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ORIGINAL COMMUNICATION

Long-term neuromuscular sequelae of critical illness

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Abstract In this observational study, we analyzed the long-term neuromuscular deficits of survivors of critical illness. Intensive care unit-acquired muscular weakness (ICU-AW) is a very common complication of critical illness. Critical illness polyneuropathy (CIP) and critical illness myopathy (CIM) are two main contributors to ICU-AW. ICU-AW is associated with an increased mortality and leads to rehabilitation problems. However, the long-term outcome of ICU-AW and factors influencing it are not well known. We analyzed the medical records of 490 survivors of critical illness, aged 18–75 years and located in the area of the study center. Intensive care unit (ICU) survivors with comorbidities that might influence neuromuscular follow-up examinations, muscle strength, or results of nerve conduction studies, such as renal or hepatic insufficiency, diabetes mellitus, or vitamin deficiency were excluded. A total of 51 patients were finally included in the study. Six to 24 months after discharge from the ICU, we measured the Medical Research Council (MRC) sum score, the Overall Disability Sum score (ODSS), and also performed nerve conduction studies and EMG. For all ICU survivors, the median MRC sum score was 60 (range 47–60) and the median ODSS score was 0 (range 0–8). CIP was diagnosed in 21 patients (41 %). No patient was diagnosed with CIM. Patients with diagnosis of CIP showed a higher median ODSS scores 1 (range 0–8) versus 0 (range 0–5); $p < 0.001$ and lower median MRC sum scores 56 (range 47–60) versus 60 (range 58–60); $p < 0.001$. The three main outcome variables MRC sum score, ODSS score and diagnosis of CIP were not related to age, gender, or diagnosis of sepsis. The MRC sum score ($r = -0.33$; $p = 0.02$) and the ODSS score ($r = 0.31$; $p = 0.029$) were correlated with the APACHE score. There was a trend for an increased APACHE score in patients with diagnosis of CIP 19 (range 6–33) versus 16.5 (range 6–28); $p = 0.065$. Patients with the diagnosis of CIP had more days of ICU treatment 11 days (range 2–74) versus 4 days (range 1–61); $p = 0.015$, and had more days of ventilator support 8 days (range 1–59) versus 2 days (range 1–46); $p = 0.006$. The MRC sum score and the ODSS score were correlated with the days of ICU treatment and with the days of ventilator support. The neuromuscular long-term consequences of critical illness were not severe in our study population. As patients with concomitant diseases and old patients were excluded from this study the result of an overall favorable prognosis of ICU-acquired weakness may not be true for other patient's case-mix. Risk factors for the development of long-term critical illness neuropathy are duration of ICU treatment, duration of ventilator support, and a high APACHE score, but not diagnosis of sepsis. Although ICU-AW can be serious complication of ICU treatment, this should not influence therapeutic decisions, given its favorable long-term prognosis, at least in relatively young patients with no concomitant diseases.

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Introduction

Intensive care unit-acquired muscular weakness (ICU-AW), as the consequence of critical illness polyneuropathy (CIP) or critical illness myopathy (CIM), is recognized as a common cause of muscular weakness, occurring in at least 50 % of critical ill patients [12]. In the majority of patients, a combination of both CIP and CIM is diagnosed [12]. Depending on the patient population, a prevalence of ICU-AW of up to 100 % of critical ill patients is described, with sepsis or systemic inflammatory response syndrome (SIRS) as one of the most important risk factors [1–3, 15, 21]. ICU-AW is a common cause of failure of weaning from ventilation, and substantially contributes to mortality and rehabilitation problems [3, 6, 17].

As important as the cause and frequency of muscular weakness during and immediately after the intensive care unit (ICU) treatment is the association with adverse long-term outcomes. In a systematic review about the long-term outcome of ICU-AW, 28 % of patients had severe disability (quadriparesis/paraparesis), with a mean duration of follow-up for 3–6 months [16], and even in patients with functional recovery varying degrees of electrophysiological abnormalities after a median of 43 months have been observed [5]. However, often these studies include only a limited number of patients or investigate within a limited follow-up period.

In this observational study, we describe the neuromuscular long-term consequences of critical illness in a group of 51 survivors of critical illness, 6–24 months after discharge from the ICU.

