The Egyptian Journal Of Intensive Care And Emergency Medicine (JICEM)

Evaluation of intensive care unit acquired weakness in patients with sepsis

Mostafa M. Elkholy, [a] , Mohammed A. Osman [b], Ahmed S. Abd El Basset [c], Sameh K. El Maraghi [d], Hamdy M. Saber [d]

[a] *Department of Clinical Neurophysiology (Neuro-Diagnostic and Research Center), Faculty of Medicine, Beni-Suef University, Egypt*

[b] *Department of Critical Care Medicine, Arish general hospital, Ministry of Health, Egypt*

[c] *Department of Radiology, Faculty of Medicine, Beni-Suef University, Egypt*

[d] *Department of Critical Care Medicine, Faculty of Medicine, Beni-Suef University, Egypt*

Abstract:

Purpose: Intensive care unit acquired weakness (ICUAW) has a negative impact on functional outcome and mortality. We aim to determine the incidence of ICUAW in septic ICU patients and to explore its significant correlations with clinical and laboratory findings. **Patients and Methods:** We included forty ICU patients diagnosed with sepsis on admission or within 48 hours later. Twenty-five ICU patients with no sepsis were included as a control group. All study populations were evaluated using clinical muscle assessment (medical research council, MRC) and muscle ultrasound at two-time points, the first was between days 2 and 5, and the second was between days 10 and 15. Laboratory workup included complete blood count, coagulation profile, arterial blood gases, liver, and kidney function tests. **Results:** There was a gradual declining neuromuscular function in all study populations and more significant in septic patients' group. The incidence of ICUAW was 60% (by MRC score <48) and 100% (by abnormal muscle ultrasound) at second evaluation point of septic patients. SOFA score, blood haemoglobin level, total leucocytic count and creatinine had significant correlations with neuromuscular dysfunction.

Conclusions: ICUAW is a prevalent complication in septic ICU patients and was correlated with SOFA score, blood haemoglobin, leucocytic count and creatinine level.

Keywords: ICU acquired weakness; muscle ultrasound, muscle weakness; neuromuscular dysfunction; sepsis

1. Introduction:

Intensive care unit acquired weakness (ICUAW) is one of the most severe complications of ICU stay and has adverse effects on both in-hospital and post-discharge morbidity and mortality. It may present as critical illness polyneuropathy (CIP), critical illness myopathy (CIM) or critical illness neuromyopathy (CINM) [1].

A widely varied incidence of ICUAW was reported in literature ranging between 10 and 80% depending on the underlying risk factors, timing and used methods of neuromuscular assessment [2, 3]. Sepsis, shock, mechanical ventilation and multiorgan failure are among the most common risk factors associated with ICUAW [4]. Early identification of ICUAW has an immense value to avoid the adverse hazards of prolonged ICU stay [5]. Diagnosis of ICUAW relies mainly on clinical muscle strength using MRC score and may be supported by other diagnostic tests such as electrophysiological assessment and muscle biopsy [1]. Ultrasonography of muscles is an easy bedside test with promising results in assessment of neuromuscular weakness [6-8].

The mechanisms underlying septic induced ICUAW is multiplex and mainly involves systemic inflammatory response that causes multiorgan failure [9, 10]. Treatment of ICUAW is mainly supportive and preventive measures included adequate blood sugar control, timely electrolyte correction and early mobilization [5, 11, 12].

The aim of the current study is to determine the incidence of ICUAW in septic ICU patients as a primary outcome and to explore any significant correlation among clinical, laboratory and ultrasonographic findings.

2. Patients and Methods:

This prospective observational study included 65 patients admitted to the critical care department Beni-Suef University Hospital from June 2021 to April. The study

protocol was approved by the local ethical committee (Approval No: FMBSUREC/01102019) and informed written consent was obtained from the patient next of kin of all participants before enrolment in the study. The participants included 40 patients diagnosed on admission or within 48 hours later as having sepsis or septic shock according to the third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [13]. Twenty-five patients with no sepsis were enrolled as a control group. Hemodynamically unstable, comatose patients and those with an acute condition like acute myocardial infarction, post-cardiac surgery or with a history of neuromuscular disorders were excluded from the study. We also excluded patients with local lower limb reason for weakness or edema, pregnancy, age less than 18 years, hypomagnesemia, chronic prolonged steroid therapy, metabolic disorder, and acute respiratory distress syndrome.

