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Long-term health related recovery and outcomes in survivors of intensive care

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Long-term health related recovery and outcomes in survivors of intensive care

by

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Abstract

Our objective was to create a follow-up clinic for survivors of critical illness in order to examine objective physical functioning, mental health and sleep quality and relate these findings to health related quality of life (HRQL) and ICU risk factors.

56 patients were evaluated at 2 months post hospital discharge and 19 patients at 4 months. At 2 months post hospital discharge we found that: Patients had reduced muscle strength and physical functioning and neither were association with ICU risk factors; Reduced muscle strength was correlated with poor physical functioning; Patients' HRQL was associated with decreased physical functioning; Anxiety was common and found to correlate with poor HRQL and physical functioning; Objective sleep quality was poor and predicted by increased severity of critical illness.

Long-term physical and mental morbidity is common in critical illness survivors and impacts HRQL. ICU follow-up clinics should be considered in all survivors of critical illness.

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List of Abbreviations

6-MWT	6-Minute Walk Test
APACHE II	Acute Physiology and Chronic Health Evaluation II
ARDS	Acute Respiratory Distress Syndrome
BP	Bodily Pain
CIM	Critical Illness Myopathy
CIN	Critical Illness Neuropathy
CINM	Critical Illness Neuromyopathy
CINMA	Critical Illness Neuro-muscular abnormalities
CIP	Critical Illness
CMAP	Compound Muscle Action Potential
D	Days
DTS	Davidson Trauma Scale
EMS	Electrical Muscle Stimulation
EQ-5D	EuroQol-5D Questionnaire
ESS	Epworth Sleepiness Scale
FMC	Foothills Medical Centre
GH	General Health
HADS	Hospital Anxiety and Depression Scale
HRQL	Health Related Quality of Life
ICU	Intensive Care Unit
ICUAP	Intensive Care Unit Acquired Paresis
ICUAW	Intensive Care Unit Acquired Weakness
IES	Impact of Events Scale
IQR	Interquartile Range
KG	Kilograms
LOS	Length of Stay
M	Meter
MCS	Mental Component Summary
MH	Mental Health

MMT	Manual Muscle Testing
MRC	Medical Research Counsel
NIMs	National Isometric Muscle Strength Database Consortium
OR	Odds Ratio
P/D	Pain/Discomfort
PCS	Physical Component Summary
PF	Physical Functioning
PQSI	Pittsburgh Sleep Quality Index
PSG	Polysomnography
PTSD	Post-Traumatic Stress Disorder
PTSS-10/14	Posttraumatic Stress Syndrome 10/14 questions inventory
RE	Role Emotional
RP	Role Physical
SC	Self Care
SD	Standard Deviation
SE	Standard Error
SF	Social Function
SF-36	Short Form 36 Questionnaire
SOFA	Sequential Organ Failure Assessment Score
SPAN	SPAN Questionnaire
TNF	Tumour Necrosis Factor
VAS	EuroQol Visual Analogue Scale
VT	Vitality

Chapter One: Introduction

According to the Society of Critical Care Medicine, the national society for critical care/intensive care physicians in the United States, over five million patients are admitted each year to an intensive care unit (ICU) in the United States [1]. Accurate estimates for Canada are not available, but based on population size, this may be as high as 500,000 patients per year in Canada. 20-30% of critically ill patients do not survive to hospital discharge and an additional 10% do not survive to 1-year post ICU admission [1, 2]. Patients admitted to the ICU require multisystem management with advanced monitoring and nursing care. Patients, who survive, are stabilized in the ICU and eventually transferred back to the hospital wards to finish their recovery. Studying outcomes of critical illness in the past has traditionally focused on short-term outcomes including, ICU and hospital mortality and length of ICU or hospital stay [3]. However, as more patients are surviving critical illness and returning home, patients may be suffering from significant morbidity that is not being appreciated by short-term study outcomes. This has created a demand to understand the potential long-term consequences critical illness can have on patients.

Over the past decade there has been an increase in the amount of research focused on assessing the long-term recovery of patients who have survived a critical illness. Several studies have concluded that survivors of critical illness have both physical and mental functional limitations greater than 1 year after discharge from the hospital [4-6]. Herridge and colleagues [5] found that patients admitted to the ICU with acute respiratory distress syndrome

(ARDS) continue to experience physical limitations 1-year after hospital discharge due to muscle deconditioning and weakness. Many authors have noted muscle wasting and subsequent muscle weakness occurring in the ICU population [7-9]. However, the body of research quantitatively examining muscle weakness and physical functioning post-critical illness is limited. Objective measure of muscle strength is limited to 1 week after ICU discharge [10], otherwise qualitative measures have been used [5, 11]. The level of muscle weakness or its relationship to functional status has yet to be objectively explored in a long-term follow-up setting [12, 13]. No literature exists accurately quantifying muscle weakness of critical illness survivors post hospital discharge. Accurately describing the physical deficits of ICU survivors is paramount to understanding how patients recover from critical illness and the effectiveness of therapies on recovery.

Several psychological abnormalities have been identified in ICU survivors including depression, anxiety and post-traumatic stress disorder (PTSD) [14]. These abnormalities have all been shown to reduce patients health related quality of life (HRQL). The prevalence of depression, anxiety and PTSD in the ICU survivor population remains unknown [15]. Several studies have been published examining psychological abnormalities however there has been a lack of consistency in the choice of screening tools, making interpretation difficult [15, 16]. Thus, it has become important to screen for psychological disorders and use instruments that have been well validated and have been used previously in the ICU population.

Sleep is a domain of health that has received little attention in the follow-up literature of critically ill patients. There have been recent studies to suggest that ICU survivors experience long-term sleep disruption [17, 18]. Only one study has been published using formal sleep evaluations [18]. Other studies have used sleep quality questionnaires that have not been well validated or found to be reliable. There is need for a detailed sleep study to properly assess the prevalence of long-term sleep disturbances in ICU survivors.

HRQL has become an important outcome in survivors of critical illness. A systematic review highlighted that the majority of studies, examining long-term HRQL, found ICU survivors had significantly lower HRQL post-ICU than the general population [6]. It is important to understand why patients are experiencing a lower HRQL and how that may be associated to particular morbidities including muscle weakness, psychiatric and sleep disorders.

It is thought that ICU follow-up clinics will have the ability to identify and treat specific complications of critical illness, which would otherwise go unrecognized [19]. ICU follow-up clinics are most common in the UK, where approximately 30% of ICUs operate follow-up clinics, typically seeing patients 2 to 3 months after hospital discharge [19]. ICU follow-up clinics also have the potential to benefit ICU medical staff because they can gain perspective on the morbidities caused by critical illness [20]. It is also important to recognize that many patients treated in Canadian ICUs may not receive any follow-up by a family doctor, due to the high prevalence of Canadian citizens not having a primary care physician, adding to the risk for morbidities caused by critical illness to go undetected and untreated [21].

There is a need for standardized follow-up of critical illness survivors by intensive care nurses and physicians as it may not be reasonable to expect general practitioners to understand the array of potential morbidities that can follow critical illness [21]. There are no reports in the literature of ICU follow-up clinics in Canada. This study reports the results of such a standardized follow-up clinic and objectively examines the physical and mental sequelae of critical illness.

Chapter Two: Literature Review

2.1 Intensive Care Unit Acquired Weakness

Critically ill patients often experience muscle weakness while in the intensive care unit (ICU). Several studies have been able to show patients experience diffuse weakness while critically ill, leading to prolonged mechanical ventilation and poorer hospital outcomes [14, 22-24]. The effects of ICU acquired weakness (ICUAW) have also been shown to debilitate patients well beyond surviving critical illness. Studies have reported physical deficits from months to up to 5 years after hospitalization, which can lead to decreased HRQL and other functional limitations [5, 25, 26] [10]. Survivors of critical illness have been shown to have poor functional status including reduced grip strength and walking ability 1 week after discharge from ICU [10]. Cardiopulmonary exercise testing within 6 weeks of hospital discharge showed ICU survivors had significant exercise limitation most likely explained by deconditioning and muscle weakness [27]. Many causes and risk factors of muscle weakness in critically ill patients have been explored, including immobilization, organ failure, systemic inflammatory response syndrome, hyperglycemia, days of ventilation, length of ICU stay, corticosteroids and neuromuscular blockades [22, 28-31]. ICUAW is a term used to described weakness derived from critical illness which results from a combination of muscle wasting, polyneuropathy and/or myopathy, as described in the subsequent review [31-33].

2.1.1 Immobility and Muscle Atrophy

Critically ill patients who have a prolonged stay in the ICU experience long durations of immobility. Patients can be inactive for several days as a result of sedation and mechanical ventilation [34]. Bed rest alone can create several complications including functional weakness caused by muscle wasting, neuropathies, joint contractures, and myocardial dysfunction [35-37]. Several studies have shown a significant loss of muscle mass caused by inactivity [38]. Rat models have shown a loss in body mass of up to 40.5% after the hind limbs were immobilized for 4 weeks [39]. Humans models have shown that individuals who were under best rest for 4 to 6 weeks lost up to 40% of their muscle strength [40]. During spaceflight, humans have been noted to have significant muscle atrophy after 5 days in the antigravity environment [41]. It is estimated an ICU patient can lose as much as 1.5kg of muscle mass per day and up to 50% of total muscle mass after 2 weeks of immobilization [42].

Skeletal muscle undergoes primary atrophy from disuse, marked by a decrease in protein content, fiber size and force generation [43]. During primary atrophy there is a shift in the equilibrium between catabolic and anabolic processes [44]. At first, protein synthesis is reduced due to decreased protein transcription and then protein degradation pathways are activated [41]. The rate of atrophy is initially the highest when immobilization is initiated and then diminishes, meaning a patient can lose significant muscle mass having only undergone a short period of immobilization [45].

During primary muscle atrophy, it has been shown certain types of muscle fibers are selectively degraded [46]. There are two main types of muscle fibers, type I (slow twitch) and type II (fast twitch). Type I fibers are capable of sustaining repeated slow contractions for a long period of time using aerobic respiration for energy; Type II fibers work for short duration, producing fast contraction using anaerobic respiration for energy. The type II muscle fibers have been shown to be degraded at a higher rate than the type I muscle fibers during disuse atrophy [33, 38, 47]. However, the anti-gravity muscles, which include the legs, back and neck, have a higher proportion of type I to type II muscle fibers and have been shown to have higher rates on type I loss during disuse [38]. These muscle groups are used to support the body of a mobile person, maintaining an upright posture. However, the anti-gravity muscle groups are not used when a patient is inactive or in a supine position [46]. It has been shown that during immobilization there is a loss of contractile proteins in antigravity muscle and increase in collagen and other noncontractile tissues, however the number of fibers remains the same [38]. Derde et al [48] examined muscle biopsies from rectus abdominis in critically ill patients and healthy controls. They found the critically ill patients had decreased myofiber size and protein synthesis, high proteolytic enzyme activity and a lower myosin to actin ratio.

Mechanical ventilation of critically ill patients removes many of the diaphragm’s normal physiologic functions, creating a unique state of disuse atrophy [49] . It is thought that weaning failure is primarily caused by atrophy and contractile dysfunction of the diaphragm [50]. In animal models the diaphragm’s ability to produce force was reduce by 30-40% after only 3 days of mechanical ventilation [49]. Much of the atrophy is thought to be caused by a decrease in protein synthesis and increased protein degradation as seen in normal disuse atrophy. Biopsies of diaphragms taken from patients diagnosed with brain death, 18-69 hours from the start of mechanical ventilation, showed significant atrophy of the myofibers when compared to healthy controls [51]. The authors concluded the amount of atrophy seen on muscle biopsy would have lead to a functional weakness in the diaphragm. A recent study found that almost 100% of long-term mechanically ventilated patients with sepsis had electrophysiological evidence of diaphragm dysfunction [13].

2.1.2 Molecular Mechanisms of Muscle Atrophy

Critically ill patients, in particular those with sepsis, have been shown to have significantly increased protein degradation [52]. The pathway primarily responsible for the heightened catabolic response in skeletal muscle is the polyubiquitin protease pathway. Muscle proteins are ubiquitinated targeting them for destruction by multisubunit proteasomes [46]. Muscle biopsies of critically ill patients have shown an up regulation of the ubiquitin-proteasome pathway [48]. The lysosomal, caplain, caspase and apoptoic pathways are also involved in proteolysis and atrophy [14, 43]. The Atrogin-1 and MuRF1 are two ubiquitin ligases that have been observed to be up regulated during muscle atrophy [53, 54]. Levine and colleges [51] reported that both atrogin-1 and MuRF1 are expressed at very high levels in diaphragms of patients who are brain dead and mechanically ventilated. The results suggested that the up regulation of these proteases would be responsible for high rates of protein degradation and atrophy that occurred in the diaphragm of these patients. In addition, critical ill patients are found to have decreased mRNA levels within the muscle responsible for the production of myofibrillar proteins [48].

Secondary muscle atrophy results from the patient's pathology and is driven by activated biochemical pathways that promote muscle degeneration. Some proinflammitory cytokines are thought to play a major role in the activation of catabolic pathways leading to muscle atrophy in critically ill patients [31, 46]. Cytokines have been found to decrease the muscle resting membrane potential and muscle contractility [42]. TNF-α, IL-6, and IL-1 [55] are cytokines that are known play a role in muscle atrophy in critically ill patients [14]. Myostatins, glucocorticoids and reactive oxygen species have all been found to be involved in activating muscle atrophy. The transcription factor NF-kB has also been found to be a key intracellular signalling protein involved in up regulation of ubiquitin ligases [14].

2.1.3 Neuromuscular Dysfunction

Neuromuscular dysfunction in the critically ill population has been giving numerous terms within the literature. Critical illness neuropathy (CIN) and critical illness myopathy (CIM) individually classify neuropathies and myopathies respectively. Critical illness neuromyopathy (CINM), ICU acquired weakness (ICUAW), ICU acquired paresis (ICUAP), and critical illness neuro-muscular abnormalities (CINMA) encompasses all neuromuscular disorders (CIM and CIP) as well as neuromuscular junction dysfunction [14, 22, 24, 56, 57]. The variability in classification of disorders has complicated the subject. It is more common for CIM and CIP to be reported together [56] because it is often difficult to distinguish between neuropathies and myopathies and the proportion each is contributing to a functional disability [7, 14, 58]. For the purposes of this review CINM will be used to denote neuromuscular disorders when studies use one of the other labels listed above.

Clinical diagnosis of myopathies and neuropathies in the ICU generally includes symptoms of muscle weakness and weaning failure. [58]. The standardized methods to quantitatively assess neuromuscular dysfunction include motor and sensory nerve conduction studies, needle EMG, direct muscle stimulation and muscle biopsy [57, 59, 60]. Although, some have considered it more important to focus on quantitative measurements of muscle strength because electromyography and nerve conduction studies do not reliably predict CINM. Evoked muscle force measurements in the ICU are capable of giving direct assessments of weakness [61, 62].

