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Muscle wasting assessed by ultrasound versus scoring systems as early predictor of outcomes of intensive care unit stay in critically ill patients

Salwa Omar El Khattab Amin, Ahmed Ali Fawaz, Hany Magdy Fahim Hana and Amr Badawy Mahmoud Badawy Elkolfat

Department of Anesthesiology, Intensive Care and Pain Management, Ain Shams University, Faculty of Medicine, Cairo, Egypt

ABSTRACT

Background: A lot of outcome predictive tools are already in use in critical care setting with different degrees of reliability aiming for possible prevention or minimization of bad outcome and better resource management. Some critical illness sequelae significantly affect patient's outcome and currently not included in the in-use predictive scoring system. Muscle wasting/weakness is one of these sequelae, and it was found to be an independent risk factor of poor outcomes.

Objective: This study was conducted to evaluate the degree of muscle wasting estimated by ultrasonography during ICU stay as a predictor of mortality, successful weaning of mechanical ventilation, ICU stay and hospital stay.

Patients and Methods: A prospective observational study was conducted in critical care units in Ain Shams University Hospitals, Cairo, Egypt over a period of 12 months.

Results: Decrease in muscle measurements was found to correlated to mortality in ICU with cutoff points from area under the curve for right QMT, left QMT, right RFCSA, left RFCSA, IEDT and EEDT were supposed to be:>9.77,>15, >16.67, >12.5, >12.63, >12.5, respectively, with best specificity and positive predictive value was found in right RFCSA (95.45, 87.5, respectively) while best sensitivity and negative predictive value was found in left RFCSA (65.38, 82, respectively). Significant negative correlation between vasoactive agent free period and maximum daily reduction in RFCSA, QMT, EIDT, and EEDT (P value = 0.001).

Conclusion: Daily reduction of the RFCSA and to lesser extent the QMT has significant correlation to mortality, prolongation of mechanical ventilation days and reduction in the vasopressor free days but has a poor correlation to the ICU and hospital stay. Pneumonia and renal disease had significant correlation with the muscle mass reduction. The left RFCSA found to be comparable to SOFA score as mortality predictor.

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ICU Aquired Weakness; critical illness polyneuropathy; critical illness neuromyopathy; ICU outcome predictive scores; muscle wasting

1. Introduction

Critically ill patients are group of patients who are sustaining a state of life-threatening organ dysfunction or at great risk of deterioration and poor outcome either in term of mortality or morbidity with prolonged hospital stay which have a great impact on medical cost. To manage those patients a great volume of clinical, laboratory, imaging . . . . data are collected at time of ICU admission and throughout patient's stay. These data are used through a multidisciplinary approach to manage and prevent potential sequelae of critical illness. It is used also to predict the possible outcome of the patient. Many outcome predictive scores are available either general or diseased-specific with different validation levels.

Some critical illness sequelae can significantly affect patient's outcome and not included in the in-use predictive scoring system, ICU-Acquired Weakness (ICUAW) is one of these sequelae. ICUAW was found to be an independent risk factor of poor outcomes in ICU [1]. that is why early detection and management is of great importance to improve patient's outcome.

The gold standard for diagnosis of ICUAW is the electrophysiology studies of the muscle [2] which is of limited use in ICU settings. So, the alternative diagnostic tool should be searched for. Bed-side muscle ultrasound is an attractive diagnostic modality being non-invasive, reproducible easy to learn and can detect the changes that develops in muscles mass in critically ill patients. These changes were found to be related to length of hospital stay in those patients [3].

This study was conducted to find out if degree of changes in muscle thickness and circumference measured by bed-side ultrasound is correlated to outcome in critically ill patients and correlate this to results of predictive scoring system so it can be used either alone or combined for better prediction of outcome (mortality and morbidity) in critically ill patients.

CONTACT Salwa Omar El Khattab Amin salwakhattab2011@hotmail.com Department of Anesthesiology, Intensive Care and Pain Management, Ain Shams University, Faculty of Medicine, ramsees st., Abbasia, Cairo 11591, Egypt

2. Patients and methods

This prospective, observational study was conducted in critical care units in Ain Shams University Hospitals, over a period of 12 months (from 2019 to 2020) after approval of our ethical committee, **Faculty of Medicine, Ain Shams University Research Ethics Committee (FMASU-REC)**. and getting informed written consent from each patient or patient's guardian (if the patient was incapable) after full explanation of the procedure.

Patients were included in this study if they were admitted to our ICU during assigned study period (whatever the diagnosis except those excluded), aged 21 years old or more and of both sexes. **Patients were excluded** if they were presented with persisted uncorrected electrolyte disturbances (hypo or hyper natremia, hypokalemia or hyperkalemia, hypocalcemia, hypophosphatemia), history of therapy with aminoglycosides, theophylline, or high-dose steroid before admission to hospital. alcohol abuse, amputated lower limb, neuromuscular diseases (myasthenia gravis, Guillain Barre syndrome . . . .), and patient presented with neuromuscular problems (cerebrovascular stroke, spine injury . . . . . .)

100 patients who admitted to ICUs and met inclusion criteria were recruited based on 12-month time frame and results of published literatures.

2.1. All included patients were subjected to the following

2.1.1. History taking

Personal data: age, sex, and occupation. Cause of admission and diagnosis. Past history of neuromuscular disease, previous ICU admission or cerebrovascular stroke and other medical morbidities. Drug history including aminoglycosides, corticosteroids, and muscle relaxants during the course of stay as there are included in exclusion criteria.

2.1.2. Clinical examination

Complete physical examination in the hospital with emphasis on: Vital signs (blood pressure, heart rate and rhythm, temperature, respiratory rate). Glasgow coma score. General, chest, abdominal and cardiac examination

2.1.3. Laboratory evaluation

Arterial blood gases and Complete blood count. Urea, creatinine, ALT, AST, sodium, potassium, calcium, total and direct bilirubin. Random blood sugar level.

2.1.4. Illness severity scoring calculation

APACHE-II on day of admission and SOFA was calculated on ICU day one and then on daily base.

2.1.5. Ultrasonographic measures

A well trained sonographer performed daily assessment of muscle of the thigh and diaphragm using PHILIPS machine and for a maximum of 28 days. A 7–10 MHz real-time linear array scan head for all patients (3.5–5 MHZ real-time curved array scan head was used in obese patients or massive edema to verify the measurements).

Thigh muscles were assessed with patient in supine position and relaxed lower limb over average of 15 minutes. Measurement taken at the junction between lower third and upper two-thirds of the distance between the superior border of the patella and the anterior superior iliac spine. A mark was put on the skin to fix the measurement point each time of assessment. The transducer was positioned strictly perpendicular to the longitudinal axis of the quadriceps femoris without compressing skin surface. Image was frozen and stored for later measurements. A mean of the three values were used for analysis.

Using planimetric technique, the inner echogenic line of the rectus femoris was outlined by a movable cursor on a frozen image of rectus femoris in the B-mode and RFCSA calculated. Then, QMT (Quadriceps Muscle Thickness) measured from the upper border of the rectus femoris muscle to lower border of vastusintermedius (VI) muscle was done. Delta change of the measure (maximum daily reduction) each day and from the first time measurement in the RFCSA and QMT was calculated each time.

Diaphragm was assessed using linear 7–10 MHz probe with the transducer perpendicular to the chest wall, between the anterior axillary and the midaxillary lines, to visualize the diaphragmatic muscle below the costophrenic sinus. The diaphragm was seen as three layers: two parallel echoic lines (the diaphragmatic pleura and the peritoneal membrane) and a hypoechoic structure between them (the muscle itself), thickness was measured across the two edges of the diaphragm. (Two hyperechoic lines). **End-Inspiratort Diaphragmatic Thickness (EIDT)** and **End-Expiratory Diaphragmatic Thickness (EEDT)** was measured as an average of three readings each. Then **Diaphragmatic thickness fraction (DTF)** was determined by equation:

$$DTF = (EIDT - EEDT)/EEDT$$

Diaphragmatic excursion (DE), measured with US probe position between the midclavicular and the anterior axillary line, during inspiration the diaphragm moves caudally toward the probe. The excursion was measured using M-mode measuring the distance from the highest to the lowest point of the diaphragm. Excursion <10 mm indicating diaphragmatic dysfunctionor and negative deflection may indicate paradoxical diaphragmatic movement.

2.2. Study outcomes

2.2.1. Primary

Mortality: ICU mortality, hospital mortality, 28-days mortality

2.2.2. Secondary

The correlating of the **Ultrasonographic measurements** with the following outcomes: total duration of mechanical ventilation. Successful weaning, failed weaning of mechanical ventilation and ICU length of stay and Hospital length of stay.

Failed weaning can be defined as "inability to maintain spontaneous breathing for at least 48 hrs, without any form of ventilatory support". Following are the criteria for failure of spontaneous breathing trial (SBT): changes in mental status, onset of discomfort, diaphoresis, RR > 35 breaths/min, haemodynamic instability (heart rate > 140, systolic blood pressure > 180 or <90 mmHg), or signs of increased work of breathing.

2.3. Statistical analysis of the data

Data were tabulated and analyzed using IBM SPSS software package version 20.0. The Kolmogorov-Smirnov test was used to verify the normality of distribution. Qualitative data expressed as range, mean, standard deviation and Quantitative data were expressed as numbers and percent. Significance of the obtained results was judged at the 5% level.

2.3.1. Chi-square test

For categorical variables, to compare between different groups. **Fisher's Exact or Monte Carlo correction** was used for chi-square when more than 20% of the cells have expected count less than 5. **Mann Whitney test** was used to compare abnormally distributed quantitative variables to compare between two studied groups. **Spearman coefficient** for correlation between abnormally distributed quantitative variables [4,5].

2.4. Results

A total of 100 patients among those admitted during study period were found to meet our inclusion/exclusion criteria initially recruited, **18** patients were discharged in the next day with no serial measurements, **seven** patients were discharged against medical advice before completing their measurements, and finally **five** cases withdrew their consents of participation.

A total of 70 patients completed the study, 26 died during ICU stay and the remaining 44 patients survived. Four had stayed in ICU more than 28 days (two survived the hospital stay and were discharged to home, another two discharged from ICU and died later after readmission to ICU). The remaining 40 patients had ICU stay of less than 28 days, two died after discharge within 28 days of ICU admission and 38 patients were discharged to home (Figure 1).

Baseline characteristic data of our population were summarized in Table 1. Our study included 43 male and 27 female patients with age range was 38.0–81.0 years old with no correlation was found between sex or age and total reductions of all measurements. (Tables 2, 3).

2.5. ICU outcomes

The measured mortality outcome in our study were, **ICU mortality**: deaths during ICU stay (26 patients, all were less than 28 days), **28-days mortality**: deaths within 28 days from admission and **hospital mortality**: mortality during total hospital-stay. Out of the 70 patients that completed the study, we had 26 patients (37%) in ICU mortality, 28 patents (26 died during ICU stay + 2 died after discharge from ICU but within 28 days) (40%) 28-days mortality and 30 patients (26 died during ICU stay + 2 died after discharge from ICU but within 28 days + 2 patients died more than 28 days of hospital stay) (42.9%) total hospital mortality. (Table 4) We found no correlation between mortality rate and different disease categories. (Table 5)

The mean **length of ICU stay** in this study was found to be 11.16 days (4.0–45.0 days), and mean length of hospital stay was 14.90 days (4.0–60.0 days). The mean percent of vasoactive-free period out of ICU stay was 65.8%, and the mean of mechanical ventilation-duration percent out of ICU stay was 54.97%. (Table 4)

2.6. Correlations between muscle measurements and primary outcomes

A positive correlation had been found between the reduction in muscle mass (percent of maximum reduction in all studied muscle measurements) and **mortality** as higher percent of reduction in daily muscle measurement was found in mortality group (with maximum reduction recorded in our population reached up to 46.9% and was in mortality group). A value of zero reduction in muscle mass was found in some of survived patients but none in mortality group.

