# The impact of sarcopenia and acute muscle mass loss on long-term outcomes in critically ill patients with intra-abdominal sepsis

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## Abstract

**Background**  Sarcopenia is a known risk factor for poor outcomes across many chronic diseases. The impact on outcomes of both pre-existing sarcopenia and acute muscle wasting (AMW) in acute critical illness caused by sepsis remain unclear.

**Methods**  We conducted a prospective longitudinal cohort study of critically ill patients with intra-abdominal sepsis utilizing abdominal computed tomography at sepsis onset to determine baseline skeletal muscle index (SMI). Biomarkers of inflammation and catabolism were measured through 28 days while hospitalized. We performed follow-up evaluations of strength and physical function at 3, 6, and 12 months, with interval CT analyses at 3 and 12 months to evaluate changes in muscle mass. Measured clinical outcomes included development of chronic critical illness (≥14 days in intensive care with persistent organ dysfunction), long-term functional status, and 1 year mortality.

**Results**  Among 47 sepsis patients enrolled (mean age 53 ± 14 years), half ($n = 23$; 49%) were sarcopenic at baseline. Overall, sepsis patients exhibited acute and persistent muscle wasting with an average 8% decrease in SMI from baseline at 3 months ($P = 0.0008$). Sarcopenic (SAR) and non-sarcopenic (NSAR) groups were similar in regards to age and comorbidity burden. SAR patients had greater acute physiologic derangement (APACHE II, 18 vs. 12.5), higher incidence of multiple organ failure (57% vs. 17%), longer hospital (21 vs. 12 days) and intensive care unit length of stays (13 vs. 4 days), and higher inpatient mortality (17% vs. 0%; all $P < 0.05$). Pre-existing SAR was a strong independent predictor of early death or developing chronic critical illness (odds ratio 11.87, 95% confidence interval CI 1.88–74.9; $P = 0.009$, area under the curve 0.880) and was associated with significantly higher risk of 1-year mortality (34.9% vs. 4.2%, $p = 0.007$). Lower baseline SMI was also predictive of poor functional status at 12 months (OR 0.89, 95% confidence interval 0.80–0.99; $p = 0.039$, area under the curve 0.867). Additionally, SAR patients had AMW with persistent muscle mass loss at 3 months that was associated with decreased health-related quality of life and SF-36 physical function domains ($P < 0.05$). Persistent AMW at 3 months was not predictive of mortality or poor functional status, with return to near-baseline muscle mass among sepsis survivors by 6 months.

**Conclusions**  Critically ill patients have an acute and persistent loss of muscle mass after intra-abdominal sepsis, which is associated with decreased health-related quality of life and physical function at 3 months. However, pre-existing sarcopenia, rather than persistent acute muscle mass loss at 3 months after sepsis, is independently associated with poor long-term functional status and increased 1 year mortality.

**Keywords**  Sarcopenia; Acute muscle wasting; Sepsis; Physical function

# Introduction

In contrast to a wide range of chronic diseases, skeletal muscle is understudied in the setting of acute critical illness. This represents a critical gap in knowledge, as muscle represents an organ system that can have significant impact on physical recovery, rehabilitation potential, and long-term function after hospitalization. Sarcopenia has no universally accepted definition, but is commonly considered a generalized loss of skeletal muscle mass with aging.[1] Many groups propose that as a syndrome it also includes a loss of muscle function.[2] While most commonly associated with the elderly, many factors other than advancing age can contribute to low muscle mass. These include chronic diseases that cause a chronic inflammatory state such as malignancy, cardiopulmonary disease, or inflammatory bowel disease.[3,4] While sarcopenia is generally considered a gradual age-related decline, acute muscle wasting is becoming recognized as a common and rapidly developing condition in acute, pro-inflammatory disease conditions that cause critical illness such as sepsis.[5]