All patients were subjected to the following:

- Clinical assessment through history taking, complete general and neurological examination.
- Routine laboratory workup: complete blood count, coagulation profile, arterial blood gases, liver, and kidney function tests.
- Evaluation of organ dysfunction and severity of illness using sepsis-related organ failure assessment (SOFA) score [14] at two time points following the onset of sepsis, the first evaluation (between days 2 and 5) and the second evaluation (between days 10 and 15).
- Clinical muscle strength assessment: Medical research council (MRC) was carried out at the same two time points following the onset of sepsis. ICUAW is defined based on clinical grounds as MRC total sum score <48 [15].

Ultrasonography assessment:

All patients were evaluated simultaneously using Mindray Dp 20 machine with a 9 to 13 MHz probe real-time linear array scanner. The initial settings were 10 MHz frequency and 49 gain with variable depth, which may be altered individually to visualize the complete muscle. All ultrasound studies were done by one operator trained in musculo- skeletal ultrasound.

Patients were examined in the supine position with extended arms and legs and relaxed muscles. The muscles selected for

analysis were bilateral biceps brachii and forearm extensors in upper limbs, tibialis anterior and quadriceps in lower limbs.

Ultrasonic echogenicity was graded according to Heckmatt and colleagues. This score differentiates ultrasonic echogenicity semi-quantitatively into four grades: Grade I: Normal, Grade II: Increased muscle echo intensity with distinct bone echo, Grade III: Marked increased muscle echo with reduced bone echo, Grade IV: Powerful muscle echo and complete loss of bone echo [16]. Total echogenicity grade was calculated as the sum of the tested eight muscle grades.

Data management and statistical analysis:

The sample size was calculated using G*Power 3.1.9.2. (Effect size 0.65, α error prob 0.05, statistical power 0.8). Data were analyzed using SPSS (statistical package for the social science software) Version 25.0. Quantitative variables were expressed by the mean and standard deviation or by median and interquartile range (IQR) (as appropriate). Paired data were compared using Paired t-test or Willcoxon test (as appropriate). Unpaired data were compared using the independent t test or Mann-Whitney U test (as appropriate).

Qualitative variables were expressed by number and percent and paired data were compared by McNemar test. Unpaired data were compared by chi-square test. Pearson correlation was used to correlate two continuous variables, otherwise, Spearman correlation was used. In all tests, p-value was considered significant if less than 0.05

3. Results:

The patient group included 40 patients with sepsis or septic shock (31 males, and their mean age was 57.3 ± 11.4 years). The Control group included 25 patients with no sepsis (14 males, their mean age was 58.8 ± 6.2). There was no significant age and gender difference between the groups (P=0.068, P=0.5, respectively). Other demographic, clinical and laboratory data are presented in **(Table 1)**

Table 1: Demographic, clinical and laboratory data of the patients and controls

		Patients (n=40)	Controls (n=25)
Age mean (SD)		57.3 (11.4)	58.8 ± 6.2
Gender Numbers (%)	**Male**	31 (77.5%)	14 (56%)
	Female	9 (22.5%)	11 (44%)
Cause of admission Numbers (%)	**Chest**	17 (42.5%)	2 (8%)
	Abdominal	12 (30%)	4 (16%)
	Cardiac	0 (0%)	5 (20%)
	Surgical	11 (27.5%)	9 (36%)
	Neurological	0 (0%)	5 (25%)
Mechanical Ventilation Numbers (%)	**1st Evaluation**	5 (12.5%)	0 (0%)
	2nd Evaluation	14 (35%)	0 (0%)
Vasopressors Numbers (%)		11 (27.5%)	0 (0%)
SOFA score Mean (SD)	**1st Evaluation**	6.56 (1.59)	
	2nd Evaluation	7.13 (3.35)	
Creatinine (mg/dL) Mean (SD)	**1st Evaluation**	3.07 (2.17)	1.56 (2.08)
	2nd Evaluation	2.6 (1.67)	1.44 (1.68)
Hemoglobin (g/dL) Mean (SD)	**1st Evaluation**	9.06 (1.63)	12.36 (1.5)
	2nd Evaluation	9.3 (1.44)	12.12 (1.13)
Total leucocytic count(thousands/cmm) Mean (SD)	**1st Evaluation**	17.88 (6.76)	12.12 (4.41)
	2nd Evaluation	20.38 (14.32)	9.88 (1.33)