Variation in test of significance was found in different muscle groups and from side to side. The **best** correlation to mortality was the percent of daily reduction in left RFCSA (area under the curve) (Figure 2) followed by right RFCSA and then left QMT (p value was 0.001 each) while the **least** correlation to mortality was in right QMT (P value was 0.049) making the RFCSA daily reduction preferred as a rough indicator of mortality. Regarding diaphragmatic measurements, reduction in EIDT and EEDT also had less significant correlation with mortality (p value = 0.015, 0.028 respectively) but better than that of right QMT. (Table 6)

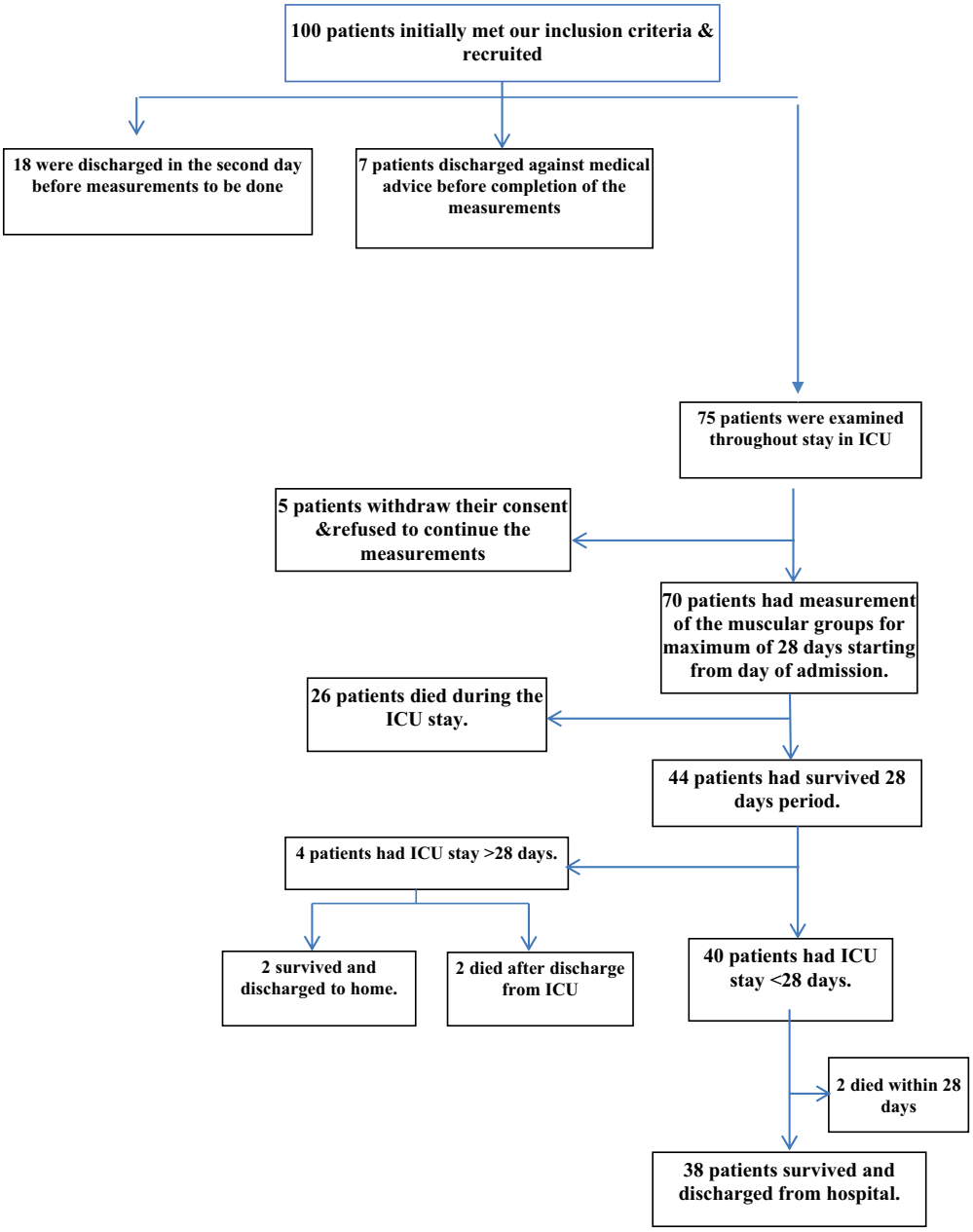

Figure 1. Flow chart of included cases in our study.

A descriptive analysis was done for non-survivors ($n = 26$), and it was found that **time of occurrence of death** was within a range of 1.38–3.12 days after record of maximum percent of daily reduction in the muscle measurement in different muscle groups (Table 7). Some patients died on the same day of measurement of the maximum percent of daily reduction. For description, maximum percent of daily reduction in the mortality group had been described with mean of days 1.38 for RFCSA, 1.46 to 2.31 for Lt Rt QMT, respectively. (Table 7)

On the other hand, the improvement in the maximum percent of the daily measures of left RFCSA, QMT (*P* value 0.001) and right RFCSA (*P* value 0.002) had a positive correlation with improvement in the survival group. (Table 8)

To set comparison between prognostic predictive value of different indicators, cutoff points from area under the Receiver Operator Characteristic (ROC) curve for both mortality predictive scores (SOFA and APACHE II scores) were compared to ultrasound muscle measurements (maximum percent of daily reduction and maximum value of reduction from first day of measurements as regard sensitivity, specificity, positive predictive values, and negative predictive values. (Table 9, Figure 2) **The best mortality predictive value** was SOFA score followed by maximum percent of daily reduction of RFCSA then APACHE II score. (Table 10)

A significant correlation was found between daily reduction in RFCSA followed by QMT and then EIDT and **28-days mortality**. EEDT showed no correlation to 28-days mortality. (Table 11)

Table 1. Baseline patients' characteristic data.

		Min. – Max.	Mean ± SD.	Median
Age		38.0–81.0	63.29 ± 10.21	65.0
	Glasgow coma score	4.0–15.0	13.12 ± 2.72	15.0
Vital signs	Blood pressure	33.20–153.1	90.32 ± 14.35	91.55
	Heart Rate	54.0–170.0	92.73 ± 19.45	90.0
	Respiratory Rate	10.0–42.0	21.35 ± 5.49	20.0
	Rectal temp	35.50–40.0	37.41 ± 0.67	37.0
ABG	PH	7.05–7.60	7.41 ± 0.11	7.42
	PaO_2	39.0–574.0	121.0 ± 61.05	110.0
	$PaCO_2$	17.0–94.0	33.96 ± 13.05	31.20
	HCO_3^-	6.0–39.0	22.14 ± 6.90	21.40
	PaO_2/FiO_2ratio	100.0–583.0	257.80 ± 95.25	252.0
Investigations	Hemoglobin	4.30–15.60	10.10 ± 1.83	10.0
	platelet count	23.0–420.0	170.6 ± 92.61	166.5
	White blood count	1.10–43.0	13.01 ± 6.70	12.0
	Urea	12.0–325.0	94.10 ± 67.10	69.0
	Creatinine	0.24–10.0	2.05 ± 2.21	1.0
	Sodium	100.0–160.0	136.1 ± 8.44	137.0
	Potassium	2.50–6.50	4.06 ± 0.70	4.0
	SOFA score	0.0–20.0	5.72 ± 4.93	4.0
	APATCH II score	3.0–35.0	15.37 ± 7.53	15.0

ABG: arterial blood gases, PaCO2: Partial pressure of carbon dioxide, PaO2: Partial pressure of oxygen, HCO3: mean arterial bicarbonate concentration.

Table 2. Correlation between sex of our patients and maximum percent of daily reduction of studied muscles.

	Sex			
Maximum % of daily reduction of muscle measures	Male ($n = 43$)	Female ($n = 27$)	U	P
Right QMT				
Min. – Max.	2.78–25.0	2.74–25.0		
Mean ± SD.	10.53 ± 5.59	10.57 ± 6.68	545.5	0.672
Median	9.09	8.97		
Left QMT				
Min. – Max.	3.75–33.55	0.0–33.33		
Mean ± SD.	12.61 ± 6.57	13.83 ± 8.76	517.5	0.447
Median	11.54	12.20		
Right RFCSA				
Min. – Max.	2.99–31.82	3.03–33.33		
Mean ± SD.	11.97 ± 6.87	11.65 ± 10.12	476.0	0.207
Median	11.43	7.14		
Left RFCSA				
Min. – Max.	4.09–32.71	4.76–46.91		
Mean ± SD.	13.81 ± 8.85	14.64 ± 13.62	512.5	0.412
Median	10.0	9.62		
EIDT				
Min. – Max.	3.77–21.88	0.0–21.88		
Mean ± SD.	9.88 ± 4.80	8.48 ± 4.88	487.0	0.259
Median	9.52	7.05		
EEDT				
Min. – Max.	0.0–22.22	3.23–16.67		
Mean ± SD.	10.35 ± 5.19	8.39 ± 4.05	437.5	0.084
Median	9.52	7.41		

U, p:U and *p* values for Mann Whitney test *: Statistically significant at $p \leq 0.05$ QMT: quadriceps muscle thickness, RFCSA: rectus femoris cross sectional area, EIDT: end inspiratory diaphragmatic thickness, EEDT: end expiratory diaphragmatic thickness.

Table 3. Correlation between age of our patients and maximum percent of daily reduction of studied muscles.

	Age	
Max. daily Reduction of	r_s	p
Right QMT	0.156	0.197
Left QMT	−0.164	0.175
Right RFCSA	0.033	0.787
Left RFCSA	0.197	0.103
EIDT	0.172	0.154
EEDT	0.138	0.256

r_s: Spearman coefficient.
*: Statistically significant at $p \leq 0.05$.
QMT:quadriceps muscle thickness, RFCSA: rectus femoris cross sectional area, EIDT: end inspiratory diaphragmatic thickness, EEDT: end expiratory diaphragmatic thickness.

Table 4. Distribution of ICU outcomes.

The measured outcome	No.	%	
ICU mortality	26	37.1	
28-days mortality	28	40.0	
Hospital mortality	30	42.9	
	Min. – Max.	**Mean ± SD.**	**Median**
Vasoactive-free periods (% out of stay)	0.0–100.0	65.79 ± 42.78	55.0
Duration of MV (% out of stay)	0.0–100.0	54.97 ± 39.41	63.96
Length of ICU stay (days)	4.0–45.0	11.16 ± 9.06	6.0
Length of hospital stay (days)	4.0–60.0	14.90 ± 13.30	8.0

MV: Mechanical ventilation.

Table 5. Relation between mortality with different disease categories.