Skeletal muscle mass can be evaluated through multiple radiographic mechanisms, including computed tomography (CT), ultrasound, bioimpedence analysis, and dual-energy x-ray absorptiometry.[6] Of these methods, CT imaging is commonly considered the gold standard method for measuring body composition at the tissue–organ level.[7] CT morphometric analysis is an accurate and precise method to determine torso muscle cross-sectional area.[6,7] Additionally, torso skeletal muscle assessments accurately estimate both extremity and whole body skeletal muscle composition.[8] CT morphometrics is particularly useful in acute critical illnesses such as intra-abdominal sepsis where images are often readily available as a diagnostic standard of care. Additionally, CT has been shown to be a valid diagnostic tool for assessment of sarcopenia and has prognostic value across multiple disease processes.[9–11] In the context of sepsis, low muscle mass has also been associated with higher inpatient mortality among older patients.[12] However, these studies are mostly retrospective in nature, limited to inpatient outcomes, or with long-term follow-up focused on solely on mortality. They also do not include information on acute changes in muscle mass after surgery or sepsis. Puthucheary *et al*. recently demonstrated using serial ultrasound assessment that critically ill patients exhibit acute lower extremity muscle wasting of greater than 10% in less than 2 weeks.[13,14] Currently, there is only a limited amount of data describing whether or not this loss of muscle mass persists over the following months to years among sepsis survivors, or if it is related to poor long-term outcomes.[15]

To investigate these questions, we performed a prospective longitudinal cohort study of critically ill patients with intra-abdominal sepsis, including 1 year functional and radiographic follow-up assessments, to determine the relationship of baseline muscle mass and acute muscle wasting with long-term outcomes after sepsis. We hypothesized that patients with sarcopenia at baseline would be subject to high sepsis-associated inpatient mortality. Additionally, we hypothesized that among sepsis survivors, those with persistent acute muscle wasting would have poor functional status at 1 year.

# Methods

## Study design, site, and patient enrolment

We performed a prospective longitudinal cohort study of critically ill patients with intra-abdominal sepsis at our academic, 996-bed quaternary medical centre. All enrolled patients had a standard-of-care diagnostic abdominal CT scan available for baseline muscle mass assessment. The parent cohort of this study was from the University of Florida Sepsis and Critical Illness Research Center (SCIRC), which is conducting an ongoing prospective, longitudinal cohort study evaluating sepsis patients treated in our surgical intensive care unit (ICU).[16] The primary research objectives of the SCIRC cohort are to investigate mechanisms of persistent inflammation, immunosuppression, and catabolism that drive the development of chronic critical illness (CCI) after sepsis, and its associated dismal long-term functional outcomes. The overall SCIRC programme, as well as this sub-cohort study, was approved by the University of Florida institutional review board (IRB201400611) and registered with clinicaltrials.gov (NCT02711709) prior to initiation. Patients eligible for this analysis were admitted to our ICU with a diagnosis of sepsis from an intra-abdominal source. Subsequent patient management was guided by evidence-based sepsis protocols, implemented within the electronic medical record to ensure timely and standardized care.[17]

Inclusion and exclusion criteria were based upon the parent SCIRC sepsis programme, with its focus on elucidating the mechanism of the dysfunctional innate immune response and poor clinical and functional outcomes of those who survive the initial septic insult.[16] Inclusion criteria consisted of the following: (i) age ≥18 years; (ii) clinical diagnosis of sepsis, severe sepsis, or septic shock as defined by the 2001 International Sepsis Definition Conference; (iii) presence of a baseline diagnostic abdominal CT scan capturing the L3 level within 48 h of sepsis diagnosis; and (iv) ability to obtain informed consent from patient or legal authorized representative. Exclusion criteria consisted of the following: (i) refractory shock (death <24 h); (ii) pre-sepsis expected lifespan <3 months; (iii) patient/proxy not committed to aggressive management (do-not-resuscitate status); (iv) severe congestive heart failure (New York Heart Association Class IV); (v) Child–Pugh Class C liver disease or pre-liver transplant; (vi) HIV diagnosis with CD4 count <200 cells per cubic

millimetre; (vii) patients on chronic corticosteroids or immunosuppressive agents, including transplant recipients; (viii) institutionalized patients; (ix) chemotherapy or radiotherapy within 30 days; (x) traumatic brain injury with Glasgow Coma Score <8; (xi) spinal cord injury resulting in permanent sensory and/or motor deficits. All enrolled study patients were prospectively adjudicated on a weekly basis to ensure an accurate sepsis diagnosis and classification.