CIM is defined as a non-necrotizing myopathy not secondary to muscle denervation [7, 14]. CIM is characterized by prolongation of the compound muscle action potential (CMAP) duration during voluntary muscle contraction, as well as, low-amplitude, short-duration polyphasic units with early recruitment [57]. There are several changes that can occur to the muscle in order to induce CIM including, changes to the muscle membrane leading to problems of cell excitability, changes to the contractile properties of the muscle fibers, reductions in protein synthesis and increases in protein degradation [63]. In a study of patients who had ICUAP all muscle biopsied patients had specific myopathies not related to any neuropathies [29]. A pro-inflammatory response, immobility, pharmacologic agents and oxidative stresses have been shown to initiate CIM. [14, 64].

Myopathic complications are very common in patients with sepsis [31]. The heightened level of pro-inflammatory cytokines during sepsis is one of the major causes of developing myopathies [65, 66]. Peripheral muscle force is decreased in septic patients and hypothesized that it is a result of a secondary atrophy or neuropathy and not a result of immobilization atrophy [67]. Sepsis has been shown to elicit several changes to myofibers at the cellular level, including changes to the contractile proteins, decreased membrane excitability [68] and activation of proteolytic pathways [65, 69].

CIP results from a primary axonal polyneuropathy [70]. One of the key components to developing CIP is change to the individual nerve fibers microvasculature, where the permeability of vessels is increased allowing toxins to cause nerve damage [64]. Electrophysiological testing typically shows decreased CMAP and sensory nerve action potential [57]. CIP is very common among patients with SIRS and sepsis. The reported prevalence ranges from 70-100% for long-term stay patients [14, 71]. Pro-inflammatory cytokines (TNF-alpha, IL-1, IL-6) can cause changes to the microcirculation of nerve fibers leading to CIP. It is thought that high serum glucose levels may lead to CIP because it was found that specific glycemic control reduces the incidence of CIP. As well, several pharmacologic agents have been thought to cause CIP [14]. Long-term follow-up (1-year) of patients with either CIM or CIP showed that patients with CIM recovered to their pre-ICU state faster than those with CIP [72, 73]. Recently it was shown that patients with CIP and CIM have much longer ICU stays and more severe weakness at ICU discharge than patients with isolated CIM [74].

De Jonghe et al [22] describes CINM as bilateral diffuse weakness occurring in the proximal part of limbs, resulting from a combination of muscle and peripheral nerve pathologies residing after the initial acute illness has resolved. This can lead to both problems in skeletal muscle movement and respiration. In 2007 Stevens and colleagues [24] conducted a systematic review of all past studies related to neuromuscular dysfunction. They found that approximately 50% of adults have CINM after reviewing over 1400 subjects. They also found that exposures most likely to induce CINM to be sepsis (OR ranged 2.4 (95% CI 0.8-6.8) to 49 (95% CI 4.7-519)), high serum glucose (OR 2.6 (95% CI 1.6-4.2), glucocorticoids (OR 14.9 (95% CI 3.2-69.8)) and neuromuscular blocking agents (OR 16.32 (95% CI 1.34-199)). De Jonghe et al [29] also found corticosteroids to be a significant risk factor for CINM. A recent randomized controlled trial examining the effects of neuromuscular blockade in patients with acute respiratory distress syndrome (ARDS) found that their use was associated with a decreased 90-day mortality and there was no difference in the incidence of ICUAW (defined using an overall MRC score < 48) between placebo and treatment [75]. In addition, high severity of illness accompanied with SIRS, female sex and organ failure have also been shown to be a major risk factor for the development of CINM [24, 29, 76]. Steven et al [24] also reported that patients with CINM had increased durations of mechanical ventilation (OR 2.4 (95% CI 1.4-4.2)), increased hospital mortality (OR 7.1 (95% CI 1.5-32.6)) and increased long-term weakness. Long-term follow-up of ARDS survivors showed combinations of compression neuropathies and changes in muscle structure found in muscle biopsies suggesting this may be contributing to the physical dysfunctions these patients experienced several months after ICU discharge [77]. In 2008 Ali and colleagues [78] found that CINM was associated with longer hospital stays, longer mechanical ventilation, decreased grip strength, and increased hospital mortality.

2.1.4 Treatment and Prevention of ICUAW

In recent years there have been a number of studies exploring ways to prevent or overcome ICUAW. It is thought that by trying to remove the risk factors associated with ICUAW, such as bed rest, pharmacologic agents and sedation, that it may be prevented [62]. Two randomized controlled trails were reviewed recently and found that intensive insulin therapy significantly decreases the incidence of CINM, length of mechanical ventilation, ICU length of stay and 180-day mortality [63, 79]. Although, a recent study examined muscle biopsies of critical ill patients and found that insulin therapy made no difference on the level of muscle atrophy and enzyme regulation. They did find that corticosteroid treatment was a primary risk factor for low myosin to actin ratio. It should also be mentioned that the NICE-Sugar trail [80], which randomized over 6000 ICU patients found that intensive insulin therapy increased mortality.

Much of the literature is focused on early mobilization and rehabilitation of critically ill patients in the ICU [81]. It is thought that by mobilizing patients early on during critical illness it can not only improve strength but decrease oxidative stress and inflammation [37]. The benefits of mobility have been shown in non-ICU patient populations, by increasing exercise capacity, decreasing hospital length of stay and the prevalence of depressive symptoms. There are several forms of mobility that can be implemented in the ICU, all with the potential to improve patient outcomes, including passive range of motion, tilt table therapy, electrical muscle stimulation (EMS) and active range of motion, such as ambulation or cycle erometry [46, 82]. Bailey et al [83] implemented early mobilization in mechanically ventilated respiratory failure patients. They determined that early mobilization is both feasible and safe for the patients and should be considered as a potential therapy for neuromuscular disorders. The literature is growing, showing the potential benefits of early mobilization. It has also been shown that passive range of motion during critical illness has the potential to maintain muscle architecture [8]. Burtin et al [84] performed a randomized controlled trail where the treatment group went through a daily exercise program of passive and active (leg ergometer) exercise. They found that at hospital discharge the treatment groups 6-MWT, quadriceps strength and subjective physical function were all significantly higher than the control group.

Others have also shown that early physical therapy can return patients to an independent functional status faster, reduce duration of delirium, reduce mechanical ventilation time and decrease both ICU and hospital length of stay [9, 85]. Many have mentioned that moving critical ill patients is both feasible and safe [9, 83-85] but there are still challenges involved in changing the ICU culture to caring for a more awake and mobile patient [36, 86]. Currently a randomized controlled trailed is underway examining the effectiveness of early rehabilitation in preventing ICUAW specific to septic patients [87].

Two recent studies examined the ability of EMS to prevent ICUAW [88, 89]. They found that EMS significantly increased the MRC score of ICU patients when compared to the control group. As well, the weaning period and prevalence of CINM was significantly lower for patients in the EMS group. One study found that EMS increased muscle strength in septic patients but did not make a difference in limb thickness or biceps thickness [90]. Currently a randomized controlled trail is being carried out to assess the effectiveness of EMS in reducing the burden of ICUAW [91].

There have been investigations into potential anabolic and anti-catabolic therapies, however they have had limited success [92]. There has been some evidence that growth hormone and insulin therapies have the potential of preventing CINM [92, 93]. Use of pyridostigmine, and an acetylcholinesterase inhibitor in rats, has improved muscle strength after immobilization, giving it the potential to prevent ICUAW in humans. Further investigations into growth hormone, androgens and other supplementations, such as glutamine and creatinine, in the critically ill population are required to determine their potential benefits in preventing ICUAW [94].

Several randomized controlled trials are currently being conducted examining the effectiveness of rehabilitation programs post hospital discharge [95, 96]. Currently there is conflict within the literature. Mcwilliams et al [97] and others [98] have found significant improvements in functional testing and HRQOL with the use of post hospital rehabilitation programs. However, Elliot et al [99] found no difference in functional status between the treatment groups, although there was improvement within both groups. Jackson et al [100] found significant improvements in cognitive status but not in physical functioning with a rehabilitation program. Cuthbertson et al [101] intervened with a nurse led rehabilitation program and didn't find any significant difference in HRQOL between the treatment and control group.

2.1.4.1 Measuring muscle strength and functional exercise capacity

Several methods are available to measure muscle strength including, manual muscle testing (MMT), hand-held isometric dynamometry, and isokinetic dynamometry [102]. Other novel methods exist including using ultrasound to assess muscle atrophy of the rectus femoris muscle which has been shown to correlate with quadriceps strength [30], although this method remains experimental. MMT is the most commonly used method to measure muscle strength and has been used in several patient populations [103, 104]. During MMT, force is applied to an examiner, who gives a subjective assessment on a rating system. The Medical Research Counsel (MRC) scale is commonly used with a scale ranging from 0 to 5 where a 0 represents no muscle contraction and a 5 represents normal power against full resistance [102, 105]. A recent study found that there was very good inter-observer agreement of the MRC and hand-held dynamometry [106]. However, the method has also been shown to have low sensitivity and questioned whether it is the most appropriate tool for testing muscle strength [103, 107]. The MRC scale does not have detailed standardization for limb positions or type of resistance applied (isometric vs. isokinetic) unlike other methods [104]. Despite this MMT has been used to assess muscle strength in critically ill patients in the ICU [33, 88, 108] and post hospital discharge [109] and found to be reliable post-ICU discharge but questionable for use in ICU. Isokinetic dynamometry is considered to be the gold standard of muscle strength testing [102]. It is capable of measuring muscle force in dynamic conditions [110]. Isokinetic measurements have been shown to be the most reliable and valid form of muscle strength measurement [102, 110]. However, the method requires a large amount of equipment, with high costs, placing limitations on the method [4]. Hand-held dynamometry measures the peak force produced during a maximum isometric contraction. The quantitative result of dynamometry yields high accuracy compared to MMT [103]. The use of handheld dynamometry to measure muscle strength has been shown to have low intra and inter observer variation and capable of accurately quantifying muscle strength [102, 111]. Hand-held isometric dynamometry is considered one of the most practical and sensitive ways to measure muscle strength, due to its cost and time efficiency, ability to be standardized, and ease of use [102, 104, 111, 112]. It has also been suggested a suitable measure when isokinetic methods are not available [102]. Two recent studies have shown that hand-held dynamometry had good inter-rater and retest reliability in critically ill patients [113, 114]. It has been recommended that hand-held dynamometry be used, over MMT, for longitudinal study of muscle weakness [114]. A limitation of hand-held dynamometry is the examiners own strength, where the patient may be able to overcome the force applied by the examiner [111]. Also, due to some measurement error with this method it is thought that moderate changes in muscle strength are required to detect changes [113]. Age, sex, weight and height standardized values are available for the major muscle groups giving the capacity for predicting patients muscle strength [32, 115-117].

Several assessments have been used to objectively evaluate functioning exercise capacity, including walk tests, stair climbing, and cardiac stress tests [118]. Recently it was demonstrated that cardiopulmonary exercise testing is a practical and safe method to assess exercise limitations [27]. Walk tests are among the most commonly used, as they are inexpensive and easy to perform [119]. Walk tests have the ability to easily give an overall assessment of global physical functioning and the pulmonary and cardiovascular systems [118, 119]. The 6-minute walk test (6MWT) has been recommended as the best walk test available for clinical or research purposes because it is easy to administer, accommodates a board spectrum of functional disability and represents activities of daily living [119]. A strong association exists between the 6-MWT and functional capacity [120]. The 6-MWT has been used in several different patient populations, including COPD, heart failure and paediatric patients [5, 119]. The use of the 6-MWT in post-ICU patients has been reported in very few studies [5, 99, 104]. The 6-MWT was used to study survivors of ARDS, where distance walked was found to be most associated with corticosteroid use, acquiring a secondary illness during critical illness, rate of resolution of lung injury score and organ failure score during the first year of recovery [5]. References values are available from several cohorts of healthy individuals [121-124].

2.2 Long-term HRQL of ICU survivors

Measures of health related quality of life (HRQL) normally assess the physical, emotional and social dimensions of health [125]. HRQL has become a popular outcome, beyond mortality, in the critical care follow-up literature [6], as it is capable of assessing the impact of critical illness on several health domains [126]. Many studies have reported that patients have reduced HRQL long-term after critical illness [6, 101, 127-133]. Some studies have shown patients' HRQL to recover over time, sometimes back the patient's pre-ICU HRQL [6, 99, 104, 134-136]. Cuthbertson et al [25] found that the physical health domains, although below the population norms at all times, recovered to pre-morbid state at 1 year, but fell again at the 5-year mark. Interestingly, the mental health domains reached the normal population level by 6 months post-ICU. Cheung et al [137] showed that at 2 years post-ICU physical health was still reduced but some of the mental health domains had returned to normal. Other studies have also shown that physical deficits remain long-term while the mental domains of health recover more rapidly [138, 139]. Besides the general ICU population HRQL has been evaluated in several patients populations within critical illness, including ARDS, COPD, trauma and sepsis [137, 140-143]. Karlsson et al [142] recently showed that patients HRQL with severe sepsis was significantly lower at 17 months post discharge than at the patients pre-ICU. Orwelius et al [144] also showed that HRQL was reduced 26 months post-ICU, although they found that a large proportion of reduced HRQL could be attributed to pre-existing disease. Conflicting results have been reports as to the ability of some ICU demographics such as severity of illness, age and admitting diagnosis to predict post ICU HRQL [133].

2.2.1.1 Measuring HRQL post-ICU

There have been several instruments used to assess HRQL in ICU populations including the, Medical Outcomes Study 36-item Short Form (SF-36), EuroQol-5D (EQ-5D), Sickness Impact Profile and Nottingham Health Profile [6]. A recent panel of experts determined that the best two instruments available to assess HRQL for ICU survivors as a long-term outcome are the SF-36 and the EQ-5D [145, 146]. Both of these instruments have been used extensively in ICU populations and have been validated repeatedly in many different study populations [137, 140, 142, 143].

The SF-36 profiles 8 dimensions of health (physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE). These 8 domains can be summarized into a Physical Component Summary (PCS) and a Mental Component Summary (MCS). Each domain can be represented as a percentage ranging from 0-100 or they have been standardized to national data so that a score of 50 represents the population average.

The EQ-5D examines 5 domains of health assessing mobility, self-care, usual activities, pain or discomfort and anxiety or depression. As well, the instrument contains a visual analogue scale (VAS), where patients are able to rate their own perception of health [146]. The scores of the EQ-5D can be represented as either the VAS alone or as a health profile based on the 5 domains of health measured. Each dimension of the EQ-5D has 3 levels of severity: no problems, some problems and severe problems (1 to 3, respectively).

2.3 Neuropsychological Sequelae of ICU

There is growing evidence within the critical care literature that survivors of critical illness can experience a range of psychological disorders, capable of reducing long-term HRQL [147, 148]. The highest reported psychological disorders included posttraumatic disorder (PTSD), depression, anxiety, cognitive impairments and delirium [149, 150]. High prevalence of psychiatric disorders have been reported within weeks and up to several years after hospital discharge [151-153], leading to delayed recovery from critical illness.