	Mortality					
	No ($n = 44$)		Yes ($n = 26$)			
	No.	%	No.	%	F2	p
Pneumonia	18	40.9	14	53.8	1.102	0.294
UTI	6	13.6	2	7.7	0.570	$^{FE}p = 0.701$
Blood stream	2	4.5	1	3.8	0.019	$^{FE}p = 1.000$
HandN infections	0	0.0	1	3.8	1.717	$^{FE}p = 0.371$
DFI	3	6.8	3	11.5	0.465	$^{FE}p = 0.664$
Others	6	13.6	7	26.9	1.908	$^{FE}p = 0.209$
DM	2	4.5	4	15.4	2.450	$^{FE}p = 0.186$
Systolic heart failure	22	50.0	8	30.8	2.468	0.116
Pulmonary disease	11	25.0	6	23.1	0.033	0.856
Neurological disease	13	29.5	6	23.1	0.346	0.557
Renal disease	6	13.6	6	23.1	1.025	$^{FE}p = 0.341$
Hepatic disease	5	11.4	4	15.4	0.236	$^{FE}p = 0.718$
Hematological disease	7	15.9	5	19.2	0.127	$^{FE}p = 0.751$
Low dose corticosteroids	16	36.4	14	53.8	2.040	0.53

X^2, p: X^2 and p values for Chi square test, ^{FE}p: p value for Fisher Exact for Chi square test.
BSI: Blood stream infection, UTI: Urinary tract infection, HandN: head and neck, DFI: diabetic foot infection DM: diabetes mellitus.

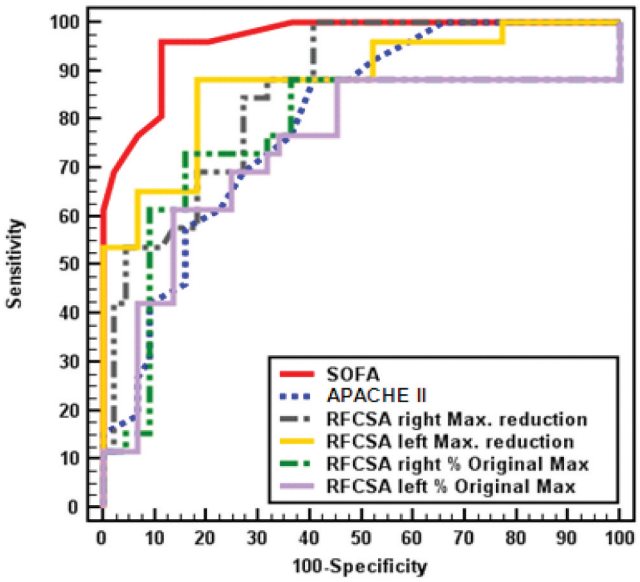

Figure 2. ROC curve to predicate mortality. $\mathbf{r_s}$:Spearman coefficient *:Statistically significant at $p \leq 0.05$

2.7. Correlations between muscle measurements and secondary outcomes

The possible correlation between maximum percent of reduction of muscle mass as judged by measuring thigh or diaphragm muscles was tested to secondary outcome parameters (vasoactive-free periods, duration of mechanical ventilation, ICU stay . . . . etc.).

A negative correlation (moderate to strong correlation) was found between percent of maximum daily reduction of the muscle measurements (the best indicative was the daily RFCSA reduction) and the **vasoactive-free periods** (vasoactive-free period decreased significantly with increase in the maximum percent of daily reduction of the measurements p value < 0.001). (Table 12, Figure 3)

Table 6. Relation between mortality and maximum percent of the daily reduction in measurements of studied muscles.

	Mortality			
Maximum value of daily reduction	No ($n = 44$)	Yes ($n = 26$)	U	P
Right QMT Min.				
Max.	2.74 18.52	3.85 25.00		
Mean ± SD.	8.98 ± 4.00	13.20 ± 7.73	410.5*	0.049*
Median	8.97	10.62		
Left QMT Min.				
Max.	0.0 16.67	4.00 33.55		
Mean ± SD.	9.98 ± 4.28	18.33 ± 8.73	229.0*	<0.001*
Median	9.92	18.18		
Right RFCSA Min.				
Max.	2.99 31.82	7.14 33.33		
Mean ± SD.	8.17 ± 5.46	18.06 ± 8.41	159.5*	<0.001*
Median	6.41	17.95		
Left RFCSA Min.				
Max.	4.09 18.97	6.10 46.91		
Mean ± SD.	8.76 ± 3.48	23.22 ± 12.94	137.0*	<0.001*
Median	8.52	25.71		
EIDT	0.0 21.05	3.70 21.88		
Min. Max.				
Mean ± SD.	8.21 ± 4.34	11.23 ± 5.13	371.5*	0.015*
Median	7.05	11.11		
EEDT	0.0 22.22	3.23 18.18		
Min. Max.				
Mean ± SD.	8.68 ± 5.03	11.14 ± 4.17	391.0*	0.028*
Median	7.28	11.11		

U and *P* values for Mann Whitney test.
**p* -value >0.05: Nonsignificant; *p*-value <0.05: Significant; *p* -value <0.01: Highly significant.

Table 7. Descriptive analysis for those who died ($n = 26$) for studied muscles.

Days before death	Min.	Max.	Mean ± SD.	Median
Right QMT	0.0	6.0	2.31 ± 1.87	2.0
Left QMT	0.0	8.0	1.46 ± 2.34	0.50
Right RFCSA	0.0	5.0	1.38 ± 1.42	1.0
Left RFCSA	0.0	4.0	1.38 ± 1.17	1.0
EIDT	0.0	7.0	2.46 ± 2.02	1.0
EEDT	0.0	12.0	3.12 ± 3.12	1.50

QMT:quadriceps muscle thickness, RFCSA: rectus femoris cross sectional area, EIDT: end inspiratory diaphragmatic thickness, EEDT: end expiratory diaphragmatic thickness.

Table 8. Relation between percent of maximum daily improvement of studied muscles measures and the mortality.

	Mortality			
Max. percent of improvement	No ($n = 44$)	Yes ($n = 26$)	U	p
Right QMT Min.				
Max.	−3.64 21.05	−3.33 5.56		
Mean ± SD.	6.46 ± 7.29	1.12 ± 2.77	318.0*	0.002*
Median	6.15	1.18		
Left QMT Min. Max.				
Max.	−4.17 19.05	−10.0 4.17		
Mean ± SD.	7.29 ± 7.0	0.59 ± 4.68	225.5*	<0.001*
Median	5.92	1.43		
Right RFCSA Min. Max.				
Max.	−7.32 20.67	−21.05 12.0		
Mean ± SD.	6.06 ± 6.48	0.76 ± 8.67	276.0*	<0.001*
Median	5.10	0.44		
Left RFCSA Min.				
Max.	−9.09 14.04	−18.0 5.88		
Mean ± SD.	4.95 ± 5.84	2.89 ± 6.71	219.0*	<0.001*
Median	5.84	0.84		
EIDT	2.47–22.22	−12.0 37.50		
Min. Max.				
Mean ± SD.	5.59 ± 7.37	5.75 ± 13.38	571.5	0.995
Median	2.50	3.23		
EEDT Min.				
Max.	−3.45 22.73	−12.0 33.33		
Mean ± SD.	7.14 ± 8.39	5.06 ± 12.14	496.5	0.357
Median	4.88	−3.33		

U, p: U and *p* values for Mann Whitney test for comparing between the two groups.
*: Statistically significant at $p \leq 0.05$.
QMT:quadriceps muscle thickness, RFCSA: rectus femoris cross sectional area, EIDT: end inspiratory diaphragmatic thickness, EEDT: end expiratory diaphragmatic thickness.

Table 9. The mortality-predictive value of percent of daily reduction in muscle mass (sensitivity, specificity, PPV and NPV).

			95% C.I						
Maximum percent of daily reduction	AUC	p	LL	UL	Cut off	Sensitivity	Specificity	PPV	NPV
Right QMT	0.641*	0.049*	0.493	0.790	>9.77	61.54	75.00	59.3	76.7
Left QMT	0.800*	<0.001*	0.681	0.918	>15	57.69	93.18	83.3	78.8
Right RFCSA	0.861*	<0.001*	0.777	0.944	>16.67	53.85	95.45	87.5	77.8
Left RFCSA	0.880*	<0.001*	0.794	0.966	>12.5	65.38	93.18	85.0	82.0
EIDT	0.675*	0.015*	0.543	0.808	>12.63	46.15	86.36	66.7	73.1
EEDT	0.658*	0.028*	0.527	0.789	>12.5	38.46	81.82	55.6	69.2

QMT:quadriceps muscle thickness, RFCSA: rectus femoris cross sectional area, EIDT: end inspiratory diaphragmatic thickness, EEDT: end expiratory diaphragmatic thickness, AUC: area under the curve, C.I: confidence interval, UL: Upper level, LL: Lower level, PPV: Positive predictive value, NPV: Negative predictive value.

Table 10. Comparison of mortality-predictive value of SOFA, APACHE II and RFCSA (daily and total reduction).

			95% C.I						
	AUC	p	LL	UL	Cut off	Sensitivity	Specificity	PPV	NPV
SOFA	0.964*	<0.001*	0.927	1.000	>9	96.15	88.64	83.3	97.5
APACHE II	0.796*	<0.001*	0.694	0.899	>17	57.69	84.09	68.2	77.1
Maximum percent of daily reduction									
Right RFCSA	0.861*	<0.001*	0.777	0.944	>16.67	53.85	95.45	87.5	77.8
Left RFCSA	0.880*	0.044*	0.794	0.966	>12.5	65.38	93.18	85.0	82.0
percent Original Max									
Right RFCSA	0.768*	<0.001*	0.637	0.900	>33.23	73.08	84.09	73.1	84.1
Left RFCSA	0.740*	0.001*	0.608	0.873	>41.86	61.54	86.36	72.7	79.2

RFCSA: rectus femoris cross sectional area, AUC: area under the curve, C.I: confidence interval, UL: Upper level, LL: Lower level, PPV: Positive predictive value, NPV: Negative predictive value.

Table 11. Relation between 28-day mortality with maximum percent of daily reduction of studied muscle measurement.

	28 days' mortality			
Maximum percent % of daily reduction	No ($n = 42$)	Yes ($n = 28$)	U	p
Right QMT				
Min. – Max.	2.74–18.52	3.85–25.0		
Mean ± SD.	8.91 ± 4.07	13.0 ± 7.48	415.0*	0.038*
Median	8.97	10.62		
Left QMT				
Min. – Max.	0.0–16.67	4.0–33.55		
Mean ± SD.	10.02 ± 4.37	17.68 ± 8.74	276.0*	<0.001*
Median	10.0	17.09		
Right RFCSA				
Min. – Max.	2.99–31.82	7.14–33.33		
Mean ± SD.	7.93 ± 5.47	17.72 ± 8.19	147.5*	<0.001*
Median	6.39	15.64		
Left RFCSA				
Min. – Max.	4.09–18.97	6.10–46.91		
Mean ± SD.	8.50 ± 3.23	22.56 ± 12.73	133.5*	<0.001*
Median	7.87	21.93		
EIDT				
Min. – Max.	0.0–21.05	3.70–21.88		
Mean ± SD.	8.30 ± 4.42	10.90 ± 5.10	407.0*	0.030*
Median	7.05	11.11		
EEDT				
Min. – Max.	0.0–22.22	0.0–18.18		
Mean ± SD.	8.94 ± 4.94	10.57 ± 4.61	458.0	0.119 §
Median	7.41	11.11		

U and *P* values for Mann Whitney test for comparing between the two groups.
*: Statistically significant at $p \leq 0.05$.
*.*p* -value >0.05: Nonsignificant; *p*-value <0.05: Significant; *p* -value <0.01: Highly significant.
§.QMT:quadriceps muscle thickness, RFCSA: rectus femoris cross sectional area, EIDT: end inspiratory diaphragmatic thickness, EEDT: end expiratory diaphragmatic thickness.

