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Long term follow-up of quality of life and functional ability in patients with ICU acquired Weakness – A post hoc analysis

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ABSTRACT

Purpose: ICU acquired Weakness (ICUaW) is a common complication of critical illness. The aim of our study was the assessment of quality of life (QoL) and functional ability of patients with ICUaW, 6 months post hospital discharge.
Material and methods: Eight hundred seventy eight consecutive patients who had been discharged from the ICU were evaluated and 128 of them, 36 with ICUaW, were eligible for the study. Muscle strength was evaluated with MRC and Hand grip dynamometry. The Functional Independence Measure (FIM) was used to evaluate the functional ability while QoL was assessed with the Nottingham Health Profile and with the SF-36 questionnaire.
Results: Patients with ICUaW continued to have low MRC at hospital discharge, [53(49–56) vs. 59(58–60), $p < 0.05$]. Patients who developed ICUaW had lower Hand grip dynamometry at ICU, hospital discharge and 6 months after ($p < 0.05$). Patients with ICUaW have significantly lower FIM score at hospital discharge, 3 and 6 months post hospital discharge ($p < 0.05$) and persistently lower QoL at 3 and 6 months post hospital discharge($p < 0.05$).
Conclusions: ICUaW is associated with persistent deficiencies in functional ability and Qol leading to a prolonged period of recovery. Further research is needed in the field of prevention and targeted rehabilitation of functionality in this patient group.

1. Introduction

Increased post ICU survival has led to a shift of the interest in the long term sequalae of critical illness [1,2]. Up to 5 years after ICU discharge survivors exhibit significant neuromuscular weakness, reduced functional ability and therefore reduced quality of life (QoL) [3,4].

Intensive care unit acquired weakness (ICUaW) is a common complication of critical illness with an estimated incidence of 25–50% depending on the diagnostic method used, and the severity of critical illness [5,6]. The cause of muscle weakness is multifactorial including Systemic Inflammatory Response Syndrome – SIRS [7,8], use of neuromuscular blockers [9,10], use of steroids [4] and long-term bed rest [11,12].

ICUaW is associated with prolonged mechanical ventilation [13], prolonged ICU and hospital stay [13-15] and increased ICU and hospital mortality [16]. After leaving the hospital, a large number of patients are led to rehabilitation centers in order to gradually return to pre - ICU functional state [17]. The long-term effects of patients with ICUaW have been limitedly studied.

We have recently conducted a randomized double-blind trial to assess the effect of neuromuscular electrical stimulation (NMES) in the muscle strength of ICU survivors at hospital discharge [18]. The whole cohort was followed for 6 months after hospital discharge aiming to investigate the impact of ICUaW on QoL, functional ability and all-cause mortality. Therefore, the primary aim was the post hoc analysis of recently published data [18] to investigate the effect of ICUaW in QoL 6 months after hospital discharge. Secondary aims were functional ability and all-cause mortality 6 months after hospital discharge.

We hypothesized that patients with ICUaW have decreased functional ability and QoL at 6 months after hospital discharge and increased all-cause mortality.

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2. Material and methods

2.1. Patients

All patients were consecutively assessed at discharge from the mixed medical-surgical 24-bed university intensive care unit during a 4-year study period. All patients on mechanical ventilation ≥72 h and patients that did have an appropriate level of consciousness adequate to respond to at least 3 of the following orders ("open/close your eyes", "look at me", "put out your tongue", "nod your head", "raise your eyebrows") were considered for inclusion in the study.

Exclusion criteria were: age < 18 and > 85 years, pregnancy, obesity (BMI > 35 kg/m^2), preexisting neuromuscular disease (e.g. myasthenia gravis), technical restrictions regarding NMES implementation (e.g. burns), terminal disease, pacemaker and trauma to the spine.

2.2. Ethical approval

The study was approved by the Scientific Council and the Ethics Committee of "Evangelismos" Hospital. Patients included in the study gave written informed consent. The study was registered in Clinical Trials (NCT01717833).

2.3. Study design

This prospective cohort study was a post hoc analysis of data collected as part of a randomized clinical trial which has been previously published [18]. In short, patients were randomized to the intervention or the control group at ICU-discharge. The intervention group received an individualized rehabilitation regime and NMES daily until hospital discharge and the control group received sham NMES along with usual care also until hospital discharge, as previously described.

For this study, all ICU survivors who had been included in the above mentioned randomized clinical trial were followed after hospital discharge. Patients were contacted at 3 and 6 months after hospital discharge. Patients living in the Athens metropolitan area were assessed with home visits and the rest were assessed with phone interviews.

Muscle strength was assessed with the MRC and handgrip dynamometry at ICU discharge, hospital discharge and in the subgroup of patients who were assessed with home visits at 3 and 6 months post hospital discharge.

Functional ability was assessed with the Functional Independence Measure scale (FIM) at hospital discharge, 3 and 6 months post hospital discharge. QoL was assessed with SF-36 questionnaire, baseline assessment at ICU discharge (QoL before ICU admission), 3 and 6 months post hospital discharge and Nottingham Health Profile (NHP) at hospital discharge, 3 and 6 months post hospital discharge.

At hospital discharge, patients were assessed with FIM score and NHP by interview and at 3 and 6 months after hospital discharge by home visit for patients living in Athens and by telephone for patients outside Athens. SF-36 was performed 3 and 6 months after hospital discharge by home-interview for patients living in Athens and by telephone for patients outside Athens.

For the baseline assessment of SF-36 patients were asked to recall their quality of life prior ICU admission.

All-cause mortality was also recorded.

2.4. Outcome measures

2.4.1. Diagnosis of ICUaW and muscle strength assessment

The MRC score for clinical assessment of muscle strength was used for the evaluation of strength and the diagnosis of ICUaW [19-21] at ICU discharge. Three muscle groups in all four limbs were assessed with the MRC scale with values ranging from 0 (quadriplegia) to 60 (normal muscle strength). The following functions were assessed: wrist flexion, forearm flexion, shoulder abduction, ankle dorsiflexion, knee extension, hip flexion. Patients who had an MRC score ≤ 48 were diagnosed with ICUaW [22,23]. The MRC score was performed by two independent investigators, that were familiar with this technique and no >24 h elapsed between the two measurements. The mean value of the MRC score of the two investigators was used for the analysis.

MRC score has been observed to have very good inter observer reliability and validity in assessing muscle strength in critical ill patients during their ICU stay and in the follow-up period [19,20,24]. On the other hand the assessing procedure requires good patient collaboration, good mobility and maximum effort which are often diminished due to sedation and the presence of delirium [19,20].

