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Ultrasonographic assessment of muscle layer thickness and its relation to patient outcome in a medical intensive care unit

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SUMMARY

Aim: Low skeletal muscle mass in ICU patients is associated with poor clinical outcome. Ultrasonography is a noninvasive method that can measure muscle thickness at the bedside. We aimed at studying the relation of the ultrasonography measured muscle layer thickness (MLT) at time of ICU admission with the patients' outcome namely mortality, duration of mechanical ventilation (MV) and ICU length of stay (LOS). In addition to define the best cut-off values that can predict mortality in medical ICU patients.

Method: this observational prospective study was conducted on 454 adult critically ill patients admitted to the medical ICU of a university hospital. At the time of admission, MLT of the anterior mid-arm and lower 1/3 thigh were assessed using ultrasonography with and without transducer compression. The clinical scores for assessment of disease severity; Acute Physiology and Chronic Health Evaluation score (APACHE-II) and Sequential Organ Failure Assessment score (SOFA) in addition to nutrition risk; modified Nutrition Risk in Critically ill score (mNUTRIC) were estimated for all patients. ICU LOS, duration on MV and mortality were reported.

Results: The mean age of our patients was 51 years ± 19. The ICU mortality rate was 36.56%. The baseline MLT was negatively associated with APACHE-II, SOFA and NUTRIC scores but not with duration of MV or ICU-LOS. The non-survivors had lower values of baseline MLT. A cut-off value of 0.895 cm (AUC: 0.649, 95% CI of 0.595–0.703) using the mid-arms as a reference point with maximum probe compression showed the highest sensitivity (90%) to predict mortality compared to other techniques however with low specificity (22%).

Conclusion: the baseline ultrasonography measured mid-arm MLT is a sensitive risk assessment tool that can reflect disease severity and predict ICU mortality.

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1. Introduction

Malnourished patients at the time of admission in an intensive care unit (ICU) are at increased risk of morbidity and mortality [1], identifying those patients to guide nutritional interventions may improve their outcomes [2]. The Nutrition Risk in Critically Ill (NUTRIC) score has been developed as a specific ICU nutritional score. It depends mainly on severity of illness, age, co-morbidities and days at hospital before ICU admission with or without IL-6 as a marker for inflammation. However it does not count for lean body mass [3,4], which indicates patients' functional status [5]. Muscle mass is the main composition of lean body mass, and it more accurately reflects both nutritional and functional status [6]. Loss of muscle mass occurs early and rapidly in the critically ill patients, and contributes to unfavorable clinical outcomes, which is thought to be higher in patients with low muscularity at the time of ICU admission [7]. Available methods for assessing muscle mass have

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limitations in ICU patients. Computed tomography (CT) and magnetic resonance imaging (MRI) have high cost, require patient transport, and require trained personnel to use them, moreover CT has risks of ionizing radiation [8]. The anthropometric measures, bio-impedance analysis and dual-energy X-ray absorptiometry (DXA) can be affected by a patient's hydration status [8]. The ultrasonography (US) has been emerged as a non-invasive, bedside tool that can predict lean body mass, as accurate as MRI and CT [9]. It is widely available in ICU, it can be repeated with no fear of ionizing radiation and it has a relative lower cost [10]. To date, the majority of US studies in ICU patients have mainly focused on its ability to detect changes in muscle thickness over a short period of time [11]. The use of US to identify sarcopenic patients at time of ICU admission has been studied with a limited number of patients [12], and a specific cut-off value that can predict mortality has not been established. Different muscle groups have been investigated with the quadriceps is the most extensively studied muscle group [13,14]. There is also variation in the amount of pressure applied to the US probe for image acquisition [13], moreover no study comparing the different methodology in relation to patients' outcomes. So, in this current study we used ultrasonography to measure the baseline muscle layer thickness (US-MLT) aiming (a) to study the relationship of baseline MLT to the patients' clinical outcomes namely ICU mortality, length of stay (LOS) and duration of mechanical ventilation. (b) To determine the best muscle group and the amount of transducer pressure (maximum versus no pressure) that can predict patient mortality. (c) To determine the cut off values that can be related to patient mortality in the ICU.

2. Patients and methods

This is an observational prospective study conducted on 454 adult critically ill patients admitted at medical ICU of the Internal Medicine Department, Kasr Alainy hospital, in the period from June 2016 to January 2018. The patients were evaluated 24 h after admission. Exclusion criteria included patients under 18 years as well as patients who died within less than 24 h of admission. A written consent was taken from the patient or his/her first-degree relatives for those who were not conscious. The study was approved by the Research Ethics Committee of Faculty of Medicine, Cairo University. The study procedures were carried out in accordance with the principles of the Declaration of Helsinki.

