Intensive Care Med (2015) 41:1433–1444
DOI 10.1007/s00134-015-3914-y

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Physical activity, muscle strength, and exercise capacity 3 months after severe sepsis and septic shock

Received: 10 February 2015
Accepted: 8 June 2015
Published online: 25 June 2015

Take-home message: The patients surviving severe sepsis and septic shock showed a reduction in physical activity of daily life in the medium term in comparison with the general population. In addition, factors such as the use of corticosteroids and length of hospital stay seem to negatively influence muscle strength and exercise capacity in these patients.

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Abstract *Purpose:* To quantify the physical activity in daily life (PADL), muscle strength, and exercise capacity in the short and medium term in survivors of severe sepsis and septic shock. *Methods:* Prospective cohort study with a follow-up from hospital admission to 3 months after hospital discharge. Seventy-two patients admitted to the ICU for severe sepsis or septic shock and a control group of healthy sedentary subjects ($n = 50$) were enrolled. All patients had their PADL quantified by an accelerometer during their hospital stay and 3 months after. Exercise capacity and handgrip and quadriceps muscle strength were also evaluated. *Results:* During hospitalization, patients spent the majority of their time inactive in a lying or sitting position (90 ± 34 % of daily time). Physical inactivity was partially reduced 3 months after (58 ± 20 % of daily time). However, the time patients spent walking was only 63 % of the time reported for healthy subjects. Patients also showed lower movement intensity when compared with controls (2.1 ± 0.3 vs 2.5 ± 0.4 m/s^2). At hospital discharge, muscle strength and exercise capacity were approximately 54 % of the predicted value, and these parameters showed significant increase in patients 3 months after (70 % of predicted value). Multivariable analysis demonstrated that the use of systemic corticosteroids and hospitalization time negatively influenced quadriceps strength and exercise capacity at the time of hospital discharge. *Conclusion:* Our results suggest that survivors of sepsis admitted to the ICU have a substantial reduction in physical activity, exercise capacity, and muscle strength compared to healthy subjects that persist even 3 months after hospital discharge.

Keywords Intensive care unit · Muscle weakness · Physical activity · Recovery of function · Sepsis · Survivors

Introduction

Sepsis is a clinical problem of great relevance within the intensive care unit (ICU) because of its high mortality rate and financial cost. In addition, survivors can suffer from severe dysfunction and symptoms, such as fatigue, dyspnea, muscle weakness, reduced physical capacity, and a decrease in health-related quality of life (HRQoL) [1–7].

The recovery from complications can take months or years for ICU survivors [6–9], and some studies have evaluated the risk factors associated with the development of morbidities, especially muscle weakness [10, 11]. De Jonghe et al. [11] found independent predictors of a poor prognosis related to muscle weakness, including gender, duration of mechanical ventilation, days of multiple system failure, and corticosteroid use. Although these factors are associated with muscle weakness in ICU survivors, sepsis continues to be the most important risk factor [12–14].

The aggressiveness of inflammation caused by sepsis can affect both muscle mass and force [15, 16]. These musculoskeletal complications may result in difficulty weaning [17] the patient from the ventilator during their ICU stay; furthermore, these problems can lead to an inability to perform physical activity in daily life (PADL) after hospital discharge. Although the association between muscle dysfunction and PADL has been demonstrated previously in patients with chronic obstructive lung disease [18, 19] and interstitial lung disease [20], to our knowledge, this link has not been investigated in sepsis survivors.

The reduction of PADL is associated with an increased mortality rate [21, 22] in the middle-aged and elderly population, which are the age groups most affected by sepsis [23]. Current data regarding the physical activity of ICU patients is based on subjective questionnaires of HRQoL. Although subjective methods are useful to evaluate a patient's functional status, this methodology presents limited validity and reliability [24, 25]. For instance, studies conducted in subjects with low back pain or patients with walking limitations suggest that subjective methods should be treated with caution because individuals overestimate their physical activity time when compared with electronic devices [26, 27]. Physical activity monitors have been shown to be reliable at evaluating different bodily positions (lying, sitting, and standing) and intensities of activity for long periods of time [28]. However, there is no information as to the PADL in sepsis survivors using this type of reliable device.

Therefore, the aim of this study was to quantify PADL, muscle strength (inspiratory muscles, handgrip, and quadriceps) and exercise capacity (6-min walking distance) in short- and medium-term survivors of severe sepsis and septic shock. These muscle groups and the exercise capacity were selected because they showed a reduction during ICU stays [4, 29, 30]. In addition, we investigated the variables collected during the study that could be associated with changes in muscle strength, exercise capacity, and PADL during hospitalization and 3 months after using a multivariable regression analysis.