2.4.2. Handgrip dynamometry

Handgrip dynamometry (Lafayette 78011, Lafayette Instrument Co, Inc., Lafayette, IN, USA), assessing maximal isometric muscle strength, was applied immediately after MRC assessment in both hands by the same experienced investigators. The handgrip measurement has been described in detail else were [25].

There is little evidence regarding its use in the diagnosis of ICUaW. Ali et al. [26] reported reduced handgrip strength in patients with ICUaW in relation to those without, and by using gender-specific thresholds identified a force value cut off for each gender for diagnosing ICUaW. In the same study handgrip strength was independently associated to increased hospital mortality. It is well documented that handgrip dynamometry has good inter observer reliability in cooperative ICU patients [24,27].

2.4.3. Functional Independence Measure

Functional ability was assessed by FIM scale [28,29]. The FIM scale assesses physical and cognitive disability. Nineteen items are scored on the level of assistance required for an individual to perform activities of daily living. The scale is widely used for its original approach to patients with mobility problems after hospital discharge and is an important instrument for measuring the patients progress and assess rehabilitation outcomes [28,29]. The scale includes 18 items, of which 13 are physical domains based on the Barthel Index and 5 are cognition items. Each item is scored from 1 (total dependence) to 7 (complete independence). Possible total scores range from 18 to 126, with higher scores indicating a higher level of independence.

2.4.4. SF-36 questionnaire

SF-36 [30,31] uses 36 items to measure 8 QoL domains: physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, energy/vitality, social functioning, role limitations due to emotional problems, and mental health. SF-36 has demonstrated reliability, validity and responsiveness in the post-ICU population [30] and is one of the most common instruments used for assessing health status in this patient cohort [19,32].

2.4.5. Nottingham Health Profile

NHP assess QoL with 38 yes/no statements in 6 domains: physical mobility, pain, sleep, energy, emotional reactions, and social isolation [31,33].

2.5. Statistical analysis

Normality of distribution was checked by employing Kolmogorov-Smirnov or Shapiro-Wilk test. Unpaired Student's *t*-test or Mann-Whitney *U* test (in case of not normal distribution) was employed for between-group comparisons. Categorical variables were compared by chi-square test. Assessments repeated >2 different times analyzed by repeated measures analysis of variance (ANOVA) with a Greenhouse-Geisser correction and Bonferroni post-hoc comparisons, where applicable. Between-gender comparisons for muscle strength indices were based on 2 × 4 (gender × time) factorial ANOVA. All variables are presented by mean ± SD or median and interquartile range in case of not

normal distribution. In all cases, statistical significance level was set at $p < 0.05$. Analyses were performed with the IBM SPSS software 23.

3. Results

3.1. Patients

During the study period, 878 patients were discharged from the ICU. From those, 734 patients fulfilled the exclusion criteria, 16 denied participation to the study and 128 met the inclusion criteria. Thirty-six patients were diagnosed with ICUaW at ICU discharge and 92 patients were not (Fig. 1).

Baseline characteristics of patients with and without ICUaW are shown in Table 1. Patients with ICUaW had longer duration of ICU and post ICU in-hospital stay, as well as longer duration of mechanical ventilation than those without ($p < 0.05$). These patients also demonstrated higher Apache II, SOFA and SAPS III scores at ICU admission ($p < 0.05$). Finally, the incidence of ICUaW was higher among women patients ($p = 0.001$).

After hospital discharge 8 patients with ICUaW (30%) were transferred to a rehabilitation center, whilst from the patients without only 7 (8%) did ($p = 0.005$). In addition, 19 (70%) patients with ICUaW had physiotherapy sessions at home, whilst from the patients without only 23 (27%) did ($p = 0.001$).

3.2. Quality of life as assessed by Nottingham Health Profile or SF-36

Quality of life as assessed by NHP questionnaire between patients with and without ICUaW at hospital discharge, 3 and 6 months post hospital discharge is presented in Table 2. At hospital discharge patients

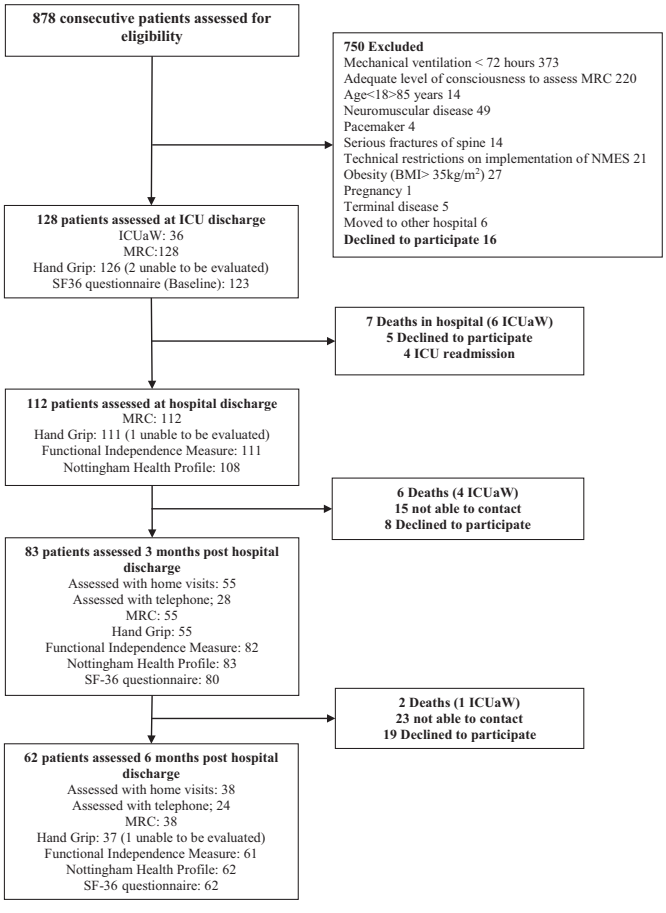

Fig. 1. Flow chart of patients included in the study and follow up.

Table 1
Baseline characteristics of patients with ICUaW and without [median (25th–75th percentile), mean ± SD].