2.1. Clinical and laboratory assessment

All patients were subjected to a thorough clinical assessment and complete clinical examination with special concern on anthropometric measures including body mass index (BMI), and mid upper arm circumference (MUAC). In conscious patients only, the muscle strength was estimated from handgrip strength using digital dynamometer. The low grip strength was defined as a value lower than 27 Kg in men and lower than 16 Kg in women, according to revised European consensus on definition and diagnosis of sarcopenia conducted by European Working Group on Sarcopenia in Older People (EWGSOP) [8].

Routine labs including complete blood count (CBC), total proteins, serum albumin and other liver function and kidney function tests were evaluated for all patients. To assess the patients' nutritional risk modified NUTRIC (mNUTRIC) score was calculated, as previously described [4]. The extent of disease severity was scored using Acute Physiology and Chronic Health disease Classification System II (APACHE II) score. While the extent of organ failure was calculated using Sequential Organ Failure (SOFA) score. All previous assessments were obtained at the time of ICU admission except for SOFA score that was repeated 48 and 96 h after admission. The ICU length of stay (LOS), number of days on mechanical ventilations and ICU mortality were also recorded.

2.2. Ultrasonography muscle assessment

Muscle layer thickness (MLT) was measured using B-mode (Philips EPIQ Elite) ultrasound machine with a broadband linear array transducer and at a frequency of 12–5 MHz. The ultrasonography (US) was done by two operators who were blinded to the clinical and biochemical data. One of the operators has more than ten years' experience in musculoskeletal ultrasonography. The other had no previous experience, he gained competency in performing the scans independently after a brief period of training (12 h workload over 3 weeks). The study was done on both sides, while the patient is relaxed and supine at the following two points (Fig. 1):

1. ***Anterior mid-arm point:*** at the flexor surface of the arm while the forearm is supinated, corresponding to the posterior point midway between the tip of the acromion and tip of the olecranon, this point corresponds to MUAC.
2. ***Anterior lower 1/3 of thigh point:*** while the knee extended, corresponding to the lower third and upper two-thirds between the anterior superior iliac spine (ASIS) and the upper pole of the patella.

The muscle layer thickness (MLT) was measured in a transverse view between the superficial fat-muscle interface to the interface between muscle and bone, from inner edge of muscle fascia to outer edge of bone cortex, using minimal and maximal compression. The machine settings regarding depth, frequency and gain were adjusted according to the examined patients, in particular those with extensive limb edema or morbid obesity. Each site was examined on both sides and then the mean measurement for both sides was obtained.

The inter/intra-rater reliability was assessed by re-producing the US images for 50 patients using randomization. The ultrasonography examination was repeated at the same day of initial assessment with about 6-h intervals. The two operators were blind to each other.

2.3. Data management and statistical analysis

Epi Info STATCALC was used to calculate the sample size by considering the following assumptions: 95% two-sided confidence level, with a power of 95%, an error of 5%, and odds ratio calculated as 4.8. The Odds ratio was preliminary calculated based on local mortality statistics with an average of 20%. The final sample size taken from the Epi- Info output was 254. Consequently, the sample size was increased to 454 subjects to accommodate any cases excluded during the study. Analysis of data was done by IBM computer using SPSS version 21 (IBM SPSS Inc., Armonk, NY, USA) and MedCalc for Windows, version 19.4.0 (MedCalc Software, Ostend, Belgium). Quantitative data were tested for normality using Shapiro–Wilk test; normally distributed variables were presented as mean (standard deviation) and non-normally distributed variables as median (interquartile range). For qualitative variables frequency and relative frequency (percentage) were used. Chi-square test was used to compare qualitative variables between groups. Fisher exact test was used when one expected cell or more are less than 5. Unpaired t-test was used to compare quantitative variables, in parametric data (SD < 50% mean). Mann Whitney-U test was used instead of unpaired t-test in non-parametric data (SD > 50%mean). Wilcoxon test was used for comparison of two related quantitative variables. Partial correlation analysis using Spearman's rank correlation coefficient was conducted to test correlation of US-MLT and other variables after