Methods

Patient selection

Medical records of ICU survivors treated in one of the ICU at the University of Bonn or of the Helios Clinic in Siegburg, Germany, between January 2004 and August 2006, aged between 18 and 75 years, and lived in the area (= not more than 50 km away from the hospital) were examined ($n = 490$). Those who met the inclusion/exclusion criteria given below were contacted by mailed letter and invited to participate in the study.

Main inclusion criterion comprised history of ICU treatment due to sepsis or systemic inflammatory response syndrome (SIRS) according to the diagnostic criteria defined by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference [18], acute respiratory distress syndrome, polytrauma, cardiac arrhythmia, or coronary heart disease. There was no pre-specified minimum duration of ICU stay or mechanical ventilation. We excluded patients with cancer and patients with cerebral or spinal lesions such as head or spinal trauma or stroke because we wanted to avoid confounders of neuromuscular performance that are not directly linked with the ICU treatment. We further excluded patients with pre-existing neuromuscular dysfunction, or diseases that might influence neuromuscular function, muscle strength or results of nerve conduction studies, such as renal or hepatic insufficiency, diabetes mellitus, vitamin deficiency, or alcohol abuse. No patient included in this study was treated with steroids other than hydrocortisone in some cases of adrenal insufficiency. No patient was treated with neuromuscular blocking agents during ICU treatment. Medical data collected during ICU treatment included diagnosis, length of ICU stay, APACHE II scores, cardiovascular data, and duration of ventilation support.

The ICU treatment of all patients was carried out according to standard clinical procedures. All patients gave a self-report of considerable muscular weakness at the time of ICU and hospital discharge. Muscular disability at ICU discharge ranged from the inability to walk >100 m without a rest to being completely bedridden. All ICU patients were discharged to a rehabilitation clinic. The length of the rehabilitation program was determined by the rehabilitation clinic. No patient received an inpatient rehabilitation program at the time of the follow-up examination. Four (=8 %) received ambulatory physiotherapy.

Study design

This study was carried out within a time period of 6–24 months after discharge from the ICU. All patients underwent diagnostic laboratory tests to exclude laboratory anomalies that could potentially influence study results. Laboratory tests performed were blood cell count, liver enzymes [serum aspartate (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT)], creatinine levels, blood coagulation parameters (PTT, INR), vitamin B12 and folic acid levels, c-reactive protein, creatine kinase, electrolytes, immunofixation, thyroid function (TSH levels, additional free T3 and T4 levels if TSH levels were abnormal), HbA1c, and hepatitis B, C, and HIV antigen levels). AST, ALT, and GGT were considered abnormal if they showed an increase of more than twofold of the standard value. For all other laboratory tests, the normal standard values were used. Patients with laboratory abnormalities were excluded from the study. We excluded patients who had renal or hepatic insufficiency before or

after their ICU stay. Patients who developed renal or hepatic insufficiency only during their ICU stay were not excluded.

Outcome measures included a neurological examination and nerve conductions studies. Neurological examination was carried out by a neurologist. Clinical findings were graded with the Medical Research Council (MRC) sum score and the Overall Disability Sum score (ODSS). The MRC sum score is a summation of MRC grades (range 0–5) given in full numbers of the following muscle pairs: upper arm abductor, elbow flexors, wrist extensors, hip flexors, knee extensors, and foot dorsal flexors. The MRC sum score ranges from 0 (complete plegia) to 60 (normal muscle strength in all examined muscles). Good validity and interobserver reliability for the MRC sum score has been demonstrated in patients with Guillain–Barré syndrome [13]. The ODSS is composed of an arm and leg disability scale with a total score ranging from 0 (no signs) to 12 (severe disability). The ODSS gives a description of arm and leg function in daily activities in a checklist form, such as dressing, doing and undoing buttons, or walking. The ODSS has shown good validity and reliability in immune mediated polyneuropathies [19].