There was gradual decline of the neuromuscular function evaluated by clinical assessment and ultrasonography and this decline was more significant in septic patients' group. Incidence of ICUAW in septic patients ranged between 60-100 % in the second evaluation depending on the assessment tool. (Tables 2 and 3)

Table 2: Comparison between patients and controls of clinical and ultrasonographic data at the two evaluations

	1st Evaluation		P-value	2nd Evaluation		P-value
	Patients (n=40)	Controls (n=25)		Patients (n=40)	Controls (n=25)	
MRC	53 (4)	59 (6)	0.001*	44 (10)	56 (3)	<0.001*
ICUAW (MRC<48)	4 (10%)	0	0.103	24 (60%)	0	<0.001*
Abnormal U/S	28 (70%)	19 (76%)	0.599	40 (100%)	25 (100%)	1
Echogenicity Grade	13 (6)	10 (4)	0.078	20 (3)	12 (3)	<0.001*

Median values (interquartile range) or numbers (percentage %) are shown. * p value < 0.05 was considered statistically significant. MRC, medical research council score; ICUAW, intensive care unit acquired weakness; U/S, ultrasonography.

Table 3: Comparison between the two evaluations of clinical and ultrasonographic data of patients and controls

	Patients (n=40)		P-value	Controls (n=25)		P-value
Evaluation time	1st	2nd		1st	2nd	
MRC	53 (4)	44 (10)	<0.001*	59 (6)	56 (3)	0.001*
ICUAW (MRC<48)	4 (10%)	24 (60%)	<0.001*	0	0	1
Abnormal U/S	28 (70%)	40 (100%)	<0.001*	19 (76%)	25 (100%)	0.031*
Echogenicity Grade	13 (6)	20 (3)	<0.001*	10 (4)	12 (3)	0.007*

Median values (interquartile range) or numbers (percentage %) are shown. * p value < 0.05 was considered statistically significant. MRC, medical research council score; ICUAW, intensive care unit acquired weakness; U/S, ultrasonography.

The SOFA score at the first evaluation was significantly correlated with MRC (P= 0.011, r = -0.417) and ultrasonographic echogenicity grade (P= <0.001, r = 0.599) at the second evaluation of the septic patients' group. Moreover, laboratory workup correlated with MRC and sonographic echogenicity at both evaluation points in the two study groups. The most significant and consistent correlations were blood hemoglobin concentration, total leucocytic count and renal function tests. Figures (1-3) show the relation between muscle weakness and Hb, TLC and creatinine.