	ICUaW $N = 36$	NO ICUaW $N = 92$	p*
Age (years)	58 ± 13	51 ± 16	0.03
Gender, (male/female)	15/21	68/24	0.001
ICU length of stay (days)	26 (13–42)	12 (9–23)	<0.001
Hospital length of stay (days)	25 (19–43)	11 (7–19)	<0.001
Duration of mechanical ventilation (days)	18 (10–36)	8 (5–15)	<0.001
APACHE II score on admission	18 (13–23)	15 (11–20)	0.03
SOFA score on admission	9 (7–11)	8 (6–10)	0.04
SAPS III score on admission	66 (55–72)	54 (46–62)	0.001
Diagnostic category at admission n (%)			
Neurologic	11 (31%)	31 (34%)	
Respiratory	7 (20%)	16 (18%)	
Cardiovascular	2 (6%)	4 (4%)	
Gastrointestinal	2 (6%)	12 (13%)	0.22
Sepsis	9 (26%)	8 (9%)	
Trauma	4 (11%)	18 (20%)	
Metabolic	–	1 (1%)	
Concomitant disease n (%)			
COPD	14 (39%)	28 (30%)	0.56
Coronary artery disease	15 (42%)	18 (20%)	0.03
Heart Failure	5 (14%)	7 (8%)	0.46
Rheumatic diseases	0 (0%)	1 (1%)	0.27
Multiple Myeloma	0 (0%)	1 (1%)	0.67
Vasculitis	1 (3%)	0 (0%)	0.23
Mental disease	11 (31%)	21 (23%)	0.17
Cancer	7 (19%)	16 (17%)	0.78
TBI	3 (8%)	18 (20%)	0.12
Spinal injury	0 (0%)	2 (2%)	0.37
Fractures	4 (11%)	16 (17%)	0.38
Stroke	1 (3%)	4 (4%)	0.68
Diabetes	8 (22%)	8 (9%)	0.04
Hypothyroidism	4 (11%)	2 (2%)	0.03
Hyperthyroidism	1 (3%)	1 (1%)	0.49

SOFA: Sequential Organ Failure Assessment, APACHE: Acute Physiology and Chronic Health Evaluation, SAPS: Simplified Acute Physiology, COPD: Chronic Obstructive Pulmonary Disease, TBI: Traumatic Brain Injury.
* p = ICUaW vs. No ICUaW.

with ICUaW had significantly reduced QoL in all domains except sleep ($p < 0.05$). Three months post hospital discharge patients with ICUaW had significantly reduced QoL in physical abilities, energy and emotional reactions ($p < 0.05$). Six months post hospital discharge patients with ICUaW had significantly reduced QoL in all domains ($p < 0.05$). The improvement in physical abilities, energy and emotional reactions in patients with ICUaW differed significantly between time points ($n = 15$, $p < 0.05$).

QoL as assessed by SF-36 questionnaire between patients with and without ICUaW before ICU admission (baseline), at 3 and 6 months post hospital discharge is presented in Table 3. At baseline assessment, patients with ICUaW had significantly reduced all the domains of the SF-36 questionnaire compared to those without ICUaW ($p < 0.05$). Three months post hospital discharge ICUaW patients had significantly reduced general health, physical function, role emotional and role functioning due to physical reasons ($p < 0.05$). Six months post hospital discharge, patients with ICUaW had also significantly reduced general health, pain, physical function and role functioning due to physical reasons ($p < 0.05$). Scores for all the domains of the SF-36 for both patients with ICUaW and without along with the normal values for Greek population [30] in 3 time points are presented in Fig. 2. The improvement in role functioning due to physical reasons in patients with ICUaW differed significantly between time points ($n = 16$, $p < 0.05$).

3.3. Muscle strength as assessed with MRC muscle strength score and Handgrip dynamometry

Muscle strength assessment between patients with and without ICUaW at ICU and hospital discharge and in 3 and 6 months post

Table 2
Results of the Nottingham Health Profile in patients with and without ICUaW at hospital discharge, 3 and 6 months post hospital discharge. A higher score (100) indicates more perceived problems [median (25th–75th percentile)].

	Hospital discharge $N = 108$			3 months post hospital discharge $N = 83$			6 months post hospital discharge $N = 62$		
	ICUaW	No ICUaW	p*	ICUaW	No ICUaW	p*	ICUaW	No ICUaW	P*
Physical abilities	79(65–91)	47(13–69)	<0.001	35(0-79)	0(0−21)	0.002	23(0–73)	0(0–4)	0.002
Energy	61(37–100)	24(0–82)	0.02	37(0-61)	0(0–24)	0.002	19(0–61)	0(0–0)	<0.001
Pain	3(0–28)	0(0–1)	0.01	0(0−21)	0(0–0)	0.01	0(0–61)	0(0–0)	0.04
Sleep	17(0–38)	16(0–50)	0.76	0(0−13)	0(0–0)	0.11	6(0–26)	0(0–0)	0.02
Emotional reactions	41(16–74)	24(7–50)	0.02	12(0–53)	0(0–9)	0.004	0(0–40)	0(0–0)	0.05
Social isolation	34(21–60)	0(0−23)	<0.001	0(0–40)	0(0–2)	0.07	0(0–42)	0(0–0)	0.04

ICU: Intensive Care Unit.
* p = ICUaW vs. No ICUaW.

hospital discharge is presented in Table 4. Patients with ICUaW had reduced muscle strength both at ICU ($p < 0.001$), hospital discharge ($p < 0.001$) and 3 months post hospital discharge ($p = 0.01$). At 6 months post hospital discharge there was no significant difference in muscle strength between groups ($p = 0.06$). Considering only patients with all time-assessments, there was significant within group improvement on MRC muscle strength score for both patients with ICUaW ($n = 10$, $p < 0.001$) and without ICUaW ($n = 23$, $p = 0.008$). There was also significant between group difference over time ($n = 33$, $p < 0.001$).

In concern to between-gender comparison, lower MRC values were observed for females at ICU- ($p < 0.001$) and hospital discharge ($p < 0.001$); A tendency for significant difference was observed 3 months post hospital discharge ($p = 0.06$); no differences were found at 6 months post hospital discharge ($p = 0.93$, Table 5). There was also significant difference between genders over time in MRC score in patients with all-time assessments ($n = 33$, $p = 0.02$). Taking into consideration, however, only patients with- and without-ICUaW, there was no significant difference between genders over time ($n = 10$, $p = 0.35$ and $n = 23$, $p = 0.29$, respectively).

Finally, muscle strength as assessed with MRC score significantly improved at 3 months after hospital discharge in patients that went to a rehabilitation center ($n = 55$, 7 ± 7 vs 1 ± 3, $p = 0.05$) in relation to those who didn't. The absolute value of MRC continued to be higher in patients that went in a rehabilitation center even when we included only patients with ICUaW ($n = 15$, 11 ± 9 vs 4 ± 4 $p = 0.04$). After 3 months patients had returned home and there was no difference between groups.

Assessing muscle strength with hand grip dynamometry showed that there was a significant difference between the two groups, with the patients with ICUaW having significantly lower strength at ICU and hospital discharge as well as at 3 and 6 months post hospital discharge (Table 6) ($p < 0.05$). This difference between groups remained significant at ICU and hospital discharge and 6 months post hospital discharge even when normative values were used in relation to age and gender [34] ($p < 0.05$) (Table 6).