Materials and methods

Study design and population

This prospective cohort study enrolled sepsis patients who were admitted to a general ICU for clinical and surgical patients at the University Hospital of the University of São Paulo from December 2008 to November 2010. The study included all consecutive patients referred to the ICU with severe sepsis or septic shock within 24 h of evolution in another unit, aged over 18 years old, of any race or gender, and able to walk without assistance before hospitalization. Furthermore, only patients who were able to perform at least two physical assessments at the time of hospital discharge and 3 months later were included.

The criteria for severe sepsis were defined according to international guidelines [31], i.e., when there was a suspicion of an infectious agent causing a systemic inflammatory response associated with hypotension (systolic blood pressure less than 90 mmHg or a 40 mmHg reduction from baseline pressure) and/or organ dysfunction. Septic shock was diagnosed when hypotension- and/or hypoperfusion-induced sepsis is refractory to fluid resuscitation and subsequently needs administration of vasopressor agents.

Patients were excluded if they had a previous or current history of stroke with physical limitations, neuromuscular disease, traumatic brain injury or subarachnoid hemorrhage, spinal cord injury, multiple traumas with fractured limbs or limb amputation, or any other disease that could affect the physical assessments. In addition, terminal patients or those with persistent coma and/or who were unable to perform at least two evaluations on the day of discharge were excluded. Finally, patients who did not attend the scheduled follow-up at 3 months after discharge were also excluded (Fig. 1). During the hospital stay, all patients received medical treatment and general care according to previously described guidelines [31]. The Hospital Research Ethics Committee (no. 796/08) approved the study and patients or their caregivers that agreed to participate provided written informed consent prior to study participation.

Rehabilitation procedures during hospitalization and after discharge

After admission to the ICU, patients received a physical therapy care protocol twice a day. In summary, if a patient was unable to perform active movements, 30 repetitions of passive movements in each upper and lower limb were performed. If a patient was able to perform partial active movements with their limbs, assisted (manual assistance) exercises were initiated in the supine position. If the

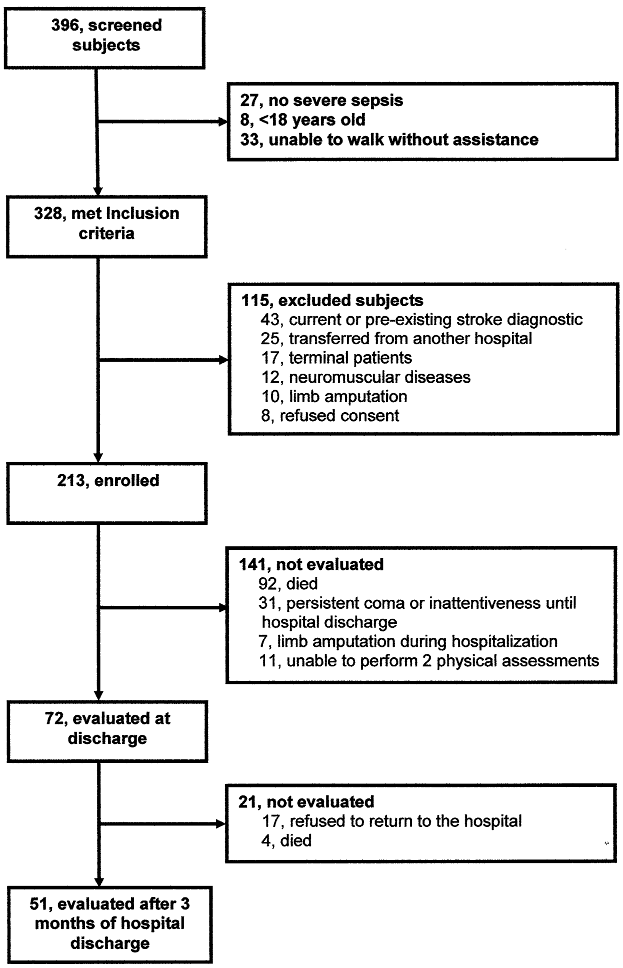

Fig. 1 CONSORT enrollment diagram. Patients diagnosed with stroke in the current hospitalization or previous stroke history with physical limitations were excluded. Patients with limb amputation during hospitalization were not evaluated

patient tolerated these exercises, they began participation in activities while sitting on their bedside or in a chair. If a patient was able to stand up, they began walking according to their maximal tolerance and acceptance. Physical therapy sessions were continued until hospital discharge; however, in the wards, sessions were performed once a day. Patients able to walk without assistance were dispensed from physical therapy care and advised to remain active and avoid staying in bed. After hospital discharge, patients were referred for medical consultations but not outpatient rehabilitation because of a lack of provider availability.