Duration of **mechanical ventilation days** during ICU stay showed weak to moderately significant increase with increase in the maximum percent of daily reduction of the measurements of both quadriceps and diaphragmatic muscle. To avoid fallacies due to different lengths of ICU stay, the **percent of MV during the ICU stay** was used, resulting in moderate correlation with RFCSA and left QMT, weak with right QMT and EIDT, EEDT the (Table 12 Figures 4, 5) with best indicative was the RFCSA readings and the least was diaphragmatic thickness in end expiration (*p* value < 0.001, <0.002 respectively). (Table 12 Figures 4, 5)

Table 12. Correlation between maximum percent of daily reduction of studied muscles and outcome parameters.

Maximum percent of daily reduction		Right QMT	Left QMT	Right RFCSA	Left RFCSA	EIDT	EEDT
percent of vasoactive-free period out of ICU stay	r_s	−0.456*	−0.533*	−0.605*	−0.645*	−0.474*	−0.403*
	P	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	0.001*
Percent of duration of mechanical ventilation out of ICU stay	r_s	0.389*	0.540*	0.617*	0.636*	0.394*	0.370*
	P	0.001*	<0.001*	<0.001*	<0.001*	0.001*	0.002*
Duration of mechanical ventilation in (days) stay in ICU	r_s	0.328*	0.401*	0.487*	0.401*	0.291*	0.450*
	P	0.006*	0.001*	<0.001*	0.001*	0.015*	<0.001*
Length of ICU stay (total patients $n = 70$)	r_s	0.108	0.039	−0.073	−0.140	−0.008	0.217
	P	0.372	0.751	0.546	0.247	0.947	0.071
Length of hospital stay (total patients $n = 70$)	r_s	0.072	−0.076	−0.105	−0.189	−0.064	0.164
	P	0.552	0.534	0.388	0.117	0.596	0.174
Length of ICU stay for survivors ($n = 44$)	r_s	0.504*	0.613*	0.283	0.254	0.357*	0.525*
	P	<0.001*	<0.001*	0.063	0.096	0.017*	<0.001*
Length of hospital stay for survivors ($n = 44$	r_s	0.515*	0.603*	0.392*	0.326*	0.283	0.454*
	P	<0.001*	<0.001*	0.008*	0.031*	0.063	0.002*

r_s: Spearman coefficient.
*: Statistically significant at $p \leq 0.05$.
QMT:quadriceps muscle thickness, RFCSA: rectus femoris cross sectional area, EIDT: end inspiratory diaphragmatic thickness, EEDT: end expiratory diaphragmatic thickness.

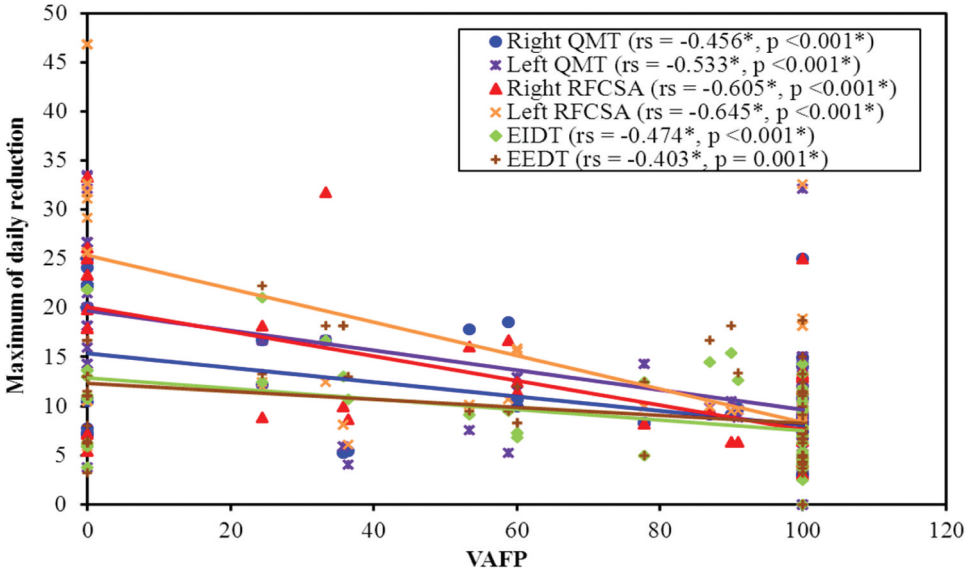

Figure 3. Correlation between maximum percent of daily reduction and percent of vasoactive agent-free period in stay (VAFP) in ICU. **r_s**:Spearman coefficient *:Statistically significant at $p \leq 0.05$

When test the correlation of **ICU and hospital length** of stay in **mortality group**, it was found that both had no test significance with maximum percent of daily reduction of all measurements. (Table 12)

When testing this correlation in **survivors** (no. 44 who skip early mortality), daily reduction of RFCSA (both sides) had a strong correlation to longer hospital (but not ICU) length of stay. **EEDT** had significant prolongation of the **hospital stay**. (Table 12, Figure 7)

The daily reduction in both right and left QMT had **moderate to highly** significant correlation with length of **ICU** and **hospital** stays. (Table 12, Figure 6)

EIDT, EEDT had **moderate** to highly significant correlation with length of ICU stay and **EEDT** had significant correlation to prolonged **hospital stay**. (Table 12, Figures 6, 7)

We can conclude that **QMT** was better than RFCSA in correlation with ICU and hospital stay while **RFCSA**, had a better correlation with the mortality. (Tables 6, 12)

When using the increase in maximum total reduction percent from the admission and over ICU stay, **QMT** measurements during all the stay had significant increase in mechanical ventilation duration and significant reduction in the vasopressor-free periods, none was found with diaphragmatic measurements. (Table 13) ICU stay and hospital stay significantly increased (weak to moderate) with increase in maximum total reduction percent from the admission and over ICU stay to left RFCSA, right QMT and diaphragmatic thickness measurements. (Table 13)

By applying length of stay for **survivors** of ICU ($n = 44$) avoiding early mortality, Maximum

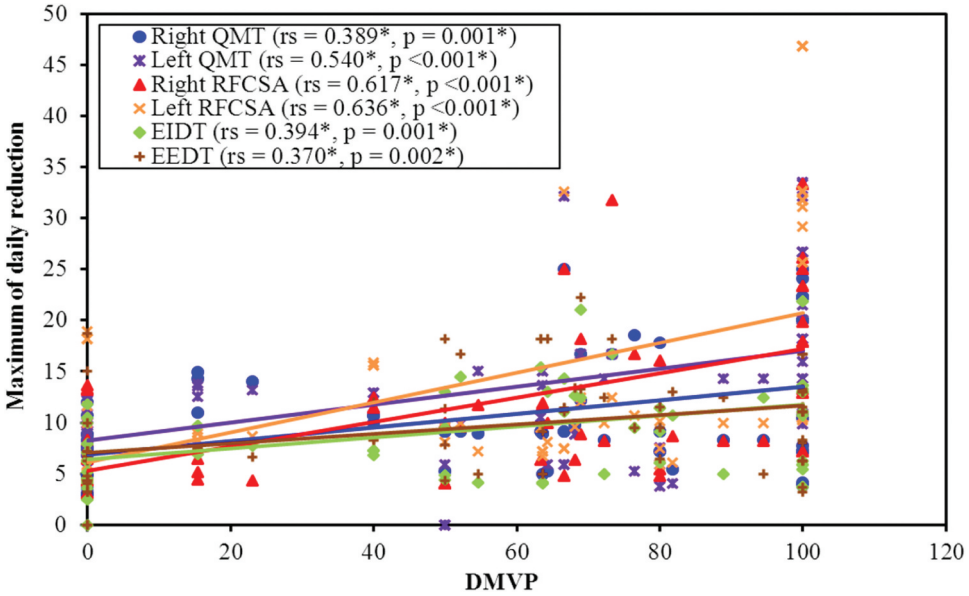

Figure 4. Correlation between maximum percent of daily reduction and duration of mechanical ventilation in %(DMVP) stay in ICU. $\mathbf{r_s}$:Spearman coefficient *:Statistically significant at $p \leq 0.05$

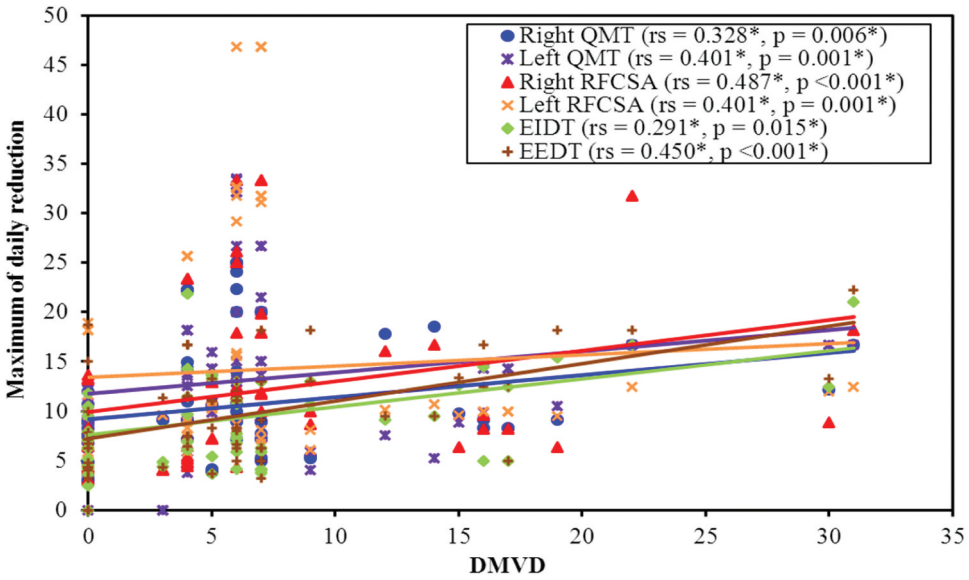

Figure 5. Correlation between maximum percent of daily reduction and duration of mechanical ventilation in days (DMVD) during stay in ICU. $\mathbf{r_s}$:Spearman coefficient *:Statistically significant at $p \leq 0.05$

reduction percent from the admission over the stay in ICU in all muscle groups had strong correlation to length of stay either in ICU or in hospital. (Table 13)

2.8. Disease-specific muscle wasting

Sepsis was the most common ICU admission diagnosis where the most common cause was pneumonia. So, we analyzed the correlation of muscle measurement reduction in case of **pneumonia**. The patient admitted with pneumonia showed higher muscle destruction in thigh and diaphragm muscles. The best proven correlation was in descending manner; left RFCSA, right QMT, EEDT, EIDT, right RFCSA and the least is eft QMT. While highest percent of reduction in muscle measurements was found in the Lt RFCSA by 46.88%, **the least was in** EIDT being zero. (Table 14).