Considering only patients with all 4 assessments, there was significant within group improvement on hand grip strength for both patients with ICUaW ($n = 10$, $p < 0.001$) and without ICUaW ($n = 21$ $p < 0.001$). There was no significant between group difference over time ($n = 31$, $p = 0.13$).

Females, as compared to males, had lower hand grip dynamometry relative values (% predicted) at ICU ($p = 0.002$) and hospital discharge ($p = 0.001$) and 3 months post hospital discharge ($p = 0.04$); no significant difference was found 6 months post hospital discharge ($p = 0.63$, Table 5). There was also significant difference between genders over time in % predicted values in patients with all-time assessments ($n = 31$, $p = 0.001$). Taking into consideration only patients with ICUaW, there was significant between-gender difference over time ($n = 10$, $p = 0.03$); considering patients without ICUaW, a tendency for significant difference over time was observed ($n = 21$ $p = 0.07$).

3.4. Functional ability as assessed by Functional Independence Measure

Patients with ICUaW had significantly reduced both total and mobility score of the FIM at hospital discharge, 3 and 6 months post hospital discharge in relation to patients without (Table 7) ($p < 0.05$). For patients with all 3-time assessments, significant within group improvement was observed for both patients with ICUaW ($n = 16$, $p < 0.001$) and without ICUaW ($n = 40$, $p < 0.001$). There was no significant between group difference over time ($n = 56$, $p = 0.22$).

3.5. Mortality

Patients with ICUaW had higher in-hospital mortality rate than those without (17% vs. 1% $p = 0.001$ $n = 124$, ICU readmission = 4). That was also the case 6 months post hospital discharge (31% vs. 5% $p = 0.04$ $n = 105$, lost to follow up =23).

Table 3
Results of SF-36 domains in patients with and without ICUaW at before ICU admission assessment (baseline), 3 and 6 months post hospital discharge. A higher score (100) indicates fewer perceived problems [median (25th–75th percentile)].

	Baseline $N = 123$			3 months post hospital discharge $N = 80$			6 months post hospital discharge $N = 62$		
	ICUaW	No ICUaW	p*	ICUaW	No ICUaW	p*	ICUaW	No ICUaW	p*
Mental Health	62(44–72)	68(52–76)	0.03	56(48–71)	68(53–80)	0.07	64(48–80)	68(54–80)	0.78
Energy	65(44–75)	70(53–80)	0.007	50(41–70)	65(46–75)	0.10	60(35–70)	65(45–83)	0.17
General Health	50(38–63)	67(52–79)	0.003	50(33–62)	67(50–83)	0.005	50(40–67)	71(50–83)	0.01
Pain	84(65–100)	100(90–100)	0.002	90(58–100)	100(65–100)	0.37	78(53–100)	100(78–100)	0.05
Physical Function	83(28–100)	100(80–100)	0.002	48(1–84)	83(45–100)	0.01	70(3–95)	90(60–98)	0.02
Role Emotional	100(0−100)	100(100−100)	0.003	83(0–100)	100(100–100)	0.006	100(33−100)	100(100–100)	0.13
Role Physical	100(0–100)	100(75–100)	0.03	0(0–100)	100(6–100)	0.004	50(0–100)	100(13−100)	0.03
Social Functioning	75(50–100)	88(63–100)	0.02	69(25–100)	88(50–100)	0.09	75(6–100)	100(56–100)	0.07

ICU: Intensive Care Unit.
* p = ICUaW vs. No ICUaW.

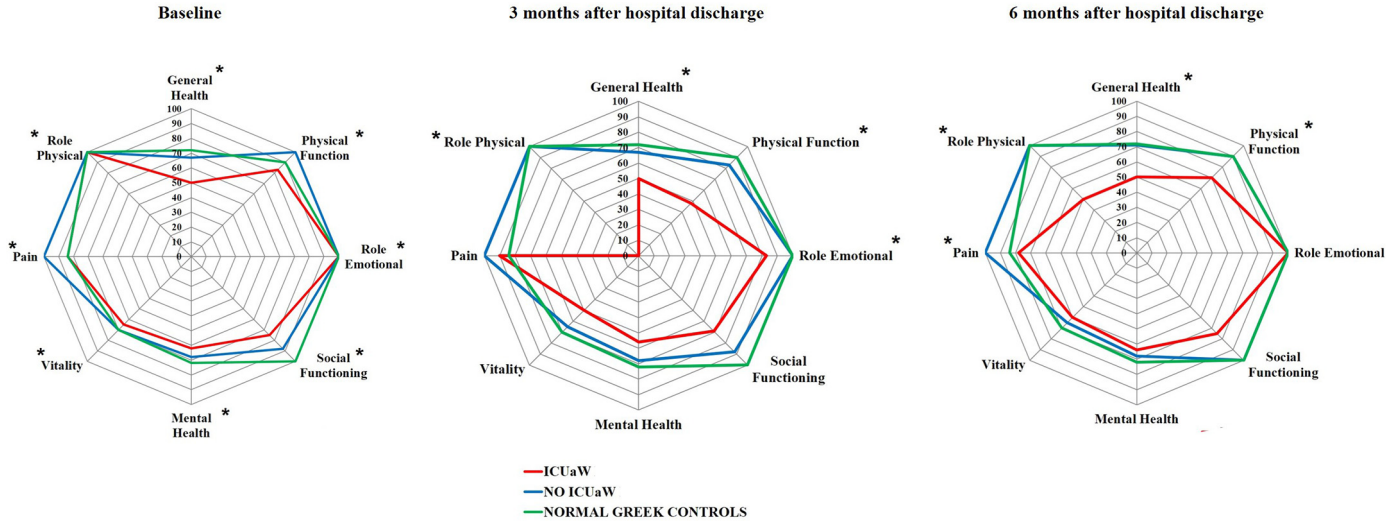

Fig. 2. Median SF-36 domain scores at baseline assessment (before ICU admission), 3 and 6 months post Hospital Discharge. A higher score (100) indicates fewer perceived problems. *p: <0.05, ICUaW vs. No ICUaW. Normal Greek controls provided by Pappa et al. [30].

4. Discussion

4.1. Quality of life and functional ability of patients with ICUaW up to 6 months post hospital discharge

The main result of this study was that patients with ICUaW had significantly worse Qol and functional ability at all time points of assessment with deficiencies persisting mainly in domains being related to physical functioning and less to psychological factors.