Nerve conduction studies were carried out by one experienced neurophysiologist using a Nicolet system (Viasis Healthcare, Nicvue 2.6.8) and record techniques according to the American Association of Electrodiagnostic Medicine. Motor studies were performed in the median, ulnar, common peroneal, and tibial nerves (one each). Sensory action potentials were recorded from the median, ulnar, and sural nerve (one each). For motor nerve conduction studies, the active electrode was placed over the muscle belly and the reference over an electrically inactive site (usually bony prominence). A ground electrode was placed between the stimulating and recording electrodes. The filter settings were a low-pass filter 30 Hz and a high-pass filter of 100 kHz. Median nerve: recorded from abductor pollicis brevis muscle, distal stimulation at the wrist, proximal stimulation below the elbow in the antecubital fossa. Ulnar nerve: recorded from the abductor digiti minimi muscle, distal stimulation at the wrist, proximal stimulation below and above the elbow near the sulcus ulnaris. Tibial nerve: recorded from the abductor hallucis muscle, distal stimulation posterior to the medial malleolus, proximal stimulation in the popliteal fossa. Peroneal nerve: recorded from the extensor digitorum brevis muscle, distal stimulation at the ankle, proximal stimulation distal and proximal of the fibula head. For sensory nerve conduction studies, the sensory nerve action potential (SNAP) was recorded orthodromically. Filter settings were 10-Hz low-pass filter and 10-kHz high-pass filter. Median and ulnar nerve: stimulation with ring electrodes on the index finger or fifth finger, recording with surface electrodes over the nerve below the wrist. Sural nerve: stimulation posterior of the lateral malleolus, recording from distal of the ending of the gastrocnemius muscle at the junction of the middle and lower third of the leg. When a co-existence of CIP and CIM could not be reliably excluded after clinical examination and nerve conduction studies ($n = 5$), an additional EMG was performed with a standard concentric needle electrode inserted in the muscle that showed the most severe weakness (Tibialis anterior muscle, Vastus lateralis muscle).

The parameters included in the motor nerve conduction studies were distal latency, conduction velocity, distal compound muscle action potential (CMAP) amplitude, conduction block (<30 % drop in proximal CMAP to distal), and minimal F-wave latency. In sensory nerve conduction, nerve conduction velocity and sensory nerve action potential (SNAP) amplitude were measured. For defining abnormality, our age-adjusted laboratory control values were used. Limbs were warmed with heat packs if necessary. EMG was analyzed for spontaneous activity at complete rest and motor unit action potential (MUAP) waveform during minimal voluntary contraction.

Criteria for the diagnosis of CIP were (1) the presence of clinical signs typical for distal symmetric polyneuropathy such as symmetric weakness and/or atrophy of muscles most prominent distally and in the legs, and absent or diminished deep tendon reflexes most prominent in the ankle reflexes, and symmetric impaired sensation most prominent distally and in the legs; (2) Nerve conduction studies showed signs typical for distal symmetric polyneuropathy; minimum criterion was an abnormality in two separate nerves, one of which must be the sural nerve or in three different nerves [4].

Criteria for CIM were (1) the presence of clinical signs typical for myopathy such as symmetric, maximal proximally weakness and/or atrophy of muscles and no impaired sensation; (2) Nerve conduction studies suggestive of myopathy, which is reduced CMAPs, normal or only minimally reduced motor nerve conduction velocity, no abnormalities in sensory nerve conduction studies; (3) EMG with reduced length and amplitude of motor unit action potential (MUAP) waveform during minimal voluntary contraction.

Data and scores are presented as median (range) and were compared between groups using the Mann–Whitney test. Spearman rank analysis was used to calculate correlations of age, days of ICU stay, days with ventilator support, and APACHE II scores with the outcome variables MRC sum scale and ODSS score as a dependent variable. Binary variables (gender, diagnosis of sepsis, and diagnosis of CIP/CIM) were compared using Fisher's exact test. To further analyze whether duration of ventilator support is a risk factor independent from the diagnosis of sepsis, we

performed a multiple logistic regression with diagnosis of CIP as a dependent variable and duration of ventilator support and diagnosis of sepsis as independent variables. Because of its skew distribution, duration of ventilator support was log-transformed for this analysis. The program IBM SPSS Statistics version 19 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Two-tailed p values <0.05 are considered statistically significant. All patients gave written informed consent to the study. The study was approved by the local ethical committee.

Results

For this study, the medical records of 490 survivors of critical illness were analyzed and 102 patients were excluded because they did not meet the exclusion/inclusion criteria. Of these 102 patients, 27 were excluded due to a neurologic disease that could possibly impair neuromuscular function including head and spinal trauma, stroke, and pre-existing polyneuropathy. Eleven were excluded due to a diagnosis of cancer, 29 because they were diagnosed with diabetes, 15 due to a diagnosis of renal impairment, 13 due to diagnosis of alcohol abuse, and 7 were diagnosed with chronic viral infection (hepatitis B/C, HIV).