Data collection

Clinical and laboratory data were collected within 24 h of patient admission to the ICU, including Acute Physiology and Chronic Health Evaluation II (APACHE), Sepsis-related Organ Failure Assessment (SOFA), sites of suspected or documented infection, serum levels of C-reactive protein, total bilirubin and fractions, blood gas analysis and levels of creatinine, urea, sodium, potassium, lactate, blood count, and glucose. During the ICU stay, additional information was also collected, including time in the ICU, comorbidities, history of smoking and alcohol consumption, duration of mechanical ventilation, days of dialysis, number of blood transfusions, and the number of failed ventilator weaning trials. The total length of the hospital stay was recorded. Medications suspected of influencing physical capacity, such as midazolam, catecholamines, corticosteroids, and neuromuscular blockers, were recorded along with the total number of days of drug administration and the cumulative dose of the drug. The cumulative dose was calculated by multiplying the number of days on the drug by the daily dosage of the drug throughout the hospitalization period, without accounting for previous administrations or the time after hospitalization.

Outcomes

At the time of hospital discharge and 3 months later, the exercise capacity and muscle strength of patients were evaluated. The PADL was assessed during the 2 days prior to hospital discharge and 3 months later.

Physical activity in daily life

The patient's PADL was determined by monitoring movements with an accelerometer (Dynaport Minimod, McRoberts, Netherlands) that was developed and validated in patients with chronic obstructive pulmonary disease (COPD) [32] and other populations [33, 34]. This small (54 × 84 × 8.5 mm) and light (45 g) high-resolution triaxial sensor quantifies the time spent performing various activities, such as sitting, lying, standing, and walking, and changes in body position and energy expenditure. The equipment was inserted into an elastic band positioned on the lower back near the second lumbar vertebra. Measurements were performed in wards after ICU discharge for 12 h per day (from 8 a.m. to 8 p.m.) for two consecutive days prior to hospital discharge. Patients were instructed to maintain their regular PADL. Three months after discharge the patient's PADL was quantified at their home for 2 days, excluding the weekend days. Assessments followed previously used protocols and were performed only on weekdays to avoid biases, i.e., those caused by potential differences in physical activity levels between weekdays and weekend days [19]. If the day of the assessment fell on a weekend, it was rescheduled for the next weekday. It was previously demonstrated that a minimum of 2 days of assessments provides an acceptable intraclass reliability coefficient for monitoring PADL in other populations [35].

The obtained signals were recorded in the accelerometer and sent via the Internet to the manufacturer for further analysis. The mean values obtained during this 2-day period were compared with a control group ($n = 50$) of healthy sedentary subjects. To form the control group, the researchers involved in the study invited people who were visiting their families in hospital with the same sexes, ages (±6 years), and BMIs (±2 kg/m^2) as the septic patients to participate in the study. The control subjects completed a form with their demographic and personal characteristics. Subjects were instructed to report any current or past health problems. Only those without physical limitations and with no history of participation in recreational (frequency less than 3 times per week) or competitive sports activities were matched. Subjects in the control group were instructed to maintain their regular PADL while using the equipment to assess PADL. The control group started using PADL monitoring equipment the day after the hospital visit and only those who would not return to the hospital in the next 48 h were included. The same instructions supplied to septic patients on the use of the equipment in the home were given to healthy individuals.

Exercise capacity

In wards on the day of hospital discharge, exercise capacity was evaluated using the 6-min walking distance (6MWD) test as previously described [36]. Briefly, patients walked as far as possible down a 30-m, flat corridor with no traffic and were verbally encouraged every minute. Interruptions in walking were allowed when patients perceived intense dyspnea or discomfort. Cardiac and respiratory rates and oxygen saturation were monitored before and after the test. Two tests were performed with a 1-h interval between tests. The farthest distance walked during both tests was recorded. The values obtained were compared with previously described values [37].

Quadriceps muscle strength

Maximal isometric voluntary muscle strength was quantified using a digital dynamometer (EMG System, Brazil). Signals were acquired and processed using software (EMGLab V1.1, EMG System, Brazil). The maximal isometric force was established by asking the patient to sustain maximal force for 5 s while receiving verbal encouragement. The highest values with a difference of less than 10 % from three tests was used for analysis. Rest was allowed between each test, and patients performed one practice trial without resistance before the test to minimize the learning effect. Patient positioning was the same as that used by other authors [38]. Muscle strength was evaluated in the dominant limb of the patient and the values obtained were compared with previously described values [38].

Inspiratory muscle strength

The inspiratory muscle strength was defined by the maximal inspiratory pressure (MIP). To determine the MIP, the patient was asked to take a normal breath and insert the mouthpiece at the moment that he or she finished exhaling the tidal volume. Next, the patient made a maximal inspiratory effort lasting at least 2 s against a closed valve. The highest value for the MIP over three reproducible (less than 10 % difference) maneuvers was recorded. The procedure was performed according to the techniques described by Black and Hyatt [39] and patient data were compared with predicted values previously described [40].

Muscle strength of upper limbs

The strength of the upper limbs was estimated by the handgrip strength of the dominant hand with a dynamometer (T18; Takei, Tokyo, Japan). The strength was established by asking the patient to sustain maximal strength for 5 s while receiving verbal encouragement. The highest values with a difference of less than 10 % from three tests were used for analysis. We conducted handgrip measurements of patients in a seated position while performing an upper limb dominant elbow flexion to 90°, adduction of the shoulder, and maintaining the wrist in a neutral position. Prior to starting the test, the patients underwent two attempts of the task to reduce learning effects. The values obtained were compared with values previously described [41].