The authors certify that the study and published manuscript adhere to all principles outlined in the ethical guidelines of the *Journal of Cachexia, Sarcopenia and Muscle*.[18]

## Computed tomography morphometric analysis

We utilized CT morphometric analysis to evaluate baseline and interval changes in torso skeletal muscle mass. Baseline CT scans were performed as standard of care for diagnosis of intra-abdominal sepsis. Interval research protocol CT scans were then performed at 3 and 12 month follow-up visits. If a patient had an abdominal CT scan for clinical purposes within 30 calendar days from scheduled follow up date, this existing imaging was used to limit unnecessary radiation exposure. We performed CT morphometric analyses using Slice-O-matic software (v. 5.0 rev 7; TomoVision, Magog, Quebec, Canada). Total axial skeletal muscle (including bilateral psoas, paraspinal, and abdominal wall muscles) cross-sectional area ($cm^2$) was identified at level of the third lumbar (L3) vertebrae. Skeletal muscle was identified using established ($-29$ to $+150$) Hounsfield unit attenuation thresholds. Skeletal muscle index (SMI, $cm^2/m^2$) value was then calculated by normalizing the skeletal muscle cross-sectional area to the patient's height squared. This same technique was used to calculate the psoas muscle index (PMI). To ensure reliability, two investigators analysed each CT scan independently with the average calculated SMI used for data analysis. Given that CT morphometric analysis includes an element of human subjectivity regarding tissue delineation, inter-observer reliability of SMI and PMI values was determined to assess for potential analytic variance.

## Patient classification, definitions, and outcomes

Baseline and clinical parameters were collected during the initial hospitalization, including patient demographics, admission diagnosis, comorbidities, sepsis source, sepsis severity, and acute physiology and chronic health evaluation (APACHE) II score. Baseline performance status (ECOG/WHO/Zubrod scale) and health-related quality of life (HRQOL; Rand SF-36, EQ-5D-3L) was assessed at the time of study entry as a 4 week, pre-sepsis recall from either the patient or patient proxy. This method has been shown to be a valid assessment tool for incapacitated critically ill patients.[16,19–21] Patients

were considered sarcopenic at baseline based on established SMI criteria, defined as male patients with an SMI $\leq 52.4$ in male patients or an SMI $\leq 38.5$ in female patients.[22–24] Primary inpatient outcomes included mortality, hospital length of stay (LOS), ICU LOS, incidence and severity of Denver criteria-based MOF, clinical trajectory, and discharge disposition. Clinical trajectory was classified as either early death, rapid recovery, or the development of CCI based on previously published definitions.[19,25] Early death was defined as death less than 14 days from sepsis protocol onset. CCI patients were those with an ICU LOS greater than or equal to 14 days with persistent organ dysfunction, as measured by sequential organ failure assessment score.[25] Rapid recovery patients were those discharged from the ICU within 14 days with organ recovery. Based on previously published definitions, a discharge disposition was considered 'good' if a patient was discharged to home or an inpatient rehabilitation facility. A disposition was deemed 'poor' for inpatient death or discharge to another acute care hospital, long-term acute care hospital, or skilled nursing facility.[19]