The reported prevalence of PTSD post-ICU ranges from 5% to 63% [15, 16, 154, 155]. A recent study by Myhren et al [156] showed that PTSD symptoms were prevalent in 27% of ICU survivors 1 year after discharge. A systematic review of PTSD in survivors of ICU reported that the median point prevalence of clinically significant symptoms for PTSD to be 22%, with most studied within one year post-ICU (n=1104) [157]. Of note, it is thought that the prevalence of PTSD may even be higher because many studies exclude patients with pre-existing psychological morbidity, which has been shown to be a predictor of post-ICU PTSD [154, 157]. It is noted that the prevalence of PTSD is unknown and unlikely capable of being quantified based on previous research due to methodological limitations, including a lack of consistent usage of the same instruments [15, 16]. Although, it is remains likely that the prevalence of PTSD in ICU survivors is significantly higher than in the general population [158]. Several studies have identified risk factors during critical illness for the development of PTSD symptoms. Delusional memories of the patients' critical illness have been repeatedly linked to the development PTSD symptoms [153, 157, 159]. Other suggested predictors of PTSD symptoms include: prior psychotic disorders, administering benzodiazepines during critical illness, long duration of mechanical ventilation and long-term ICU length of stay [147, 157, 160, 161]. It has also been shown the presence of PTSD symptoms is associated with reduced long-term HRQL [157, 159, 162]. Recently it was shown in a large study that ICU diaries written for the patient could reduce the incidence of PTSD to 5% from 13% in the control group at 3 months post-ICU [163].

The prevalence of depression in the ICU survivor population has ranged from 10% [138] to 47% [160]. A recent systematic review [164] found the median point prevalence of depression symptoms to be 26% (n=1213). The prevalence of anxiety post-ICU has been found to be between 11% and 47% [138, 150]. Rattray et al [165] recently showed that the prevalence of anxiety and depression did not decrease from 2 to 6 months post ICU discharge, although this was contrary to previous results published by the authors.

Ringdal et al [140] showed that trauma patients who had delusional memories from their critical illness had higher prevalence of depression (51% vs. 29%) and anxiety (48% vs. 26%). Other studies have also shown a connection between ICU memories and psychiatric symptoms [165, 166]. Risk factors such as sequential organ failure, surgical patients, benzodiazepines, mechanical ventilation, ICU LOS, days of sedation and poor sleep quality have been linked to depression [147, 161, 167, 168]. A study assessing ARDS survivors found that being a younger patient, female sex or having an alcohol dependence was predictive of depression post-ICU and that Pa02/Fi02 ratio and number of days ventilated was predictive of anxiety post-ICU [169]. It has also been shown that there is an association between the presence of depression and anxiety and poor HRQL [140, 147]. Sukantarat et al [150] suggested that the reduction in functional status of ICU survivors might contribute to the prevalence of psychiatric disorders present in this patient population.

A recent study implemented an early intra-ICU psychological intervention and found that it significantly reduced rates of anxiety (8.9% vs. 17.4%), depression (6.5% vs. 12.8%) and risk of PTSD (21.1% vs. 57%) [170]. Of note a substantially lower number of patients in the treatment group were on psychiatric medication at 12 months (41.7% vs. 8.1%).

2.3.1.1 Measuring PTSD, anxiety and depression

The 'gold standard' method for the diagnosis of PTSD is through an assessment by a psychiatrist, although several instruments have been developed to screen for symptoms of PTSD [15, 16, 171]. Some of the well validated PTSD screening instruments used in the ICU follow-up literature include, The Davidson Trauma Scale (DTS) [101, 172], the Impact of Events Scale (IES) [153, 156, 160, 165] and the Posttraumatic Stress Syndrome 10/14-questions inventory (PTSS-10/14) [159, 162, 173].

The Davidson Trauma Scale (DTS) is a validated self-rating scale that has been used to screen for PTSD in patients who have undergone a traumatic event, including critical illness [172, 174]. It is a 17-item scale that assesses all of the DSM-IV symptoms of PTSD. The SPAN scale is a shorter 4-item scale derived from the DTS that has been shown to have equivalent sensitivity and specificity to the original DTS [175]. Brody et al [175] developed the SPAN scale using the four items from the DTS that have the greatest difference in severity between subjects with PTSD and without, these include: Startle, Physiological arousal, Anger, and Numbness. Each item scores between 0-4 on the severity of the symptom, a total score of 5 or greater has been shown to indicate greatest likelihood of developing PTSD. The advantage of the SPAN scale is that it is a brief diagnostic screening test. However, it is not sufficient to formally diagnose PTSD, and only designed to be used as a screening tool of symptoms of PTSD.

Several screening tools for anxiety and depression have been developed [164, 176]. Within the ICU follow-up literature some studies have examined depression or anxiety individually [151, 176], however the majority of studies have used the Hospital Anxiety and Depression Scale (HADS) [101, 138, 140, 153, 156, 160, 165, 167, 170, 177]. The HADS is a 14-item questionnaire, measuring both depression and anxiety on separate scales [178]. The HADS scale is designed to detect mild levels of disorder, while avoiding questions dealing with suicide and somatic items. Scores can range from 0 to 21 for each of the depression and anxiety scales. Different cut points exist for different levels of disorder, a score of less than 8 is not a case, 8 to 10 is a probably case and greater than 10 represents a definite case of the disorder for either subscale. A review of several anxiety measurements found that the HADS has high reliability and validity, while taking less than 5 minutes to complete [125].

2.4 Sleep Disorders in ICU survivors

The study of sleep has predominantly been focused on patients while they are in the ICU. A number of studies have been published describing sleep in the ICU, stating that is it disrupted [179, 180]. In the ICU, patients experience increased arousals and awakenings and decreased time is spent in rapid eye movement and slow wave stages of sleep [179, 181]. The causes of sleep disruption in the ICU are primarily unknown. Noise disruption has been found to account for less than 20% of arousals [181]. The mode of mechanical ventilation, severity of illness and pain have all been shown effect sleep quality [182, 183]. Sleep deprivation is thought to contribute to increased physical and psychological morbidities leading to delayed recovery [180, 184]. It is also thought that in septic patients, sleep deprivation may lead to increased mortality [185].

There has been little study examining long-term sleep quality of patient once discharged from the ICU. Only two studies exist reporting on the sleep quality of ICU survivors. Orwelius et al [17] examined sleep disturbances at 6 and 12 months after ICU discharge. They examined sleep disturbances using the Basic Nordic Sleep Questionnaire, 723 patients responded at 6 months and 497 at 12 months. They found that there was no decrease in sleep quality from pre-ICU to 6-months after discharge. They did find however that the ICU group had poorer quality of sleep, longer sleep latency, and shorter lengths of sleep compared to a 6000-person reference group. Concurrent disease, along with ICU admission, was associated with sleep disturbances, where as severity of illness, length of stay and admitting diagnosis were not. They also found a minor correlation to HRQL and sleep disturbances, where body pain, general health, vitality and limitations due to physical problems were associated with increases in certain aspects of sleep disturbances. The major limitation with this study, as mentioned by the authors, is the validity of the sleep questionnaire chosen. Lee et al [18] conducted a small case series study of 7 patients, examining long-term sleep disorders in patients with ARDS who required an ICU stay. These patients were part of larger cohort but were individuals that developed sleep difficulties, 6 months after ICU, that were not present before their critical illness. They examined these patients sleep at least 6 months after ICU discharge using both questionnaires and polysomnography (PSG). All patients showed PSG abnormalities. The subjective assessment sleep showed that all patients have insomnia after ICU discharge. All patients were shown to have chronic sleep disorders, 5 patients had chronic conditioned insomnia, 1 patient had parasomnia and 1 patient had obstructive sleep apnea. It is important to recognize the limitations of this study due to the small study sample.

2.4.1.1 Measuring sleep quality

PSG is the 'gold standard' method for conducting a sleep study and analyzing sleep quality [186]. However, this method is not always practical because of its high cost and high resource demands. Other methods have been developed for measuring sleep disruption that are much less labour intensive and have equivalent accuracy to PSG, including Actigraphy. The Actigraph device is a wrist watch that is capable of tracking the movements of the patient during sleep and determine if the patient is sleeping [186]. The watch records the duration, intensity and frequency of the patient's movements. Actigraphy has been previously used in the ICU, however no reports exists using the device to follow-up on patients sleep quality [187].

Subjective sleep questionnaires are also a valid method to assess sleep dysfunction. Devine el at [188] conducted a systematic review, assessing 22 different sleep questionnaires that have been used to study sleep dysfunction. According to the review two of the highest cited questionnaires were the Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale (ESS). The PQSI is an effective self-reported instrument that differentiates "poor" quality sleep from "good" quality sleep in seven areas: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications and daytime dysfunction over the last month [189]. Thus, the PSQI has the ability to assess general sleep quality.

The ESS is a questionnaire that assesses a patient's subjective daytime sleepiness [190]. Higher scores have been able to positively screen individuals with sleep problems [191]. The scale asks the individual 8 questions regarding their chances on sleeping during generally low level stimulating activities. Scores range from 0 to 24, individuals scoring greater than 9 are recommended to see a sleep specialist.

The PSQI and ESS have both been validated in numerous patient populations and shown to have high reliability and validity [188, 189, 192]. The instruments have also been shown to be stable over long periods of measurement [192]. The PQSI has also been shown to correlate with psychological dysfunction [188, 193]. However, it is important to recognize that these questionnaires are only capable of assessing perceived sleep-wake symptoms, which may not be representative of patient's objective sleep quality [193].

2.5 Conclusion

The current literature has highlighted the need for additional long-term follow-up data on ICU survivors. A quantitative measurement of long-term ICU survivor's peripheral muscle strength and its relationship to physical function and HRQL does not exist. No study has used the recommended method, hand-held dynamometry, to assess longitudinal muscle strength in ICU survivors [114]. The risk factors for muscle weakness and impaired physical functioning remain unresolved. The long-term prevalence of psychological abnormalities, sleep disorders and their relationship to HRQL and physical functioning remains unknown. Several studies have found that sepsis is major risk factor for morbidity following critical illness including, neuromuscular dysfunction, sleep problems and reduced HRQOL. Understanding the physical and mental health recovery from intensive care remains in its infancy. Given the data available has shown these patient likely suffer long-term morbidity from critical illness, further study into these sequelae is needed. Therefore, the goal of this study is to: 1) Quantitatively examine long-term muscle weakness and physical functioning and their relationship to HRQL in ICU survivors. 2) Assess the long-term prevalence of psychological abnormalities and sleep issues amongst ICU survivors and their relationship to HRQL and physical functioning.

Chapter Three: Objectives

3.1 Research Question 1

In survivors of ICU at 2 months post hospital discharge is there evidence of a reduction in peripheral muscle strength measured by hand-held dynamometry or physical functioning when compared to age and sex normative data and non-ICU trauma patients?

3.1.1 As secondary questions:

i. Does sepsis increase the degree of muscle weakness and decreased physical functioning at 2 months post hospital discharge?

ii. If a reduction in physical functioning is present does it improve between the 2 and 4-month follow-up time points?

iii. Is there a relationship between a decline in peripheral muscle strength and physical functioning?

iv. Is there is a relationship between long-term muscle weakness or physical functioning and HRQL?

v. Does severity of illness, organ dysfunction, days of mechanical ventilation and ICU or hospital length of stay predict a decline in long-term muscle weakness or decreased physical function.

3.2 Research Question 2

Is there evidence of reduced physical and mental HRQL at the 2 and 4 months post hospital discharge in survivors of critical illness.

3.3 Research Question 3

What is the prevalence of anxiety, depression and PTSD in critical illness survivors at 2 and does it change at 4 months post hospital discharge?

3.3.1 As secondary questions:

i. Does the presence of sepsis increase the prevalence of psychiatric abnormalities at 2 months post hospital discharge?

ii. Is the presence of psychiatric abnormalities associated with a decrease in HRQL or physical functioning?

3.4 Research Question 4

Is there evidence of long-term reduced sleep quality and increased sleep disruptions in survivors of critical illness at 2-months post hospital discharge?

3.4.1 As secondary questions:

i. Does the presence of sepsis increase the prevalence of reduced sleep quality at 2 months post hospital discharge?

ii. Is the presence of sleep abnormalities associated with a decrease in HRQL or increased prevalence of psychological abnormalities?

iii. Does severity of illness, days of mechanical ventilation, ICU or hospital length of stay predict a reduction in long-term objective sleep quality?

Chapter Four: Methods

4.1 Study Design

This was a prospective longitudinal cohort study of patients who were admitted to the ICU or Trauma Unit at the Foothills Medical Center (FMC) between July 1st, 2008 and July 31, 2012. All patients admitted to the ICU or Trauma Unit were screened for eligibility to be followed-up post hospital discharge. Patients were followed-up in a clinic setting where a variety of outcome measures were examined.

4.2 Study Sample

At the time of study sample enrolment, the FMC contained a 24-bed multidisciplinary ICU, which also served as the trauma center for southern Alberta. Trauma patients who are not critically ill are admitted to the Trauma Unit at the FMC. All adult patients (≥18 years) admitted to the FMC ICU during the study timeframe were considered for enrolment based on specific set of inclusion criteria (table 1). Patients had to have a minimum 4-day length of ICU stay and expected to survive to discharge in the ICU or Trauma Unit. During the study period more patients were eligible for enrolment than could be accommodated at the follow-up clinic because of limited resources. Patients eligible for enrolment were added until the clinic appointments were full, resulting in patients who met the inclusion criteria being declined enrolment.

Table 1. Inclusion and exclusion criteria of the ICU follow-up clinic

Inclusion criteria	Exclusion criteria
Patients ≥ 18 years of age. Patients resident in the Calgary Health Region to enable long-term follow-up. Any patient staying longer than 4 days in the ICU or Trauma unit.	Patients not meeting specific inclusion criteria. Head injured patients that will be unable to complete the follow-up questionnaires. Patients with pre-existing cognitive impairment, or with acute brain injury who in the opinion of the ICU attending physician were expected to have significant cognitive dysfunction. Patients not expected to survive to hospital discharge. Patients enrolled in other types of follow up or rehabilitation programs. Patients who were expected to survive, but require discharge to a long-term care facility. Patients who cannot speak English or without a family member who can speak English that is committed to attending the clinic with them on an ongoing basis.

Patients in the ICU were screened for eligibility during the initial 48 hours and approached for follow-up once they had been admitted to the ICU for a minimum of 4 days. Attendance at the clinic was presented as a natural continuation of care following hospitalization, which they had the option to refuse. We sought permission from these patients to include their clinic data in our study.

Likewise, all trauma patients were followed in a Trauma follow-up clinic. A member of the Trauma team sought permission for us to approach these individuals for consent to participate in the study.