It is well documented that patients with ICUaW fail to reach, retrospectively estimated, pre-ICU admission baseline values of functional ability at hospital discharge [35]. Additionally, in a recent study [36], it was reported that patients that had reduced muscle strength during their ICU stay, had diminished functionality and as a consequence diminished QoL at 6 months after ICU discharge. Thomas et al. [37] reported that QoL was limited up to 12 months. In patients with ARDS was also noted reduced QoL and functional ability at ICU discharge in relation to healthy population at 6 and 12 months post hospital discharge [32].

Although, patients with ICUaW remained compromised in relation to patients without, when assessed at 6 months after hospital discharge, they showed significant improvement over time at the domains of physical disability, energy and emotional reaction when assessed by NHP, significant improvement in role functioning in SF36 questionnaire and significant improvement in Functional ability as assessed with FIM.

This finding is in accordance with the study of Fan et al. that also reported that recovery of muscle strength and functional ability generally occurs within 12 months after acute lung injury, yet substantial impairments continued beyond 24 months in relation to general population [35]. Mehrholz et al. reported significant improvement after a 2-month rehabilitation program [38].

It is worth mentioning that patients with ICUaW had reduced QoL even before their ICU admission in relation to those without. Yet, there are questions regarding the validity of such a retrospective method of assessment because it may be subject to bias due to traumatic experience [39]. Similar results have been reported in other studies as well along with that previous poor QoL is an independent predictor of QoL worsening [40]. It is also of interest that QoL before ICU admission was reduced compared to Greek normal values.

ICUaW may cause significant functional deficiencies, which seriously affect QoL after hospital discharge through different mechanisms. In ICUaW muscle and nerves are affected both on a functional and structural level [5]. Confined membrane excitability may lead to muscle and nerve dysfunction and this could resolve quickly [41] as this was recorded in the results MRC and hand grip. On the contrary, structural changes may cause long term functional deficiencies [42,43]. Nerve involvement has been linked to worse outcomes [42,43].

Another important finding was the destination of patients once discharged from hospital. In our study 30% of patients with ICUaW were transferred to a rehabilitation facility but only 7% of patients without. Recent studies have reported similar findings to ours [40,44,45]. It should be noted that rehabilitation costs are not covered by the public health system; therefore, the economic burden is huge for the patients and the families. Considering the economic situation of Greece in recent years, it would be possible to assume that we could have a bigger percentage from both groups and only severely disabled and more affluent patients made the decision to cover the cost privately. In any case, it's possible that post-hospital rehabilitation, more commonly offered to ICUaW patients in rehabilitation centers (from hospital discharge to 3 months post), improved rate of strength recovery; so that both ICUaW and non-ICUaW groups had clinically comparable strength levels at 6-month assessment.

Table 4
MRC of muscle strength in patients with and without ICUaW assessed at ICU discharge, at hospital discharge, 3 and 6 months post hospital discharge [median, (25°–75° percentile)].

	ICUaW	No ICUaW	p*
ICU Discharge $N = 128$	37 (29–44)	57 (54–60)	<0.001
Hospital Discharge $N = 112$	53 (49–56)	59 (58–60)	<0.001
3 months post hospital discharge $N = 55$	59 (57–60)	60 (59–60)	0.01
6 months post hospital discharge $N = 38$	60 (57–60)	60 (60–60)	0.06

MRC: Medical Research Council, ICU: Intensive Care Unit.
* p = ICUaW vs. No ICUaW.

4.2. Muscle strength of patients with ICUaW up to 6 months post hospital discharge

According to our results, patients with ICUaW present with significantly reduced muscle strength, as assessed by MRC score, in relation to those without at hospital discharge with muscle strength being back to normal values at 6 months post hospital discharge. Although same strength deficiencies have been reported by handgrip

Table 5
Absolute MRC values and hand grip dynamometry (right hand[¶], % predicted[ŧ]) between genders at ICU and hospital discharge, 3 and 6 months post hospital discharge [median, (25°–75° percentile)].

	MRC absolute values			Hand grip dynamometry % predicted[ŧ]		
	Male	Female	p*	Male	Female	p*
ICU discharge	57(51–60) $N = 128$	51(39–56)	<0.001	41(25–59) $N = 126$	25(8–46)	0.002
Hospital discharge	59(57–60) $N = 112$	56(53–59)	<0.001	53(33–75) $N = 111$	41(14–54)	0.001
3 months post Hospital discharge	60(59–60) $N = 55$	59(58–60)	0.06	85(77–95) $N = 55$	70(49–86)	0.04
6 months post Hospital discharge	60(59–60) $N = 38$	60(59–60)	0.93	84(70–105) $N = 37$	86(69–100)	0.63

MRC: medical research council score for muscle strength.
¶ All patients assessed were right handed.
ŧ Handgrip dynamometry absolute values were transformed to relative values (% predicted), according to the norms provided by Schlussel et al. [34].
ICU: Intensive Care Unit.
* p = Male vs. Female.

dynamometry at hospital discharge, it is noted that deficiencies were prolonged up to 6 months but with good improvement. This difference between MRC score and hand grip maybe due to the fact that hand grip is a quantitative assessment method whilst MRC score is qualitative. Also MRC is known to have a ceiling effect [24]. Recent studies that have used the MRC score for muscle strength and hand grip dynamometry in patients with ICUaW have reported similar findings to ours [25,26,35,46].

In a recent multicenter study [35] of 222 patients with Acute Lung Injury (ALI), it was noted reduced muscle strength 3, 6, 12 and 24 months post ICU discharge in patients with ICUaW, but after 12 months there were signs of improvement. MRC score was increased from a median of 50 at hospital discharge to 57 two years post ALI [35].

There are many contributors to the development of ICUaW. Prolonged bedrest leads to significant reduction of muscle protein synthesis (MPS), increased muscle wasting and reduction of muscle mass of lower limbs [47]. Immobility increases the production of inflammatory cytokines resulting to triggering of muscle proteolytic pathways leading to muscle protein loss and reduction of muscle strength [48,49]. Muscle protein degradation in critical ill patients could reach up to 2% of body weight per day [50]. Sepsis and systemic inflammation combined with immobilization leads to an increased loss of muscle mass in relation to immobility alone. Immobile septic patients have significant reduction in MPS, increased nitrogen excretion (indicates increased muscle catabolism) and reduction in muscle mass especially in lower limbs [47].

In our study, female patients demonstrated lower muscle strength at ICU discharge and an increased rate of recovery up to 3 or 6 months post-hospital. This issue has been pointed out in other studies [51]. Gandora et al. have suggested that this observation could be attributed to hormonal reasons. It has been hypothesized that differences in sex steroid hormone concentrations might represent a mechanism which affects mortality rate between males and females [52,53]. The same mechanism could also potentially affect strength recovery. Whether increased rate of muscle strength recovery in females affects all patients, either with- or without-ICAaW, remains to be decided.