The remaining 388 ICU survivors were invited to participate in the study. There were 327 ICU survivors that did not answer the invitation or refused to participate, so that 61 survivors (response rate 15.7 %) came to the hospital for the follow-up examination. Ten were excluded because of laboratory abnormalities or because they refused to participate in nerve conduction studies, and in the end, 51 ICU survivors could be included in the study (Fig. 1).

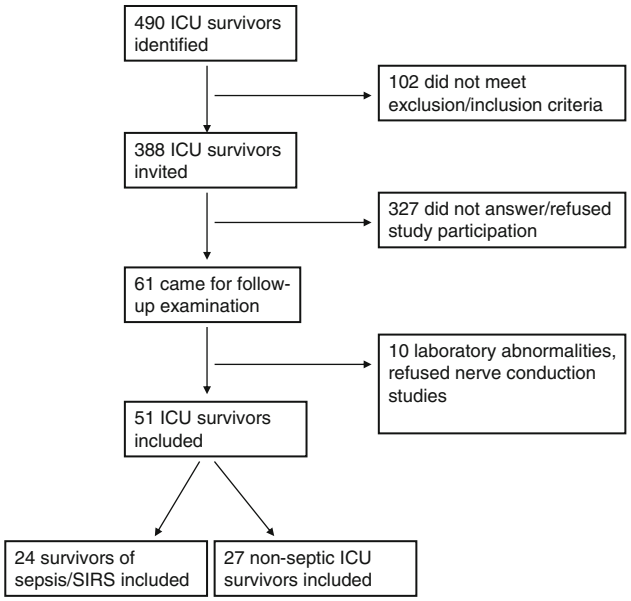

Fig. 1 Summary of patient recruitment

Demographic and clinical characteristics

All data are presented as median (range). The median time from intensive care unit discharge to follow-up was 11 months (range 6–24). The median age of the patients was 57 years (range 19–75) (female 47 %). Twenty-four patients (47 %) were diagnosed with severe sepsis or septic shock during ICU treatment. Seven (14 %) had coronary artery bypass surgery because of coronary artery heart disease or cardiac arrhythmia, six (12 %) were diagnosed with acute respiratory distress syndrome, 14 (27 %) were trauma patients. Median length of ICU treatment was 5 days (range 1–74). Median length of ventilator support was 3 days (range 1–59), median APACHE II score was 17 (range 3–33). Sepsis survivors did not differ from non-septic ICU survivors in age or gender. Sepsis survivors stayed longer on the ICU (13 days (range 3–74) versus 3 days (range 1–12); $p < 0.001$, showed a higher APACHE II Score of 20 (range 8–33) versus 14.5 (range 6–22); $p < 0.001$, and more days with ventilator support 10.5 (range 1–59) versus 1 (range 1–9); $p < 0.001$.

Neuromuscular scores and results of nerve conduction studies

For all ICU survivors, the MRC sum score was 60 (range 47–60) and the ODSS score was 0 (range 0–8). CIP was diagnosed in 21 patients (41 %). Please see Table 1 for details of nerve conduction studies. Patients with diagnosis of CIP showed a higher ODSS scores 1 (range 0–8) versus 0 (range 0–5); $p < 0.001$ and lower MRC sum scores 56 (range 47–60) versus 60 (range 58–60); $p < 0.001$. All patients with an MRC score <58 were diagnosed with CIP. All patients diagnosed with CIP had abnormalities in motor and sensory nerve conduction. No patient had reduced CMAPs as the exclusive abnormality in nerve conduction, indicative of myopathy (= CIM). If the co-existence of CIP and CIM could not be excluded on the basis of the clinical examination and nerve conduction studies, we additionally performed EMG ($n = 5$). All EMGs showed neurogenic changes. Therefore, no patient was diagnosed with CIM or co-existing CIM/CIP.