Statistical analysis

At first, the variables collected during the study that could affect muscle strength, exercise capacity, and PADL were selected a priori on the basis of the findings of other studies [10, 26] and our own observations and all of them are listed in "Data collection". Then, to evaluate associations between exercise capacity, muscle strength, and PADL and other quantitative variables collected during the study we used univariable regression. The *t* test and Mann–Whitney *U* test were used for the comparison of quantitative variables and the Chi-square test was used for the comparison of qualitative variables. Variables collected during the study with $p < 0.05$ in the univariable analysis, *t* test, or Mann–Whitney *U* were then considered in a backward multivariable linear regression analysis to identify the independent contributors to the decline in

Table 1 Clinical characteristics of patients admitted to the ICU with severe sepsis and septic shock

Outcome	Physical assessments performed ($n = 72$)	Physical assessments not performed ($n = 141$)	p value
Age, years	53.4 ± 17.6	61.2 ± 19.0	<0.01*
Sex, male, n (%)	36 (50)	77 (55)	0.56
Comorbidity			
Diabetes mellitus, n (%)	15 (20.8)	44 (31.2)	0.14
Chronic renal failure, n (%)	20 (27.8)	37 (26.2)	0.87
Alcohol abuse, n (%)	17 (23.7)	20 (14.2)	<0.01*
Systemic artery hypertension, n (%)	22 (30.6)	55 (39)	0.23
COPD, n (%)	4 (5.6)	12 (8.5)	0.58
Chronic heart failure, n (%)	7 (9.7)	25 (17.7)	0.15
HIV, n (%)	1 (1.4)	3 (2.1)	1.00
Surgical patient, n (%)	8 (11.1)	44 (31.2)	<0.01*
Source of sepsis, n (%)			
Pneumonia	26 (36.2)	60 (42.6)	0.36
Urinary tract infect	17 (23.7)	15 (10.6)	0.01
Intra-abdominal infection	12 (16.7)	33 (23.5)	0.25
Infection of unknown source	10 (13.8)	22 (15.6)	0.74
Catheter-related infection	5 (6.9)	5 (3.5)	0.26
Other	2 (2.7)	6 (4.2)	0.59
ICU admission patients' characteristics			
APACHE	20.0 ± 6.6	22.2 ± 5.7	<0.01*
Total SOFA	9.0 (6–12)	12.0 (10–14)	<0.01*
Septic shock, n (%)	28 (38.9)	116 (82.3)	<0.01
Blood glucose	154.1 ± 59.2	141.4 ± 71.5	0.21
Serum creatinine, mg dL^{-1}	1.8 ± 1.2	2.5 ± 2.7	0.02*
Bilirubin, mg dL^{-1}	1.7 ± 2.3	2.1 ± 3.9	0.34
PaO_2/FIO_2	265.9 ± 101.3	243.7 ± 114.0	0.18
Hematocrit, %	33.6 ± 7.1	32.1 ± 7.8	0.15
pH	7.35 ± 0.1	7.30 ± 0.2	<0.01*
Lactate, mg dL^{-1}	18.1 ± 12.1	26.4 ± 25.0	0.01*
CRP, mg dL^{-1}	207.3 ± 130.7	190.5 ± 114.8	0.38
INR	1.6 ± 1.1	1.6 ± 0.7	0.88
WBC count μL^{-1}	14,763.9 ± 8589.5	10,958.9 ± 6793.8	0.01*
Use of MV	37 (51.4)	125 (88.7)	<0.01*
Duration of MV, days	7.5 ± 6.2	8.5 ± 8.9	0.51
ICU length of stay, days	10.4 ± 11.1	12.4 ± 11.8	0.25
Medication			
Corticosteroids, n (%)	42 (58.4)	91 (64.5)	0.45
Dosage cumulative (mg)	1068.6 ± 827.5	1486.6 ± 1978.3	0.5
Midazolam, n (%)	37 (51.4)	125 (88.7)	<0.01*
Dosage cumulative (mg)	493.4 ± 403.3	793.1 ± 570.2	<0.01
Norepinephrine, n (%)	33 (45.9)	116 (82.3)	<0.01*
Dosage cumulative (mg)	81.5 ± 48.1	110.9 ± 67.1	<0.01
Neuromuscular blockers, n (%)	7 (9.7)	12 (8.5)	0.80
Dosage cumulative (mg)	7.4 ± 2.0	10.7 ± 4.6	0.09

Values are presented as mean ± standard deviation or as number subjects (percentage), except in the variable SOFA [median (IQR)] *ICU* intensive care unit, *HIV* human immunodeficiency virus, *COPD* chronic obstructive pulmonary disease, *APACHE* Acute Physiology and Chronic Health Evaluation, *SOFA* Sequential Organ Failure Assessment, *CRP* C-reactive protein, *INR* international normalized ratio, *WBC* white blood cell, *MV* mechanical ventilation

* $p < 0.05$ when compared between groups. Statistical analysis was performed with the unpaired t and Mann–Whitney U test (quantitative variables) and Chi-square test (qualitative variables)

exercise capacity, muscle strength, and PADL. Quantitative variables were expressed as the mean and standard deviation, and categorical variables were expressed as the total number and percentage of patients.