Patients enrolled in the study were assessed according to one of three groups, severe sepsis in the ICU, non-sepsis ICU and non-ICU trauma. The non-ICU trauma patient group will serve as a comparator cohort representing patients with a severe illness characterized by a systemic inflammatory response, but not severe enough to require ICU admission. To be considered as severe sepsis patients had to meet 2 of 4 SIRS criteria based on established guidelines, have a confirmed source of sepsis and a minimum of one organ dysfunction during their ICU stay. All other ICU patients seen in the clinic that did not meet the above criteria were considered as non-sepsis ICU. For trauma patients they required an ISS of >11 based on established guidelines and 2 of 4 SIRS criteria at time of admission..

4.3 Follow Up Design

All enrolled patients from the ICU were followed-up at approximately 2 months post hospital discharge. Patients willing to return and thought to benefit from an additional clinic visit were subsequently followed-up at 4 months post hospital discharge. Trauma patients were only followed-up at 2 months because this is the only time point the Trauma Services follows these patients.

Once the inclusion criteria were met ICU patients were approached either in the ICU or the hospital ward, and given information about the ICU follow-up clinic. Patients or their family members were given a brochure regarding the clinic and we discussed the potential importance of ICU follow-up. When the patient was discharged from the hospital an appointment at the follow-up clinic was scheduled for 2-months after their hospital discharge date. Trauma Services organized the follow-up of trauma patients at 2-months after hospital discharge.

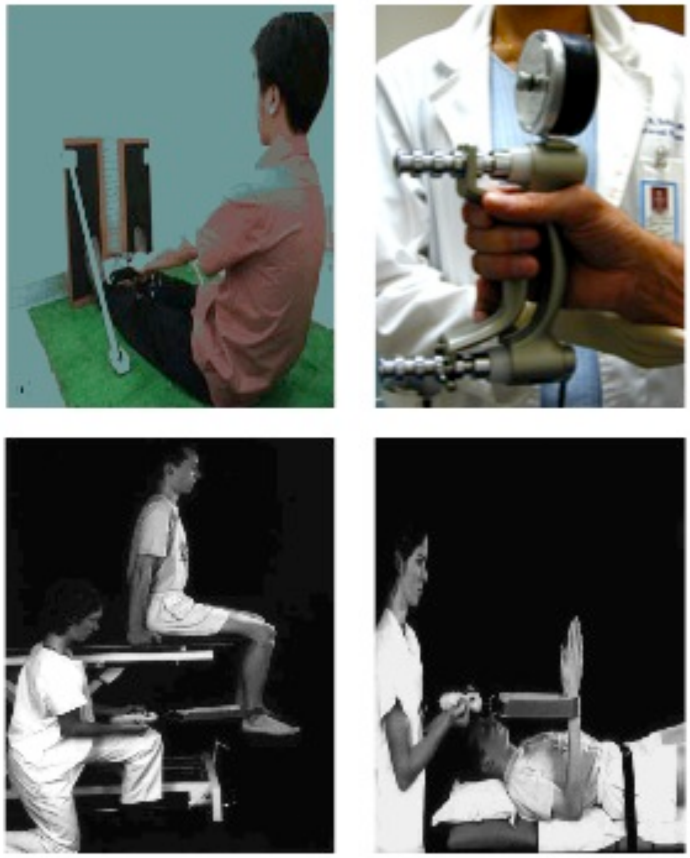
During the ICU patients' clinic visit, detailed surveys were filled out first then the 6-MWT and muscle strength testing were performed, normally taking 2 hours to complete. The surveys (described in detail below) included assessments of health related quality of life (HRQL), screening for anxiety, depression, PTSD and sleep abnormalities. Trauma patients were only subjected to the muscle strength-testing component.

4.4 Data Measurement

4.4.1 Muscle strength testing

Hand-held dynamometry was used in the clinic to measure muscle strength (Figure 1). This method was chosen due to its ease of use, low cost, ability to standardize and well established published methods for measurement. The Jamar hydraulic hand dynamometer and the Chatillon hand-held dynamometer (K-MSC-200), which is capable of measuring forces up to 100kgs at 0.01kg increments, were used. All measurements were made in kilograms to the nearest hundredth of a kilogram.

Figure 1. Examples of hand-held dynamometry and the standardized positions [115, 194]



During the strength testing each muscle group was measured according to previously validated protocols, with specific positioning of each muscle group [32]. These methods ensure reliability and accuracy for comparison of multiple tests. Table 2 lists the muscle groups in the order they were tested, which includes the handgrip, triceps, biceps, foot dorsiflexors, hamstrings and quadriceps. During the muscle strength-testing portion of the patient's clinic visit the patient was asked to exert a maximal force for 3-4 seconds (the time required to exert maximal strength) against the dynamometer held stationary. Standardized phrases for encouragement, such as "push as hard as you can", were used. Three measurements were collected for each muscle group, alternating between sides after each trial, giving at least 15 seconds of rest between each trial. One examiner performed all of the strength testing for the study. There is no published recommendation on which measure to report. At the end of the three measurements, the maximum result in each muscle group was used. The National Isometric Muscle Strength (NIMs) Database Consortium [32] was used for age and sex standardized normative values. The NIMS database was chosen over the other reference values [115-117], because it used the largest sample size (n=493) and had a large age range of included subjects (18 to 80 years).

Table 2. Muscle groups measured by hand-held dynamometry and the standardized position and setup to test each muscle group [32]

Muscle group	Muscle action	Patient position	Strap Position
Hand and wrist-finger flexors	Prehension	Seated, elbow flexed 90°	n/a
Biceps	Elbow flexion	Supine, elbow flexed 90°	At wrist
Triceps	Elbow extension	Supine, elbow flexed 90°	At wrist
Tibialis anterior	Dorsiflexion	Supine, ankle flexed 90°	Around metatarsals
Quadriceps	Knee extension	Seated, knee flexed 90°	Around malleolus
Hamstrings	Knee flexion	Seated, knee flexed 90°	Around malleolus

4.4.2 Global physical functioning

The 6MWT was used for an objective assessment of functional exercise capacity and overall global physical functioning. The guidelines and procedures set by the American Thoracic Society for the 6MWT were followed [118], and are summarized in the remainder of the paragraphs. If the patient arrived at the clinic with a history of using a walker, other walking aids or supplemental oxygen, they were then also used during the test. Patients were given at least a 20-minute rest period before the test begun. The 6MWT was performed indoors along a hallway 30m in length. The patients were asked to walk as fast as they could without running, down the hallway and turning back at a marked spot to complete a lap of 60m. Patients were told that they could rest if needed and stop the test at any time if they were not feeling well. During the test the technician remained at the starting area and followed the standardized protocol using predetermined phrases for instructions and encouragement. The total distance covered over the 6 minutes was recorded. Values were rounded to the nearest meter. During the rest period before the test began and after the test had finished, oxygen saturation, dyspnea, and overall fatigue was measured using a pulse oximeter and the Borg scale. Population age and sex standardized normative values for the 6MWT were obtained from Enright et al [121] and Chetta et al [122].

During the clinic patients first filled out all the surveys and then were taken to do the 6-MWT. After the 6-MWT patients were given at least 20 minutes of rest time before being asked to perform the muscle strength testing. Patient's height and weight were measured using a clinic scale.

4.4.3 HRQL Measurements

The following instruments were used to assess HRQL in our population. The questionnaires were administered during the follow-up clinic prior to the 6-

MWT and muscle strength testing by a team member with prior experience using the questionnaires.

4.4.3.1 Short Form-36

The SF-36 version 2.0, 4-week recall was used in the clinic. Scores for each domain and composite score can be calculated and referenced to scores of the general Canadian population [195]. The SF-36 scores were calculated according the guidelines published by the issuing body of the questionnaire [196]. Scores for each domain and composite score were reported both as a percentage ranging from 0 to 100 and a norm based score for the Canadian populations ranging from 0 to 100, where a value of 50 represents a normal score.

4.4.3.2 EuroQol-5D

The EQ-5D questionnaire was used to further assess HRQL. Each domain was assessed and reported as either a 1, 2 or 3 which represented no problems, some problems or severe problems, respectively.

4.4.4 Anxiety and Depression Screening

The HADS was used to assess anxiety and depression [178]. The HADS was used because of its already extensive use in the ICU follow-up literature, ease of administration and reliability and validity. The administration of the psychological questionnaires was standardized as described in 4.4.3.

4.4.5 PTSD Screening

The SPAN scale was chosen to screen for PTSD in our population it was administered and standardized as described in 3.4.3.

4.4.6 Sleep Quality Assessments

4.4.6.1 Sleep Questionnaires

In order to assess the quality of sleep in ICU patients after hospital discharge, by means of questionnaire, the PSQI was used. A second sleep questionnaire used in the clinic was the ESS. The administration of the questionnaires was standardized as described in 4.4.3.

4.4.6.2 Actigraphy

We used Actigraphy in our patient population, as an objective measure of sleep disruption and sleep quality. The Actigraph device was given to patients to take home and be worn for three days and then mailed back to us. The patients were also sent home with a simple questionnaire asking them to comment on sleep quality and other sleep related questions. Not all patients were assessed with Actigraphy because there were a limited number of watches and it can take up to two weeks before the watch is returned to the clinic in the mail. Patients were selected at random to receive an Actigraph watch. Previously validated algorithms, provided by Ambulatory Monitoring Inc, New York, USA, were used to analyze sleep and wake cycles [197].

4.5 Data Entry and Management

A trained technician entered all clinic data into an Excel database. Data was managed using Stata 11.0. ICU specific data was exported from the ICU TRACER database. All clinic data was reviewed for errors after being entered into the database.

4.6 Data Analysis

All data analysis was performed using Stata 11.0 (Stata Corp, College Station, TX).

4.6.1 Analysis of Research Question 1

Each variable was summarized using descriptive statistics and boxplots. Within and between group comparisons were analyzed using the appropriate Student's t-test or Wilcoxon Rank-Sum test, depending on data characteristics. To summarize the strength testing results, the maximum value recorded of the three trials was used for each muscle group and indexed with the patient's predicted peak force for that specific muscle group. The specific muscle group indexes were then averaged into an upper (grip, triceps and biceps) or lower extremity group (quadriceps, hamstrings and dorsiflexors) (anti-gravity), distal (grip and dorsiflexors) and proximal group (biceps, triceps, hamstrings and quadriceps) and an overall group. Comparisons were made for each muscle grouping within and between the severe sepsis, non-sepsis ICU and non-ICU trauma for the 2 months follow-up time point. Comparisons of the muscle strength results were made between the 1st and 2nd follow-ups. Slopes for change in strength were calculated and compared by subtracting the 2nd follow-up result from the 1st follow-up result and dividing this by the time that had elapsed in days.

4.6.1.1 Analysis of Secondary Questions

To assess the relationship between muscle strength and the 6-MWT linear regression models were created to independently evaluate each muscle group. To assess the relationship between HRQL and muscle weakness linear and logistic regression models were used, with muscle weakness as an independent variable, and the SF-36 health domains and the component scores and the EQ-5D domains as dependent variables. The risk factors of muscle weakness and physical function were analyzed using univariate linear regression models. We examined ICU and hospital lengths of stay (LOS), severity of illness, level of organ failure and number mechanical ventilation days as independent variables.

4.6.2 Analysis of Research Question 2

Descriptive statistics and statistical comparisons were used as described in 4.6.1 to summarize the HRQL data across the follow-up time points and between the patient groups.

4.6.3 Analysis of Research Question 3

Descriptive statistics were used as described in 4.6.1 to report the prevalence of depression, anxiety and PTSD. Odds ratios were used to assess whether problems reported on the EQ-5D domain increased the odds of psychological abnormalities. A logistic regression was used to independently assess how muscle strength, physical functioning or chronic health points may influence the odds of having psychological abnormalities.

4.6.4 Analysis of Research Question 4

Descriptive statistics were used as described in 4.6.1 to report the prevalence of poor sleep quality measured with the PQSI and ESS questionnaires and the Actigraph device. A univariate linear regression was used to assess the relationship between reported and objective sleep quality. A logistic regression was used to independently assess how domains of the EQ-5D and anxiety and depression influence the odds of reporting poor perceived sleep quality. Finally, a linear regression was used to assess the same risk factors described in 3.6.1.1 for poor objective sleep quality.

4.7 Ethical Concerns

Ethical approval for this study was obtained from the Conjoint Health Research Ethics Board of the University of Calgary. Consent was obtained from all patients to include their clinic data in our study. All hardcopy data was stored in a secure location and electronic data was stored on a password protected computer. All patient names and identifiers were replaced with unique study identifiers. Data collected from the patients was provided back to the responsible physician.

Chapter Five: Results

5.1 Patient Characteristics

A total of 56 patients that met the inclusion criteria during the study period were followed up at least one time post hospital discharge (table 3). An additional 19 patients were seen during a second follow-up visit. 13 patients admitted for traumatic injuries but not admitted to the ICU were seen once. The median age and percent male of patients followed-up with sepsis in the ICU, non-sepsis in the ICU and non-ICU trauma patients was 59, 62, and 43 years and 57%, 48%, 69% males respectively. The “2 month” follow-up period was at an average of 74 days post hospital discharge. Similarly the “4 month” follow-up period was at an average of 146 days (4.8 months) post hospital discharge. The mean follow-up time was considerably shorter for the trauma controls than the ICU patients (34 days vs. 74 days). The median ICU and hospital length of stay was 13 and 12 days respectively for septic patients compared to 11 days for both the ICU and hospitals stays of non-sepsis patients. The median hospital stay of the non-ICU trauma patients was slightly lower at 7 days. The patients with sepsis had higher mean APACHE II and SOFA scores (measure of illness severity and organ failure) than the non-septic patients (22 and 13 vs. 16 and 9 respectively).

Table 3. Patient demographics by patient group

Variable	Sepsis ICU	Non-Sepsis ICU	Trauma non-ICU
No. of patients			
1st follow-up	35	21	13
2nd follow-up	12	7	-
Age, yrs (median, iqr)	59 (45, 67)	62 (38, 70)	43 (24, 46)
Sex, % male	57	48	69
Diagnostic category, n (%)			
Respiratory	74	57	-
Cardiovascular	0	0	-
Gastrointestinal	9	19	-
Genitourinary	11	0	-
Other	6	24	-
Chronic health points, (%)			-
Yes	32	10	-
No	68	90	-
APACHE II score (mean, SD)	21 (6)	16 (4)	-
SOFA maximum value (mean, SD)	13 (3)	9 (3)	-
Ventilator, days (median, iqr)	9.5 (6, 14)	7 (4, 10)	0
Length of ICU stay, days (median, iqr)	13 (7, 19)	11 (6, 12)	-
Length of hospital stay, days (median, iqr)	12 (6, 23)	11 (8, 16)	7 (6, 10)
Mean time to first follow-up, days (SD)	72 (28)	78 (28)	34 (13)
Mean time to second follow-up (SD)	143 (34)	150 (34)	-

5.2 Physical Function

The results of the muscle strength testing and 6-MWT at 2 months follow up are presented in table 4. Amongst all ICU patients peripheral muscle strength was reduced comparatively in all muscle group when compared to age and sex standardized data. The median percent predicted muscle strength for the quadriceps was 59% for ICU patients, which was the weakest muscle group measured. The dorsiflexors (0.62) and grip strength (0.65) were the next weakest respectively. The overall composite median for all muscle groups was 72% of predicted muscle strength. The lower body and proximal muscle groups were weaker comparatively to the upper body and distal muscle groups measured. All muscle groups median percent predicted muscle strength, excluding the triceps, were significantly lower than 1.0 ($P<0.01$). Figure 2 displays boxplots of the percent-predicted muscle strength for all ICU patients by muscle group and an overall composite average.