Long-term follow-up assessments were completed at 3, 6, and 12 months following sepsis onset. These visits were performed at the University of Florida Institute on Aging, the patient's home, or via telephone in that preferential order. We conducted monthly telephone interviews with all patients to optimize retention and assess for interval changes in health status. Long-term outcomes included assessments of HRQOL, physical performance, and mortality. Additionally, hand dynamometry grip strength and short physical performance battery (SPPB) assessments were performed and at 3, 6, and 12 months. For patients lost to follow-up, the United States Social Security Death Index (SSDI) database was cross-referenced for mortality assessment. Performance status was evaluated using the Eastern Oncology Group/World Health Organization/Zubrod (i.e. 'Zubrod') score.[26] The Zubrod score is a 6-point scale that measures the functional status of a patient's ambulatory nature and ability to perform independent activities: (0) asymptomatic (fully active), (1) symptomatic but completely ambulatory (restricted in physically strenuous activity), (2) symptomatic, <50% in bed during the day (ambulatory and capable of all self-care but unable to perform any work activities), (3) symptomatic, >50% in bed, but not bedbound (capable of only limited self-care), (4) Bedbound (completely disabled and incapable of any self-care), and (5) death. Baseline (i.e. pre-sepsis) Zubrod scores were independently adjudicated by three investigators based on patient/proxy 1 month recall assessment that was obtained within 1 week of initial enrolment. We selected the Zubrod score as our metric for functional status as it is validated, easy to perform, and can be assessed remotely if necessary.[26] Zubrod scores were compared at 3, 6, and 12 month follow-up visits to baseline for those patients with values recorded at both time points.

## Biomarker analysis

Based on previously described markers of catabolism, muscle wasting, and cancer cachexia, a series of biomarkers was measured sequentially to evaluate possible mechanisms of ongoing muscle loss.[27–29] Plasma levels of IL-6, IL-8, and TNF-alpha, as well as urinary 3-methylhistidine/creatinine ratio were determined from samples collected on days 1, 4, 7, 14, and 21 days after enrolment, while hospitalized.

## Statistical analysis and predictive models

Data are presented as frequency and percentage for categorical variables, and as mean with standard deviation, or median with interquartile range, for continuous variables. We used Fisher's exact test for comparison of categorical variables and the Kruskal–Wallis test for comparison of continuous variables, while paired *t* tests were used to assess differences from baseline measurements. For CT morphometric results, inter-rater agreement was calculated by the concordance correlation coefficient.[30] The log-rank test was used to compare Kaplan–Meier product limit estimates of survival between groups. All significance tests were two sided, with *P* value ≤0.05 considered statistically significant. Statistical analyses were performed with SAS version 9.4 (Cary, NC, USA).

We utilized CT morphometric values (SMI/PMI, and sarcopenia as previously defined) to develop multivariate prediction models of both inpatient clinical trajectory (early death/CCI) and poor long-term outcome (Zubrod score of 4 or 5 at 12 months). Following univariate analysis, we performed positive stepwise logistic regression analysis considering individual CT-derived morphometrics (SMI, PMI, and sarcopenia) while controlling for age, sepsis severity, and comorbidity burden.[25,31]

# Results

## Enrolment

Over the 2 year study period (April 2016 to June 2018) a total of 1491 patients were screened for the parent prospective sepsis cohort. Of these potential septic patients, 1137 failed to meet inclusion and/or met exclusion criteria, 59 were adjudicated as non-septic after initial diagnosis, and in 90 informed consent could not be obtained (see CONSORT diagram; supplement information, *Supporting information, Figure S1*). Of the remaining 205 patients, 77 patients had a non-abdominal source of sepsis, 65 patients had no baseline diagnostic standard-of-care CT scan, 11 declined interval research CT imaging at follow-up, and 2 patients had unusable

CT scans due to artefact (e.g. photon starvation and peripheral beam hardening). Three patients withdrew from the study prior to hospital discharge, leaving 47 patients for the final analytic cohort. The vast majority of subjects in the final analytic cohort (*n* = 44/47, 94%) presented acutely to the hospital with intra-abdominal sepsis as their primary admitting diagnosis and were enrolled within 48 h of admission (median 0 days, interquartile range 0–1). There were only three patients that were enrolled later in an established hospital course (Days 10, 16, and 23) after developing intra-abdominal sepsis and becoming critically ill.