The three main outcome variables (MRC sum score, ODSS score, and diagnosis of CIP) were not related to age, gender, diagnosis of sepsis, or time from ICU discharge to follow-up. The MRC sum score and the ODSS score was correlated with the APACHE score. There was a trend for an increased APACHE score in patients with diagnosis of CIP 19 (range 6–33) versus 16.5 (range 6–28); $p = 0.065$. Patients with the diagnosis of CIP had more days of ICU treatment 11 days (range 2–74) versus 4 days (range

Table 1 Percentages for a normal/abnormal/unrecordable result of nerve conduction studies for all patients ($n = 51$) and every nerve examined

DL distal latency, *CMAP* compound muscle action potential, *SNAP* sensory nerve action potential, *CV* conduction velocity

Nerve	DL	CMAP/SNAP	CV	F-wave latency
Median (motor)	82/16/2	88/10/2	84/14/2	80/18/2
Median (sensory)	–	84/16/0	77/23/0	–
Ulnar (motor)	92/2/0	90/10/0	94/6/0	–
Ulnar (sensory)	–	80/18/2	82/16/2	–
Peroneal	84/10/6	53/41/6	67/27/6	–
Tibial	98/2/0	80/18/2	75/23/2	84/16/0
Sural	–	47/45/8	55/37/8	–

Table 2 Correlation of the three outcome variables of MRC sum score, ODSS score, diagnosis of critical illness polyneuropathy (= CIP) with the independent variables age of the patient, time from ICU discharge to follow-up, APACHE score, days of treatment on ICU, and days of ventilator support

	MRC sum score	ODSS	CIP
Gender (male)	$p = 0.07$	$p = 0.22$	$p = 0.43$
Age (years)	$r = -0.04$; $p = 0.80$	$r = 0.03$; $p = 0.84$	$p = 0.43$
ICU discharge (months)	$r = -0.41$; $p = 0.77$	$r = 0.76$; $p = 0.60$	$p = 0.08$
Sepsis	$p = 0.87$	$p = 0.32$	$p = 0.52$
APACHE II score	$r = -0.33$; $p = 0.021$	$r = 0.31$; $p = 0.029$	$p = 0.065$
ICU treatment (days)	$r = -0.27$; $p = 0.053$	$r = 0.39$; $p = 0.004$	$p = 0.015$
Ventilator support (days)	$r = -0.33$; $p = 0.017$	$r = 0.47$; $p < 0.001$	$p = 0.006$

The Spearman rank correlation coefficient (r) and the corresponding p levels are shown. In case of binary variables (gender, diagnosis of sepsis, diagnosis of critical illness polyneuropathy (= CIP)), the Mann–Whitney test was applied. Direct comparison of two binary variables was done with Fisher's exact test

1–61); $p = 0.015$, and had more days of ventilator support 8 days (range 1–59) versus 2 days (range 1–46); $p = 0.006$. The MRC sum score and the ODSS score were correlated with the days of ICU treatment and with the days of ventilator support (Table 2).

As mentioned above, the diagnosis of sepsis is associated with a longer duration of ventilator support. Logistic regression with the diagnosis of CIP as a dependent variable and duration of ventilator support (log-transformed) and the diagnosis of sepsis as independent variables showed that duration of ventilator support is an independent risk factor for diagnosis of CIP (OR 2.3, 95 % CI 1.3–4.2, $p = 0.004$ with each doubling of the duration of ventilator support), while sepsis is no independent risk factor ($p = 0.10$) as it was in the univariate analysis.

Discussion

In our study population, the neuromuscular long-term consequences of critical illness were not severe, suggesting a favorable prognosis of ICU-acquired muscular weakness. Other authors described a less favorable outcome with around 10–25 % of ICU survivors suffering from sustained and severe neuromuscular disability ranging from reduced 6-min walking distance up to tetraplegia [8–10, 14]. The difference between these studies and the current one might be explained by patient selection. For this study, patients with diseases that might influence neuromuscular function were carefully excluded. Also, the average age of 56 years in the study population was relatively low, and speculatively, elderly ICU survivors experience more long-term neuromuscular deficits. Another reason for the good neuromuscular outcome may be the minimal use of neuromuscular blocking agents and steroids in our study population, as this has been described to be a risk factor for CIM and CIP by several authors [14]. In addition to this, early rehabilitation in the ICU or immediately thereafter improves the functional recovery and independence [14] and this has been applied in all our patients. It is possible that there was some selection bias in that patients who saw themselves as unable to return to the hospital for the follow-up examination may have been more severely disabled than those who agreed to participate. Unfortunately, we do not have any means to estimate the degree of this potential selection bias. Therefore, the conclusion of a favorable outcome of ICU-acquired weakness might only apply to healthy and younger ICU survivors, and may not be true for other patients' case-mix. On the other hand, this study shows that under optimal conditions (complete resolution of the underlying disease, no relevant concomitant

diseases, relatively young age, and rehabilitation), the long-term prognosis of ICU-acquired weakness is favorable.