Also, **renal diseases** were the most common comorbidity in our patients. It was found that it was associated with higher muscle destruction in studied muscles with the highest proven correlation were in descending manner right QMT, EEDT, right RFCSA, EIDT, and left RFCSA. No correlation was found for left QMT. While highest percent of reduction in muscle measurement was found in the right RFCSA by 31.82%, the least was in left RFCSA being zero. (Table 15)

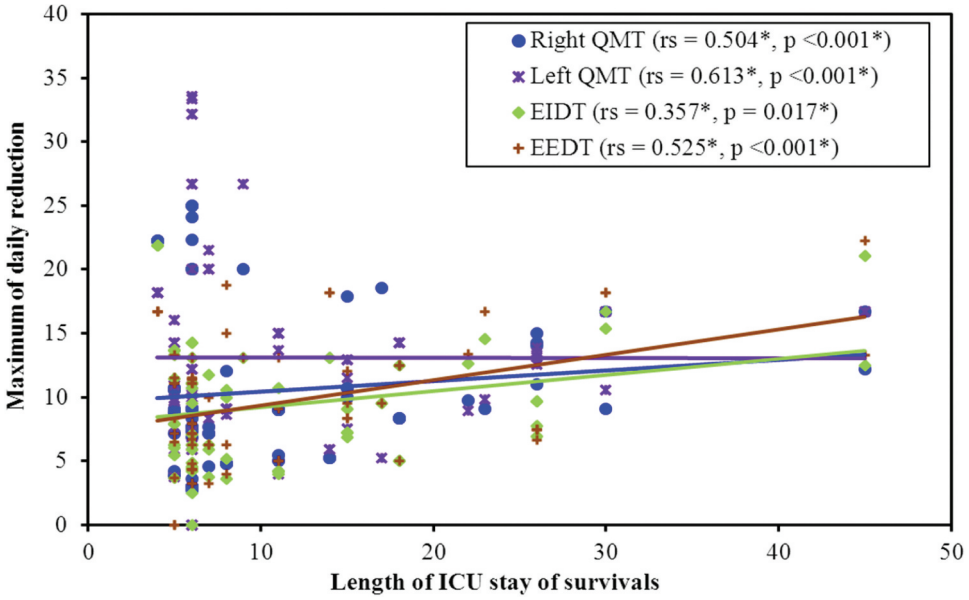

Figure 6. Correlation between maximum percent of daily reduction and length of ICU stay of survivals. $\mathbf{r_s}$:Spearman coefficient *: Statistically significant at $p \leq 0.05$

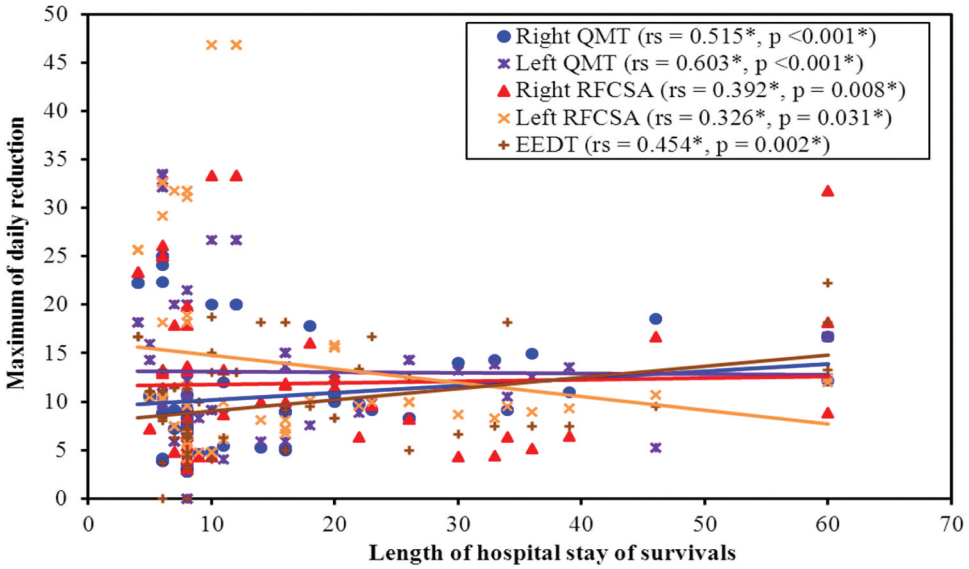

Figure 7. Correlation between maximum percent of daily reduction length of hospital stay of survivals. $\mathbf{r_s}$:Spearman coefficient *: Statistically significant at $p \leq 0.05$

2.9. Correlation between reduction in muscle measurements and predictive scores

The correlation between reduction in studied muscle measurements and **predictive scores** were analyzed. A weak positive correlation was found between **SOFA score** and QMT measurements and very weak correlation in EIDT and EEDT measurements.

The low spearman coefficient can be explained by large sample (as all the studied days were included) so the maximum percent of daily reduction in the stay in each patient was correlated with the corresponding SOFA scores at the same day resulting in more significant values. (Table 16)

Regarding value of **SOFA** score occurring in the day of maximum reduction in muscle measurement, left RFCSA had strong significant correlation while on right one had moderate significant correlation with weak significant correlation with the QMT. (Table 17)

The maximum **SOFA** score value during the stay was correlated with corresponding daily reduction in the same day for each patient. Weak to moderate significant correlation between SOFA and

Table 13. Correlation between percent of maximum reduction from original measurement of studied muscles at time of admission and over ICU stay and outcome parameters.

Maximum percent of shortage from original thickness		Total patients					Survived patients	
		percent of vasoactive agent free period during stay in ICU	Duration of mechanical ventilation during stay in ICU		Length of ICU stay ($n = 70$)	Length of hospital stay ($n = 70$)	Length of ICU stay ($n = 44$)	Length of hospital stay ($n = 44$)
			%	Days				
Right QMT	r_s	−0.337*	0.314*	0.491*	0.287*	0.291*	0.422*	0.484*
	p	0.004*	0.008*	<0.001*	0.016*	0.015*	0.004*	0.001*
Left QMT	r_s	−0.526*	0.480*	0.504*	0.201	0.160	0.609*	0.616*
	p	<0.001*	<0.001*	<0.001*	0.095	0.185	<0.001*	<0.001*
Right RFCSA	r_s	−0.549*	0.421*	0.504*	0.198	0.156	0.429*	0.495*
	p	<0.001*	<0.001*	<0.001*	0.100	0.198	0.004*	0.001*
Left RFCSA	r_s	−0.515*	0.430*	0.588*	0.306*	0.266*	0.509*	0.547*
	p	<0.001*	<0.001*	<0.001*	0.010*	0.026*	<0.001*	<0.001*
EIDT	r_s	−0.093	0.105	0.346*	0.319*	0.249*	0.506*	0.462*
	p	0.442	0.386	0.003*	0.007*	0.038*	<0.001*	0.002*
EEDT	r_s	−0.125	0.184	0.499*	0.460*	0.359*	0.677*	0.597*
	p	0.303	0.127	<0.001*	<0.001*	0.002*	<0.001*	<0.001*

r_s: Spearman coefficient *: Statistically significant at $p \leq 0.05$.
QMT:quadriceps muscle thickness, RFCSA: rectus femoris cross sectional area, EIDT: end inspiratory diaphragmatic thickness, EEDT: end expiratory diaphragmatic thickness.

Table 14. Relation between pneumonia and maximum of percent daily reduction of studied muscles.

Maximum percent of daily reduction	Pneumonia		U	p
	No ($n = 38$)	Yes ($n = 32$)		
Right QMT Min.				
Max.	2.74–20.0	3.85–25.0		
Mean ± SD.	8.59 ± 4.50	12.86 ± 6.74	379.50*	0.007*
Median	8.57	9.09		
Left QMT Min.				
Max.	4.0–26.67	0.0–33.55		
Mean ± SD.	11.23 ± 4.28	15.29 ± 9.62	432.50*	0.038*
Median	10.66	14.29		
Right RFCSA Min.				
Max.	2.99–33.33	4.0–33.33		
Mean ± SD.	9.40 ± 5.84	14.75 ± 9.65	429.0	0.035*
Median	7.92	11.24		
Left RFCSA Min.				
Max.	4.09–46.91	5.86–46.88		
Mean ± SD.	10.72 ± 8.15	18.18 ± 12.31	350.50*	0.002*
Median	8.22	10.32		
EIDT				
Min. Max.	0.0–13.64	2.50–21.88		
Mean ± SD.	7.85 ± 3.54	11.10 ± 5.60	416.0*	0.024*
Median	7.15	11.11		
EEDT				
Min. Max.	0.0–18.75	3.23–22.22		
Mean ± SD.	8.31 ± 4.59	11.11 ± 4.76	407.0*	0.018*
Median	7.28	11.43		

U, p: U and p values for Mann Whitney test .
*: Statistically significant at $p \leq 0.05$.
QMT:quadriceps muscle thickness, RFCSA: rectus femoris cross sectional area, EIDT: end inspiratory diaphragmatic thickness, EEDT: end expiratory diaphragmatic thickness.

corresponding percent of daily reduction was documented in both sides RFCSA and left QMT, not in right QMT, EIDT or EEDT. (Table 18)

Significant increase in the **APACHE II** score was correlated with maximum percent of daily reduction of both right- and left-sided RFCSA and to lesser extent the left sided QMT. (Table 19)

2.10. Correlation between reduction in measurements in different muscle group with each other's

A positive correlation was found between the **maximum percent of daily reduction** in the right QMT, both RFCSA and EIDT. EEDT was significant only with right QMT. (Table 20, Figures 8, 9)

Table 15. Relation between renal diseases with percent of maximum daily reduction of studied muscles.

	Renal disease			
Maximum percent of daily reduction	No ($n = 58$)	Yes ($n = 12$)	U	p
Right QMT Min.				
Max.	2.74 25.0	7.69 22.22		
Mean ± SD.	9.49 ± 5.61	15.64 ± 5.23	128.0*	0.001*
Median	8.80	16.67		
Left QMT Min.				
Max.	0.0 33.55	5.26 18.18		
Mean ± SD.	12.95 ± 7.96	13.74 ± 4.42	273.5	0.245
Median	10.89	14.82		
Right RFCSA Min.				
Max.	2.99 33.33	6.50 31.82		
Mean ± SD.	10.78 ± 8.02	16.95 ± 7.40	175.5*	0.007*
Median	8.16	16.39		
Left RFCSA				
Max.	4.09 46.91	6.67 25.71		
Mean ± SD.	13.79 ± 11.56	15.74 ± 6.55	197.0*	0.019*
Median	9.60	14.07		
EIDT	0.0 15.38	6.83 21.88		
Min. Max.				
Mean ± SD.	8.46 ± 3.93	13.57 ± 6.59	192.0*	0.015*
Median	7.81	11.01		
EEDT	0.0 18.75	7.14 22.22		
Min. Max.				
Mean ± SD.	8.84 ± 4.54	13.22 ± 4.81	174.0*	0.007*
Median	7.64	12.67		

U, p: U and p values for Mann Whitney test .
*: Statistically significant at $p \leq 0.05$.
QMT:quadriceps muscle thickness, RFCSA: rectus femoris cross sectional area, EIDT: end inspiratory diaphragmatic thickness, EEDT: end expiratory diaphragmatic thickness.

Table 16. Correlation between SOFA with percent of daily reduction of studied muscles.

	SOFA	
percent of reduction of	r_s	P
Right QMT	0.204*	<0.001*
Left QMT	0.290*	<0.001*
Right RFCSA	0.357*	<0.001*
Left RFCSA	0.292*	<0.001*
EIDT	0.146*	<0.001*
EEDT	0.182*	<0.001*

r_s: Spearman coefficient.
*: Statistically significant at $p \leq 0.05$.
QMT:quadriceps muscle thickness, RFCSA: rectus femoris cross sectional area, EIDT: end inspiratory diaphragmatic thickness, EEDT: end expiratory diaphragmatic thickness.

