	7.10 ± 0.95	183.500*	<0.001*
Median (IQR)	6.0 (5.15–6.30)	7.15 (6.15–7.90)		
Hand grip strength (kg)				
Min. – Max.	11.0 – 26.0	17.0 – 32.0		
Mean ± SD.	19.09 ± 5.78	24.66 ± 4.86	261.500*	0.001*
Median (IQR)	23.0 (13.0–24.50)	25.50 (20.0–29.0)		
Physical performance (m/s)				
Min. – Max.	0.60 – 1.0	0.90 – 1.30		
Mean ± SD.	0.78 ± 0.12	1.05 ± 0.15	83.0*	<0.001*
Median (IQR)	0.80 (0.70–0.90)	1.0 (0.90–1.20)		

IQR: Inter quartile range, **SD:** Standard deviation, **EWGSOP-2:** The European Working Group on Sarcopenia in Older People, **ASMI**: Appendicular skeletal muscle index, **U:** Mann Whitney test**, p**: p value for comparing between the two studied groups, *: Statistically significant at p ≤ 0.05

Table 3 represents the routine laboratory investigations of both groups; sarcopenic patients had significantly lower haemoglobin levels compared to the controls (p=0.016). No statistical difference was detected between studied participants regarding other laboratory investigations.

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Table (3): Comparison between both studied groups regarding their routine laboratory investigations:

	Group I (Sarcopenic group) (n=32)	Group II (Control group) (n=32)	t	P
Hb (g/dl) Min. – Max. Mean ± SD. Median (IQR)	 10.40 – 15.10 12.89 ± 1.05 12.95 (12.20–13.60)	 11.0 – 13.80 12.33 ± 0.69 12.30 (11.85–12.80)	2.489*	0.016*
TLC (× 10^9/L) Min. – Max. Mean ± SD. Median (IQR)	 4.28 – 9.98 6.92 ± 1.70 6.84 (5.50–8.34)	 4.50 – 11.0 7.70 ± 2.10 7.85 (5.90–9.65)	1.639	0.106
PLT (× 10^9/L) Min. – Max. Mean ± SD. Median (IQR)	 26.0 – 451.0 256.69 ± 80.04 251.0 (198.0–316.50)	 10.90 – 375.0 252.90 ± 75.07 264.0 (202.0–306.0)	0.195	0.846
Urea (mg/dL) Min. – Max. Mean ± SD. Median (IQR)	 17.0 – 32.0 24.81 ± 4.0 25.0 (22.50–27.50)	 19.0 – 32.0 26.28 ± 3.26 26.0 (24.0–29.0)	1.612	0.112
Creatinine (mg/dL) Min. – Max. Mean ± SD. Median (IQR)	 0.76 – 1.10 0.89 ± 0.10 0.89 (0.80–0.97)	 0.76 – 1.10 0.89 ± 0.08 0.88 (0.82–0.95)	0.248	0.805
ALT (IU/L) Min. – Max. Mean ± SD. Median (IQR)	 22.0 – 35.0 28.59 ± 3.49 28.50 (25.0–31.0)	 22.0 – 35.0 28.56 ± 3.43 28.50 (25.0–31.0)	0.036	0.971
AST (IU/L) Min. – Max. Mean ± SD. Median (IQR)	 21.0 – 38.0 28.50 ± 4.59 29.0 (24.50–31.0)	 21.0 – 35.0 28.34 ± 4.34 29.0 (24.50–31.0)	0.140	0.889
FBS (mg/dL) Min. – Max. Mean ± SD. Median (IQR)	 81.0 – 121.0 100.50 ± 10.81 100.50 (92.0–107.50)	 82.0 – 120.0 97.81 ± 10.83 94.50 (89.50- 107.50)	0.994	0.324
CRP (mg/L) Min. – Max. Mean ± SD. Median (IQR)	 1.10 – 3.40 2.19 ± 0.58 2.30 (1.80–2.60)	 1.20 – 3.60 2.25 ± 0.70 2.20 (1.70–2.80)	0.392	0.697
T4 (ug/ml) Min. – Max. Mean ± SD. Median (IQR)	 0.84 – 11.20 1.96 ± 2.57 1.15 (0.99–1.35)	 0.84 – 6.70 1.42 ± 1.05 1.22 (0.97–1.33)	U= 502.500	0.898
TSH (mIU/mL) Min. – Max. Mean ± SD. Median (IQR)	 0.39 – 213.0 8.89 ± 37.26 2.18 (1.54–3.33)	 0.41 – 3.94 2.28 ± 0.92 2.31 (1.65–3.01)	U= 497.500	0.846