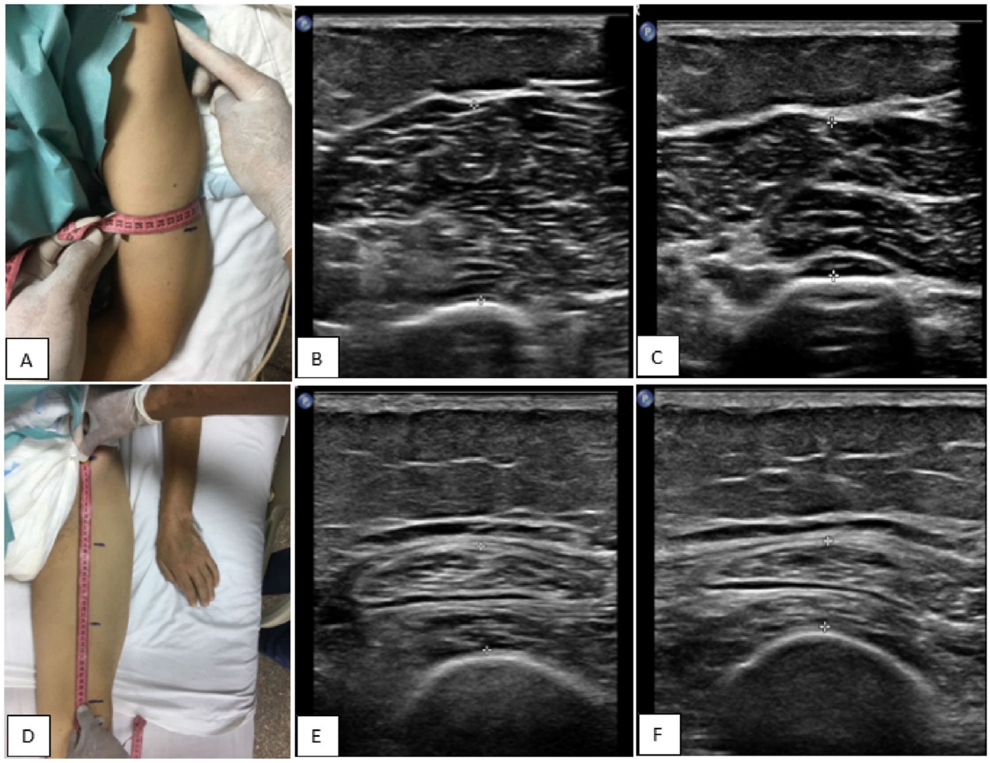

Fig. 1. (A–F): Reference points for measuring muscle thickness and representative ultrasound images (A) reference point for anterior mid-arm (B) ultrasound image of representative flexor arm muscles without transducer compression and (C) with compression (D) reference point for lower 1/3 of the thigh (E) ultrasound image of representative quadriceps muscle without transducer compression and (F) with compression.

controlling for age and gender. Receiver Operator Characteristic (**ROC**) Curve was used to determine the best cut off points of the MLT using the mortality outcome as a reference. Multiple regression analysis was conducted to find the significant predictors for mortality outcome (not survived/survived), the independent variables entered in first step were age, baseline APACHE-II, baseline SOFA, and US-MLT of anterior mid arm as well as of anterior lower thigh with/without transduced pressure. The most significant variable of US-MLT then entered with APACHE-II score in binary logistic regression analysis. This model was used to calculate a new probability variable to study the impact of combined effect of APACHE-II and US-MLT on the mortality. Inter and intra-rater agreement was calculated using intra-class correlation coefficient (ICC), and was considered poor to moderate if ICC = 0.61–0.67, good if ICC = 0.74–0.86, excellent if ICC = 0.92–0.99. P-values less than 0.05 were considered as statistically significant.

3. Results

454 patients with multiple diagnoses at the time of ICU admission were included in this study. The frequent causes of ICU admissions were respiratory (33.3%), cardiac (32.4%), renal (32.4%) followed by hemodynamic instability (30%). The infection was encountered in 75% of our patients, the chest infection was the prevalent source (45%). 20% of the patients were admitted with bed sores or developed them during their ICU admission. The patients' demography, clinical, and their ICU scores as well as anthropometric measures were illustrated in (Table 1). 59% of our patients were under 60 years old and more than half of them were females (60.8%). Based on BMI classifications, 34.8% of them had average weight, whereas 13% were underweight, 27% were overweight and only one patient had morbid obesity. The hand grip strength measured only in conscious patients (313 patients out of 454), the low muscle strength was detected in 280 patients; 167 females and 113 males.

The ICU mortality was around 37%. There was no difference between the non-survivors and survivors regarding the gender, BMI, and MUAC (Table 1). However, in comparison to those who survived, the non survivors were older (56.83 years ± 16.55 versus 48.34 years ± 19.48 in survivors, p value < 0.001) and had more severe disease as reflected by higher baseline APACHE-II (20.94 ± 6.83 versus 13.8 ± 6.01in survivors, p value < 0.001) and higher baseline SOFA (7.61 ± 3.53 versus 4.01 ± 3.01 in survivors, p value < 0.001) scores. In addition, they had higher nutritional risk as assessed by mNUTRIC score (5.14 ± 1.79 versus 2.91 ± 1.81 in survivors, p value < 0.001), and had lower muscle strength as assessed by hand grip (5.19 Kg ±5.66 versus 11.7 Kg ±7.78 in survivors, p value < 0.001). Regarding the laboratory findings, anemia, impaired creatinine, impaired liver enzymes, hypoalbuminemia and hypocalcemia were more encountered in non-survivor group (Table 1).

During the ICU stay, 37% of the patients needed mechanical ventilation with higher frequency in non-survivors. There was no significant difference between the survivors and non-survivors regarding the duration of mechanical ventilation (Table 1), also there was no significant difference between them regarding the ICU-LOS (Table 1).