## Baseline characteristics

*Table 1* shows the baseline characteristics of the overall study analytic cohort, as well as comparison between the sarcopenic and non-sarcopenic groups. Overall, the patients were non-elderly (mean age 53 years), with approximately 80% of patients under the age of 65. Approximately half (*n* = 23) of patients met CT morphometric criteria for pre-existing sarcopenia. The sarcopenic group did have significantly lower median baseline body mass index and contained a higher proportion of Caucasian patients (*Table 1*). Sarcopenic patients had significantly worse baseline performance status as assessed by Zubrod scale (0.8 ± 0.27 vs. 2.0 ± 0.31, *P* = 0.0083), and physical function as measured by SF-36 physical functioning component (34.8 ± 3.6 vs. 45.4 ± 3.0, *P* = 0.029; *Table S1*). Additionally, sarcopenic patients had worse baseline health related quality of life as demonstrated by lower EQ-5D 3L Utility Index (0.5 ± 0.006 vs. 0.7 ± 0.07, *P* = 0.038) and higher descriptive system scores (9.2 ± 0.6 vs. 7.3 ± 0.6, *P* = 0.025; *Table S1*). Although there were trends towards worse values in the sarcopenic cohort, there were no statistically significant differences in sepsis severity or comorbidity burden as measured by Charlson Comorbidity Index (*Table 1*).[32] However, sarcopenic patients did have worse initial physiologic derangement as quantified by APACHE II score measured at 24 h after sepsis onset (*Table 1*).

## In-hospital clinical outcomes

Inpatient and short-term outcomes were generally worse in the sarcopenic group, including significantly greater ICU and hospital LOS, and higher inpatient mortality (*Table 2*). Sarcopenic patients also had a higher incidence of multiple organ failure and were more likely to have a clinical trajectory of early death or CCI, as opposed to that of rapid recovery (*Table 2*). Finally, sarcopenic patients were more likely to have a 'poor' hospital discharge disposition (*Table 2*).

**Table 1** Study population demographics and disease severity

|  | Overall (n = 47) | Sarcopenic (n = 23) | Non-sarcopenic (n = 24) | P |
|---|---|---|---|---|
| Male, n (%) | 14 (29.8) | 8 (34.8) | 6 (25) | 0.53 |
| Age in years, mean (SD) | 53.1 (14.3) | 55.5 (15.2) | 50.8 (13.2) | 0.22 |
| Age ≥65, n (%) | 10 (21.3) | 6 (26.1) | 4 (16.7) | 0.49 |
| Race, n (%) |  |  |  | 0.02 |
|   Caucasian (White) | 40 (85.1) | 22 (95.7) | 18 (75) | — |
|   African American | 6 (12.8) | 0 (0) | 6 (25) | — |
|   Unknown | 1 (2.1) | 1 (4.3) | 0 (0) | — |
| BMI, median (25th, 75th) | 32.6 (28.4, 43.6) | 29.5 (25.1, 37.8) | 38 (30.9, 45.7) | 0.01 |
| Charlson CI, median (25th, 75th) | 1 (0, 3) | 2 (1, 5) | 1 (0, 3) | 0.15 |
| Sarcopenia-associated comorbidities, n (%) |  |  |  |  |
|   History of severe COPD | 8 (17.0) | 5 (21.7) | 3 (12.5) | 0.46 |
|   History of decompensated CHF | 0 (0) | 0 (0) | 0 (0) | — |
|   Disseminated cancer | 0 (0) | 0 (0) | 0 (0) | — |
|   Chemotherapy within 30 days | 0 (0) | 0 (0) | 0 (0) | — |
|   ESRD with HD | 2 (4.3) | 2 (8.7) | 0 (0) | 0.23 |
| APACHE II, median (25th, 75th) | 14 (10, 20) | 18 (12, 24) | 12.5 (8.5, 16.5) | 0.01 |
| Sepsis severity[a], n (%) |  |  |  | 0.058 |
|   Sepsis | 12 (25.5) | 6 (26.1) | 6 (25) | — |
|   Severe sepsis | 25 (53.2) | 9 (39.1) | 16 (66.7) | — |
|   Septic shock | 10 (21.3) | 8 (34.8) | 2 (8.3) | — |

BMI, body mass index; CI, comorbidity index; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; ESRD, end-stage renal disease with haemodialysis; APACHE II, Acute Physiology And Chronic Health Evaluation two score.
[a]Sepsis-2 Consensus Conference definitions.