The level of significance was set to 5 % ($p < 0.05$), and the statistical analysis was performed using a software package (SPSS 17, SPSS Inc., USA). All statistical analyses were performed independently of the PADL equipment manufacturer.

Results

Seventy-two patients underwent physical assessments prior to hospital discharge, and 51 patients returned 3 months later for reassessments (Fig. 1). The baseline characteristics of patients admitted to the ICU for severe sepsis and septic shock are described in Table 1. The characteristics of patients who could not be evaluated prior to hospital discharge were compared to those who

Table 2 Anthropometric characteristics and presence of comorbidities in septic patients and in healthy individuals

Comorbidity	Septic patients ($n = 72$)	Healthy individuals ($n = 50$)	p
Age, years	53.4 ± 17.6	54.6 ± 17.0	0.60
Sex, male, n (%)	36 (50)	25 (50)	1.00
BMI, kg/m^2	25.5 ± 4.8	24.2 ± 2.9	0.08
Systemic arterial hypertension, n (%)	22 (30.6)	20 (40)	0.31
Diabetes, n (%)	15 (20.8)	8 (16)	0.47
COPD, n (%)	4 (5.6)	2 (4)	0.67
Chronic heart failure, n (%)	7 (9.7)	0 (0)	0.02*
Chronic renal failure, n (%)	20 (27.8)	0 (0)	<0.01*
HIV, n (%)	1 (1.4)	0 (0)	0.39

Values are presented as mean ± standard deviation or as number subjects (percentage)
HIV human immunodeficiency virus, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease

* $p < 0.05$ difference between septic patients and healthy individuals. Statistical analysis was performed with the unpaired t (quantitative variables) and Chi-square or Fisher's exact test (qualitative variables)

were successfully assessed (Table 1); the reasons why patients did not undergo evaluations are displayed in Fig. 1. Patients who were not evaluated prior to hospital discharge were significantly different in age, histories of alcohol abuse, number of surgical patients, laboratory test results, prognostic scores at ICU admission, and medications taken when compared with patients who had received an assessment ($p < 0.05$; Table 1). Patients admitted with severe sepsis who then developed septic shock during hospitalization were analyzed in the septic shock group. There was no difference between the septic patients and the healthy individuals in the variables age, gender, and body mass index ($p > 0.05$) (see Table 2).

Physical activity in daily life

Figure 2 shows the time spent per day completing different activities in various bodily positions by sepsis survivors and healthy individuals in the ward and 3 months later. Septic patients demonstrated a lower walking time per day when compared with healthy subjects in the ward (1.9 ± 1.6 vs 10.1 ± 4.4 %, $p < 0.05$) and 3 months later (6.3 ± 3.0 vs 10.1 ± 4.4 %, $p < 0.05$). Notably, each percent of the total time represents 7.2 min/day. Patients remained inactive during the majority of their hospitalization and spent up to 89.2 % of their time sitting or lying down. After hospital discharge, the time spent inactive in a sitting or lying position was reduced to 58 % ($p < 0.05$). There was no significant difference between walking times among patients with severe sepsis and septic shock 3 months after hospital discharge. Sepsis patients had a lower movement intensity during walking after their hospital discharge when compared with healthy subjects (2.1 ± 0.3 vs 2.5 ± 0.4 m/s^2, respectively, $p < 0.05$). At 3 months post-hospitalization, approximately 60 % of septic patients walked more than 30 min a day, whereas this value reached 85 % in healthy subjects. None of the septic patients reported performing regular physical activity at least 3 times a week 3 months after discharge.

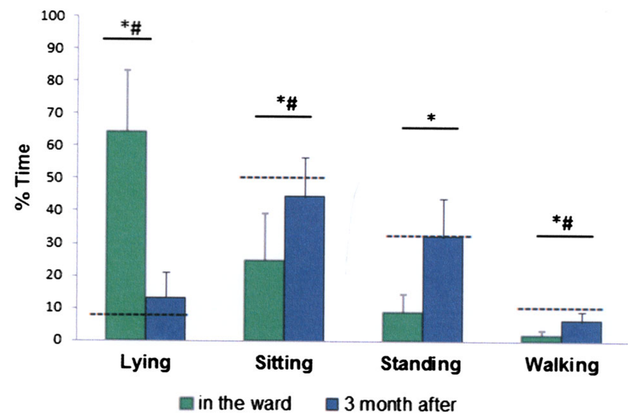

Fig. 2 Time spent per day executing different activities in septic patients and in controls in the ward and at a 3-month follow-up. Data in septic patients are presented as mean and standard deviation. Data in healthy controls are presented with *dotted line* indicating the mean time spent in each activity. *$p < 0.05$ comparison between hospitalization (in the ward) and 3-month follow-up. $^{\#}p < 0.05$ comparison between septic patients and healthy subjects