The values of muscle layer thickness measured by ultrasonography (US-MLT) at time of ICU admission are illustrated in (Fig. 2). The means of US-MLT of all studied muscle groups were significantly greater in those patients who survived compared to the non-survivors (p value < 0.001) (Fig. 3).

Additional Table (1) illustrated the correlation between US-MLT with anthropometric, NUTRIC score, ICU scores, LOS and duration of mechanical ventilation after controlling for age and gender. US-MLT showed significant positive correlation with BMI (p value < 0.001), MUAC (p value < 0.001) and hand grip strength (p values < 0.001,

Table 1
Demographic, clinical, and laboratory data of the studied group with comparison between non survivors and survivors.

		All patients	Outcome		
			Non-Survivors	Survivors	P Value
Number (%)		454	166 (37)	288 (63)	
Gender N (%)	**Female**	276 (61)	101 (61)	175 (61)	1.000
	Male	178 (39)	65 (39)	113 (39)	
Age (Mean ± SD)		51 ± 19	56.83 ± 16.55	48.34 ± 19.48	**<0.001**
BMI (Mean ± SD)		25.9 ± 6.4	26.03 ± 7.08	25.96 ± 6.05	0.916
MUAC (Mean ± SD)		28 ± 6.1	27.82 ± 6.82	28.24 ± 5.68	0.151
Hand grip strength	Tested patients N (%)	324 (72)	74 (45)	250 (87)	
	Normal muscle strength N (%)	26 (8)	0	26 (10)	**0.003**
	Low muscle strength N (%)	298 (92)	74 (100)	224 (90)	
	Strength/kg [Median (IQR)]	10 (3–15)	3 (0–8)	12 (5–16)	**<0.001**
Total Calories (Mean ± SD)		1683.8 ± 369.5	1648 ± 391.7	1699.8 ± 368.2	0.168
Laboratory (Mean ± SD)	**Hemoglobin**	9.95 ± 2.76	9.61 ± 2.56	10.16 ± 2.86	**0.036**
	TLC	13.48 ± 12.84	14.75 ± 18.41	12.75 ± 7.98	0.162
	Platelet count	231.99 ± 140.02	200.12 ± 143.48	250.35 ± 134.85	**<0.001**
	Creatinine	3.29 ± 3.38	3.56 ± 2.98	3.14 ± 3.59	**<0.001**
	Corrected total Ca	8 ± 1.3	7.87 ± 1.39	8.03 ± 1.18	0.057
	Albumin	2.72 ± 0.79	2.46 ± 0.7	2.87 ± 0.79	**<0.001**
ICU scores	**APACHE-II** (Mean ± SD)	16.4 ± 7.2	20.94 ± 6.83	13.8 ± 6.01	**<0.001**
	SOFA-0 [Median (IQR)]	5 (2.5–8)	8 (5–10)	4 (2–5.75)	**<0.001**
	SOFA-48 [Median (IQR)]	4 (2–7)	8 (6–11)	3 (1–4)	**<0.001**
	SOFA-96 [Median (IQR)]	4 (2–8)	8.5 (5–11.8)	3 (1–4)	**<0.001**
	mNUTRIC (Mean ± SD)	3.7 ± 2.1	5.14 ± 1.79	2.91 ± 1.81	**<0.001**
LOS [Median (IQR)]		6 (4–10)	5 (3–11)	7 (4–10)	0.155
Mechanical ventilation	N (%)	168 (37)	120 (72.3)	51 (17.7)	**<0.001**
	Duration [Median (IQR)]	4 (2–7)	4 (2–7.25)	3 (2–6)	0.413

APACHE: Acute Physiology and Chronic Health Evaluation, AST: aspartate amino transferase, BMI: body mass index, LOS: length of stay, MLT: muscle layer thickness, MUAC: mid upper arm circumference, mNUTRIC: modified Nutrition Risk in Critically ill, SD: standard deviation, SOFA: Sequential Organ failure Assessment, TLC: total leucocytic count.

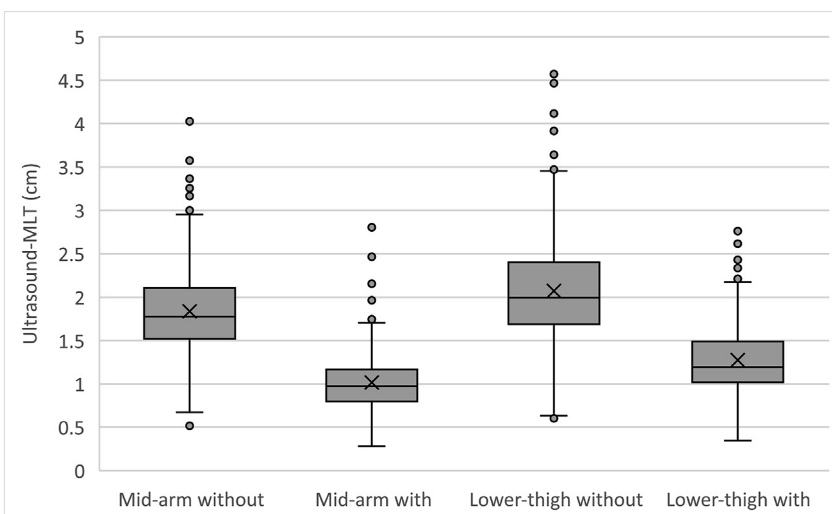

Fig. 2. Values of ultrasonography MLT of studied muscles without and with pressure.