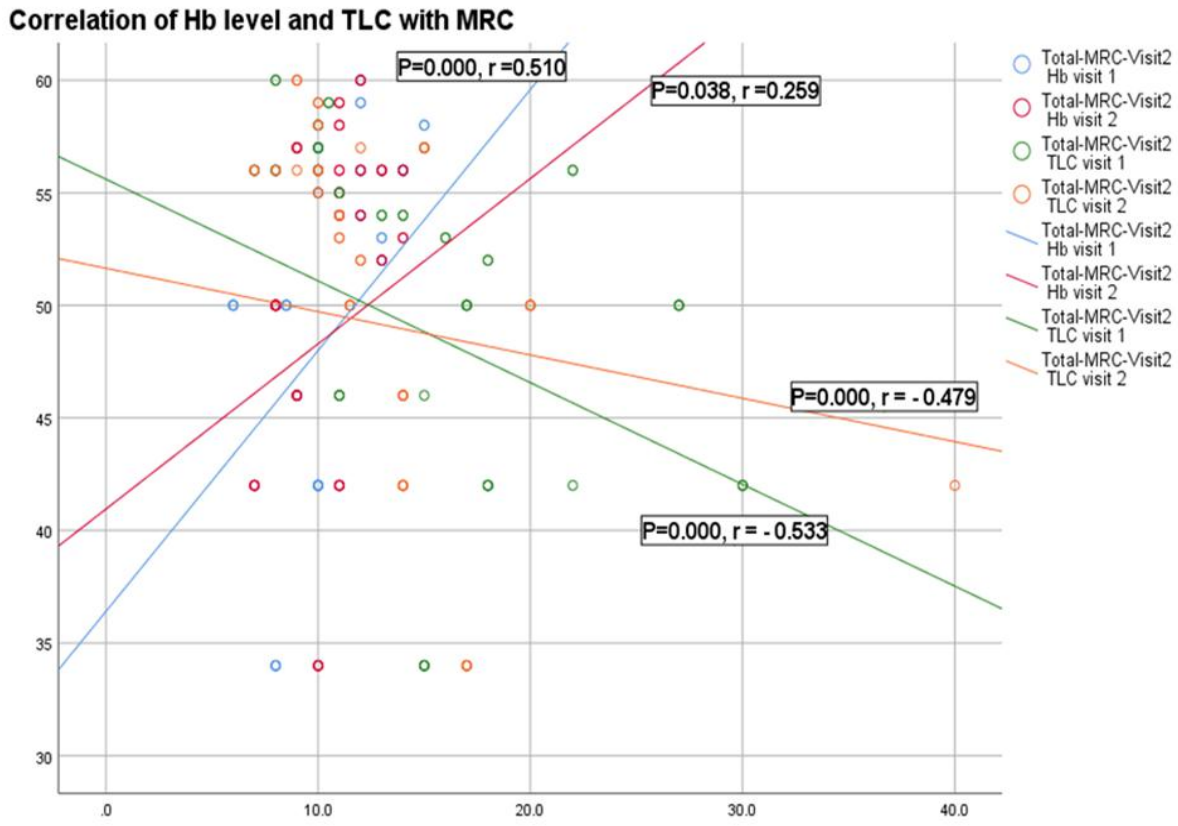

Figure 1: Correlation of blood hemoglobin and leucocytic count with total MRC score