Muscle strength and exercise capacity

Figure 3a displays the muscle strengths and exercise capacity of the sepsis survivors at hospital discharge and 3 months after. Briefly, patients had lower values than predicted, with mean values of 45.9 ± 25.9, 50.9 ± 22.3, 54.6 ± 20.9, and 63.7 ± 32.1 % in assessments of 6MWD, quadriceps strength, handgrip strength, and MIP, respectively (Fig. 3a). These values increased to 69.0 ± 30.3, 68.5 ± 24.9, 66.5 ± 23.9, and 72.0 ± 26.5 % (Fig. 3a), respectively, 3 months after hospital discharge; however, these data remained lower than expected ($p < 0.05$, Fig. 3a).

To evaluate the influence of severity of sepsis on muscle strength and exercise capacity, patients with severe sepsis were assessed separately from those with septic shock (Fig. 3b). Patients who developed septic shock presented with lower quadriceps and handgrip strengths

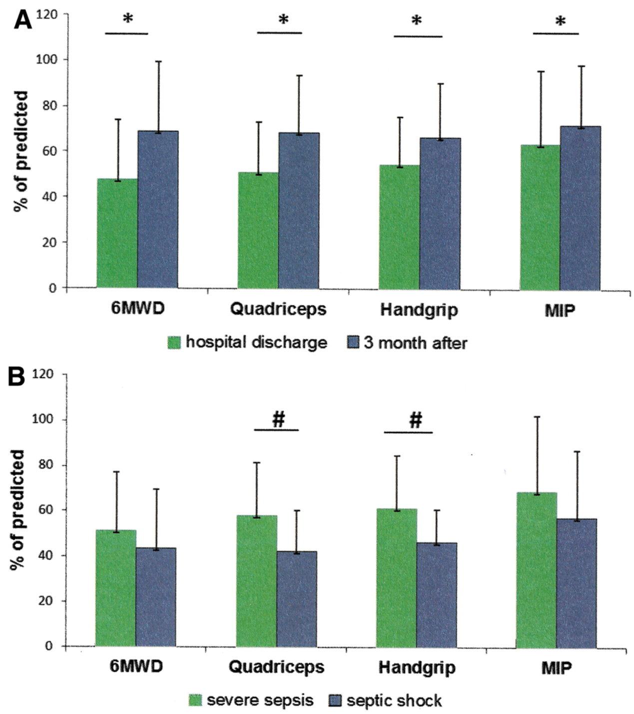

Fig. 3 **a** Represents the values obtained during assessments of exercise capacity and muscle strength at hospital discharge and 3 months after discharge compared to predicted values described in the literature [37–41]. **b** Represents the values obtained during assessments of exercise capacity and muscle strength at hospital discharge in patients with severe sepsis and septic shock. *6MWD* six-min walking distance, *Quadriceps* quadriceps muscle strength, *Handgrip* handgrip strength, *MIP* maximal inspiratory pressure. Data are presented as a percentage of predicted values of six-min walking distance [37], quadriceps strength [38], handgrip strength [41], and maximal inspiratory pressure (MIP) [40]. $^{*}p < 0.05$ comparison between hospital discharge and 3 months after (paired *t* test) and also the comparison between the value obtained and predicted (unpaired *t* test). $^{\#}p < 0.05$ comparison between patients with severe sepsis and septic shock (unpaired *t* test)

compared to patients with severe sepsis ($p < 0.05$); however, no difference was observed between them in the 6MWD and MIP tests on the day of hospital discharge ($p > 0.05$; Fig. 3b). After 3 months, the patients with severe sepsis and septic shock had similar values for muscle strength and exercise capacity ($p > 0.05$).

Factors associated with exercise capacity and muscle strength during hospitalization

The variables collected during the study that entered the backward multivariable linear regression model with the dependent variables muscle strength and exercise capacity obtained on the day of hospital discharge are displayed in Table 3. There were no variables associated with inspiratory muscle strength and PADL during hospitalization. Furthermore, none of the variables were associated with exercise capacity, muscle strength, and PADL results from 3 months after discharge.