<0.001, 0.002 & 0.062 for mid-arm and lower-thigh with and without compression respectively).

In relation to ICU scores, the baseline US-MLT of all examined sites showed negative significant correlation with baseline APACHE score (p value < 0.001), baseline SOFA score and SOFA score assessed 48 h after admission. However, the baseline US-MLT showed no significant correlation with SOFA score assessed 96 h after admission (additional Table 1). A negative correlation was also found with NUTRIC score (p value < 0.001) (additional Table 1). No significant correlation has been found with the LOS and the duration of mechanical ventilation on any of the examined sites (additional Table 1). The ROC curves were done for the measured US-MLT to determine the best cut-off values that can predict patients' mortality. The cutoff values for isolated reference points on each side had high sensitivity ranged 80–82% but rather low specificity ranging between 33 and 39% (not shown). Using the mean value of both sides for single reference points improves the specificity to 23–61% (Table 2).

It is worth noting that adjustment of the US measured MLT for height and BMI did not improve the AUC (not presented), so we preferred to use the measures without adjustment in order to give priority to simplicity.

In the final model of multiple step wise regression with mortality outcome (non-survived vs survived) as the dependent variable, the baseline SOFA, baseline APACHE-II scores and the baseline mid-arm US-MLT with and without transducer pressure were significant predictors (r square 0.410) (Table 3).