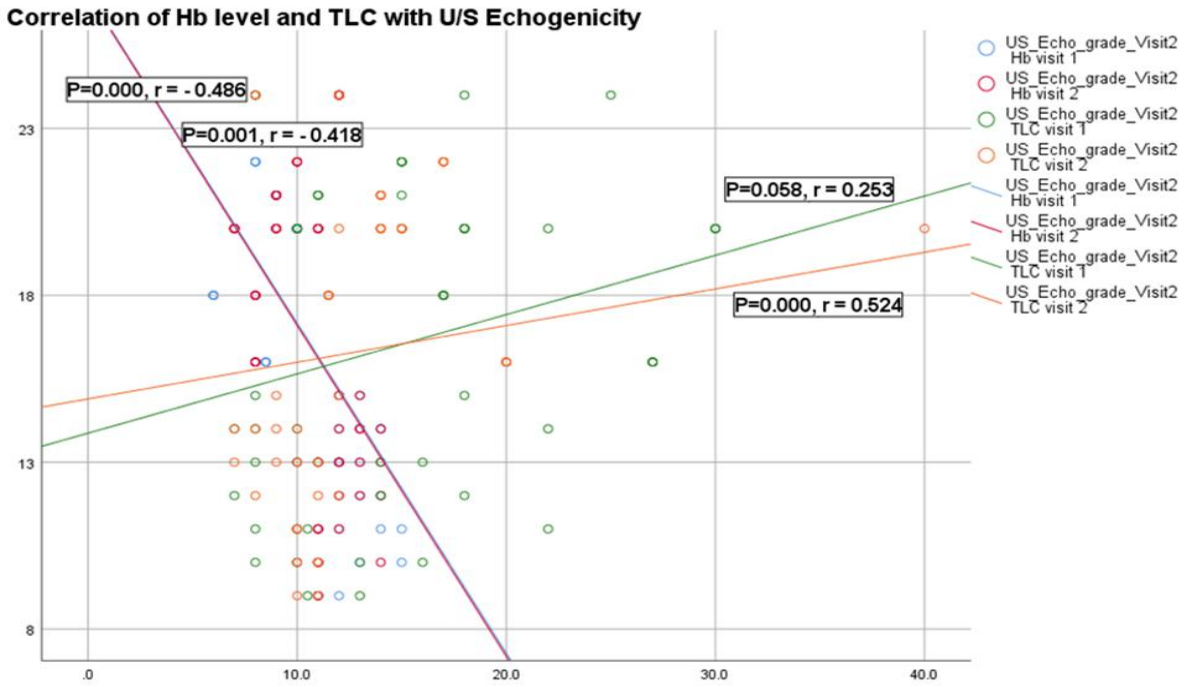

Figure 2: Correlation of blood hemoglobin and leucocytic count with total echogenicity score

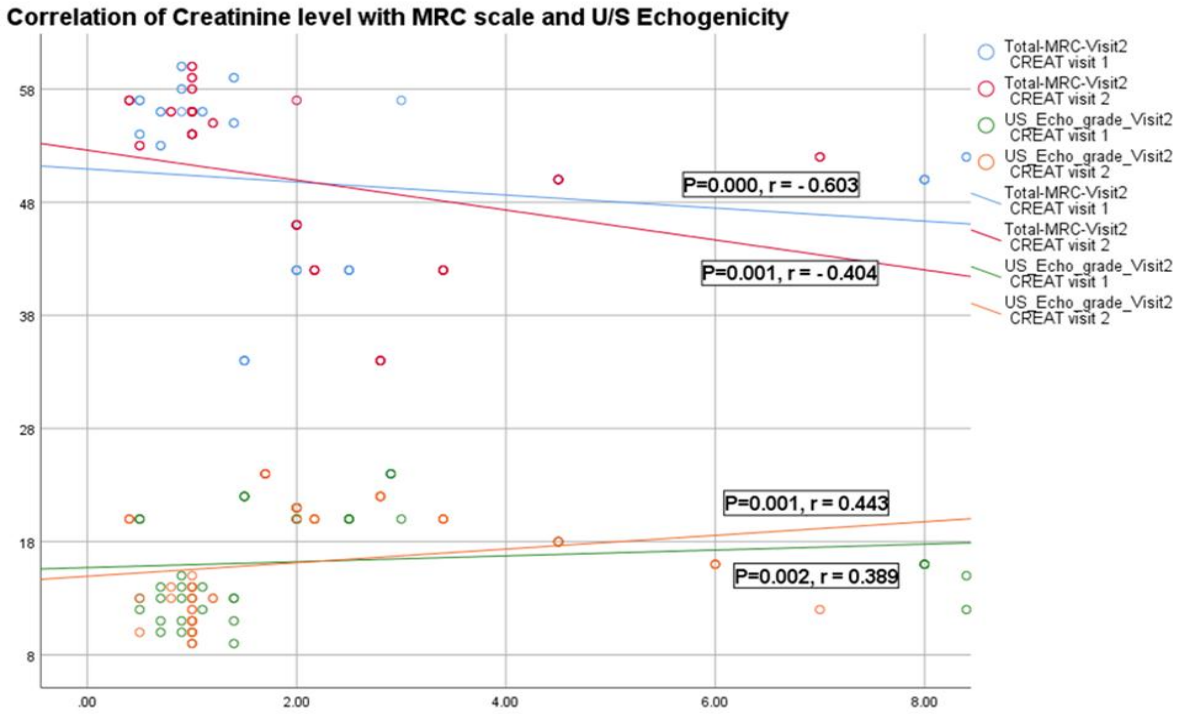

Figure 3: Correlation of creatinine level with total MRC and echogenicity scores

4. Discussion:

This prospective case control study was designed to explore the incidence and significant correlations of ICUAW in patients with sepsis.

The main findings of this study were gradual neuromuscular deterioration in ICU patients, however, more marked in septic patients' group. The incidence of ICUAW at the second evaluation time point was dependent on the assessment tool, 60% by clinical MRC score and 100% by ultrasonographic assessment. SOFA score and especially blood hemoglobin, leucocytic count and creatinine level had significant association with neuromuscular dysfunction.