Table 17. Correlation between SOFA occurring in the day of maximum value of daily muscular reduction and muscle daily reduction.

SOFA Occurrence during max daily reduction in stay	r_s	p
Max. QMT RT vs SOFA	0.366	0.002
Max. QMT LT vs SOFA	0.581	<0.001
Max. RFCSA RT vs SOFA	0.555	<0.001
Max. RFCSA LT vs SOFA	0.612	<0.001
Max. EIDTvs SOFA	0.336	0.005
Max. EEDTvs SOFA	0.276	0.022

r_s: Spearman coefficient *: Statistically significant at $p \leq 0.05$ QMT: quadriceps muscle thickness, RFCSA: rectus femoris cross sectional area, EIDT: end inspiratory diaphragmatic thickness, EEDT: end expiratory diaphragmatic thickness.

Table 18. Correlation between the maximum daily reductions occurring in the day of maximum SOFA with corresponding maximum SOFA.

	Maximum of SOFA	
Corresponding daily reduction	r_s	p
Right QMT	0.164	0.176
Left QMT	0.407*	<0.001*
Right RFCSA	0.340*	0.004*
Left RFCSA	0.371*	0.002*
EIDT	0.093	0.446
EEDT	0.201	0.095

r_s: Spearman coefficient.
*: Statistically significant at $p \leq 0.05$.
QMT:quadriceps muscle thickness, RFCSA: rectus femoris cross sectional area, EIDT: end inspiratory diaphragmatic thickness, EEDT: end expiratory diaphragmatic thickness.

Using maximum percent of **total reduction from original measurements** on admission and over ICU stay, positive correlation was found between RFCSA and both EIDT and EEDT. (Table 21)

2.11. Correlation of diaphragmatic measurements to outcome parameters

A disease-specific diaphragmatic measurements affection was existed. A significant reduction in the minimum of the

Table 19. Correlation between maximum percent of daily reduction of studied muscles and APACHE on admission.

Maximum percent of daily reduction		Right QMT	Left QMT	Right RFCSA	Left RFCSA	EIDT	EEDT
APACHE II on admission	r_s	0.118	0.262*	0.465*	0.526*	0.147	0.093
	P	0.330	0.029*	<0.001*	<0.001*	0.224	0.443

r_s: Spearman coefficient.
*: Statistically significant at $p \leq 0.05$.
QMT:quadriceps muscle thickness, RFCSA: rectus femoris cross sectional area, EIDT: end inspiratory diaphragmatic thickness, EEDT: end expiratory diaphragmatic thickness.

Table 20. Correlation between maximum percent of daily reduction in QMT, RFCSA and diaphragm.

	EIDT		EEDT	
Maximum percent of daily reduction	r_s	p	r_s	p
Right QMT	0.510*	<0.001*	0.376*	0.001*
Left QMT	0.169	0.161	0.093	0.442
Right RFCSA	0.243*	0.043*	0.224	0.062
Left RFCSA	0.348*	0.003*	0.217	0.071

r_s: Spearman coefficient.
*: Statistically significant at $p \leq 0.05$.
QMT:quadriceps muscle thickness, RFCSA: rectus femoris cross sectional area, EIDT: end inspiratory diaphragmatic thickness, EEDT: end expiratory diaphragmatic thickness.

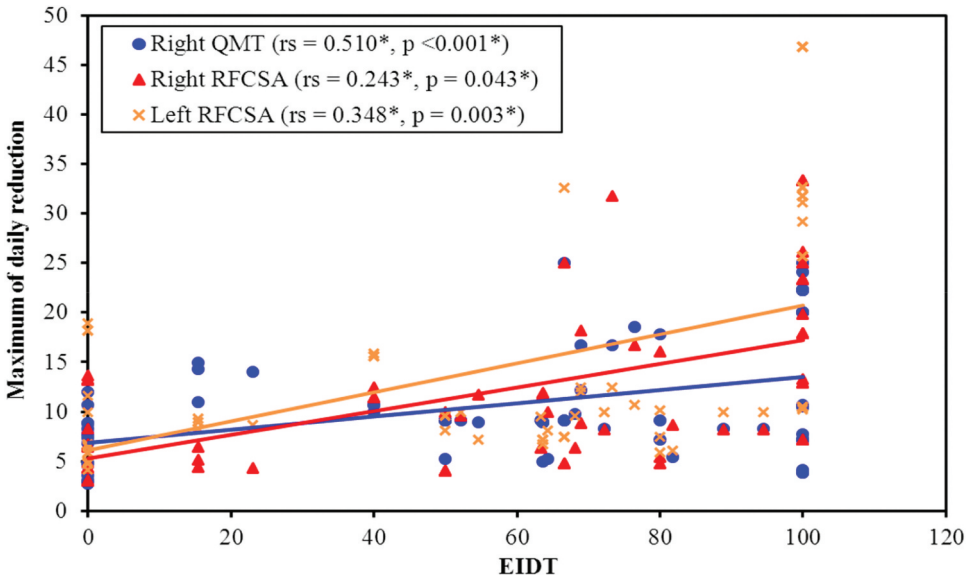

Figure 8. Correlation between maximum percent of daily reduction in muscle mass in QM and diaphragm. r_s:Spearman coefficient *:Statistically significant at $p \leq 0.05$

Diaphragmatic Thickness Fraction (DTF) occurred with presence of pneumonia and systolic heart failure, none had occurred in other categories of diseases. (Table 22)

For correlation between minimum of **DTF** and outcome parameters, it was found that moderate correlation between reduction in the minimum of DTF and increase in duration of mechanical ventilation and decrease vasoactive-free periods in ICU. (Table 23, Figure 10) No correlation was found between the minimum of DTF and length of stay of

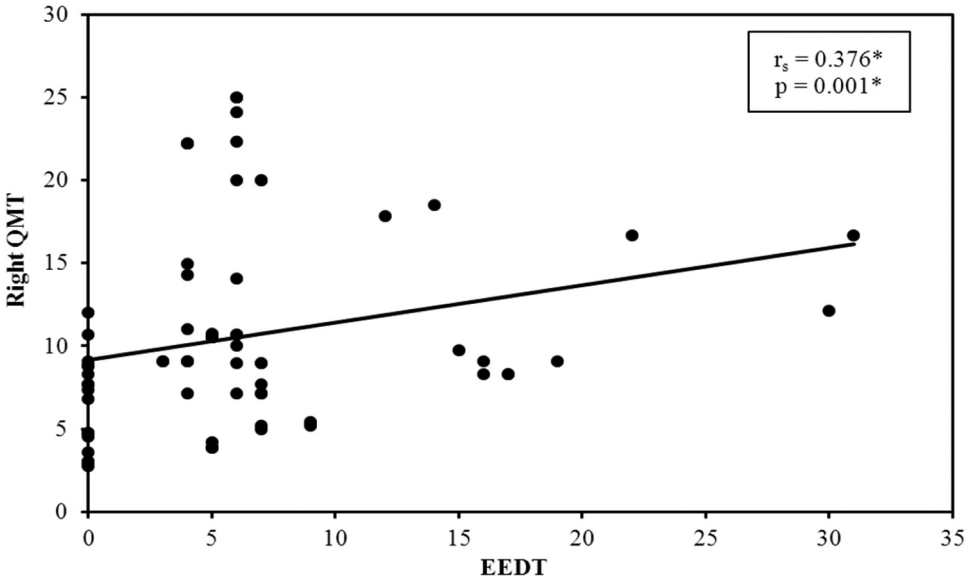

Figure 9. Correlation between maximum percent of daily reduction in muscle mass in QM and diaphragm. **r_s**:Spearman coefficient *:Statistically significant at $p \leq 0.05$

Table 21. Correlation between maximum percent of total reduction in muscle mass in QMT, RFCSA and diaphragm.

	Diaphragmatic thickness end inspiration		Diaphragmatic thickness end expiration	
Maximum percent of shortage from original thickness	r_s	p	r_s	p
Right QMT	0.138	0.256	0.205	0.089
Left QMT	0.221	0.066	0.203	0.092
Right RFCSA	0.369*	0.002*	0.335*	0.005*
Left RFCSA	0.379*	0.001*	0.344*	0.004*

r_s: Spearman coefficient.
*: Statistically significant at $p \leq 0.05$.
QMT:quadriceps muscle thickness, RFCSA: rectus femoris cross sectional area, EIDT: end inspiratory diaphragmatic thickness, EEDT: end expiratory diaphragmatic thickness.

Table 22. Relation between minimum of DTF with different disease parameters.

	Minimum of DTF				U	p
	Min.	Max.	Mean ± SD.	Median		
Sex	0.0	0.47	0.07 ± 0.12	0.01	564.0	0.833
Pneumonia	0.0	0.47	0.10 ± 0.12	0.06	281.0*	<0.001*
UTI	0.0	0.14	0.07 ± 0.06	0.05	190.0	0.257
Others	0.0	0.47	0.06 ± 0.10	0.02	346.0	0.695
DM	0.0	0.47	0.06 ± 0.10	0.01	188.0	0.929
Systolic heart failure	0.0	0.47	0.09 ± 0.12	0.03	426.0*	0.029*
Pulmonary disease	0.0	0.47	0.07 ± 0.11	0.03	358.0	0.180
Neurological disease	0.0	0.47	0.06 ± 0.11	0.01	456.5	0.696
Renal disease	0.0	0.47	0.05 ± 0.09	0.03	346.0	0.974
Hepatic disease	0.0	0.47	0.06 ± 0.10	0.02	266.0	0.875
Hematological disease	0.0	0.47	0.06 ± 0.10	0.02	341.0	0.908
Low dose corticosteroids	0.0	0.36	0.07 ± 0.11	0.02	563.5	0.647
Blood Stream infection	0.0	0.06	0.02 ± 0.03	0.0	77.0	0.471

U, p: U and *p* values for Mann Whitney test .
*: Statistically significant at $p \leq 0.05$.
UTI: Urinary tract infection, DM: diabetes mellitus.

Table 23. Correlation between DTF and days and percent of duration of mechanical ventilation during stay in ICU.

	Minimum of DTF	
	r_s	P
Days of Duration of mechanical ventilation during stay in ICU	−0.358*	0.002*
percent of Duration of mechanical ventilation during stay in ICU	−0.347*	0.003*
Vasoactive agent free period in percent stay in ICU	0.271*	0.023*

r_s: Spearman coefficient.
*: Statistically significant at $p \leq 0.05$.
QMT:quadriceps muscle thickness, RFCSA: rectus femoris cross sectional area, EIDT: end inspiratory diaphragmatic thickness, EEDT: end expiratory diaphragmatic thickness.

both ICU and hospital stay in mortality group, but when analyzing s**urvivors**, a moderate correlation was found with length of stay both ICU and hospital. (Table 24)

As regard the **diaphragmatic excursion (DE)**, a correlation was found between a minimum of mean DE **and mortality outcome measures (**ICU mortality, 28-days mortality and hospital mortality). (Table 25)

For other outcome parameters, it was found that longer mechanical ventilation duration and less vasoactive-free days was associated with decrease in minimum of mean **DE**, (Table 11) but no correlation was found between length of ICU or hospital stay and minimum of DE. (Table 26, Figure 11)

The possible correlations of failed **weaning off mechanical ventilation** and reduction of diaphragmatic measurements were searched for in subgroup analysis. We had 52 mechanically ventilated patients; 19 patients never had a chance to get off mechanical ventilation while the remaining 33 patients met weaning criteria. 24 patients were successfully weaned while 9 failed the first weaning trial, 3 patients successfully weaned after second trial, one patient weaned after third trial and 3 patients have died before a second weaning trial.