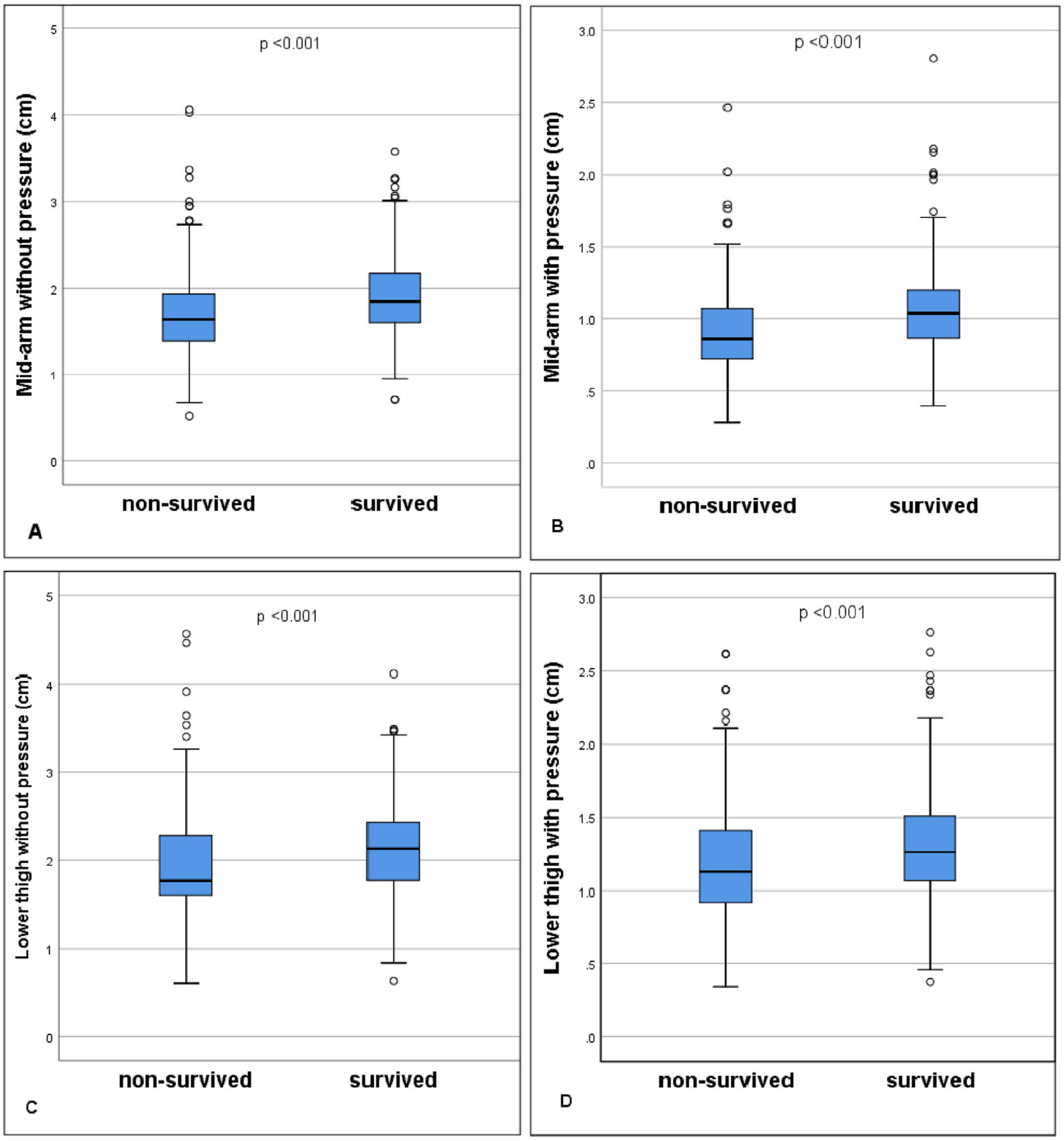

Fig. 3. A–D: comparison of ultrasonography- MLT in non-survived and survived. A & B: mid-arm points without and with pressure respectively. C & D: lower thigh points with and without pressure respectively.

Table 2
Sensitivity and specificity of US-MLT cutoff values to predict mortality.

Gender	Site	Transducer pressure	AUC	p value	95% CI	Best cut off value (cm)	Sensitivity (%)	Specificity (%)
All patients	Mid Arm	Without	0.622	<0.001	0.567–0.677	> 1.76	76.39	49.40
		With	0.649	<0.001	0.595–0.703	> 0.895	90.62	22.89
	Lower Thigh	Without	0.613	<0.001	0.558–0.669	> 1.725	64.58	61.45
		With	0.606	<0.001	0.550–0.661	> 0.913	67.71	61.45
Male	Mid Arm	Without	0.656	0.001	0.581–0.725	> 1.6	80.53	46.97
		With	0.678	0.001	0.604–0.746	0.72	92.04	28.79
	Lower Thigh	Without	0.634	0.003	0.559–0.704	> 1.73	80.53	48.48
		With	0.646	0.001	0.572–0.716	> 0.88	93.81	27.27
Female	Mid Arm	Without	0.598	0.007	0.537–0.656	> 1.39	88	24
		With	0.628	0.001	0.568–0.685	> 0.72	90.86	24
	Lower Thigh	Without	0.600	0.007	0.539–0.658	> 1.76	74.29	48
		With	0.580	0.028	0.519–0.639	> 0.93	87.43	20

AUC: area under the curve, CI: confidence interval.

The mid-arm US-MLT with transducer pressure, being the most significant US-MLT variable in predicting the mortality, was entered with APACHE-II score in binary logistic regression analysis. The model was significant (p value < 0.001) and, both variables can explain the change in mortality by 33.9% (r square 0.339). This model was used to calculate a new probability variable to study the impact of the combined effect of APACHE-II and US-MLT on mortality. The discriminatory power of APACHE-II and mid-arm MLT in predicting mortality was compared using ROC curves as single variables and then combined. AUC of combined variables becomes larger which reflects the discriminatory ability of combined effect when compared with AUC for APACHE-II and mid-arm MLT (Table 4).

Inter/intra-rater reliability tests (additional Table 2) showed excellent agreement between the two raters (1st = trainee & 2nd = trainer) in measuring mid-arm and lower-thigh MLT without and with maximal compression (ICC was 0.957, 0.898, 0.908, and 0.931 respectively).

In addition, there was excellent agreement between the two readings of the same rater in measuring mid-arm MLT without and with maximal compression (ICC was 0.983, 0.964) and lower-thigh muscle thickness without maximal compression (ICC was 0.99), but poor to moderate agreement in measuring lower-thigh muscle thickness with maximal compression (ICC was 0.675).

Table 3
Multiple stepwise regression: mortality outcome[a] as dependent variable.

	B	P value	OR[b]
Age	−0.014	0.051	0.987
Baseline APACHE-II	−0.104	< 0.001	0.901
Baseline SOFA	−0.207	< 0.001	0.813
Mid arm US-MLT without transducer pressure	−0.884	0.069	0.413
Mid arm US-MLT with transducer pressure	2.691	0.001	14.742
Constant[c]	3.174	< 0.001	23.91

[a] Mortality outcome: not survived/survived.
[b] OR: odds ratio.
[c] Constant is y intercept.

Table 4
Area under the curve for the predicted mortality assigned by binary logistic regression model.

	AUC	p value	95% CI
probability	0.801	< 0.001	0.762 to 0.837
Baseline APACHE	0.791	< 0.001	0.751 to 0.828
Mid arm US-MLT with transducer pressure	0.648	< 0.001	0.602 to 0.692

AUC: area under the curve, CI: confidence interval.