CIP could be diagnosed in 41 % of patients. It is very unlikely that the clinical signs and symptoms and the abnormalities in the nerve conduction found in these patients were attributable to other causes than CIP, as only selected patients with normal laboratory results were included in the study. The abnormalities in nerve conduction studies were moderate and were not accompanied by a disabling reduction of arm and leg function as expressed in a low ODSS score in those patients diagnosed with CIP. The ODSS score for all ICU survivors including those without nerve conduction abnormalities was very low indicating minor symptoms in the arms or in walking without affection of daily activities.

Accordingly, the median MRC sum score of 60 in all ICU survivors suggests that a thorough neurological examination could reveal minimal muscular weakness in the majority of patients. Twenty-nine of 51 patients (57 %) showed no muscular weakness at all (MRC sum score of 60). MRC sum scores were lower in patients diagnosed with CIP, while patients without CIP showed no muscle weakness.

Differentiating CIP from CIM can be difficult clinically during ICU treatment and often both syndromes occur at the same time causing ICU-acquired muscular weakness. Nerve conduction studies can be helpful to differentiate CIP from CIM. Especially the depression or absence of sensible nerve action potentials (SNAP) amplitudes is a strong indicator of CIP, since SNAPs are normal in pure myopathic disease. All patients diagnosed with CIP had abnormalities in sensory nerve conduction studies. When the presence of additional CIM could not be excluded on basis of clinical examination and nerve conduction studies, we performed EMG that showed neurogenic changes in all examined muscles. This means that in our study sample, there was no patient with muscular weakness that was only or mainly attributable to CIM, indicating that CIM has a more favorable prognosis than CIP. This is well in line with previous reports, where CIP was the main diagnosis associated with persistent disability, while CIM is often associated with a more rapid and complete recovery [8, 16].

Prospective trials have shown that the development of ICU-acquired muscular weakness is associated with the severity of illness as measured by severity of illness scores, the presence of sepsis or SIRS, duration of ICU stay, and the duration of mechanical ventilation [7, 11]. In part, this is also the case for the long-term outcome of ICU-acquired muscular weakness. MRC score, ODSS score, and diagnosis of CIP are correlated with the risk factors APACHE Score, duration of ICU treatment, and duration of ventilator support. It is surprising, however, that the diagnosis of sepsis, which is a very important risk factor for the development of ICU-acquired muscular weakness during ICU stay, does not impair the long-term neuromuscular outcome of ICU survivors. Although sepsis leads to an extension of ICU treatment and duration of ventilator support, the diagnosis of sepsis does not constitute an additional independent risk factor.

The most important predictor of long-term neuromuscular outcome was the duration of ventilator support. Speculatively, the duration of neuromuscular inactivity induced by the analgo-sedation necessary for ventilator support is important for this correlation, but inactivation was reported to lead to loss of muscle bulk and not development of neuropathy [20]. Therefore, the underlying disease that led to a long duration of ventilator support and muscular inactivation may be more important in your study population than prolonged bed rest itself. Age and gender do not predict the long-term neuromuscular outcome of critical illness.

Taken together, this study indicates that the long-term prevalence and severity of ICU-AW is slight 6–24 months after ICU treatment in relatively young patients with no concomitant diseases. Even patients in the highest quartile of duration of ventilator support still show an acceptable outcome (mean MRC score 56.93 and mean ODSS score of 2.14). Although ICU-acquired muscular weakness is a serious complication of ICU treatment, this should not influence therapeutic decisions, given its possible favorable long-term prognosis even in the presence of risk factors such as high APACHE score, long duration of ICU treatment, or long duration of ventilator support and patients and their relatives should be advised accordingly.

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Conflicts of interest The authors declare that they have no competing interests.

Ethical standards The authors hereby declare that the research documented in the submitted manuscript have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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