A significant correlation was found between minimum of DTF and DE and the success of weaning off mechanical ventilator. (Table 27) The cutoff points of minimum of DTF and DE that can predict success of weaning can be obtained from area under Receiver Operator Characteristic curve (ROC) was ≥0.28, ≤1.2 for of DTF and DE respectively. (Table 28, Figure 12)

To summarize, maximum percent daily reduction of Rt and Lt RFCSA was associated with higher percent of duration of mechanical ventilation during stay in ICU and lower vasoactive agent free period percent of ICU stay. Lt daily reduction alone had negative correlation with length of hospital stay.

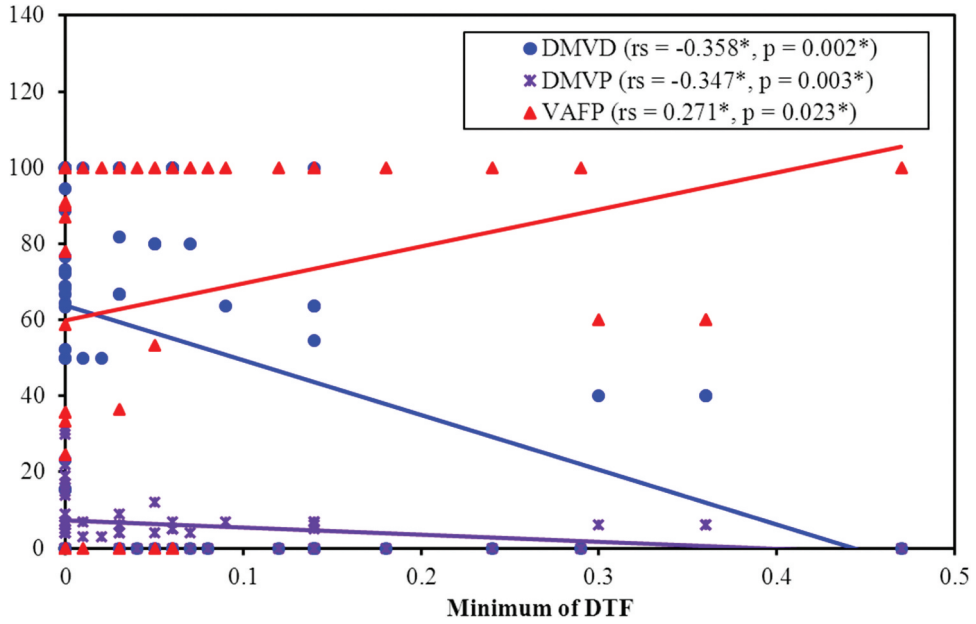

Figure 10. Correlation between DTF and days and percent of duration of mechanical ventilation during stay in ICU. **r_s**:Spearman coefficient *:Statistically significant at $p \leq 0.05$

Table 24. Correlation between the minimum of DTF and length of ICU and hospital stay.

	Minimum of DTF	
	r_s	p
Total patients		
Length of ICU stay	−0.185	0.125
Length of hospital stay	−0.160	0.186
Survived patients		
Length of ICU stay	−0.441*	0.003*
Length of hospital stay	−0.439*	0.003*

r_s: Spearman coefficient.
*: Statistically significant at $p \leq 0.05$.
QMT:quadriceps muscle thickness, RFCSA: rectus femoris cross sectional area, EIDT: end inspiratory diaphragmatic thickness, EEDT: end expiratory diaphragmatic thickness.

Minimum of DTF was the only correlated measurement with Length of ICU stay, while DE had no correlation with any of the secondary outcomes of ICU stay. (Table 29)

3. Discussion

This study was conducted to find out if ultrasound-measured muscle atrophy in critically ill patients can be used as an outcome predictor either in term of mortality, duration of mechanical ventilation, and success of weaning or length of stay.

Maximum daily reduction of Rectus Femoris Cross Sectional Area (RFCSA) was found to be more indicative of muscle weakness than that of Quadriceps Muscle Thickness (QMT).

In a study of Puthucheary et al, 54 patients' cohorts were studied for their delta RFCSA and delta QMT on ICU days, 1, 7, and 10 where QMT was found to underestimates muscle atrophy compared to RFCSA [6].

During early ICU stay, RFCSA was found to be a reliable indicator of muscle weakness and can be

Table 25. Relation between minimum of excursion with mortality.

		Minimum of excursion					
	No.	Min. Max.	Mean ± SD.	Median	IQR(25 75)	U	p
ICU mortality							
Survived	44	0.0 2.80	1.46 ± 0.66	1.37	0.90 1.97		
						278.5*	<0.001*
Died	26	0.30 2.64	0.94 ± 0.61	0.80	0.48 1.18		
						278.5*	<0.001*
28 days mortality							
Survived	42	0.0 2.80	1.42 ± 0.65	1.29	0.90 1.82	350.0*	0.004*
Died	28	0.30 2.64	1.03 ± 0.69	0.80	0.50 1.53		
Hospital mortality							
Survived	40	0.0 2.80	1.44 ± 0.65	1.37	0.93 1.87	345.0*	0.002*
Died	30	0.30 2.64	1.03 ± 0.67	0.83	0.50 1.38		

r_s: Spearman coefficient.
*: Statistically significant at $p \leq 0.05$.
QMT:quadriceps muscle thickness, RFCSA: rectus femoris cross sectional area, EIDT: end inspiratory diaphragmatic thickness, EEDT: end expiratory diaphragmatic thickness.

Table 26. Correlation between minimum of excursion ($n = 70$).

	Minimum of DE	
	r_s	P
Days of Duration of mechanicalventilation during stay in ICU	−0.566*	<0.001*
percent of Duration of mechanical ventilation during stay in ICU	−0.582*	<0.001*
Vasoactive agent free period in percent stay in ICU	0.459*	<0.001*
Length of ICU stay	−0.186	0.124
Length of hospital stay	−0.121	0.316

r_s: Spearman coefficient.
*: Statistically significant at $p \leq 0.05$.
QMT:quadriceps muscle thickness, RFCSA: rectus femoris cross sectional area, EIDT: end inspiratory diaphragmatic thickness, EEDT: end expiratory diaphragmatic thickness.

Table 27. Relation between weaning of MV and maximum percent of studied muscles, measurements during SBT of DTF and DE.

		Successful Weaning			
		Failed ($n = 11$)	Yes ($n = 30$)	U	P
Maximum of % reduction	Right QMT Min. Max.	5.20 20.0	5.0 18.52	92.0	0.580
	Mean ± SD.	10.76 ± 4.70	10.67 ± 3.74		
	Median	10.36	9.09		
	IQR (Min. Max.)	6.66 13.29	8.65 14.18		
	Left QMT Min. Max.	5.88 26.67	0.0 16.67	75.0	0.204
	Mean ± SD.	13.81 ± 6.47	9.83 ± 5.57		
	Median	12.96	12.55		
	IQR (Min. Max.)	8.14 17.50	5.57 14.29		
	Right RFCSA	6.34 33.33	4.0 31.82		
	Min. Max.	14.0 ± 7.74	9.18 ± 6.52	53.0*	0.028*
	Mean ± SD.	11.43	8.16		
	Median	9.71 18.01	4.60 11.67		
	IQR (Min. Max.)				
	Left RFCSA Min. Max.	8.11 46.91	5.88 12.50	39.5*	0.006*
	Mean ± SD.	17.62 ± 12.36	8.88 ± 1.63		
	Median	14.07	9.52		
	IQR (Min. Max.)	9.21 19.87	7.28 10.0		
	EIDT	3.77 21.05	4.0 16.67		
	Min. Max.				
	Mean ± SD.	11.04 ± 4.90	8.53 ± 4.20	75.5	0.212
	Median	12.57	7.72		
	IQR (Min. Max.)	7.15 13.04	4.62 11.97		
	EEDT	3.23 22.22	4.35 18.18		
	Min. Max.				
	Mean ± SD.	13.02 ± 5.57	9.55 ± 4.29	59.0	0.051
	Median	13.19	9.09		
	IQR (Min. Max.)	8.33 18.18	5.73 12.02		
Minimum of	DTF	0.0 0.30	0.03 0.59		
	Min. Max.	0.08 ± 0.12	0.30 ± 0.12	33.0*	<0.001*
	Mean ± SD.	0.01	0.30		
	Median	0.0 0.32	0.0 0.06		
	IQR (Min. Max.)				
	DE	0.30 2.60	0.94 2.24		
	Min. Max.				
	Mean ± SD.	1.05 ± 0.59	1.42 ± 0.36	65.0*	0.003*
	Median	1.0 0.54 0.90	1.32		
	IQR (Min. Max.)		0.85 1.21		

r_s: Spearman coefficient.
*: Statistically significant at $p \leq 0.05$.
QMT:quadriceps muscle thickness, RFCSA: rectus femoris cross sectional area, EIDT: end inspiratory diaphragmatic thickness, EEDT: end expiratory diaphragmatic thickness.

used as a biomarker of muscle loss and development of weakness of proximal muscle of lower limb [7].

The lower significance of QMT compared to RFCSA can be **attributed** to the ultrasound appearance of rectus femoris muscle which appears as globular structure and sometimes as transversely spread sheet of muscle with the vastus intermedius muscle contributing to the reduction of thickness but this can't be proved as each muscle thickness was not measured separately during the examination.

Regarding **mortality** outcome, it was reported that in the 1st week of critical illness, there is 5% increase in 60-days mortality for each 1% reduction in quadriceps measures [8].

In our study, a positive correlation between **mortality** and maximum daily reduction (delta changes) in all studied muscle measurements had been found, being best correlated to the RFCSA daily reduction percent (P value < 0.001); it was least in EIDT, EEDT then right QMT ones.

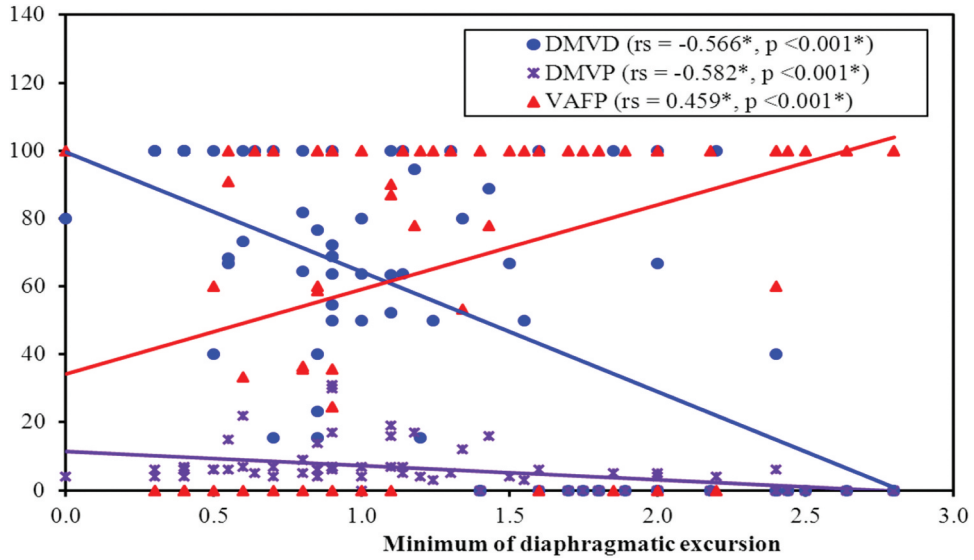

Figure 11. Correlation between minimum of DE ($n = 70$) and DMVP: duration of mechanical ventilation percentage, DMVD: duration of mechanicalventilation duration, VAFP: vasoactive agent free period percent of stay in ICU. $\mathbf{r_s}$:Spearman coefficient *: Statistically significant at $p \leq 0.05$

Table 28. Agreement (sensitivity, specificity, PPV, NPV) in weaning of MV.