Table 3 Multivariable regression analysis with clinical and laboratory factors for muscle strength and exercise capacity obtained on the day of hospital discharge

Variables	B-coefficients	Standard error	*T*	*p*
6MWD				
Intercept	0.5212	0.0585	8.91	<0.01
Used corticosteroids	−0.1258	0.0571	−2.16	0.03*
SOFA	−0.0079	0.0088	−0.90	0.37
Hospital stay	−0.0050	0.0015	−3.63	<0.01*
Noradrenaline time	−0.0073	0.0119	−0.61	0.54
Quadriceps strength				
Intercept	0.5247	0.0494	10.63	<0.01
Used corticosteroids	−0.1206	0.0479	−2.52	0.01*
C-reactive protein	−0.0001	0.0002	−0.84	0.40
Hospital stay	−0.0048	0.0013	−3.81	<0.01*
Noradrenaline time	−0.0184	0.0094	−1.95	0.06
Handgrip strength				
Intercept	0.6020	0.0369	16.33	<0.01
Body mass index	0.0180	0.0044	4.06	<0.01*
SOFA	−0.0034	0.0068	−0.50	0.61
Used noradrenaline	−0.0577	0.0507	−1.14	0.25
Hospital stay	−0.0046	0.0011	−4.20	<0.01*

6MWD six-min walking distance

* $p < 0.05$ clinical or laboratory factors independently associated with the physical evaluation of the hospital discharge day

Discussion

This study clearly demonstrated that patients referred to the ICU for severe sepsis or septic shock had a significant reduction in short- and medium-term PADL when compared with healthy subjects. Furthermore, a significant reduction in movement intensity was observed during walking even at 3 months after discharge. We demonstrated that sepsis survivors partially recover peripheral muscle strength and exercise capacity after hospital discharge; however, these outcomes remain below the expected values.

To the best of our knowledge, no previous study has quantified PADL in sepsis survivors during hospitalization. Our results show that patients remained largely inactive (sitting and lying = 89.2 %) during hospitalization. The physical inactivity observed in hospitalized patients has previously been described in the elderly [42] and patients with chronic lung disease [18, 19]. Villumsen et al. [42] demonstrated that elderly patients nearing hospital discharge spent approximately 10 min/day walking. In COPD patients, the average daily walking time during hospitalization was less than 10 min/day [18, 19]. This inactivity was also observed in our patients

(14 min/day), allowing us to conclude that this is a common occurrence in several populations of hospitalized patients. Potential reasons for physical inactivity include disease severity, the effects of diseases on the musculoskeletal system, fear of worsening symptoms, low confidence, and the hospital environment. In addition, the hospital environment favors inactivity because all basic needs such as eating, drinking, and going to the bathroom are carried out in bed or near the bed. The potentially harmful effects of immobility in short- and medium-term sepsis survivors have not been established. Therefore, further studies using exercises, specific strategies [43], or walking programs can help to reduce physical inactivity and may be promising strategies for these patients.

The level of physical inactivity observed in our patients after hospital discharge is not surprising. Previous studies using the physical function domain of the Short Form-36 (SF-36) questionnaire suggested that the level of physical activity in these patients may be compromised [2, 6]. However, questionnaires are unable to produce detailed information about a patient's PADL. Thus, this is the first study to demonstrate the differences between sepsis survivors and healthy subjects in terms of time spent completing different activities in various body positions and the intensity of movement during walking. Septic patients had a lower intensity of movement than healthy subjects (2.1 ± 0.3 vs 2.5 ± 0.4 m/s^2). The values obtained in our study for healthy subjects are close to those obtained in other studies (2.4 and 2.3 m/s^2) [19, 35]. Physical inactivity was clearly demonstrated with patients spending approximately 14 % of their time lying down compared with 8 % in healthy subjects. This highlights an important health issue because physical activity guidelines recommend a daily physical activity time of at least 30 min [44]. In our study, 60 % of patients were able to achieve this recommendation, whereas 85 % of healthy subjects reached this goal. This was similar to previous results in Brazilian COPD patients, where 72 % of patients were able to achieve 30 min/day of walking compared to 93 % of healthy volunteers [45]. In contrast, only 37 % of Australian ICU survivors spent at least 30 min/day walking [46]. The differences obtained in the walking times of Brazilian patients in relation to other countries have been demonstrated previously [47] and can be explained in part by the low socioeconomic status of Brazilian patients, who do not have access to public and private transport and, therefore, have to walk more during activities of daily life. Other hypotheses included climatic differences and size differences between cities that could directly influence the time spent on activities such as walking. These results suggest a need for the establishment of rehabilitation programs for medium- and long-term ICU survivors that aim to improve physical activity.

It was previously demonstrated that ICU survivors showed a reduced muscle strength, health status, and HRQoL [2–4]. However, few studies have analyzed muscular strength and exercise capacity in depth in short- and medium-term patients referred to the ICU for severe sepsis and septic shock [16, 48]. In our study, patients had a muscle strength and physical capacity that was only 55 % of the predicted value. Eikermann et al. found a reduction of approximately 30 % in skeletal muscle strength in septic patients [16]. In addition, peripheral muscle weakness has been shown using electrophysiological measurements [48]. The causes of muscle dysfunction in sepsis have been attributed to many factors, including the reduction of membrane excitability, sarcolemma membrane damage, altered calcium homeostasis, increased proteolytic degradation, and decreased protein synthesis [49]. However, the association among these variables, clinical measurements, and muscle strength and exercise capacity needs further investigation. The reduction in muscle strength and exercise capacity observed at hospital discharge in our study has also been observed in the long term [8], which may suggest an increase in patient morbidity and expenses related to health care; however, this remains to be investigated.