The trauma patients not admitted to the ICU had higher median percent predicted muscle strength in all muscle groups when compared to all ICU patients. The median maximum grip ($P=0.005$), biceps ($P=0.04$) and hamstrings ($P=0.03$) strength of ICU patients were significantly lower than the non-ICU trauma patients. The median percent predicted grip strength of ICU patients was the only individual muscle group statistically lower than trauma patients (0.65 vs. 1.24 $P=0.01$). The median indexed ICU overall composite strength score was also statistically lower than the trauma patients (0.7 vs. 1.1, $P=0.08$).

When comparing the median indexed muscle strength of sepsis to non-sepsis ICU patients, grip strength (0.53 vs. 0.67) and triceps (0.67 vs. 0.79) were on average lower, however not statistically significant. There was no difference between the groups with respect to the triceps and quadriceps. Interestingly, the average index for the lower body muscle groups was greater in the patients who had sepsis vs. non-sepsis, although no differences were statistically significant (hamstrings 0.79 vs. 0.68 and dorsiflexors 0.62 vs. 0.53).

The median distance walked during the 6-MWT was 382m for all ICU patients at the 2-month follow up period. The median percent predicted distance walked for all patients was 72% ($P<0.001$). The median percent predicted distanced walk was greater in the sepsis group when compared to the non-sepsis group (0.77 vs. 0.69, $P=0.16$).

Table 4. The maximum and indexed muscle strength and distance walked during the 6-MWT by patient group at 1st follow-up after hospital discharge

Muscle group, (median, iqr)		All ICU	Sepsis ICU±	Non- Sepsis ICU	Trauma non-ICU
Grip∗	**Maximum (kg)∫**	20.4 (9.1, 30.6)	19.7 (8.8, 28,4)	24.3 (11.3, 34.0)	36.3 (20.4, 43.1)
	Indexed∫	0.65 (0.25, 1.08)	0.53 (0.24, 1.0)	0.67 (.27, 1.2)	1.24 (0.46, 1.5)
Triceps	**Maximum (kg)**	12.3 (8.7, 16.7)	11.1 (8.4, 15.5)	12.9 (10.7, 17.6)	16.9 (10.9, 18.4)
	Indexed	0.71 (0.45, 1.26)	0.67 (.41, 1.3)	0.79 (0.53, 1.4)	1.25 (0.57, 1.36)
Biceps∗	**Maximum (kg)∫**	14.5 (11.7, 19.0)	14.3 (11.7, 18.7)	16.1 (11.7, 20.5)	22.1 (16.3, 24.4)
	Indexed	0.72 (0.45, 1.26)	0.72 (0.45, 1.1)	0.73 (0.44, 1.4)	1.18 (0.61, 1.33)
Hamstrings∗	**Maximum (kg)∫**	13.2 (10.3, 17.6)	13.2 (11.2, 16.8)	14.6 (10.0, 19.28)	18.1 (14.6, 22.4)
	Indexed	0.77 (0.47, 1.14)	0.79 (0.48, 0.96)	0.68 (0.47, 1.3)	0.96 (0.63, 1.3)
Quadriceps∗	**Maximum (kg)**	20.3 (16.4, 25.6)	19.7 (16.4, 25.1)	20.9 (17.7, 28.3)	24.8 (20.1, 28.1)
	Indexed	0.59 (0.35, 0.88)	0.59 (0.33, 0.88)	0.58 (0.37, 0.88)	0.72 (0.44, 0.86)
Dorsiflexors∗	**Maximum (kg)**	13.7 (10.6, 17.2)	14.1 (9.9, 17.1)	13.0 (11.8, 17.3)	17.4 (15.3, 18.8)
	Indexed	0.62 (0.42, 0.92)	0.62 (0.42, 0.92)	0.53 (0.4, 0.96)	0.83 (0.55, 0.91)
Overall∗	**Indexed**	0.72 (0.41, 1.07)	0.72 (0.41, 0.99)	0.79 (0.42, 1.12)	1.1 (0.53, 1.2)
Upper∗	**Indexed**	0.78 (0.42, 1.16)	0.78 (0.39, 1.1)	0.88 (0.43, 1.14)	1.22 (0.52, 1.4)
Lower∗	**Indexed**	0.66 (0.45, 0.93)	0.66 (0.44, 0.91)	0.58 (0.45, 1.0)	0.85 (0.53, 1.4)
Proximal∗	**Indexed**	0.49 (0.35, 0.88)	0.49 (0.33, 0.81)	0.62 (0.35, 1.0)	0.83 (0.41, 0.90)
Distal∗	**Indexed∫**	0.64 (0.32, 1.02)	0.64 (0.32, 0.91)	0.62 (0.35, 1.1)	1.1 (0.51, 1.1)
6-MWT∗	**Maximum (m)**	382 (291, 480)	381 (313, 495)	410 (240, 460)	
	Index	0.72 (0.55, 0.88)	0.77 (0.57, 0.9)	0.69 (0.53, 0.77)	

∗ Wilcox rank-sum test p-value <0.05 comparing median indexed muscle groups to a median value of 1

∫ Wilcox rank-sum test p-value <0.05 comparing indexed medians between all ICU patients and non-ICU trauma patients

± No p-values <0.05 comparing sepsis vs. non-sepsis indexed muscle groups

Figure 2. Boxplots of all ICU patients' indexed muscle strength at 1st follow-up after hospital discharge

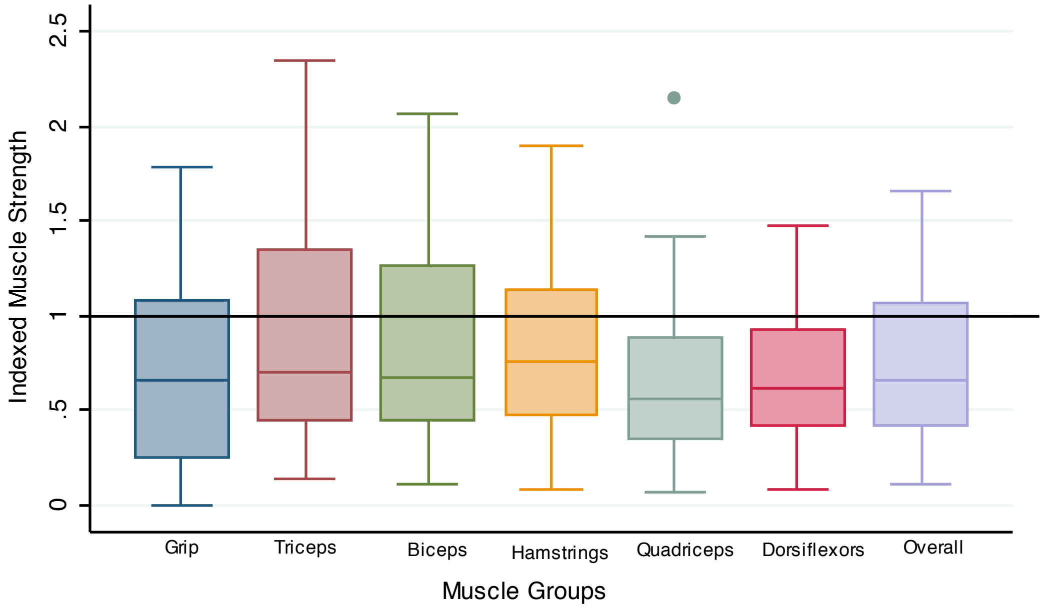


Table 5 shows a comparison of 19 patients muscle strength and distanced walked from their first follow-up to the second follow-up visit. All muscle groups, except grip strength, had an increase in maximum and percent-predicted muscle strength. At the 4-month follow-up time point the median percent predicted muscle strength remained less than 100% for grip (0.86), hamstrings (0.94), quadriceps (0.73) and dorsiflexors (0.71). Triceps and biceps all had median predicted muscle strength greater than 100% at the 4-month follow-up. The overall composite median percent predicted for all muscle groups increased to 104% from 86%. It should be noted that the 19 patient who returned for follow up had considerably higher percent predicted strength results at the 2-month time period when compared to all ICU patients (86% vs. 52%, respectively for overall composite percent predicted muscle strength) in table 3. The median maximum grip strength decreased slightly at the second follow-up (21.3 to 20.4), although the median percent predicted grip strength increased from 0.79 to 0.88. The discrepancy between a decrease in median grip strength and an increase in median percent predicted grip strength is due to small changes in max strength having a large impact on percent predicted for patients with low predicted strength relative to others.

The median percent predicted distance walked during the 6-MWT did not change from 77%, although the 25th and 75th percentile increased at the second follow-up.

Table 5. The maximum and indexed muscle strength and distance walked during the 6-MWT at first and second follow-up after hospital discharge for all ICU patients with a second follow-up

Muscle group (median, iqr) n=19		1st Follow-up	2nd Follow-up
Grip	**Maximum (kg)**	21.3 (11.3, 36.3)	20.4 (18.1, 36.3)
	Indexed	0.79 (0.40, 1.3)	0.88 (0.40, 1.3)
Triceps	**Maximum (kg)**	12.6 (10.4, 16.6)	16.0 (11.2, 17.3)
	Indexed	1.0 (0.50, 1.4)	1.36 (0.60, 1.7)
Biceps	**Maximum (kg)**	15.5 (12.2, 20)	16.2 (13.9, 22.8)
	Indexed	1.01 (0.50, 1.3)	1.04 (0.6, 1.7)
Hamstrings	**Maximum (kg)**	13.9 (8.8, 19.0)	14.9 (13.1, 22.6)
	Indexed	0.82 (0.43, 1.4)	0.94 (0.60, 1.6)
Quadriceps	**Maximum (kg)**	21.1 (17.8, 25.6)	24.7 (18.1, 28.4)
	Indexed	0.72 (0.35, 0.90)	0.76 (0.4, 1.0)
Dorsiflexors	**Maximum (kg)**	14.7 (9.9, 19.0)	14.1 (9.0, 19.3)
	Indexed	0.77 (0.40, 0.96)	0.77 (0.30, 1.0)
Overall	**Indexed**	0.86 (0.38, 1.1)	1.04 (0.5,0 1.3)
6-MWT	**Maximum (m)**	380 (295, 480)	440 (307, 467)
	Indexed	0.77 (0.59, 0.87)	0.77 (.62, .99)

± No p-values <0.05 comparing 1st follow-up vs. 2nd follow-up indexed muscle groups

The rate of muscle strength change for each muscle group and distance walk was calculated to assess whether patients physical function changes over time. The patient's strength values were subtracted between the 2nd and 1st follow up visits and divided by the time that had elapsed between follow-ups. This analysis takes into consideration the variation in the time intervals between the first and second follow-ups for each patient, as the interval between follow-ups was not uniform. Table 6 displays the mean rate of change between the 1st and 2nd follow-up for maximal strength of each muscle group and the distance walked during the 6-MWT. All muscle groups and the distance walked had a positive mean slope. The triceps (0.078, P=0.0368), biceps (0.048, P=0.0106), hamstrings (0.079, P=0.0145) and quadriceps (0.040, P=0.0342) all had positive slopes that were significantly greater than zero. There was considerable variation for which muscle group had a greater mean rate of change for septic patients vs. non-septic patients. Again each group had all positive rates of change in maximal muscle strength and distance walked for each muscle group. However, no statistical differences were found the between the septic and non-septic patients for each muscle group or the 6-MWT.

Table 6. The rate of change of patients maximal muscle strength and distance walked during the 6-MWT between 1st and 2nd follow-ups after hospital discharge by patient group

Muscle group, mean (SD)	**All ICU** (n=19)	**Sepsis ICU** (n=12)	**Non-Sepsis ICU** (n=7)
Grip	0.024 (0.011)	0.025 (0.012)	0.021 (0.084)
Triceps	0.042 (0.078) ∗	0.027 (0.060)	0.064 (0.010)
Biceps	0.032 (0.048) ∗	0.035 (0.057)	0.026 (0.030)
Hamstrings	0.049 (0.079) ∗	0.032 (0.039)	0.080 (0.120)
Quadriceps	0.040 (0.071) ∗	0.036 (0.072)	0.045 (0.075)
Dorsiflexors	0.17 (0.080)	0.142 (0.089)	0.021 (0.067)
6-MWT	0.19 (1.1)	0.29 (1.2)	0.01 (1.0)

∗ $p<0.05$ one-sample t-test for all-ICU patients comparing mean slope to 0.
β $p<0.05$ two-sample t-test comparing sepsis vs. non-sepsis ICU

Table 7 examines the relationship between patient's distance walked during the 6-MWT and each muscles group's maximum strength. All of the muscle group's maximum muscle strength independently correlated with distance walked during the 6-MWT. Lower peripheral muscle strength produced lower distances walked over the 6 minutes. Maximum grip, triceps, biceps, and quadriceps strength accounted for the most variation in the distance walked

(R^2=0.28, 0.31, 0.28, and 0.3, respectively). An exploratory multivariate analysis was attempted however no associations were significant.

Table 7. A univariate linear regression analysis examining the relationship between the distance walked during the 6-MWT and peripheral muscle strength at 1st follow-up after hospital discharge

Muscle group (n=45)	**6-MWT β-coefficient (SE)**	**R^2**	**P value**
Grip	5.4 (1.3)	0.28	<0.001
Triceps	12.7 (3.0)	0.31	<0.001
Biceps	10.8 (2.7)	0.28	<0.001
Hamstrings	11.5 (2.7)	0.14	<0.001
Quadriceps	4.13 (1.6)	0.30	0.013
Dorsiflexors	11.5 (2.7)	0.13	<0.001

An additional assessment comparing patient's indexed 6-MWT to the indexed combined muscle groups was done using a univariate regression analysis (table 8). All of the muscle groupings were statistically associated with patient's indexed 6-MWT. Surprisingly the upper body muscle groups had a higher beta-coefficient and accounted for more variation than the lower body muscle groups when compared to the indexed 6-MWT (β=1.05 R^2= 0.25 vs. β=0.58 R^2=0.18, respectively).