			95% C.I						
Before weaning	AUC	p	LL	UL	Cut off	Sensitivity	Specificity	PPV	NPV
DTF	0.900*	<0.001*	0.789	1.0	0.28	81.82	63.33	45.0	90.48
Diaphragmatic excursion	0.803*	0.003*	0.623	0.983	1.2	90.91	63.33	47.6	95.0

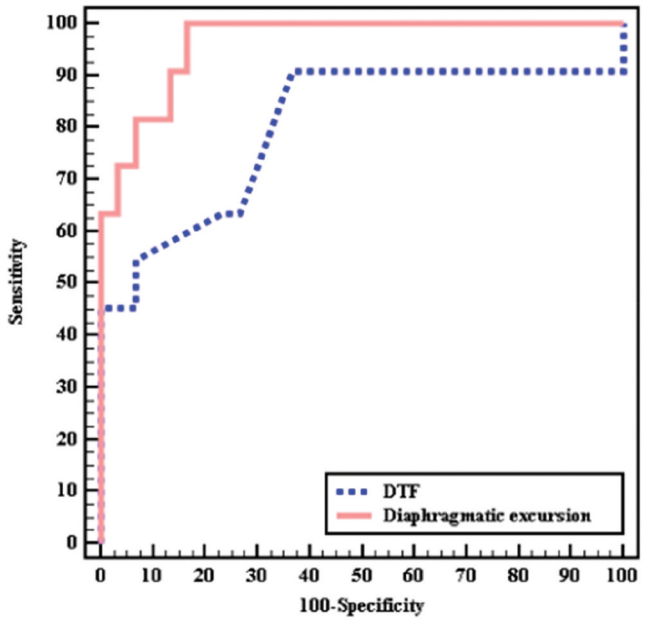

Figure 12. ROC curve to predicate weaning of MV.

Difference in significance of quadriceps measurements were found from side to side so that, left QMT was more indicative of mortality than the right one. This can be explained by different motor activity from side to side or special configuration of the muscular structure on the left side. TO solve this issue a proper measurement of motor activity of the tested limb should be included in future studies.

Using area under Receiver Operating Characteristic (ROC) curve showing the best mortality predictive value was RFCSA (best positive predictive value, negative predictive value and sensitivity). This matches the previously mentioned finding of better significance of FRCSA as indicative of muscle wasting and weakness.

As no correlation had been found between **disease-specific mortality and ultrasound muscle measure-**

Table 29. Correlation between maximum percent of studied muscles, the minimum of DTF/DE and the outcome parameters.

		Maximum percent of daily reduction							
		Thickness		RFCSA		Diaphragmatic thickness			
		Right	Left	Right	Left	End Inspiration	End Expiration	Minimum of DTF	Minimum of DE
Length of ICU stay	r_s	0.010	−0.112	−0.187	−0.227	−0.103	0.084	−0.302*	0.017
	p	0.942	0.428	0.184	0.105	0.466	0.552	0.030*	0.907
Length of hospital stay	r_s	−0.029	−0.209	−0.222	−0.288*	−0.158	0.055	−0.271	0.032
	p	0.836	0.137	0.114	0.039*	0.265	0.701	0.052	0.821
Days of Duration of mechanical ventilation during stay in ICU	r_s	−0.102	0.209	0.317*	0.101	0.019	0.277*	−0.286*	−0.101
	p	0.471	0.137	0.022*	0.478	0.892	0.047*	0.040*	0.478
percent of Duration of mechanical ventilation during stay in ICU	r_s	0.070	0.532*	0.595*	0.583*	0.223	0.097	−0.073	−0.179
	p	0.624	<0.001*	<0.001*	<0.001*	0.112	0.494	0.605	0.205
Vasoactive agent free period in percent stay in ICU	r_s	−0.336*	−0.560*	−0.571*	−0.660*	−0.370*	−0.247	0.100	0.236
	p	0.015*	<0.001*	<0.001*	<0.001*	0.007*	0.078	0.479	0.092

ments (development of muscle atrophy is associated with higher risk of mortality irrespective to type of illness), so muscle loss could be considered as an independent predictor of mortality.

In sub-group analysis, mortality group (26 patients) versus survival group (44 patients), death occurrence was within 0–5 days (with median of 1.38) of the day of maximum percent of the daily RFCSA reduction which is an extra proof of previously mentioned correlation between muscle atrophy and mortality. Improvement of muscle mass measurements (reflected in the negative values of daily changes) had a negative correlation with mortality so can be consider as a good prognostic indicator of survivals. On the other hand, improvement in EIDT and EEDT measurements failed to prove any significance thus limiting its importance as a prognostic value of mortality.

A zero percent reduction of muscle mass measurements was documented in **survival group** of patients, further studies needed to prove that zero reduction of the QMT or RFCSA can be used as predictor of protection against mortality.

Comparing the mortality predictive ability of muscle measurement to standard predictive scoring systems (SOFA and APACHE II), using ROC curve cutoff points of **RFCSA** (being the most indicative for mortality as previously mentioned) versus cutoff points **SOFA** and **APACHE II** scores from the present study, he best mortality predictor was SOFA score followed by RFCSA reduction assessment followed by the APACHE II score, in agreement with the study done by Vijay et al, 2018 which found the same result. The study included 70 patients with sepsis, muscle thickness was measured at the level of the mid-arm and mid-thigh using bedside US on days 1, 3, 5, 7, 10, and 14 and then weekly till discharge or death. Patients were followed up for 90 days after discharge [9].

Regarding the **length of stay** outcome, analysis of total population howed poor correlation between muscle mass measurements (both QMT and RFCSA) and length of stay either ICU or hospital but when analyzing survival group (those who skipped early mortality) a positive correlation was found between QMT on both sides to lesser extent RFCSA and length of stay. This can be explained by the better correlation of the RFCSA with mortality thus less stay in ICU [3]. Anyway, it was reported that, more than 10% loss of rectus femoris cross-sectional area was associated with longer ICU length of stay ($p = 0.038$) and hospital length of stay ($p = 0.014$) [7].

Duration of mechanical ventilation in days had been increased with increased reduction in the studied muscles, with a better correlation with the use of the percent of MV during the ICU stay rather than the use of mechanical ventilation days. Right QMT, left QMT, right RFCSA, left RFCSA, EIDT, and EEDT had Spearman coefficient 0.328, 0.401, 0.487, 0.401, 0.291, 0.450 for days and 0.389, 0.540, 0.617, 0.636, 0.394, 0.37 for percentage of MV. Muscle measurements (quadriceps femoris muscle cross sectional area and thickness were significantly reduced in prolonged ventilated critically ill patients compared to healthy volunteers [10].

Increasing severity of critical illnesses was associated of higher risk of muscle atrophy and hence weakness this was proved by association between significantly high daily reduction of muscles mass in cases of high severity of SOFA and APACHE II scores reflecting the effect of multiorgan affection on muscle mass loss.

The significant correlation between diaphragmatic muscle and quadriceps muscle wasting representing ventilatory and skeletal muscle affection respectively, being both significantly correlated with mortality and illness severity (SOFA score) denoting the systemic nature of muscular affection during the ICU stay.

Considering the risk of development muscle atrophy in specific admission diagnosis, result of this study showed that pneumonia was recorded in 32 patients and had significant correlation with muscle mass reduction. Which agree with the study done by Januel et al. that found pneumonia was the second cause of hospital infection and the most common cause of death from ICU acquired death [11].

Presence of renal disease had a positive correlation with the muscle mass loss, this has been proven in

study of WANG et al, conducted on CKD patients using pathological prove of increased cellular protein loss and increased morbidity and mortality [12].

Diaphragmatic ultrasound measures, minimum of Diaphragmatic Thickness Fraction (DTF) used as a functional indicator for the muscle wasting which had a significant correlation with some of our study outcomes as prolonged mechanical ventilation days (*P* value 0.002), less vasoactive agent free periods but no correlation to mortality.

No correlation had been found between minimum of DTF reduction and prolongation in length of ICU and hospital stay but in subgroup analysis a significant correlation was present in survival group.

Ultrasound diaphragmatic measures had been assessed as a predictor of success of extubation in patients tolerating spontaneous breathing trials (SBT). It was reported that measures as DE, EIDT, EEDT and DTF were found to be higher with successful extubation [13].

We assessed Diaphragmatic Excursion (DE) measurement in ventilated and non-ventilated patients; it had been correlated to mortality, prolonged mechanical ventilation days and less vasoactive free periods but not correlated to length of ICU and hospital stay.

Diaphragmatic dysfunction as assessed by ultrasound measurement of diaphragmatic excursion was found in medical critically ill patients ventilated more than 48 hours and was correlated to early and delayed weaning failure and could be used to identify patients at risk of difficulty weaning [14].

Predictive value of DE could be improved if different DE measures at different points of time to be evaluated during SBT and the delta changes from measure to measure also could be used [15].

In subgroup analysis of mechanically ventilated patients (52 patients), the measurements of DE, DTF, Lt RFCSA and Rt RFCSA in descending manner correlated to success of weaning.

DE on t-piece trial before weaning had cutoff point of more than or equal to 12 mm had sensitivity of 90.9% and specificity of 63.33%. different cut-off values were reported by different studies which range from 10–11 mm with different levels of sensitivity and specificity [16–18].

Using the area under ROC curve cutoff points of DTF for predictive of successful weaning was ≥ 28%, with sensitivity, specificity, positive predictive value, and negative predictive value: 81.82, 63.33, 45.0, 90.48. Different values were reported by different studies which may be attributed to different study settings, point of time of measurement during SBT and other factors in study design [13,18].

Combining diaphragmatic parameters with other conventional predictors of weaning as respiratory rate and extubation success have been studied aiming to improve their predictive ability [19].

This study had several limitations; the baseline preadmission muscle status, muscle power, nutritional status was not evaluated and post ICU functional status was not evaluated. Patients were not followed up after hospital discharge. Measurements were time consuming. Also, patients were not categorized as surgical, trauma and medical and ICU readmission was not considered.

In conclusion, critical illness had a negative impact on muscle mass either the skeletal or ventilatory ones in a degree related to severity of critical illness and organ affection. Ultrasound assessed muscle mass reduction in critically ill patients can be used as predictor of many outcomes' parameter, RFCSA as an index for mortality was inferior to SOFA score but equivalent to APACHE score in prediction of mortality. QMT could predict length of stay, DE and DTF were good in prediction of weaning success. Reliability of prediction ability of different measures could be better if combined with other conventional measures of different ICU outcomes. Further studies are needed to test different combinations of muscle measurements and validate different measurement protocols.

Further studies are recommended to find out specific muscle group wasting in different disease categories, to find out the difference between surgical and medical patients. Larger sample size, multicenter studies, studying different combinations between muscle measurements and other predictive tools is highly needed.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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