Muscle weakness was reported to start in the early few days after ICU admission with 4% daily reduction of muscle fiber cross sectional area and an average 1-1.3% daily loss of overall muscle strength were reported in the literature [10, 17, 18].

Previous studies demonstrated a widely variable incidence of ICUAW in different cohorts ranging from 10% to 80%. This variation was attributed to differences in populations studied, timing and used diagnostic methods, presence and severity of underlying risk factors and lack of standard diagnostic criteria [3, 4].

The incidence was lower when evaluated by clinical tools alone than electrophysiological assessment [3]. This is consistent with our results that showed lower incidence by clinical assessment than ultrasonographic evaluation. We used ultrasonography as an easy applicable bedside test with fewer limitations and higher compliance compared to electrophysiological testing and invasive muscle biopsy. Muscle ultrasound was previously used as a promising alternative method for evaluation of neuromuscular dysfunction in ICU patients using different parameters such as cross-sectional area, muscle layer thickness and echogenicity grade [6-8].

Sepsis, septic shock and multiorgan failure are important risk factors for developing ICUAW, with reported incidence of 50-100% [19, 20]. In accordance with these data, our study showed a significant correlation of SOFA score with declining neuromuscular function. Moreover, higher leucocytic count was found to correlate with clinical weakness on MRC score and increased ultrasound muscle echogenicity grade that indicates muscle fiber necrosis and degeneration.

The underlying pathophysiology of septic induced ICUAW is multifactorial and includes microcirculatory, metabolic,

cellular, and electrical disturbances. Critical illness and sepsis include systemic inflammatory responses with resulting multiorgan failures including neuromuscular dysfunction [9, 10, 21].

The significant correlation of reduced blood hemoglobin with muscle weakness in our study could be explained by the anemic tissue hypoxia or both disorders are secondary to the sepsis and critical illness inflammatory responses.

The significant association of renal function biomarkers with neuromuscular dysfunction in the current study is supported by a previous report that included a large cohort of 104 ICU survivors and demonstrated that patients with stage 2 or 3 AKI had increased severity of muscle weakness and impaired ability to return to work or driving [22].

The mechanisms behind this kidney-skeletal muscles relationship are multiple, including systemic inflammation, metabolic acidosis, mitochondrial dysfunction, impaired protein synthesis, disrupted insulin signaling, and malnutrition inducing mediators of muscle protein catabolism such as ubiquitin-proteasome system (UPS), caspase 3, lysosomes, and myostatin [23, 24].

Our study has some limitations including the small sample size and the collection of all data from a single ICU. The current study highlights the importance of early assessment for muscle weakness in all septic patients and following them meticulously during the early phase which allows for an optimum intervention at an early reversible stage of ICUAW.

5. Conclusions:

ICUAW is a prevalent complication in septic ICU patients and is correlated with SOFA score and creatinine level.

Abbreviations:

CIM; Critical illness myopathy

CINM; critical illness neuromyopathy

CIP; critical illness polyneuropathy

ICUAW; intensive care unit acquired weakness.

IQR; interquartile range

MRC; medical research council

SOFA; Sepsis-related organ failure assessment

U/S; ultrasonography

6. References:

1. Kramer CL. Intensive care unit–acquired weakness. Neurol Clin. 2017;35(4):723-36.
2. Diaz Ballve LP, Dargains N, Urrutia Inchaustegui JG, Bratos A, Milagros

Percaz Mdl, Bueno Ardariz C, et al. Weakness acquired in the intensive care unit. Incidence, risk factors and their association with inspiratory weakness. Observational cohort study. Rev Bras Ter Intensiva. 2017;29:466-75.