Hb: haemoglobin, **TLC:** total leucocyte count**, PLT:** platelet count**, ALT:** Alanine aminotransferase, **AST:** Aspartate aminotransferase**, FBS:** Fasting blood glucose, **CRP:** C-reactive protein, **T4:** Thyroxine hormone**, TSH**: Thyroid Stimulating Hormone**, IQR:** Inter quartile range, **SD:** Standard deviation**, t:** Student t-test**, p:** p value for comparing between the two studied groups**,***: Statistically significant at $p \leq 0.05$, **U:** Mann Whitney test.

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Table 4 shows Serum Myostatin level and the 36-Item Short Form Health Survey score of the studied groups. The Serum Myostatin mean in the sarcopenic patients was 32.73 ± 5.0 (IU/dl), and was 26.49 ± 6.44 (IU/dl) in the control group. Serum myostatin was significantly higher in Sarcopenic patients (p<0.001). The mean SF-36 score in the sarcopenic group was 74.19 ± 5.04, while it was 84.84 ± 3.33 in the control group. The controls had significantly higher values of SF-36 (p<0.001).

Table (4): Comparison between the two studied groups regarding their Serum Myostatin & SF-36:

	Group I (Sarcopenic group) (n=32)	Group II (Control group) (n=32)	T	P
Serum Myostatin (IU/dl)				
Min. – Max.	20.36 – 45.40	10.10 – 43.80		
Mean ± SD.	32.73 ± 5.0	26.49 ± 6.44	4.329*	<0.001*
Median (IQR)	32.05 (30.10–35.50)	28.10 (22.40–29.70)		
SF-36				
Min. – Max.	67.0 – 81.0	80.0 – 90.0		
Mean ± SD.	74.19 ± 5.04	84.84 ± 3.33	9.971*	<0.001*
Median (IQR)	72.50 (69.50–79.50)	85.0 (82.0–88.0)		

IQR: Inter quartile range, **SD**: Standard deviation, **SF-36:** The 36-Item Short Form Health Survey, **t:** Student t-test, **p**: p value for comparing between the two studied groups, *: Statistically significant at p ≤ 0.05

Table 5 shows that serum myostatin and SF-36 scores differed significantly in a negative manner in the sarcopenic patients equated to the controls. [Figure 1]

Table (5): Correlation between Serum Myostatin and SF-36 in each group and total sample:

	Serum Myostatin (IU/dl)					
	Total (n=64)		Sarcopenic group (n=32)		Control group (n=32)	
	r	p	r	p	r	P
SF-36	-0.345*	<0.001*	-0.008	0.965	0.152	0.408