**Table 2** Inpatient outcomes

|  | Overall (n = 47) | Sarcopenic (n = 23) | Non-sarcopenic (n = 24) | P* |
|---|---|---|---|---|
| In-hospital mortality, n (%) | 4 (8.5) | 4 (17.4) | 0 (0) | 0.049 |
| 30-day mortality, n (%) | 4 (8.5) | 4 (17.4) | 0 (0) | 0.049 |
| ICU LOS, median (25th, 75th) | 7 (3, 17) | 13 (5, 26) | 4 (3, 9) | 0.005 |
| Hospital LOS, median (25th, 75th) | 15 (8, 23) | 21 (9, 33) | 12 (7.5, 19.5) | 0.024 |
| Max. SOFA score, median (25th, 75th) | 7 (3.5, 9.5) | 8 (4, 11) | 5 (2, 7) | 0.058 |
| MOF incidence, n (%) | 17 (36.2) | 13 (56.5) | 4 (16.7) | 0.007 |
| Clinical trajectory, n (%) |  |  |  | 0.002 |
|   Early death | 1 (2.1) | 1 (4.3) | 0 (0) |  |
|   CCI | 13 (27.7) | 11 (47.8) | 2 (8.3) |  |
|   RAP | 33 (70.2) | 11 (47.8) | 22 (91.7) |  |
| Discharge disposition, n (%) |  |  |  | 0.016 |
|   'Good' disposition | 34 (72.3) | 13 (56.5) | 21 (87.5) |  |
|     Home | 15 (31.9) | 3 (13) | 12 (50) |  |
|     Home with healthcare services | 18 (38.3) | 9 (39.1) | 9 (37.5) |  |
|     Rehabilitation facility | 1 (2.1) | 1 (4.3) | 0 (0) |  |
|   'Poor' disposition | 13 (27.7) | 10 (43.5) | 3 (12.5) |  |
|     Long-term acute care facility | 5 (10.6) | 4 (17.4) | 1 (4.2) |  |
|     Skilled nursing facility | 4 (8.5) | 2 (8.7) | 2 (8.3) |  |
|     Inpatient death | 4 (8.5) | 4 (17.4) | 0 (0) |  |

CCI, chronic critical illness (ICU LOS ≥ 14 days with ongoing organ dysfunction); early death, death <14 days from sepsis onset; ICU, intensive care unit; LOS, length of stay; MOF, multiple organ failure; RAP, rapid recovery (ICU LOS < 14 days with organ dysfunction resolution); SOFA, sequential organ failure assessment.
*Sarcopenic vs. non-sarcopenic group comparison.

## Functional and long-term outcomes associated with pre-existing sarcopenia

Loss to outpatient follow-up was extremely low, with 95% subject retention at 3 months and 91% retention at 6 and 12 months (*Figure S1*). *Figure 1* shows the baseline and long-term performance status of sarcopenic as compared with non-sarcopenic patients. While sarcopenic patients reported worse baseline (pre-hospitalization) performance status than non-sarcopenic patients, overall functional status of

the study population was good at mildly symptomatic (non-sarcopenic) to moderately symptomatic (sarcopenic). Sarcopenic patients also had worse overall performance status at all follow-up time points (*Figure 1*). Sarcopenic patients had lower hand grip strength measured at 3 (16.7 ± 2.8 vs. 8.5 ± 1.1, P = 0.013) and 6 months (20.9 ± 2.7 vs. 33.2 ± 3.9, P = 0.018; *Table S1*). Additionally, sarcopenic patients exhibited worse physical function as measured by SPPB at 3 (3.5 ± 1.5 vs. 8.5 ± 1.1, P = 0.013) and 6 months (4.0 ± 1.6 vs. 10.4 ± 0.7, P = 0.001) after sepsis onset (*Table S1*). Of

note, as grip strength and SPPB are objective rather than sub-jective measurements, and given sepsis is a condition of acute onset critical illness, we were unable to measure baseline/pre-sepsis status for comparison between groups or to later follow-up assessments. Finally, sarcopenic patients were found to have significantly higher 1 year mortality than non-sarcopenic patients (34.9% vs. 4.2%, *p* = 0.007; *Figure 2*).