In previous studies the relationship between muscle strength, functional ability and QoL is well demonstrated. [4,32]. Not unexpectedly the significant improvement in muscle strength over time had a beneficial effect in QoL. Yet, we should consider what was noted by Fan et al. that persistent limitation in QoL could not be attributed alone to ICUaW, but we should consider other factors such as mental health [35].

Functional ability is significantly affected in patients with ICUaW, highlighted by other researchers [35,38,44,46]. The relationship between muscle wasting - weakness and functional deterioration is significant. We also noted that significant improvement of muscle strength was followed by significant improvement of functionality. Intiso et al. also noted good functional recovery on patients with critical illness polyneuromyopathy [54].

4.3. Mortality

The hospital mortality of patients with ICUaW was 17% in our study. This finding highlights the fact that ICUaW is related to ICU complications that increase hospital mortality. Sharshar et al. [16], found 23% in hospital mortality and noted that mortality rate increased with severity of muscle weakness, a point also concluded by Ali et al. [26]. It has been suggested that increased mortality in ICUaW patients is related to the increased risk of developing infections [16,36]. Although increased in- and post-hospital mortality rate has also been reported in the study of Hermans et al. [45] when patients were matched for baseline

Table 6
Hand grip Dynamometry (right hand[¶]) in patients with and without ICUaW assessed at ICU discharge, at hospital discharge, 3 and 6 months post hospital discharge [median, (25° – 75° percentile)].

	ICUaW	No ICUaW	p*	% Predicted ICUaW ŧ	% Predicted No ICUaW ŧ	p*
ICU Discharge $N = 126$	3(0–7) Kg	14(9–24) Kg	<0.001	11(0–27)%	44(26–61)%	<0.001
Hospital Discharge $N = 111$	7(3−13) Kg	16(11–28) Kg	<0.001	22(12–53)%	52(36–71)%	<0.001
3 Months post hospital discharge $N = 55$	16(13–23) Kg	31(19–39) Kg	0.002	82(46–86)%	84(63–95)%	0.15
6 Months post hospital discharge $N = 37$	22(16–24) Kg	31(25–41) Kg	0.001	76(67–88)%	89(79–105)%	0.05

¶ All patients assessed were right handed,
ŧ Handgrip dynamometry absolute values were transformed to relative values (% predicted), according to the norms provided by Schlussel et al. [34].
ICU: Intensive Care Unit.
* p = ICUaW vs. No ICUaW.

Table 7
Results of the Functional Independence Measure score, physical domain score and total, in patients with and without ICUaW at hospital discharge, 3 and 6 months post hospital discharge [median (25th–75th percentile)].

		ICUaW	No ICUaW	p*
Hospital Discharge	Physical domain score	32 (21–55)	79 (54–89)	<0.001
$N = 111$	FIM total	65 (53–87)	111 (86–122)	<0.001
3 months post hospital Discharge	Physical domain score	87 (51–91)	91 (90–91)	0.001
$N = 82$	FIM total	116 (73–126)	126 (121–126)	0.002
6 months post hospital Discharge	Physical domain score	90 (57–91)	91 (89–91)	0.009
$N = 61$	FIM total	116 (87–126)	126 (124–126)	0.001

FIM: Functional Independence Measure.
* p = ICUaW vs. No ICUaW.

characteristics there was no difference at in-hospital mortality rate between weak and non-weak patients. However, there was still a significant difference in mortality after 1 year.

4.4. Limitations

There are several potential limitations of this study. First, as with all observational studies, due to a lack of randomization, we cannot assess causality of the associations reported. Second the small number of patients could restrict generalization of the results, due to the clinical diagnosis of the ICUaW which requires patients with adequate level of consciousness. Third limitation is the large number of patients that were lost in follow up; however, most of them were not Athens residents and visiting at home for follow-up evaluation was not feasible. In addition, results were similar when considering only patients with all-time evaluations. Significant difference was observed between ICUaW and no-ICUaW group on MRC score over time. This was not the case for hand grip strength and functional ability; however, sample size is a potential confounding factor.

5. Conclusions

ICUaW is associated with persistent deficiencies in functional ability and QoL leading to a prolonged period of recovery. Although there is a significant improvement in global muscle strength it seems that functional recovery takes more time. Patients with ICUaW are those that should be early recognized even during the acute phase of illness. Rehabilitation strategies should be carefully chosen in relation to patients' co-operation from the first day of admission to ICU. Further investigation is needed in the field of prevention and targeted rehabilitation of functionality.

Author contributions

The authors declare no conflict of interest. All authors have contributed to the submitted work and have approved the final manuscript.