r: Pearson coefficient, *: Statistically significant at p ≤ 0.05

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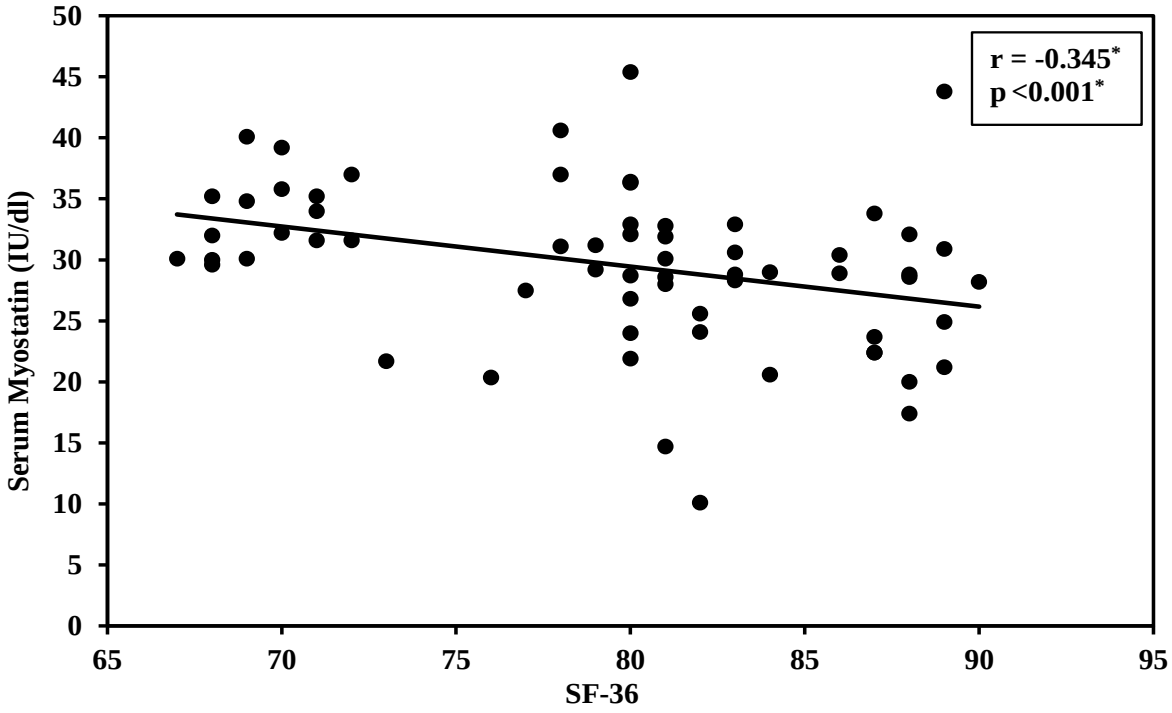

Figure (1): Correlation between Serum Myostatin and SF-36 in each group and total sample

Table 6 shows that serum myostatin level at values more than 29(IU/dl) has high sensitivity (87.5%) and high specificity (75%) in discriminating sarcopenic patients from healthy elders. [Figure 2]

Table (6): Validity (AUC, sensitivity, specificity) for Serum Myostatin (IU/dl) to discriminate the Sarcopenic group from the control one:

	AUC	p	95% C.I	Cut off#	Sensitivity	Specificity	PPV	NPV
Serum Myostatin (IU/dl)	0.812	<0.001*	0.701 – 0.922	**>29**	87.50	75.0	77.8	85.7

AUC: Area Under a Curve, **p** value: Probability value, **CI:** Confidence Intervals, **NPV:** Negative predictive value, **PPV:** Positive predictive value, *: Statistically significant at $p \leq 0.05$, #Cut off was choose according to Youden index

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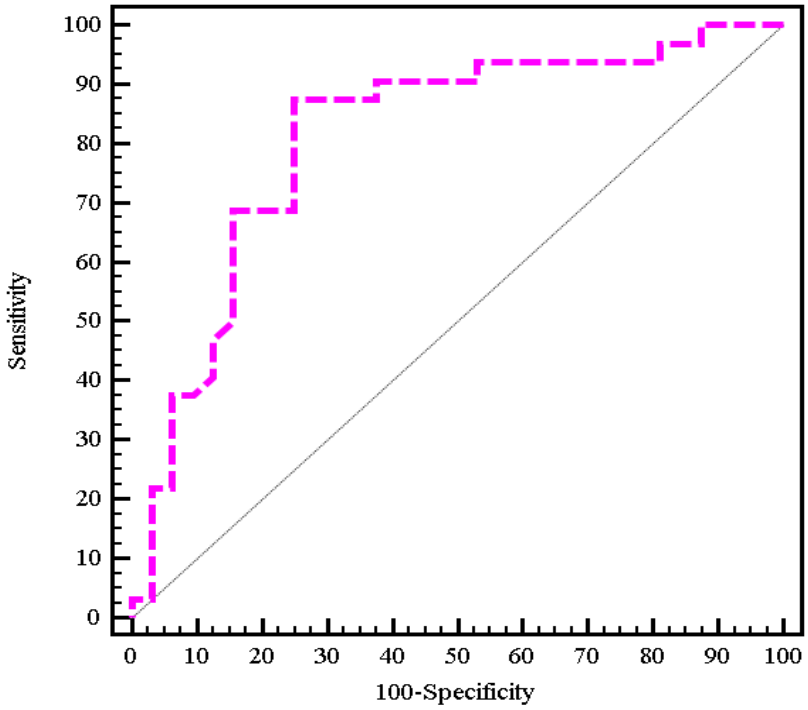