3. Appleton RTD, Kinsella J, Quasim T. The incidence of intensive care unit-acquired weakness syndromes: a systematic review. J Intensive Care Soc. 2015;16(2):126-36.
4. García-Martínez MÁ, González JCM, y Mateos AG-d-L, Teijeira S. Muscle weakness: Understanding the principles of myopathy and neuropathy in the critically ill patient and the management options. Clin Nutr. 2020;39(5):1331-44.
5. Eggmann S, Luder G, Verra ML, Irincheeva I, Bastiaenen CH, Jakob SM. Functional ability and quality of life in critical illness survivors with intensive care unit acquired weakness: A secondary analysis of a randomised controlled trial. PLoS One. 2020;15(3):e0229725.
6. Le Neindre A, Philippart F, Luperto M, Wormser J, Morel-Sapene J, Aho SL, et al. Diagnostic accuracy of diaphragm ultrasound to predict weaning outcome: a systematic review and meta-analysis. Int J Nurs Stud. 2021;117:103890.
7. Toledo DO, de Freitas BJ, Dib R, do Amaral Pfeilsticker FJ, Dos Santos DM, Gomes BC, et al. Peripheral muscular ultrasound as outcome assessment tool in critically ill patients on mechanical ventilation: An observational cohort study. Clin Nutr ESPEN. 2021;43:408-14.
8. Paolo F, Silvia C, Tommaso P, Elena C, Martin D, John JM, et al. The possible predictive value of muscle ultrasound in the diagnosis of ICUAW in long-term critically ill patients. J Crit Care. 2022;71:154104.
9. McClafferty B, Umer I, Fye G, Kepko D, Kalayanamitra R, Shahid Z, et al. Approach to critical illness myopathy and polyneuropathy in the older SARS-CoV-2 patients. J Clin Neurosci. 2020;79:241-5.
10. Rodriguez B, Larsson L, Z'Graggen WJ. Critical Illness Myopathy: Diagnostic Approach and Resulting Therapeutic Implications. Curr Treat Options Neurol. 2022:1-10.
11. edu TSIchm. Early mobilization and recovery in mechanically ventilated patients in the ICU: a bi-national, multi-centre, prospective cohort study. Crit Care. 2015;19:1-10.
12. de Jonghe B, Lacherade J-C, Sharshar T, Outin H. Intensive care unit-acquired

weakness: risk factors and prevention. Crit Care Med. 2009;37(10):S309-S15.

13. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). Jama. 2016;315(8):801-10.
14. Vincent J-L, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med: Springer-Verlag; 1996.
15. Stevens RD, Marshall SA, Cornblath DR, Hoke A, Needham DM, De Jonghe B, et al. A framework for diagnosing and classifying intensive care unit-acquired weakness. Crit Care Med. 2009;37(10):S299-S308.
16. Heckmatt JZ, Leeman S, Dubowitz V. Ultrasound imaging in the diagnosis of muscle disease. J Pediatr. 1982;101(5):656-60.
17. Dos Santos C, Hussain SNA, Mathur S, Picard M, Herridge M, Correa J, et al. Mechanisms of chronic muscle wasting and dysfunction after an intensive care unit stay. A pilot study. Am J Respir Crit Care Med. 2016;194(7):821-30.
18. Jolley SE, Bunnell AE, Hough CL. ICU-acquired weakness. Chest. 2016;150(5):1129-40.
19. Tennilä A, Salmi T, Pettilä V, Roine RO, Varpula T, Takkunen O. Early signs of critical illness polyneuropathy in ICU patients with systemic inflammatory response syndrome or sepsis. Intensive Care Med. 2000;26(9):1360-3.
20. Latronico N, Bolton CF. Critical illness polyneuropathy and myopathy: a major cause of muscle weakness and paralysis. Lancet Neurol. 2011;10(10):931-41.
21. Schefold JC, Wollersheim T, Grunow JJ, Luedi MM, Z'Graggen WJ, Weber-Carstens S. Muscular weakness and muscle wasting in the critically ill. J Cachexia Sarcopenia Muscle. 2020;11(6):1399-412.
22. Mayer KP, Ortiz-Soriano VM, Kalantar A, Lambert J, Morris PE, Neyra JA. Acute kidney injury contributes to worse physical and quality of life outcomes in survivors of critical illness. BMC Nephrol. 2022;23(1):1-10.
23. Teixeira JP, Mayer KP, Griffin BR, George N, Jenkins N, Pal CA, et al. Intensive Care Unit–Acquired Weakness in Patients With Acute Kidney Injury: A Contemporary Review. Am J Kidney Dis. 2022.

24. Wang XH, Mitch WE. Mechanisms of muscle wasting in chronic kidney disease. Nat Rev Nephrol. 2014;10(9):504-16.