Initially, we believed that patients who developed septic shock would experience greater effects on their exercise capacity and peripheral muscle strength compared to patients with severe sepsis because the mortality rate is higher in patients with septic shock [31]. Therefore, the survivors of septic shock could recover with a higher number of sequelae. Surprisingly, patients with septic shock showed no difference in 6MWD and MIP results when compared to patients with severe sepsis. We believe that this was observed for MIP because patients generate negative inspiratory pressures constantly throughout the day to hold their breath, which would reduce the effects of sepsis on inspiratory muscle strength. As for 6MWD, the rehabilitation protocol applied at the institution may have attenuated the differences between the groups because the protocol aims to encourage ambulation of patients as early as possible. This result differs from the quadriceps and handgrip strength tests, for which the institution's rehabilitation protocols had no specific strength training objectives. After 3 months, the differences between septic patients disappeared, allowing us to suggest that these effects are more restricted to the hospitalization period.

We observed an association between the use of corticosteroids and both quadriceps weakness and 6MWD. A prospective observational study reported that the use of corticosteroids was the highest risk factor for the development of muscle weakness in patients submitted to mechanical ventilation in the ICU; however, no association was observed with the total dose or duration of therapy with corticosteroids [11]. On the other hand, a recent study found no association between corticosteroids and 6MWD or physical function outcome results during a follow-up study in acute lung injury survivors [50]. To date, the role of systemic corticosteroids in the development of muscle weakness is unclear and controversial [51–53]. Interestingly, a recent study reported that hyperglycemia may partially mediate the deleterious effects of corticosteroids on the neuromuscular system [54]. However, we did not find an association between glucose levels and physical dysfunction. Another risk factor in our study suggests that hospital stay lengths are associated with the development of weakness and reduced exercise capacity. These findings are similar to previous results [48] and may reflect the severity of side effects suffered by patients during times when a longer hospital stay is necessary for treatment.

This study had some limitations. First, the tests used to measure muscle strength were dependent on the patient's motivation. However, we tried to minimize this effect by only considering the three greatest values that had a maximum difference of 10 % between tests and by determining the muscle strength on the basis of the greatest value. We were unable to obtain baseline measurements of muscle strength, exercise capacity, or PADL because of the severity and speed of disease onset; thus, the full magnitude of the changes caused by sepsis could not be determined. However, we used healthy subjects and normative data from the general population for our assessments. Second, PADL was quantified for 2 instead of 7 days, as previously described [46]. In addition, we also performed evaluations on weekdays only. However, this decision can be explained by the following: (1) there is evidence that 2 days of assessment provides an acceptable reliability for assess PADL and (2) our data obtained from septic patients was compared with healthy subjects, who are known to walk less on weekends. Third, it was impossible to pair the septic patients with matched controls for all comorbidities and anthropometric characteristics mainly because several septic patients only were diagnosed with human immunodeficiency virus infection, chronic renal failure, and other comorbidities after admission, unlike the control group who filled out a form about the diseases that they knew they currently had. However, in a secondary analysis (data not shown) we compared the septic patients with human immunodeficiency virus or chronic renal failure or chronic heart failure history with other septic patients and found no difference in PADL after 3 months. Therefore patients were matched only by gender and anthropometric characteristics. Furthermore, other studies on PADL also paired the control patients through anthropometric characteristics and not comorbidities [55, 56]. Fourth, myopathy and polyneuropathy have been identified as the main causes of muscle weakness in the ICU [57]; these were previously shown to be prognostic markers in the recovery process of patients and mortality [58, 59]. Despite this, the electrophysiological testing required for the diagnosis of myopathy and polyneuropathy were not performed in our study because it is highly time-consuming, technically difficult to perform, expensive, and not available in all ICUs [60, 61]. Lastly, it was not possible to quantify the effects of the institution's rehabilitation program on the results obtained in septic patients because this was not one of the study objectives.

Conclusion

Patients referred to the ICU for severe sepsis or septic shock had a substantial reduction in their short-term and medium-term PADL that was associated with a reduction in peripheral muscle strength and exercise capacity. Although patients exhibited a general recovery of muscle strength and exercise capacity, their performance was below that of healthy subjects. The use of corticosteroids and hospitalization time influenced quadriceps muscle weakness and exercise capacity in sepsis survivors.

Acknowledgments We thank the physical therapy staff of the University Hospital for technical support and postgraduate students in respiratory physiotherapy.

Conflicts of interest The authors declare that they have no conflict of interest.

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