Table 8. A univariate linear regression analysis examining the relationship between indexed distance walked during the 6-MWT and indexed muscle groups at 2 months post hospital discharge

Muscle grouping	**6-MWT β-coefficient (SE)**	**R^2**	**P value**
Upper	1.05 (0.28)	0.25	<0.001
Lower	0.58 (0.19)	0.18	0.004
Distal	0.82 (0.23)	0.23	0.001
Proximal	0.71 (0.21)	0.22	0.001
Overall	0.86 (0.24)	0.23	0.001

A univariate linear regression analysis was created to determine if there is an association between reduced percent predicted muscle strength or physical functioning and perceived quality of life measured by the SF-36 questionnaire (table 9). Each muscle group and the 6-MWT was independently analysed with each domain of the SF-36 and the physical and mental component summaries (PCS / MCS) that are standardized to Canadian normative data. The only muscle groups statistically associated with the physical function domain were grip strength (P=0.019) and the hamstrings (P=0.026). The other lower body muscle groups were close to statistical significance (quadriceps, P=0.061 and dorsiflexors, P=0.063). Interestingly the strength in all muscle groups, expect the triceps, were associated with the general health domain. The percent predicted walked during the 6-MWT was statistically associated with all of the domains of the SF-36, except for social function, bodily pain and mental health. In addition, the 6-MWT was the only measure of physical function that was statistically associated with the overall PCS (P=0.001).

Table 9. A univariate linear regression analysis examining the relationship between age/sex standardized muscle strength and distance walked during the 6-MWT to the SF-36 health domains at 2 months post hospital discharge

Muscle group n=50	**PF**	**RP**	**BP**	**GH**	**VT**	**SF**	**RE**	**MH**	**PCS**	**MCS**
Grip										
β coefficient	**18.3 (7.5)**	12.7 (8.1)	2.4 (9.2)	**15.4 (5.6)**	**13.2 (5.5)**	**19.4 (8.4)**	**14.2 (6.6)**	6.1 (5.8)	4.5 (3.3)	4.5 (2.9)
P value	**0.019**	0.123	0.802	**0.009**	**0.021**	**0.025**	**0.037**	0.291	0.183	0.129
Triceps										
β coefficient	10.0 (7.3)	-2.26 (7.9)	-2.2 (8.6)	9.5 (5.6)	5.4 (5.6)	6.3 (8.4)	8.9 (6.4)	1.4 (5.5)	0.01 (3.1)	1.0 (2.9)
P value	0.177	0.776	0.801	0.094	0.335	0.457	0.171	0.804	0.998	0.717
Biceps										
β coefficient	13.1 (8.1)	4.8 (8.7)	2.6 (9.5)	**17.0 (5.9)**	9.3 (6.1)	15.0 (9.1)	9.9 (7.1)	6.33 (6.1)	3.8 (3.4)	2.6 (3.2)
P value	0.112	0.587	0.784	**0.006**	0.131	0.107	0.167	0.301	0.266	0.411
Hamstrings										
β coefficient	**19.8 (8.6)**	8.7 (9.4)	6.7 (10.2)	**17.3 (6.6)**	11.5 (6.4)	13.7 (9.9)	11.9 (7.7)	7.3 (6.5)	6.1 (3.7)	2.8 (3.4)
P value	**0.026**	0.356	0.515	**0.009**	0.078	0.169	0.129	0.272	0.105	0.418
Quadriceps										
β coefficient	19.1 (10.0)	8.6 (10.7)	8.6 (11.9)	**20.9 (7.0)**	9.2 (7.4)	16.6 (10.7)	14.8 (8.7)	11.7 (7.3)	6.9 (4.2)	4.0 (3.9)
P value	0.061	0.426	0.475	**0.005**	0.222	0.129	0.096	0.118	0.111	0.314
Dorsiflexors										
β coefficient	22.5 (11.8)	11.7 (12.9)	8.5 (13.9)	**19.5 (8.7)**	11.1 (8.6)	24.0 (13.2)	16.7 (10.6)	5.7 (8.9)	5.4 (5.3)	3.4 (4.6)
P value	0.063	0.369	0.543	**0.031**	0.202	0.075	0.121	0.531	0.319	0.459
6-MWT Distance										
β coefficient	**56.7 (12.6)**	**39.3 (15.8)**	29.2 (16.9)	**40.7 (10.7)**	**34.4 (11.2)**	33.0 (16.7)	**36.9 (12.7)**	22.1 (11.9)	**22.2 (6.1)**	10.1 (6.3)
P value	**<0.001**	**0.017**	0.091	**<0.001**	**0.004**	0.055	**0.006**	0.070	**0.001**	0.116

PF, Physical Functioning; RP, Role-Physical; BP, Bodily Pain; GH, General Health; VT, Vitality; SF, Social Functioning; RE, Role-Emotional; MH, Mental Health; PCS, Physical Component Summary; MCS, Mental Component Summary

The relationship between those patients who report any degree of problems with the individual EQ-5D health domains and indexed muscle strength and 6-MWT at 2 months post hospital discharge was examined using a univariate logistics regression (table 10). The odds of reporting problems in the mobility domain of the EQ-5D were independently associated the patients indexed grip, hamstrings and quadriceps muscle groups (OR=0.27, P=0.035; OR=0.20 P=0.028; OR=0.12, P=0.028, respectively). None of the other EQ-5D domains (self-care, usual activities, pain/discomfort, anxiety/depression) had statistically significant associations with any of the muscle groups. The quadriceps muscle group appears to most drastically affect the odds of a patient reporting a problem with mobility (OR=0.12), when compared to the other muscle groups.

The patients indexed 6-MWT distance was found to be statistically associated with patients reporting problems in the mobility, usual activities and pain and discomfort domains of the EQ-5D (OR=0.01, P=0.007; OR=0.02 P=0.029; OR=0.01, P=0.011, respectively). Using a univariate linear regression model the 6-MWT was the only physical function measure that was statistically associated with patients reported visual analogue scale of the EQ-5D (β=0.05, P=0.025).

Table 10. A univariate logistic regression analysis examining the relationship between age/sex standardized muscle strength and distance walked during the 6-MWT to those who reported problems in the EuroQol-5D health domains at 1st follow-up after hospital discharge

Muscle group n=50	Mobility	Self-care	Usual Activities	Pain/ Discomfort	Anxiety/ Depression	Visual analogue scale*
Grip						
Odds ratio	**0.27 (0.167)**	0.55 (0.411)	0.48 0.318)	0.87 (0.521)	0.77 (0.475)	0.4 (0.5)
P value	**0.035**	0.428	0.269	0.814	0.814	0.428
Triceps						
Odds ratio	0.44 (0.248)	0.51 (0.379)	1.12 (0.717)	1.13 (0.625)	0.70 (0.416)	0.3 (0.5)
P value	0.145	0.366	0.854	0.825	0.548	0.534
Biceps						
Odds ratio	0.35 (0.223)	0.46 (0.369)	0.96 (0.668)	0.72 (0.451)	0.84 (0.541)	0.2 (0.5)
P value	0.100	0.322	0.950	0.596	0.782	0.662
Hamstrings						
Odds ratio	**0.20 (0.146)**	0.3 (0.278)	0.77 (0.577)	0.77 (0.516)	1.03 (0.702)	0.4 (0.6)
P value	**0.028**	0.193	0.728	0.694	0.971	0.480
Quadriceps						
Odds ratio	**0.12 (0.117)**	0.21 (0.252)	1.01 (0.864)	0.74 (0.563)	1.17 (0.909)	-0.2 (0.6)
P value	**0.028**	0.193	0.983	0.689	0.839	0.759
Dorsiflexors						
Odds ratio	0.23 (0.221)	0.22 (0.264)	0.20 (0.217)	0.56 (0.531)	1.08 (1.061)	-0.3 (0.8)
P value	0.128	0.211	0.137	0.543	0.939	0.746
6-MWT Distance						
Odds ratio	**0.01 (0.019)**	0.04 (0.074)	**0.02 (0.040)**	**0.01 (0.020)**	0.14 (0.198)	**0.05 (0.02)**
P value	**0.007**	0.071	**0.029**	**0.011**	0.158	**0.025**

*Univariate regression analysis as the Visual analogue scale is linear

Table 11 examines the relationship between muscle strength and physical function to risk factors from patients ICU characteristics. No statistical association were found between any of the muscle groups or the 6-MWT with respect to patients' ICU and hospital length of stay, number of days ventilated, severity of illness (APACHE II) or organ dysfunction (SOFA score). The 6-MWT approached statistical significance for the ICU LOS (P=0.072), hospital LOS (P=0.067) and number of days ventilated (P=0.062).

Table 11. A univariate regression analysis examining the relationship between age/sex standardized muscle strength and distance walked during the 6-MWT and risk factors at 1st follow-up after hospital discharge

Muscle group n=50	ICU LOS	Hospital LOS	Number of ventilation days	APACHE II score	SOFA score
Grip					
β coefficient	-0.002 (0.003)	-0.001 (0.004)	0.002 (0.004)	-0.002 (0.011)	0.022 (0.0018)
P value	0.956	0.708	0.971	0.868	0.229
Triceps					
β coefficient	-0.008 (0.010)	0.002 (0.005)	-0.009 (0.011)	-0.008 (0.013)	0.021 (0.021)
P value	0.409	0.711	0.418	0.515	0.325
Biceps					
β coefficient	-0.004 (0.009)	0.004 (0.005)	0.000 (0.009)	0.003 (0.11)	0.027 (0.019)
P value	0.631	0.375	0.973	0.802	0.167
Hamstrings	0.000 (0.002)	0.000 (0.003)	0.000 (0.003)	0.003 (0.010)	0.020 (0.016)
β coefficient	0.890	0.855	0.873	0.755	0.219
P value					
Quadriceps					
β coefficient	0.000 (0.003)	0.003 (0.003)	0.002 (0.003)	0.011 (0.009)	0.019 (0.014)
P value	0.874	0.281	0.621	0.212	0.174
Dorsiflexors					
β coefficient	-0.001 (0.002)	0.001 (0.002)	0.000 (0.003)	0.006 (0.007)	0.017 (0.012)
P value	0.800	0.692	0.958	0.397	0.154
6-MWT					
β coefficient	**-0.003 (0.002)**	**-0.003 (0.001)**	**-0.004 (0.002)**	-0.003 (0.006)	0.011 (0.009)
P value	**0.072**	**0.067**	**0.062**	0.642	0.257

5.3 HRQL

Table 12 outlines the results of the SF-36 questionnaire. For each domain the scores can range from 0-100 and are adjusted to Canadian normative data (a score 50 is considered normal). At 1st follow-up the patients' mean adjusted scores for each health domain were below the Canadian national average. The domains Physical Functioning (36.9), Role Physical (38.2) and Social Functioning (38.0) had the lowest mean adjusted scores. The mean PCS was considerably lower than the national norm (36.2), whereas, the mean MCS was just below the national average (47.6).

Table 12. Mean (SD) Short-form 36 domains and composite scores adjusted to Canadian normal population values* at 1st follow-up

Variable	All ICU (n=56)	Sepsis ICU (n=35)	Non-Sepsis ICU (n=21)
PF	36.9 (15.0)	40.6 (13.9)	30.7 (15.0)
RP	38.2 (9.6)	39.7 (9.9)	35.8 (8.9)
BP	42.3 (13.4)	42.4 (14.3)	42.1 (12.2)
GH	40.1 (12.0)	40.9 (12.8)	38.8 (10.6)
VT	40.5 (11.0)	42.3 (12.5)	37.9 (10.7)
SF	38.0 (15.7)	37.2 (15.8)	39.3 (15.7)
RE	47.0 (8.1)	47.4 (8.0)	46.3 (8.4)
MH	47.8 (13.4)	48.2 (12.5)	47.1 (15.1)
PCS	36.2 (11.8)	38.5 (12.1)	32.6 (10.5)
MCS	47.6 (10.9)	47.2 (10.7)	48.4 (11.4)

PF, Physical Functioning; RP, Role-Physical; BP, Bodily Pain; GH, General Health; VT, Vitality; SF, Social Functioning; RE, Role-Emotional; MH, Mental Health; PCS, Physical Component Summary; MCS, Mental Component Summary

Table 13 outlines the unadjusted mean SF-36 domains for patients who had both a 1st follow-up and 2nd follow-up. All of the health domains increased between 1st and 2nd follow-up except for Vitality and Mental Health. The mean PCS also increased between follow-ups (35.2 to 39.8), whereas the mean MCS decreased slightly (48.1 to 47.2).

Table 13. Mean (SD) unadjusted Short-form 36 domains and composite scores at 1st and 2nd follow-up after hospital discharge for all ICU patients with 2 follow-ups

Variable n=19	**1st Follow-up**	**2nd Follow-up**
PF	58.2 (25.5)	62.3 (23.1)
RP	38.8 (27.8)	48.0 (26.4)
BP	48.9 (26.7)	64.2 (26.2)
GH	61.6 (18.8)	62.2 (19.1)
VT	55.9 (14.5)	55.9 (16.6)
SF	64.5 (27.1)	73.7 (21.2)
RE	71.9 (23.4)	78.5 (25.2)
MH	76.1 (15.9)	71.3 (18.8)
PCS	35.2 (10.6)	39.8 (11.2)
MCS	48.1 (9.7)	47.2 (10.1)

PF, Physical Functioning; RP, Role-Physical; BP, Bodily Pain; GH, General Health; VT, Vitality; SF, Social Functioning; RE, Role-Emotional; MH, Mental Health; PCS, Physical Component Summary; MCS, Mental Component Summary

The rate of change of unadjusted SF-36 health domains was calculated for each patient between the 1st and 2nd follow-up (table 14). This analysis accounts for variation in follow-up intervals between patients. Bodily pain was the only slope that was statically greater than 0 (Slope=0.248, P=0.0227). All of the domains had positive slopes except for Vitality, Mental Health and the MCS. The PCS also had a mean slope significantly greater than 0 (Slope=0.072, P=0.0468).