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References

[1] Halpern NA, Pastores SM. Critical care medicine in the United States 2000-2005: an analysis of bed numbers, occupancy rates, payer mix, and costs. Crit Care Med 2010; 38:65–71. https://doi.org/10.1097/CCM.0b013e3181b090d0.
[2] Zimmerman JE, Kramer AA, Knaus WA. Changes in hospital mortality for United States intensive care unit admissions from 1988 to 2012. Crit Care Lond Engl 2013;17:R81. https://doi.org/10.1186/cc12695.
[3] Herridge MS, Tansey CM, Matté A, Tomlinson G, Diaz-Granados N, Cooper A, et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med 2011;364:1293–304. https://doi.org/10.1056/NEJMoa1011802.
[4] Herridge MS, Cheung AM, Tansey CM, Matte-Martyn A, Diaz-Granados N, Al-Saidi F, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. N Engl J Med 2003;348:683–93. https://doi.org/10.1056/NEJMoa022450.
[5] Stevens RD, Dowdy DW, Michaels RK, Mendez-Tellez PA, Pronovost PJ, Needham DM. Neuromuscular dysfunction acquired in critical illness: a systematic review. Intensive Care Med 2007;33:1876–91. https://doi.org/10.1007/s00134-007-0772-2.
[6] Nanas S, Kritikos K, Angelopoulos E, Siafaka A, Tsikriki S, Poriazi M, et al. Predisposing factors for critical illness polyneuromyopathy in a multidisciplinary intensive care unit. Acta Neurol Scand 2008;118:175–81. https://doi.org/10.1111/j.1600-0404.2008.00996.x.
[7] Jaber S, Petrof BJ, Jung B, Chanques G, Berthet J-P, Rabuel C, et al. Rapidly progressive diaphragmatic weakness and injury during mechanical ventilation in humans. Am J Respir Crit Care Med 2011;183:364–71. https://doi.org/10.1164/rccm.201004-0670OC.
[8] Levine S, Biswas C, Dierov J, Barsotti R, Shrager JB, Nguyen T, et al. Increased proteolysis, myosin depletion, and atrophic AKT-FOXO signaling in human diaphragm disuse. Am J Respir Crit Care Med 2011;183:483–90. https://doi.org/10.1164/rccm.200910-1487OC.
[9] Garnacho-Montero J, Madrazo-Osuna J, García-Garmendia JL, Ortiz-Leyba C, Jiménez-Jiménez FJ, Barrero-Almodóvar A, et al. Critical illness polyneuropathy: risk factors and clinical consequences. A cohort study in septic patients. Intensive Care Med 2001;27:1288–96. https://doi.org/10.1007/s001340101009.
[10] Hermans G, Wilmer A, Meersseman W, Milants I, Wouters PJ, Bobbaers H, et al. Impact of intensive insulin therapy on neuromuscular complications and ventilator dependency in the medical intensive care unit. Am J Respir Crit Care Med 2007;175: 480–9. https://doi.org/10.1164/rccm.200605-665OC.
[11] Levine S, Nguyen T, Taylor N, Friscia ME, Budak MT, Rothenberg P, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. N Engl J Med 2008; 358:1327–35. https://doi.org/10.1056/NEJMoa070447.
[12] Papazian L, Forel J-M, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010; 363:1107–16. https://doi.org/10.1056/NEJMoa1005372.
[13] Garnacho-Montero J, Amaya-Villar R, García-Garmendía JL, Madrazo-Osuna J, Ortiz-Leyba C. Effect of critical illness polyneuropathy on the withdrawal from mechanical ventilation and the length of stay in septic patients. Crit Care Med 2005;33:349–54. https://doi.org/10.1097/01.CCM.0000153521.41848.7E.
[14] De Jonghe B, Bastuji-Garin S, Durand M-C, Malissin I, Rodrigues P, Cerf C, et al. Respiratory weakness is associated with limb weakness and delayed weaning in critical illness. Crit Care Med 2007;35:2007–15. https://doi.org/10.1097/01.ccm.0000281450.01881.d8.
[15] Sidiras G, Gerovasili V, Patsaki I, Karatzanos E, Papadopoulos E, Markaki V, et al. Short and long term outcomes of icu acquired weakness. Health Sci J 2013;7: 188–200.
[16] Sharshar T, Bastuji-Garin S, Stevens RD, Durand M-C, Malissin I, Rodriguez P, et al. Presence and severity of intensive care unit-acquired paresis at time of awakening are associated with increased intensive care unit and hospital mortality. Crit Care Med 2009;37:3047–53. https://doi.org/10.1097/CCM.0b013e3181b027e9.
[17] Kaukonen K-M, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. JAMA 2014;311:1308–16. https://doi.org/10.1001/jama.2014.2637.
[18] Patsaki I, Gerovasili V, Sidiras G, Karatzanos E, Mitsiou G, Papadopoulos E, et al. Effect of neuromuscular stimulation and individualized rehabilitation on muscle strength in Intensive Care Unit survivors: a randomized trial. J Crit Care 2017;40:76–82. https://doi.org/10.1016/j.jcrc.2017.03.014.
[19] Fan E, Cheek F, Chlan L, Gosselink R, Hart N, Herridge MS, et al. An official American Thoracic Society Clinical Practice guideline: the diagnosis of intensive care unit-acquired weakness in adults. Am J Respir Crit Care Med 2014;190:1437–46. https://doi.org/10.1164/rccm.201411-2011ST.
[20] Hough CL, Lieu BK, Caldwell ES. Manual muscle strength testing of critically ill patients: feasibility and interobserver agreement. Crit Care Lond Engl 2011;15:R43. https://doi.org/10.1186/cc10005.
[21] Fan E, Ciesla ND, Truong AD, Bhoopathi V, Zeger SL, Needham DM. Inter-rater reliability of manual muscle strength testing in ICU survivors and simulated patients. Intensive Care Med 2010;36:1038–43. https://doi.org/10.1007/s00134-010-1796-6.
[22] Latronico N, Gosselink R. A guided approach to diagnose severe muscle weakness in the intensive care unit. Rev Bras Ter Intensiva 2015;27:199–201. https://doi.org/10.5935/0103-507X.20150036.
[23] De Jonghe B, Sharshar T, Lefaucheur J-P, Authier F-J, Durand-Zaleski I, Boussarsar M, et al. Paresis acquired in the intensive care unit: a prospective multicenter study. JAMA 2002;288:2859–67. https://doi.org/10.1001/jama.288.22.2859.