Figure (2): ROC curve for Serum Myostatin (IU/dl) to discriminate Sarcopenic group from control

Discussion:

Sarcopenia is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength and it is strictly correlated with physical disability, poor quality of life and increased mortality [22]. The complex and multifaceted nature of Sarcopenia poses a significant barrier in terms of diagnosis. The precise mechanisms involved in the development and prediction of Sarcopenia are not completely understood. Nevertheless, a set of biomarkers has been identified that could potentially aid in understanding the various mechanisms of Sarcopenia. These biomarkers can be used to identify individuals with early-stage Sarcopenia as well as create a personalized and effective management strategy for preventing and treating this condition [23].

Myostatin is a myokine, and a potent negative regulator of growth that is highly enriched in the skeletal muscle, there has been great interest in it as a potential mediator of Sarcopenia [16]. Recent investigations have identified myostatin as a potential biomarker for neuromuscular disorders [24]. The aim of the present study was to evaluate the accuracy of the serum myostatin as a predictor of Sarcopenia in elders and to study the correlation between this biomarker and the quality of life in such patients.

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Our case-control study involved 64 elderly patients aged 65 years and older. Participants were divided into two groups: Group (I): 32 elderly patients diagnosed with Sarcopenia according to the EWGSOP-2 definition [18], and Group (II): 32 age and sex-matched healthy participants acted as a control group. We did not find a statistical gender difference between sarcopenic patients and healthy participants. This was in accordance with Shafiee et al. [25] who analysed a meta-analysis involved 58,404 participants from 35 researches, and found equal prevalence of Sarcopenia in men and women. On contrary, Yang et al.[26] followed 3404 community-dwelling elders for 8 years for incident Sarcopenia, Sarcopenia was 20% more likely to occur in females than in males.

The discrepancy of findings between studies could be attributed to the fact that the incidence of Sarcopenia varies in men and women depending on a variety of internal and external factors as hormonal alteration for example.

Initial assessment of sarcopenic patients can be performed using anthropometric measurements [27].

In our study, the mean body weight in sarcopenic patients (73.44 ± 5.88 Kg) was significantly lower than that in the controls (78.72 ± 5.16 Kg) ($p<0.001$). This was in accordance with other studies [27-29]. We detected no significant difference regarding mean height, hip circumference, & waist circumference between studied groups ($p=0.787$, 0.535, and $p=0.947$, respectively). Beaudart et al. [30] gave similar results to ours, but on contrary, they reported lower waist circumferences in sarcopenic subjects compared to the healthy participants.

A Chinese trial by Yin et al. [31] stated that sarcopenic patients were significantly shorter than healthy controls. Also, they had significantly lower weight, waist, hip, mid-arm circumferences ($P<0.001$).

We found that the mean Appendicular skeletal muscle index (ASMI), hand grip strength, and physical performance in the sarcopenic group were significantly lower than that in the control group ($p<0.001$). These results indicated that sarcopenic patients had a loss of muscle mass, and a decrease in the muscle strength which can lead to poor physical disability, physical performance, and increase the risk of falls in such patients. This emphasizes the importance of early assessment, identification in addition to intervention of Sarcopenia that may prevent disability and other adverse health outcomes. Several studies had given similar findings [32-35].

Inflammation contributes to the onset of functional impairment and weak muscles. It has been postulated that inflammation brought on by aging or chronic

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diseases can lead to catabolic effects on the muscle, which in turn can diminish physical functioning [36].

Previous studies [36-38], showed that CRP is related to muscle cell dysfunction in Sarcopenia. In the current study, CRP levels were found to be raised in both sarcopenic & non-sarcopenic subjects but with no significant statistical difference between both groups (p=0.697). This may be explained by the chronic state of inflammation of elders; inflammaging, also elderly people have a lot of comorbid diseases, not only Sarcopenia, that may elevate the CRP levels.