Table 14. Mean (SD) rate of change of patients SF-36 domains between 1st and 2nd follow-ups after hospital discharge by patient group

Variable	All ICU (n=19)	Sepsis ICU (n=12)	Non-Sepsis ICU (n=7)
PF	0.056 (0.38)	-0.014 (0.25)	0.176 (0.42)
RP	0.180 (0.43)	-0.004 (0.40)	0.298 (0.19)
BP	0.248 (0.43)∗	0.271 (0.45)	0.208 (0.44)
GH	0.026 (0.21)	0.008 (0.14)	0.053 (0.31)
VT	-0.004 (0.20)	-0.05 (0.15)	0.070 (0.27)
SF	0.090 (0.33)	0.064 (0.39)	0.145 (0.25)
RE	0.056 (0.51)	-0.059 (0.55)	0.252 (0.40)
MH	-0.080 (0.29)	-0.114 (0.34)	0.027 (0.16)
PCS	0.072 (0.15)∗	0.055 (0.12)	0.101 (0.19)
MCS	-0.028 (0.13)	-0.060 (0.15)	0.028 (0.09)

∗ $p<0.05$ one-sample t-test for all-ICU patients comparing mean slope to 0

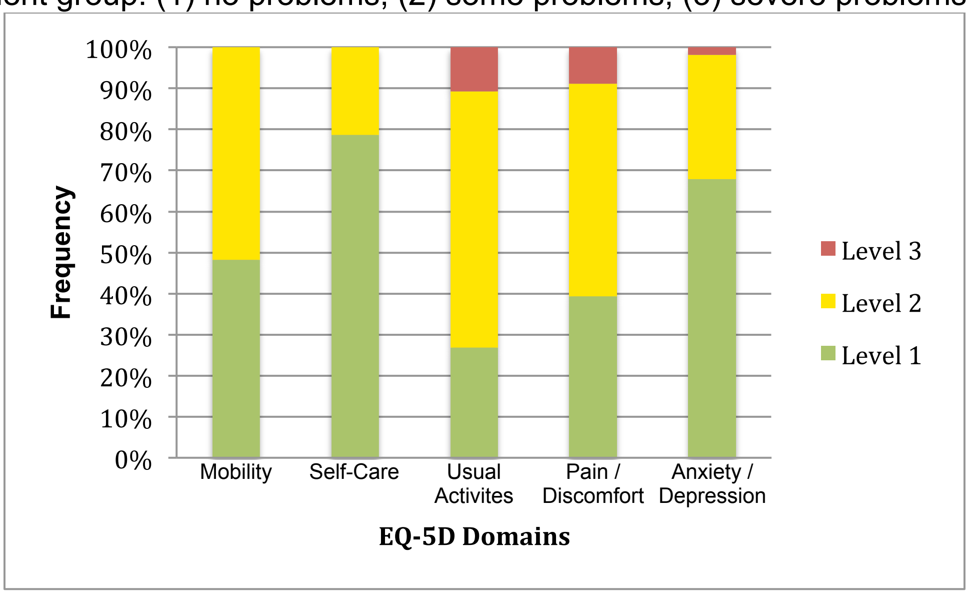
PF, Physical Functioning; RP, Role-Physical; BP, Bodily Pain; GH, General Health; VT, Vitality; SF, Social Functioning; RE, Role-Emotional; MH, Mental Health; PCS, Physical Component Summary; MCS, Mental Component Summary

Table 15 and Figure 3 outlines the results of the EQ-5D questionnaire. Each dimension of the EQ-5D has 3 levels of severity: no problems, some problems and severe problems (1 to 3, respectively). More than half of the patients seen at 1st follow-up reported some problems with mobility (52%, level 2), however no patients reported severe problems. Self-care was the dimension patients reported the fewest number of problems (79%, level 1). Patients usual activities was reported as having the greatest number of problems, with 62% reporting some problems and 11% reporting severe problems. 61% of patients reported problems with pain/discomfort (52% some problems, 9% severe problems). 30% of patients reported some problems with anxiety and depression and 2% reported severe problems.

Table 15. Frequency (proportion) of levels of dysfunction on the EuroQol-5D dimensions and mean (SD) of the reported Visual Analogue Scale of patients at 1st follow-up by patient group

EQ-5D Dimension		All ICU	Sepsis ICU	Non-Sepsis ICU
Mobility	Level 1	27 (48)	19 (54)	8 (38)
	Level 2	29 (52)	16 (46)	62 (62)
	Level 3	0 (0)	0 (0)	0 (0)
Self-Care	Level 1	44 (79)	28 (80)	16 (76)
	Level 2	12 (21)	7 (20)	5 (24)
	Level 3	0 (0)	0 (0)	0 (0)
Usual Activities	Level 1	15 (27)	13 (37)	2 (10)
	Level 2	35 (62)	19 (54)	16 (76)
	Level 3	6 (11)	3 (9)	3 (14)
Pain / Discomfort	Level 1	22 (39)	17 (49)	5 (24)
	Level 2	29 (52)	14 (40)	15 (71)
	Level 3	5 (9)	4 (11)	1 (5)
Anxiety / Depression	Level 1	38 (68)	26 (74)	12 (57)
	Level 2	17 (30)	8 (23)	9 (43)
	Level 3	1 (2)	1 (3)	0 (0)
VAS		6.3 (2.0)	6.5 (2.0)	6.3 (1.9)

Figure 3. Proportion of levels on EQ-5D dimensions of patients at 1st follow-up by patient group: (1) no problems, (2) some problems, (3) severe problems



The changes in proportion of reported problems on the EQ-5D dimensions and mean visual analogue scale between 1st and 2nd follow-up are shown in table 16. The proportion of patients reporting problems decreased in all health dimensions between 1st and 2nd follow-up. The dimensions self-care and pain/discomfort had the greatest decrease in the proportion of patients reporting problems (SC: 26% to 11% and P/D 74% to 58%). The usual activities and pain dimensions remained to have the highest proportions of patients reporting problems at 2nd follow-up (68% and 58% respectively).

Table 16. Frequency (proportion) of patients at 1st and 2nd follow-up with reported problems on EQ-5D dimensions and mean (SD) reported Visual Analogue Scale score

EQ-5D Dimension		**1st (n=19)**	**2nd (n=19)**
Mobility	No Problems	9 (47)	11 (58)
	Problems	10 (53)	8 (42)
Self-Care	No Problems	14 (74)	17 (89)
	Problems	5 (26)	2 (11)
Usual Activities	No Problems	3 (16)	6 (32)
	Problems	16 (74)	13 (68)
Pain / Discomfort	No Problems	5 (26)	8 (42)
	Problems	14 (74)	11 (58)
Anxiety / Depression	No Problems	9 (47)	10 (53)
	Problems	10 (53)	9 (47)
VAS	-	6.2 (1.5)	6.7 (1.6)

5.4 Neuropsychological outcomes

Table 17 outlines the prevalence of anxiety, depression and PTSD in patients at 1st follow-up. 11% of patients scored as probable cases for depression on the HADS. 24% of patients scored in the probable range for anxiety. Using the SPAN scale, 8% of patients scored in the probable range for having PTSD. There were no obvious differences between the sepsis and non-sepsis patients.

Table 17. Frequency and proportion of anxiety, depression and PTSD at 1st follow-up by patient category measured by the Hospital Anxiety and Depression Scale and SPAN scale

Variable	Cut-off*	All ICU	Sepsis ICU	Non-Sepsis ICU
Depression	≤ 7	49 (89)	30 (88)	19 (90)
	8-10	3 (5.5)	2 (6)	1 (5)
	≥ 11	3 (5.5)	2 (6)	1 (5)
Anxiety	≤ 7	42 (76)	27 (79)	15 (71)
	8-10	6 (11)	2 (6)	4 (19)
	≥ 11	7 (13)	5 (15)	2 (10)
PTSD	≥ 5	4 (8)	2 (7)	2 (10)

* HADS: ≤ 7: non-case; 8-10: probable case; ≥ 11 likely case
SPAN: ≥ 5 likely case

At 2nd follow-up the prevalence of depression increased from 5% to 11% in patients who had both 1st and 2nd follow-ups (table 18). The prevalence of anxiety remained the same between 1st and 2nd follow-ups, with 26% of patients screening positive. Finally, the prevalence of PTSD decreased from 10% to 6%.

Table 18. Frequency and proportion of anxiety, depression and PTSD at 1st and 2nd follow-up

Variable n=19	**Cut-off***	**1st** follow-up	**2nd** follow-up
Depression	≤ 7	18 (95)	17 (89)
	8-10	0 (0)	2 (11)
	≥ 11	1 (5)	0 (0)
Anxiety	≤ 7	14 (74)	14 (74)
	8-10	2 (11)	3 (16)
	≥ 11	3 (15)	2 (10)
PTSD	≥ 5	2 (10)	1 (6)

* HADS: ≤ 7: non-case; 8-10: probable case; ≥ 11 likely case
SPAN: ≥ 5 likely case

Table 19 examines the relationship between patients who screened positive for depression, anxiety, or PTSD and patients who reported problems for each of the EQ-5D domains. The odds of reporting problems in any of the EQ-5D domains did not increase if a patient scored as a depression case on the HADS. As well, if a patient scored as a PTSD case on the SPAN scale it did not increase the odds of reporting problems in any of the EQ-5D domains. However, the odds of reporting problems in mobility (OR=4.9, P=0.028), usual activities (OR=6.5, P=0.085), pain/discomfort (OR=13, P=0.018) and anxiety/depression (OR=6.6, P=0.005) were statistically increased if the patient scored as an anxiety case on the HADS.

Table 19. A univariate case control analysis comparing the HADS positive anxiety and depression cases and SPAN positive PTSD cases to each domain of the EQ-5D (dichotomized to no problem vs. problem) at 1st follow-up after hospital discharge

Variable n=56	**Mobility**	**Self-care**	**Usual activities**	**Pain / Discomfort**	**Anxiety / Depression**
Depression case					
Odds Ratio	2.6 (2.3)	3.3 (2.8)	-	1.7 (1.5)	0.8 (0.7)
P value	0.279	0.156	-	0.539	0.829
Anxiety Case					
Odds Ratio	**4.9 (3.5)**	2.7 (1.9)	**6.5 (7.1)**	**13 (14.1)**	**6.6 (4.4)**
P value	**0.028**	0.141	**0.085**	**0.018**	**0.005**
PTSD Case					
Odds Ratio	2.2 (1.5)	2.3 (1.6)	1.1 (0.8)	2.28 (1.7)	1.1 (0.7)
P value	0.251	0.264	0.875	0.261	0.921

Table 20 examines the relationship between patients who screened positive for psychiatric abnormalities and overall muscle strength, the 6-MWT and chronic health problems. The indexed 6-MWT was statistically associated with anxiety, in that as the patient's percent predicted 6-MWT decreased the odds of screening positive for anxiety increased (OR=0.003, P=0.023). There were no other statistical associations found between the psychiatric abnormalities and physical functioning or chronic health issues.

Table 20. A univariate logistic regression analysis examining the relationship between psychiatric abnormalities and the mental and physical composite scores of the SF-36 at 1st follow-up after hospital discharge

Variable n=50	Indexed 6-MWT	Composite muscle strength	CHP
Anxiety case			
Odds Ratio	**0.003 (0.005)**	0.23 (0.21)	0.96 (0.16)
P value	**0.023**	0.105	0.809
Depression case			
Odds Ratio	0.18 (0.34)	1.00 (1.10)	1.01 (0.21)
P value	0.355	0.999	0.958
PTSD case			
Odds Ratio	0.25 (0.41)	**0.07 (0.08)**	0.95 (0.17)
P value	0.399	**0.033**	0.790

CHP, Chronic health points

5.5 Sleep Function

The results of the PQSI and ESS questionaries' are shown in table 21. 62% of patients at 1st follow-up achieved a score that is associated with poor sleep quality. 24% of patients also reported significant daytime sleepiness as measured by the ESS questionnaire.

Table 21. Frequency and proportion of poor sleep quality and daytime sleepiness at 1st follow-up by patient category measured by the Pittsburgh Sleep Quality Index and Epworth Sleepiness Scale

Variable (n=55)	Cut-off*	All ICU	Sepsis ICU	Non-Sepsis ICU
Poor Sleep Quality	≥ 5	34 (62)	22 (65)	12 (57)
Daytime sleepiness	≥ 10	10 (24)	6 (25)	4 (22)

* PSQI: ≥ 5: poor sleep quality
ESS: ≥ 10 sleep specialist advice recommended

Table 22 outlines the patients sleep characteristics collected by the Actigraph sleep watch. The mean time the data collection occurred post hospital discharge was 101 days. Patients average total sleep time was 6.15 hours, with a sleep efficiency of 78%. The mean time to fall asleep was 12 minutes. Patients had an average of 11 awakenings per night and were awake for an average of 7 minutes during the awakenings.

Table 22. The mean (SD) Actigraph sleep characteristics

Variable (n=12)	**Mean (SD)**
Time elapsed since hospital discharge, days	101 (51)
Sleep Time (hours)	6.15 (3.4)
Sleep Percent, (%)	78 (18)
Number of Awakenings, (n)	11 (5)
Time awake during an awakening, (minutes)	7 (5)
Sleep Onset Latency, (minutes)	12 (11)

To examine the relationship between patients reported sleep quality and the quantitative sleep data the PQSI and Actigraph results were compared using a linear regression model (table 23). There were no statistical associations found between patients perceived sleep quality and total sleep time (β=-9.4, P=0.223), sleep efficiency (β=-1.7, P=0.193) or number of sleep disruptions (β=-0.17, P=0.693), as measured by Actigraphy.

Table 23. A univariate linear regression analysis examining the relationship between reported sleep quality and Actigraphy at 1st follow-up after hospital discharge

Variable n=12	Sleep time	Sleep efficiency	Sleep disruptions
Reported sleep quality			
β coefficient	-9.4 (7.3)	-1.7 (1.2)	-0.17 (0.40)
P value	0.233	0.193	0.693

Table 24 shows a comparison of patients who screened positive for poor sleep quality and anxiety cases, depression cases, and patients with problems in the pain/discomfort or anxiety/depression domains of the EQ-5D. The odds of having poor sleep quality were increased for patients who screened positive for anxiety on the HADS (OR=10.7, P=0.028). Having screened positive for depression on the HADS or reporting problems in the pain/discomfort or anxiety/depression domains of the EQ-5D did not increase the odds of screening positive for poor sleep quality.

Table 24. A univariate logistic regression analysis examining the relationship between reported poor sleep quality and psychiatric abnormalities and HRQL at 1st follow-up after hospital discharge

Variable n=55	Anxiety case	Depression case	EQ-5D Pain/discomfort	EQ-5D Anxiety/depression
Poor Sleep quality				
Odds Ratio	**10.7 (11.6)**	1.5 (1.3)	2.0 (1.1)	1.7 (1.1)
P value	**0.028**	0.675	0.224	0.396

Table 25 examines the relationship between patients severity of illness, days of ventilation, and ICU and hospital length of stay to quantitative sleep characteristics measured by the Actigraph watch. Patients' severity of illness, as measured by the APACHE II score, was statistically associated with lower total sleep time (β=-12.6, P=0.019), reduced sleep efficiency (β=-1.18, P=0.042) and higher number of sleep disruptions (β=0.64, P=0.023). The number of days ventilated or ICU and hospital length of stay was not statically associated with the sleep parameters.