## Longitudinal computed tomography morphometric analysis and persistent muscle loss

As per study inclusion criteria, all of the 47 patients enrolled in the study had baseline standard of care CT imaging for ax-ial morphometric analysis at the L3 level. The overwhelming majority (*n* = 45; 96%) of the baseline imaging scans were
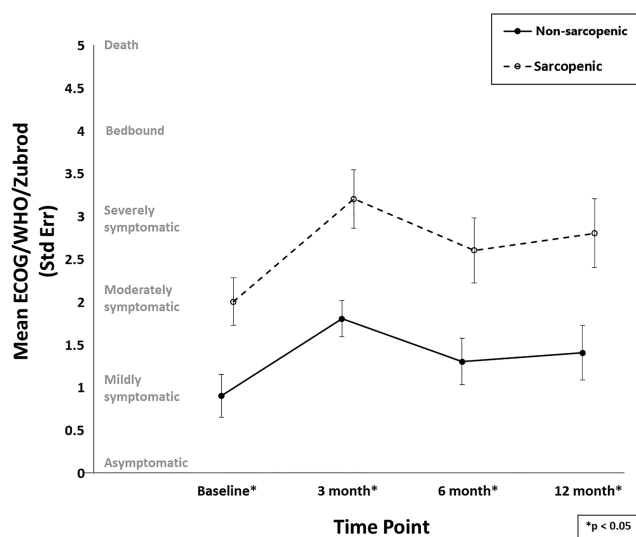


**Figure 1** Functional status over time among sepsis patients with and without baseline sarcopenia. Functional status is measured by ECOG/WHO/Zubrod score by baseline patient/proxy recall reporting and at 3, 6, and 12 month follow-up. *\*P < 0.05*.
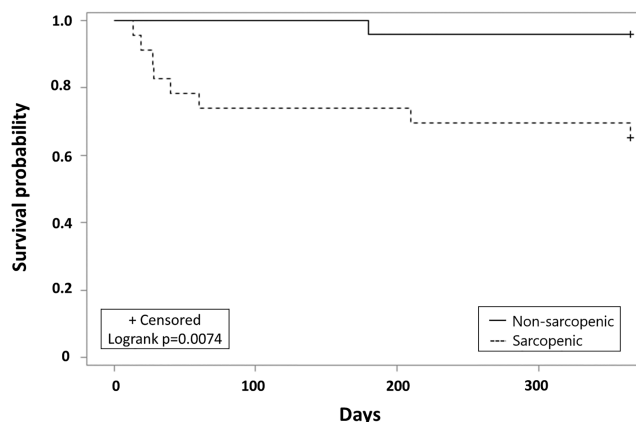


**Figure 2** One year survival analysis of sepsis patients with and without baseline sarcopenia.

obtained either immediately prior to or within 24 h of sepsis diagnosis. The remaining two baseline scans were obtained within 48 h of enrolment. The inter-rater correlation coeffi-cient for the dual assessed morphometric analyses was strong, being slightly higher in SMI [0.956 (95% confidence in-terval 0.935–0.970)] than PMI [0.885 (0.833–0.922)]. There was approximately 50% attrition to CT image acquisition at 3 and 12 months, primarily due to subjects not willing, able or alive to return for on-site assessment (*Table 3, Figure S1*).