Both the contractile function & the regeneration of skeletal muscles rely on the signaling of thyroid hormones [39]. Aging is associated with alteration in thyroid hormone levels, changed signaling pathways, changes in nutritional status, and sickness which contribute to alteration of muscle metabolism [40]. We observed that thyroid hormones (T3, and T4), and TSH were higher among sarcopenic patients than controls, however, the results did not achieve significant statistical difference (p=0.114, 0.898, & p=0.846, respectively).

A Brazilian study by Szlejf et al. [41] stated that T3 was negatively associated with muscle mass, and that minor thyroid malfunction was linked to Sarcopenia. In comparison, Yin et al.[31] reported patients with Sarcopenia had lower levels of T3 but higher levels of T4 than the healthy.

Few researches had investigated the serum myostatin in sarcopenic cases but data were scarce. A negative association between age & serum myostatin levels has been demonstrated in earlier studies [42, 43]. The results of the current trail showed that sarcopenic patients had significantly higher levels of serum Myostatin level (p<0.001). In accordance with our results, a cross-sectional research by Yarasheski et al.[44] investigated the skeletal muscle mass, and serum myostatin-immunoreactive protein levels in three age groups: group I aged between 19 and 35 years old, group II aged between 60 and 75 years old, and group III aged between 76 and 92 years old frail women. They discovered that as people get older, both genders experience a loss of muscle mass. Women in the physically fragile category had the highest serum myostatin levels. Serum myostatin levels were greater in the middle-aged group compared to the younger group. Consistent with the theory that the human myostatin gene product inhibits skeletal muscle growth with age, they determined that serum myostatin could be a biomarker of geriatric Sarcopenia.

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Likewise, Léger et al. [45], investigated myostatin mRNA, and its serum levels in young and elderly males. They reported that myostatin mRNA in addition to its serum levels were significantly raised in elderly sarcopenic men. They concluded that myostatin is increased in human Sarcopenia, and can be considered as a potential candidate influencing anabolic perturbation in Sarcopenia. Similar research by Roh et al. [46] showed that myostatin gene expression increased in sarcopenic patients; however, serum myostatin levels were not estimated.

Bergen et al. [47], measured myostatin concentrations in 80 young subjects (<40 years), 80 elders without Sarcopenia (>65 years), and 80 elderly sarcopenic patients of both genders. Serum myostatin concentrations were higher in both elders and elderly sarcopenic women by more than 23 % than in young women, but young males had more myostatin levels compared to elderly males with or without Sarcopenia. Authors stated that myostatin may increase the incidence of Sarcopenia in both men and women.

Tay et al. [48], investigated 200 community independent dwelling elders aged 50 years and more for comorbidities, cognitive and functional abilities, levels of physical activity, and dietary health. Myostatin was one of the biochemical characteristics measured. A greater serum myostatin level is independently linked to an increased risk of Sarcopenia.

Han et al. [49], stated that elevated serum myostatin levels contributed to an increased risk of Sarcopenia. While the simple correlation analysis found no correlation between myostatin, and muscular mass, the logistic regression model found that myostatin increased the likelihood of pre-Sarcopenia. This can be explained that Myostatin is not the only factor that influences muscle mass; the metabolic milieu in which the muscle is located as well as the amount of activity it undergoes also have a role.

A cross-sectional study by Echeverria et al. [50], consisted of 84 post-hospitalized patients aged 70 years and more immediately after discharge. Serum myostatin concentrations were measured. People with Sarcopenia have a decreased levels of myostatin. They concluded that Myostatin could be a helpful biomarker for Sarcopenia in elderly patients discharged from the hospital.

On contrary to our results, Hofman et al. [51], investigated a number of serum biomarkers, including myostatin to determine their relation to Sarcopenia in elderly women. Their results showed that serum biomarkers, age and fat mass

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predicted muscle mass. Neither a single nor a combined set of tested biomarkers reflected the presence of Sarcopenia in elderly women.

Concerning the quality of life in our work, the mean score of SF-36 questionnaire was significantly lower in the sarcopenic group ($p<0.001$), indicating poorer quality of life (Qol) among sarcopenic patients.