Table 25. A univariate linear regression analysis examining the risk factors of decreased sleep time, sleep efficiency, and sleep interruptions as measured by Actigraphy at 1st follow-up after hospital discharge

Variable n=11	APACHE II score	ICU LOS	HOSP LOS	Days mechanically ventilated
Sleep time				
β coefficient	**-12.6 (4.4)**	-5.27 (4.7)	-0.47 (2.13)	-4.57 (4.88)
P value	**0.019**	0.290	0.831	0.373
Sleep efficiency				
β coefficient	**-1.8 (0.8)**	-0.12 (0.82)	0.19 (0.35)	-0.28 (0.84)
P value	**0.042**	0.884	0.603	0.746
Sleep disruption				
β coefficient	**0.64 (0.23)**	0.04 (0.25)	-0.05 (0.10)	0.12 (0.26)
P value	**0.023**	0.870	0.644	0.644

Chapter Six: Discussion

This is the first study to use quantitative hand-held dynamometry to measure muscle strength in survivors of critical illness. We demonstrated that survivors of critical illness have reduced muscle function after hospital discharge. At 2 months post hospital discharge, patients muscle strength in all muscle groups was below their age and sex predicted values. The quadriceps were the weakest muscle group measured, with the median percent-predicted strength achieved being 59%. Patients median overall composite score for predicted muscle strength was only 72% at 2 months after discharge. Additionally, the lower and proximal muscle groups were found to be the weakest. This is in keeping with the current thought that proximal muscle groups are impacted the most by ICUAW [22]. Patients with sepsis were on average found to be weaker than non-sepsis patients although the differences were not significantly different. This suggests that sepsis may cause increased muscle weakness. Furthermore, when comparing the ICU patients to non-ICU trauma patients the ICU patients were found to be weaker in all muscle groups. This suggests that critical illness exposes patients to risk factors leading to muscle weakness that other in-hospital patients are not exposed to. The non-ICU trauma patients were also followed-up on average at 34 days post hospital discharge versus the 74 days for ICU patients, suggesting that the gap in muscle strength may be even larger given the ICU patients had an additional month to recover.

Survivors of critical illness demonstrated impaired physical functioning, as measured by the 6-MWT. The median percent predicted distanced walked was

72% at 2 months and did not change at the 4-month follow-up time point. Surprisingly the patients with sepsis had less impaired physical functioning compared to the non-sepsis patients (77% vs. 69%, respectively). Herridge and colleges [5] in 2003 assessed the physical functioning, using the 6-MWT, of approximately 80 survivors of ARDS at 3, 6 and 12 months post hospital discharge. At 3-months follow-up the patients percent predicted score was 49% and at 6-months was 64%. The more severe limitations in physical function seen in the Herridge et al [5] study versus our study, may be attributed to their cohort having higher severity of illness, longer number of days on the ventilator and longer ICU and hospital length of stays, which were variables they found to be predictive of the 6-MWT.

For patients who received a second follow-up we were able to show that they had improvement in muscle strength from their first follow-up. A number of the muscle groups had statistically significant slopes, representing improvement between patient follow-ups. The median percent predicted value for some muscle groups crossed the 100% mark, including the overall composite strength score (86% to 104%) meaning they had reached normal muscle strength. However, the cohort of patients followed-up a second time had greater strength at their first follow-up compared to the other patients not seen a second time (86% vs. 52% overall composite strength score). This suggests that it is likely if all individuals were examined at the second follow-up, despite improved muscle strength, they would remain below normative values.

Despite the improvements seen in patients' muscle strength the 6-MWT at the second follow-up remained well bellow the expected median distance walked. The median percent predicted distance walked did not change between follow-ups and remained at 77%, however the quartiles did increase. This result demonstrates that the distance an individual walks during the test is multifactorial and likely involves more than the patient's peripheral muscle strength.

Despite the minimal improvement in the 6-MWT and improved overall muscle strength between the follow-ups, we were able to show that the strength, of all the muscle groups measured, independently predict the patient's distance walked during the 6-MWT. The quadriceps and triceps accounted for the most variability in the 6-MWT (R^2=0.30 and R^2=0.31, respectively). It is reasonable that the quadriceps can best predict the distance a patient walks, given their importance in ambulation. This is the first time that quantitative peripheral muscle strength has been correlated with overall physical functioning in ICU survivors. Novak et al [198] examined the relationship between MMT and a walk test but did not find any associations. This is likely a result of the MMT method lacking the sensitivity to detect differences in muscle strength when minimal disability is present. Where as by using hand-held dynamometry we were able to detect differences among patients without severe weakness and link this variability to performance on the 6-MWT.

We are able to demonstrate that there is a relationship between patients' peripheral muscle strength and overall physical functioning with their reported HRQL using the SF-36 and EQ-5D instruments. Grip strength was associated with a number of the SF-36 health domains including physical function, general health, vitality, social function and role emotional. All of the muscle groups, except triceps, were associated with patients' perceived general health on the SF-36. The EQ-5D showed similar results where grip strength, hamstrings, and quadriceps were all associated with patients reporting problems with mobility. We found the distanced walked during the 6-MWT was associated with all of the SF-36 domains, except, bodily pain, social functioning and mental health and was the only measure associated with the PCS. Additionally, the 6-MWT was also associated with patients reporting problems in mobility, usual activities, having pain or discomfort and the visual analogue scale (a measure of perceived overall health).

Benington et al [27] examined exercise capacity using cardiopulmonary exercise testing in 50 survivors of critical illness at 6 weeks after hospital discharge but they did not find any correlations between patient's exercise capacity and HRQL. However, we have shown that peripheral muscle strength plays a role in survivors of critical illness views on their overall health status, specifically general health. Patients' grip strength, was associated with the most HRQL domains, suggesting it may play an important role in patients overall HRQL. Compared to peripheral muscle strength, patients' performance on the 6-MWT is associated with a greater number of the physical and mental components of HRQL. The 6-MWT is likely more sensitive to changes in a patients perceived HRQL as it takes into account not only peripheral muscle strength, but exercise capacity, bodily pain, motivation and other factors that may not be accounted for when measuring muscle strength or cardiopulmonary exercise capacity.

Although we were able to show that patients have dysfunction in muscle strength and physical function we did not find any ICU characteristics that could predict patients' muscle strength or 6-MWT. These included ICU and hospital LOS, number of days ventilated, severity of illness (APACHE II) and organ dysfunction (SOFA score). ICU and hospital LOS and ventilation days were near statistical significance, but did not have a p value <0.05, for predicting the 6-MWT. These results are contrary to the study findings of Herridge et al [5], which examined the predictors of the 6-MWT in 83 survivors of ARDS at 3 months. They found all of the risk factors identified above to be statistically associated with the distance walked in the 6-MWT. It is not clear why we found this discrepancy but it may highlight that the determinants of muscle strength and overall physical function is multifactorial and may not be account for by these simple ICU measures.

At 2-months post hospital discharge we found that patients had reduced HRQL. All of the mean health domains of the SF-36 were below the Canadian normative values. At 4-months post hospital discharge patients continued to have significant reduction in physical health domains, but had recovered to normal population means for mental health. Surprisingly the patients who had sepsis reported better HRQL than the non-septic patients. The results that we found were similar to other studies published [25, 137]. The results of the EQ-5D were in keeping with the SF-36, where patients reported the most problems in the physical domains (mobility, usual activities and pain or discomfort). At the 4-month follow-up period the EQ-5D domain that had the most improvement was self-care, where only 11% of patents reported problems versus 26% at 2-months. Where as, the mobility and usual activities domains continued to have a very high prevalence of reported problems (42% and 68%, respectively). This result shows that simple activities such as self-care likely recover in a short period after hospital discharge, where we are seeing it takes much longer for patients to be able to return their normal activities. Again the patients with sepsis reported fewer problems in all of the EQ-5D domains compared to patients without sepsis. It is not understood why the patients with sepsis were reporting higher HRQL than the non-septic patients as they also had higher severity of illness, organ failure and ICU and hospital length of stays.

The prevalence of depression was 11% in our cohort at 2 months post hospital discharge and remained elevated at the 4-month follow-up. A systematic review examining 14 studies found the median point prevalence of depression to be 28% in the ICU survivor population [164]. It is unsure why our population has a lower prevalence of depression than what previous studies have found, however it may be due to the heterogeneity of instruments used to assess depression in the literature. The prevalence of anxiety was 24% and PTSD was 8% at 2-months post hospital discharge. The prevalence of anxiety and PTSD is in keeping with what previous studies have shown, where the prevalence of anxiety has ranged from 10%-47% [138, 160] and PTSD ranged from 5% to 63% [16]. The prevalence of anxiety and PTSD both remained elevated and did not decrease by the 2nd follow-up time point. There were no distinct trends seen between sepsis and non-sepsis patients within the neuropsychological testing. It is concerning to find that the prevalence of depression and anxiety and PTSD did not decrease by 2nd follow-up, which is consistent with what previous studies found [165] and suggests these psychiatric abnormalities may be long-term.

We were able to show that the odds of having reduced quality life increases if psychological abnormalities are present. The presence of anxiety increased the odds of patients reporting problems in mobility, usual activities, pain/discomfort and anxiety/depression of the EQ-5D. The presence of depression or PTSD did not increase the odds of patients reporting problems in any of the EQ-5D domains. Sukantarat et al [150] also found that anxiety measured using the HADS was associated with decreased HRQL measured using the SF-36 in 45 patients 3-months post ICU discharge, but they also found depression correlated HRQL. Our lack of association between HRQL and depression may be explained by the relatively low prevalence of depression in our population. Other studies have shown a relationship between PTSD and decreased HRQL, however we did not find this correlation [157, 159, 162]. The presence of anxiety was also associated with the distanced walked on the 6-MWT, but not associated with overall muscle strength or chronic health points. This result is in keeping with Sukantarat et al [150] who showed subjective physical function is correlated with both anxiety and depression. The overall composite muscle strength score was found to significantly increase the odds of patients screening positive for PTSD. Depression was not related to either muscle strength or physical functioning. We had expected depression to most likely be associated with problems of mobility, bodily pain, and thus physical functioning however we found that anxiety may play a more important role in influencing patient's HQRL and physical functioning. A limitation of this analysis is that we cannot assess the temporality between the neuropsychological abnormalities and HRQL or physical functioning. Despite this, it is still important to recognize that a relationship exists and that by preventing either neuropsychological problems or physical impartment it may prevent the other from occurring. Given these results it will be important to properly screen for neuropsychological disorders in all survivors of critical illness.

Our sleep analysis identified 62% of patients report poor sleep quality. There were no obvious differences between septic vs. non-septic patients. Orwellus et al [17] found that 20% of 497 patients at 6-months post hospital discharge reported poor sleep quality. It is difficult to interpret the differences found in sleep quality between studies as different subjective questionnaires were used, but it is likely our population had higher rates of sleep problems. The Actigraph results showed that total sleep was reduced with patients sleeping an average of 6.15 hours per night. There were a surprisingly high number of mean awakenings per night (11 awakenings) for a prolonged period of time (7 minutes). These patients did not appear to have any issues with sleep initiation. There was no association between the quantitatively measured Actigraph sleep data and patients preserved sleep quality measured with the PQSI questionnaire. Buysse et al [193] also found that the PQSI was not associated with polysomnography results in healthy individuals but it was more closely related to psychological abnormalities. This highlights that the PSQI and Actigraph may be assessing different variables. Patients may be poor at assessing their sleep quality and rate it as low although they have adequate sleep times. A limitation of the Actigraphy device is that it can only assess when a patient is asleep but not the patients sleep architecture. Given this, patients may be detected as being asleep by the device, but not reaching deep stages of sleep and thus not feeling rested and reporting poor sleep quality. Just as Buysse et al [193] had found, our patients who reported having anxiety had much higher odds of reporting poor sleep quality however depression, and pain/discomfort did not. Our results highlight the fact that perceived sleep quality is complex and it is difficulty to predict who will report having impaired sleep.

We were able to show using the Actigraph device that severity of illness predicts sleep time, sleep efficiency and the number of sleep disruptions in this population. There was no relationship between the Actigraph sleep assessment and ICU or hospital LOS or the number of days mechanically ventilated. Previous studies have not found any associations between sleep quality and ICU demographics such as severity of illness [17]. This is the first study, post-ICU, to recognize that patients have high level of sleep dysfunction as measured by the Actigraph device and this dysfunction can be in part attributed to the patients' severity of illness while critically ill [183]. In addition, this data emphasises the importance of using quantitative sleep measures in assessing sleep quality in the

ICU survivor population as deficiencies may be missed using conventional sleep measures.

Anecdotally, many patients feel that the clinic helped immensely in their recovery as they had the opportunity to speak with an Intensivist, go through medical concerns they had and learn that the experience they were going through is common for many survivors of critical illness. It helped relieve many fears patients had with regards to returning to their daily activities, work and social life. Several patients reported having vivid dreams from during their admission to the ICU. Including, memories of health care workers trying to harm them and harm being done to their loved ones while they could do nothing about it. For some patients these memories were very difficult to deal with, but found it reassuring to discuss them in the clinic and learn that they can be common and distressing to other survivors of critical illness. Patients also reported issues with their short-term memory and problems completing simple cognitive tasks. The anecdotal evidence, which is supported in the literature [149], of cognitive impairment, short-term memory problems and issues with frightening memories of the ICU highlights the need for continued ICU follow-up and future study into neurocognitive function.

A limitation of this study involves the number of patients missing for 2nd follow-up. As the clinic was designed to be a normal continuation of the patients care, only some patients were given the opportunity to return to the clinic if it was felt they would benefit from seeing an Intensivist a second time. As well, logistically the clinic was running at full capacity and more emphasis was given to seeing first time patients at the 2-month mark over following-up patients for a second time. It is possible that the patients not screened a second time may have been healthier. However, given that the patients we screened a second time had higher muscle strength and 6-MWT results compared to patients not seen again, this is unlikely. A second limitation of the study is that not all patients who were eligible for the study were seeing in the follow-up clinic. The clinic was only able to operate at a certain capacity and was not able to see all patients. However, given that the patients selected for the clinic were randomly selected from eligible ICU patients we feel this should have helped reduce selection bias. A 3rd limitation of the study is that we only follow-up patients until 4 months post hospital discharge. Given that significant morbidity was still seen at this make is many of the patients it is unknown when or if they return to normal function. Future studies should consider following patients up to 1 year after hospital discharge.

The ICU follow-up clinic has been able to identify patients who have decreased muscle strength and physical functioning, and report poor HRQL, psychological dysfunction and poor sleep quality up until 4 months after hospital discharge. It is currently not clearly understood what predicts long-term physical dysfunction or how long this dysfunction may last. Despite what was predicted sepsis does not appear to predict increase morbidity after critical illness. These results highlight the need for follow-up in all ICU survivor population. By assessing the physical and psychological abnormalities through questionnaires and interviews it gives the patients time to reflect on their health status and help detect morbidities that may have otherwise been missed through regular routine medical check-ups. The ICU follow-up clinic has also demonstrated that objective physical functioning can be assessed in a controlled environment. Quantitative assessment, using hand-held dynamometry is a reasonable and accurate method to assess muscle strength. It should become the standard in measuring muscle strength in the post-ICU population. Given the growing body of evidence that survivors of critical illness have decreased physical functioning, and it may be impacting their HRQL, it is important to study interventions in the ICU to try and prevent post-ICU morbidity. The recent literature has highlighted the potential benefit of early patient mobilization in the ICU. The outcomes of these studies would be best studied in an ICU follow-up clinic setting where muscle strength, physical function and HRQL can be quantitatively assessed.

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