4. Discussion

In the current study we used ultrasound to measure MLT at the time of ICU admission. We preferred measuring MLT of group of muscles; from the facial border to the bone interface, as in critically ill patient, the muscle echogenicity may increase making cross sectional area (CSA) measurement or measuring the MLT of single muscle more difficult due to less delineation of muscle boundaries [15]. The study showed that lower baseline US-MLT was associated with increased disease severity at the time of ICU admission as reflected by higher baseline APACHE-II and SOFA-0 scores and was associated with progression of organ failure two days after admission as assessed by SOFA-48 in addition it was associated with increased ICU mortality. After including the age, basal APACHE-II, basal SOFA, different US-MLT protocols in a multivariable regression model, the multiple step wise regression analysis showed that the baseline mid-arm US-MLT together with SOFA, and APACHE-II scores were significant predictors for the mortality, and when the baseline mid-arm US-MLT with transducer pressure combined with the baseline APACHE-II score, the risk estimation of APACHE-II score in predicting the mortality was increased.

We also found that lower baseline US-MLT was associated with lower muscle strength, as measured by the hand grip, which may

Additional table (1)
Correlation between mean MLT with clinical, ICU scores, LOS and duration of mechanical ventilation (after controlling for age and gender).

	Mid Arm				Lower Thigh			
	Without pressure		With pressure		Without pressure		With pressure	
	r	p value	r	p value	r	p value	r	p value
BMI	**0.652****	**< 0.001**	**0.570****	**< 0.001**	**0.572****	**< 0.001**	**0.569****	**< 0.001**
MUAC	**0.695****	**< 0.001**	**0.608****	**< 0.001**	**0.606****	**< 0.001**	**0.603****	**< 0.001**
Hand grip strength	**0.281**	**< 0.001**	**0.297***	**< 0.001**	**0.242***	**< 0.001**	**0.188***	**< 0.001**
ICU-LOS days	−0.050	0.295	−0.005	0.912	−0.030	0.523	0.005	0.917
Duration of mechanical ventilation	−0.037	0.444	−0.012	0.797	−0.040	0.408	−0.021	0.666
APACHE-II	**−0.129***	**0.006**	**−0.127***	**0.007**	**−0.128***	**0.007**	**−0.111***	**0.018**
SOFA-0	**−0.103***	**0.029**	**−0.123***	**0.009**	**−0.096***	**0.042**	**−0.094***	**0.047**
SOFA-48	**−0.142***	**0.002**	**−0.178***	**< 0.001**	**−0.115***	**0.014**	**−0.117***	**0.013**
SOFA-96	−0.063	0.266	−0.08	0.16	−0.044	0.443	−0.039	0.492
mNUTRIC	**−0.160***	**0.001**	**−0.169***	**< 0.001**	**−0.195***	**< 0.001**	**−0.160***	**0.001**

APACHE: Acute Physiology and Chronic Health Evaluation, AST: aspartate amino transferase, BMI: body mass index, LOS: length of stay, MLT: muscle layer thickness, MUAC: mid upper arm circumference, mNUTRIC: Modified Nutrition Risk in Critically ill, SOFA: Sequential Organ failure Assessment.

Additional table (2)
Inter-rater reliability and Intra -rater reliability.

	Site	Pressure	Reader 1 Mean ± SD	Reader II Mean ± SD	ICC	95% CI
Inter-rater reliability	**Mid Arm**	without	1.47 ± 0.44	1.52 ± 0.41	0.957	0.957 (0.925–0.975)
		with	0.79 ± 0.35	0.8 ± 0.28	0.898	0.898 (0.827–0.941)
	Lower Thigh	without	1.9 ± 0.7	1.9 ± 0.55	0.908	0.908 (0.844–0.947)
		with	1.09 ± 0.5	1.04 ± 0.4	0.931	0.931 (0.881–0.96)
	Site	**Pressure**	**Reading 1 Mean ± SD**	**Reading II Mean ± SD**	**ICC**	**95% CI**
Intra −rater reliability	**Mid Arm**	without	1.85 ± 0.49	1.83 ± 0.49	0.983	(0.979–0.986)
		with	1.02 ± 0.33	1.01 ± 0.32	0.964	(0.957–0.97)
	Lower Thigh	without	2.08 ± 0.58	2.07 ± 0.57	0.99	(0.988–0.992)
		with	1.28 ± 0.4	1.29 ± 0.54	0.675	(0.622–0.723)

CI: confidence interval, ICC: inter correlation coefficient.

reflect the functional status of the patients. It was also associated with an increased nutritional status risk as indicated by a higher mNUTRIC score, lower BMI, and lower MAUAC. Accordingly, we hypothesized that baseline US-MLT could reflect the functional as well as nutritional status of critically ill patients, which may explain its ability to predict ICU mortality.