Kull et al.[52], reported a reduced quality of life assessed by the SF-36 questionnaire in terms of physical function, vitality, and role-emotional domains in sarcopenic patients.

Also, Sayer et al.[53], investigated the relationship of the strength of hand grip, as a predictor of Sarcopenia, and Health-related QoL, using SF-36 score, in 2987 subjects aged from 59 to 73 years of age. They demonstrated a correlation between decreased grip strength as well as poorer HRQoL in the elderly, implying a connection between Sarcopenia and overall fragility. Smith et al., showed that participants with severe Sarcopenia have a lower quality of life score than non-severe Sarcopenia participants [54].

The current study showed that serum myostatin correlated negatively with SF-36 scores in the sarcopenic group compared to the control group ($r= -0.345$; $p<0.001$).

To assess the accuracy of serum myostatin in discriminating sarcopenic patients from healthy elders, ROC curve analysis was performed. Serum myostatin level at values > 29 IU/dl has high sensitivity (87.5%) and high specificity (75%), indicating a good and acceptable performance of serum myostatin to detect and diagnose patients with Sarcopenia. We suggested that serum myostatin is a promising serum biomarkers that can help in diagnosing Sarcopenia. Similar findings were reported by Han et al. who stated that serum myostatin can be used as a to predict pre-Sarcopenia in males [49]. Also, Tay et al.[48] using multiple logistic regression, observed that myostatin is a significant risk factor for only sarcopenic men. Furthermore, a previous work by Smith et al.[55] centered on the function of myostatin inhibitors in the management of illnesses characterized by the atrophy of muscular mass in elderly Sarcopenia patients. They discovered that serum myostatin is a possible serum marker for evaluating the therapy of Sarcopenia.

Conclusion:

In conclusion; Sarcopenia that geriatric condition may pose a public health risk owing to the numerous clinical features that appear to be connected with it.

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In order to mitigate the detrimental effects of the disease on the quality of life of sarcopenic individuals, it is necessary to implement strategies for both preventive and interventional care. The treatment of Sarcopenia would advance significantly if a cost-effective way could be developed to detect and track the condition. Our findings point to serum myostatin as a possible blood-based biomarker for Sarcopenia diagnosis as well as quality of life assessment in such population. Further researches with more sample sizes are required to confirm our outcomes. The cause-and-effect relationship between myostatin as well as Sarcopenia can be better understood with the results of future longitudinal studies. Using serum myostatin as a biomarker for sarcopenia & promoting its incorporation into standard practice would increase healthcare professionals' awareness of Sarcopenia.

The main limitation of our trial was the small sample size, however, even though on a small sample, we have showed the correlation between myostatin as a potential biomarker for Sarcopenia and its correlation with the quality of life. We didn't use the specified Sarcopenia QoL questionnaire, a specific tool to measure QoL in Sarcopenia, instead, we applied the general SF-36 score since the SarQoL questionnaire is yet to be validated.

List of abbreviation:

ActRIIB: Activin type IIB receptor.
AKt: Ak strain transforming.
ASMI: appendicular skeletal muscle mass index.
AST: Aspartate aminotransferase.
ALT: Alanine aminotransferase.
BIA: Bioelectrical impedance assessment.
BMI: Body mass index.
CBC: complete blood count.
CRP: C-reactive protein.
CT: Computed tomography.
(14). Also, myostatin induces activation of Smad2 and Smad3 that inhibit the IGF-1/Akt/
DEXA: Dual energy X-ray absorptiometry.
ELIZA: enzyme-linked immunosorbent assay.
EWGSOP: European Working Group on Sarcopenia in Older People.
ESR: Erythrocyte sedimentation rate.
GGT: gamma-glutamyl transferase
Kg: Kilogram
IGF-1: Insulin like growth factor-1.
m: meter.
mRNA: messenger RiboNucleic Acid
mTOR: Mammalian target of rapamycin
MRI: magnetic resonance imaging.

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QoL: Quality of life.
SF-36: The Short Form 36 Health Survey Questionnaire.
T3: Triidotyrosin.
T4: thyroxin level.
TSH: thyroid stimulating hormone
US: Ultrasound.
WHO: world health organization.

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