[24] Hermans G, Clerckx B, Vanhullebusch T, Segers J, Vanpee G, Robbeets C, et al. Interobserver agreement of Medical Research Council sum-score and handgrip strength in the intensive care unit. Muscle Nerve 2012;45:18–25. https://doi.org/10.1002/mus.22219.
[25] Karatzanos E, Gerovasili V, Zervakis D, Tripodaki E-S, Apostolou K, Vasileiadis I, et al. Electrical muscle stimulation: an effective form of exercise and early mobilization to preserve muscle strength in critically ill patients. Crit Care Res Pract 2012; 2012:432752. https://doi.org/10.1155/2012/432752.
[26] Ali NA, O'Brien JM, Hoffmann SP, Phillips G, Garland A, Finley JCW, et al. Acquired weakness, handgrip strength, and mortality in critically ill patients. Am J Respir Crit Care Med 2008;178:261–8. https://doi.org/10.1164/rccm.200712-1829OC.
[27] Vanpee G, Segers J, Van Mechelen H, Wouters P, Van den Berghe G, Hermans G, et al. The interobserver agreement of handheld dynamometry for muscle strength assessment in critically ill patients. Crit Care Med 2011;39:1929–34. https://doi.org/10.1097/CCM.0b013e31821f050b.
[28] Scott V, Votova K, Scanlan A, Close J. Multifactorial and functional mobility assessment tools for fall risk among older adults in community, home-support, long-term and acute care settings. Age Ageing 2007;36:130–9. https://doi.org/10.1093/ageing/afl165.
[29] Masedo AI, Hanley M, Jensen MP, Ehde D, Cardenas DD. Reliability and validity of a self-report FIM (FIM-SR) in persons with amputation or spinal cord injury and chronic pain. Am J Phys Med Rehabil 2005;84:167–76 quiz 177–9, 198.
[30] Pappa E, Kontodimopoulos N, Niakas D. Validating and norming of the Greek SF-36 Health Survey. Qual Life Res Int J Qual Life Asp Treat Care Rehabil 2005;14:1433–8. https://doi.org/10.1007/s11136-004-6014-y.
[31] de Sèze M, Petit H, Wiart L, Cardinaud JP, Gaujard E, Joseph PA, et al. Critical illness polyneuropathy. A 2-year follow-up study in 19 severe cases. Eur Neurol 2000;43: 61–9. https://doi.org/10.1159/000008137.
[32] Needham DM, Wozniak AW, Hough CL, Morris PE, Dinglas VD, Jackson JC, et al. Risk factors for physical impairment after acute lung injury in a national, multicenter study. Am J Respir Crit Care Med 2014;189:1214–24. https://doi.org/10.1164/rccm.201401-0158OC.
[33] Vidalis A, Syngelakis M, Papathanasiou M, Whalley D, Mc Kenna S. The Greek version of the Nottingham Health Profile: features of its adaptation. Hippokratia 2002;1: 79–82.
[34] Schlüssel MM, dos Anjos LA, de Vasconcellos MTL, Kac G. Reference values of handgrip dynamometry of healthy adults: a population-based study. Clin Nutr Edinb Scotl 2008;27:601–7. https://doi.org/10.1016/j.clnu.2008.04.004.
[35] Fan E, Dowdy DW, Colantuoni E, Mendez-Tellez PA, Sevransky JE, Shanholtz C, et al. Physical complications in acute lung injury survivors: a two-year longitudinal prospective study. Crit Care Med 2014;42:849–59. https://doi.org/10.1097/CCM.0000000000000040.
[36] Wieske L, Dettling-Ihnenfeldt DS, Verhamme C, Nollet F, van Schaik IN, Schultz MJ, et al. Impact of ICU-acquired weakness on post-ICU physical functioning: a follow-up study. Crit Care Lond Engl 2015;19:196. https://doi.org/10.1186/s13054-015-0937-2.
[37] Thomas S, Mehrholz J. Health-related quality of life, participation, and physical and cognitive function of patients with intensive care unit-acquired muscle weakness 1 year after rehabilitation in Germany: the GymNAST cohort study. BMJ Open 2018;8:e020163. https://doi.org/10.1136/bmjopen-2017-020163.
[38] Mehrholz J, Mückel S, Oehmichen F, Pohl M. First results about recovery of walking function in patients with intensive care unit-acquired muscle weakness from the General Weakness Syndrome Therapy (GymNAST) cohort study. BMJ Open 2015; 5:e008828. https://doi.org/10.1136/bmjopen-2015-008828.
[39] Scholten AC, Haagsma JA, Steyerberg EW, van Beeck EF, Polinder S. Assessment of pre-injury health-related quality of life: a systematic review. Popul Health Metr 2017;15:10. https://doi.org/10.1186/s12963-017-0127-3.
[40] Busico M, Intile D, Sívori M, Irastorza N, Alvarez AL, Quintana J, et al. Risk factors for worsened quality of life in patients on mechanical ventilation. A prospective multicenter study. Med Intensiva 2016;40:422–30. https://doi.org/10.1016/j.medin.2016.01.002.
[41] Batt J, dos Santos CC, Cameron JI, Herridge MS. Intensive care unit-acquired weakness: clinical phenotypes and molecular mechanisms. Am J Respir Crit Care Med 2013;187:238–46. https://doi.org/10.1164/rccm.201205-0954SO.
[42] Koch S, Wollersheim T, Bierbrauer J, Haas K, Mörgeli R, Deja M, et al. Long-term recovery in critical illness myopathy is complete, contrary to polyneuropathy. Muscle Nerve 2014;50:431–6. https://doi.org/10.1002/mus.24175.
[43] Koch S, Spuler S, Deja M, Bierbrauer J, Dimroth A, Behse F, et al. Critical illness myopathy is frequent: accompanying neuropathy protracts ICU discharge. J Neurol Neurosurg Psychiatry 2011;82:287–93. https://doi.org/10.1136/jnnp.2009.192997.
[44] Dettling-Ihnenfeldt DS, Wieske L, Horn J, Nollet F, van der Schaaf M. Functional recovery in patients with and without intensive care unit-acquired weakness. Am J Phys Med Rehabil 2017;96:236–42. https://doi.org/10.1097/PHM.0000000000000586.
[45] Hermans G, Van Mechelen H, Clerckx B, Vanhullebusch T, Mesotten D, Wilmer A, et al. Acute outcomes and 1-year mortality of intensive care unit-acquired weakness. A cohort study and propensity-matched analysis. Am J Respir Crit Care Med 2014; 190:410–20. https://doi.org/10.1164/rccm.201312-2257OC.
[46] Fletcher SN, Kennedy DD, Ghosh IR, Misra VP, Kiff K, Coakley JH, et al. Persistent neuromuscular and neurophysiologic abnormalities in long-term survivors of prolonged critical illness. Crit Care Med 2003;31:1012–6. https://doi.org/10.1097/01.CCM.0000053651.38421.D9.
[47] Kortebein P, Ferrando A, Lombeida J, Wolfe R, Evans WJ. Effect of 10 days of bed rest on skeletal muscle in healthy older adults. JAMA 2007;297:1772–4. https://doi.org/10.1001/jama.297.16.1772-b.
[48] Stäuble CG, Helming M, Martyn JAJ, Blobner M, Fink H. Neuromuscular recovery is prolonged after immobilization or superimposition of inflammation with immobilization compared to inflammation alone: data from a preclinical model. Crit Care Med 2016;44:e1097–110. https://doi.org/10.1097/CCM.0000000000001845.
[49] Parry SM, Puthucheary ZA. The impact of extended bed rest on the musculoskeletal system in the critical care environment. Extreme Physiol Med 2015;4. https://doi.org/10.1186/s13728-015-0036-7.
[50] Puthucheary Z, Montgomery H, Moxham J, Harridge S, Hart N. Structure to function: muscle failure in critically ill patients. J Physiol 2010;588:4641–8. https://doi.org/10.1113/jphysiol.2010.197632.
[51] Gandotra S, Lovato J, Case D, Bakhru RN, Gibbs K, Berry M, et al. Physical function trajectories in survivors of acute respiratory failure. Ann Am Thorac Soc 2019;16: 471–7. https://doi.org/10.1513/AnnalsATS.201806-375OC.
[52] Eachempati SR, Hydo L, Barie PS. Gender-based differences in outcome in patients with sepsis. Arch Surg Chic Ill 1960 1999;134:1342–7.
[53] Mahmood K, Eldeirawi K, Wahidi MM. Association of gender with outcomes in critically ill patients. Crit Care Lond Engl 2012;16:R92. https://doi.org/10.1186/cc11355.
[54] Intiso D, Amoruso L, Zarrelli M, Pazienza L, Basciani M, Grimaldi G, et al. Long-term functional outcome and health status of patients with critical illness polyneuromyopathy. Acta Neurol Scand 2011;123:211–9. https://doi.org/10.1111/j.1600-0404.2010.01414.x.