Our findings confirmed the study done by Galindo Martín et al., in a relatively small sample of 59 adult patients admitted in medical-surgical ICU and used single reference point, they found that the baseline US-MLT of quadriceps muscle could predict the mortality and improve the performance of baseline SOFA score. Similar to our results, non-survivors were older, had greater baseline SOFA and APACHE-II scores as well as had lower muscle thickness [16]. The mean quadriceps MLT using maximum probe compression was 1.44 cm in survivors, 0.98 cm non survivors, that were different to our measurements, that is contributed to different point of measurements as they used an anterior mid-thigh as a reference point [16]. The mid-thigh point is mathematically easier; however more probe pressure and depth adjustment are needed particularly in obese patients to get the bone interface. Sabatino et al. showed no difference between the two points; mid-thigh and lower-third in critically ill patients with acute kidney injury [17]. Pardo et al. [18] also found that both points were strongly correlated with the muscle loss with a r coefficient of 0.96 at mid-point and 0.93 at the lower-third. However the former point acts better [18].

It is not surprising that the baseline US-MLT showed no significant correlation with progression of organ failure four days after ICU admission as assessed by SOFA-96 as this may emphasize the importance to repeat the US measurement during the ICU stay. This was shown by other studies that serial US muscle measurement was correlated with muscle loss and increasing SOFA score [19,20].

Among the studied muscle groups and various screening protocols; with versus without transducer pressure, the mid-arm US-MLT with transducer pressure was most significant in predicting mortality. It is thought that the transducer compression may improve measurements accuracy in the critically ill patients as it could abolish the effect of edema that is frequently occurred due to increased extracellular fluid volume in such patients [16]. In addition the biceps thickness was found most to be closely correlated with lean body mass derived by DXA compared to the anterior thigh as illustrated by Campbell et al. [21].

One of main shortcomings of US-MLT is the absence of cutoff values for muscle thickness. In the current study we reached cutoff values in relation to mortality using the ROC curve. A cutoff value of 0.895 cm at the mid-arm US-MLT with transducer pressure had high sensitivity (91%) but rather low specificity (23%). While lower-thigh US-MLT with transducer pressure showed increased sensitivity (68%) and specificity (62%) at cutoff value of 0.913 cm. When used CSA of rectus femoris, Mueller et al. demonstrated that a cutoff value of 5.2 cm^2 can predict sarcopenia in critically ill surgical patients (sensitivity 73%, specificity 69%) [20]. These differences are related to the differently used measurement and outcome variables.

Regarding the ICU LOS and the duration of mechanical ventilation (MV), the current study found no significant correlation of previous outcomes with the initial US-MLT of any of the examined sites. This is in line with a multivariable regression model done by Mueller et al. that demonstrated that US detected sarcopenia independently could not predict the duration of surgical ICU stay. However it can predict the total hospital LOS [20]. In addition, in study of Galindo Martín et al. no difference was found in ICU LOS between survivors and non survivors [16]. Instead, a serial decline in muscle thickness was found to be associated with a prolonged ICU stay [19,22,23] and increased periods of MV [24]. The quadriceps group was found to have greater implications compared with other muscle groups on ICU LOS as demonstrated by Paris et al. [23].

Ultrasonography has been viewed as one of the most operator dependent imaging techniques. The current study demonstrated excellent inter- and intra-observer reliability for all examined sites. These results are consistent with previous studies that showed good intra- and inter-observer reliability of anterior thigh [18,25,26] and mid-arm muscle thickness [27] measured in critically ill patients. It is worth to mention that, Pardo et al. reported that the agreement were higher when the lower-thigh point used compared to the mid-thigh [18]. We also confirmed the reliability of measurements made by a recently trained physician with no previous experience in ultrasonography with relatively short learning curve. That was in line with other studies that demonstrated excellent agreement for quadriceps MLT in healthy volunteers [28], and for mid-arm muscle thickness in critically ill patients with sepsis [27], when performed by providers with no prior ultrasound experience.

4.1. Strength and limitations

The main strength of the current study includes enrollment of large population of critically ill patients and the calculation of US-MLT cutoff values at different reference points that can predict patients' mortality. We also have limitations. We did not evaluate the predictive value of US-MLT on long-term outcomes such as post discharge mortality and quality of life.

5. Conclusion

This study demonstrated that muscle thickness measured by ultrasound can significantly reflect the nutritional and functional status of critically ill patients as assessed by mNUTRIC score and handgrip, respectively. It showed that the baseline US-MLT can be used as a reliable risk assessment tool in addition to other scores for ICU patients, it can reflect the baseline disease severity, and predict the disease severity progression, at least at the first 48-h of ICU admission. The baseline mid-arm US-MLT with maximum transducer pressure can predict mortality together with other ICU scores and it also improves the performance of baseline APACE-II score. Also, this study provides cutoff values for US-MLT in relation to mortality. Verification of these cut-off values through guiding nutritional support policy; intensified compared to an ordinary one, for critically ill patients with lower values with respect to their outcome is an interesting point for future research. Finally, the US-MLT can be performed by any appropriately trained clinician with good intra- and inter-observer reliability.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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