Of the 26 sepsis patients alive and with follow-up imaging at 3 months, 18 (69%) showed evidence of persistence of acute muscle wasting (as measured by a decrease in SMI from baseline) at 3 months with an average 8% loss in muscle mass (*Figure 3*). A set of representative CT analysis images of a patient with 8% loss of muscle mass at 3 months is shown in *Figure S2*. The only clinical factors associated with a persis-tent loss of muscle mass was a lower overall comorbidity bur-den (Charlson Comorbidity Index, 1.4 ± 0.6 vs. 3.8 ± 0.9, *P* = 0.02) and better baseline HRQOL (EQ-5D-3L Utility Index, 0.7 ± 0.1 vs. 0.5 ± 0.1, *P* = 0.026; and Descriptive system score, 7.3 ± 0.5 vs. 9.6 ± 0.76, *p* = 0.019; *Table S2*). There were no differences in incidence of baseline sarcopenia [*n* = 7/18 (40%) vs. *n* = 4/8 (50%); *P* = 0.68] or average SMI [median, 47.6 (37.8, 56.5) vs. 43.6 (38.9, 46.9); *P* = 0.54] be-tween those with and without persistent muscle loss at 3 months. Those with persistent muscle loss at 3 months had a worse SF-36 physical component summary (22.7 ± 4.2 vs. 34.7 ± 3.2, *P* = 0.035), general health (31.7 ± 2.5 vs. 42.3 ± 2.4, *P* = 0.006) and physical role limitation (19.0 ± 2.8 vs. 33.1 ± 4.7, *P* = 0.018) scores, but no difference in SPPB performance or hand grip strength (*Table S2*). How-ever, by 6 months, there were no differences in HRQOL, phys-ical function, or strength in subjects with or without persistent muscle loss at 3 months (*Table S2*).

Of the 24 patients alive and with follow-up imaging at 12 months, 16 (67%) had evidence of residual muscle mass loss (average ΔSMI −3%; *Figure 3*). However, this was statis-tically equivalent to their baseline muscle mass (*Table 3*). Non-sarcopenic patients at baseline had a decrease in SMI of 8% at 3 months, with a persistent 4% decrease from base-line at 12 months (*Table 3*). In contrast, sarcopenic patients showed a 10% decrease in SMI at 3 months, which subse-quently returned to baseline at 12 months (*Table 3*). It should be noted that the sarcopenia group had significantly higher mortality between Months 3 and 12 compared with the non-sarcopenic group (*Figure 2*), which may confound this apparent muscle mass increase at 12 months via survival bias.

## Biomarker analysis

Overall, there were no statistically significant (*P* < 0.05) dif-ferences in early inflammatory or catabolic biomarkers (Days 1–21) between patients who showed persistent loss of

**Table 3** Skeletal muscle mass changes from baseline at 3 and 12 months after sepsis onset

| Change from baseline muscle mass | Overall | P | Sarcopenic | P | Non-sarcopenic | P |
|---|---|---|---|---|---|---|
| SMI | | | | | | |
| Baseline to 3 month ΔSMI, mean (SD) | −8.4% (11.8%) [n = 26] | <0.001 | −9.5% (14.8%) [n = 11] | 0.066 | −7.6% (9.5%) [n = 15] | 0.001 |
| Baseline to 12 month ΔSMI, mean (SD) | −2.9% (11.3%) [n = 24] | 0.09 | −1.1% (14.8%) [n = 11] | 0.78 | −4.4% (7.5%) [n = 13] | 0.023 |
| PMI | | | | | | |
| Baseline to 3 month ΔPMI, mean (SD) | −4.7% (20.3%) [n = 26] | 0.21 | −0.2% (23.0%) [n = 11] | 0.78 | −7.6% (18.9%) [n = 15] | 0.003 |
| Baseline to 12 month ΔPMI, mean (SD) | 0.3% (22.4%) [n = 24] | 0.49 | 3.4% (25.9%) [n = 11] | 0.8 | −1.4% (20.5%) [n = 13] | 0.023 |

PMI, psoas muscle index; SMI, skeletal muscle index; ΔPMI, change in psoas muscle index; ΔSMI, change in skeletal muscle index.
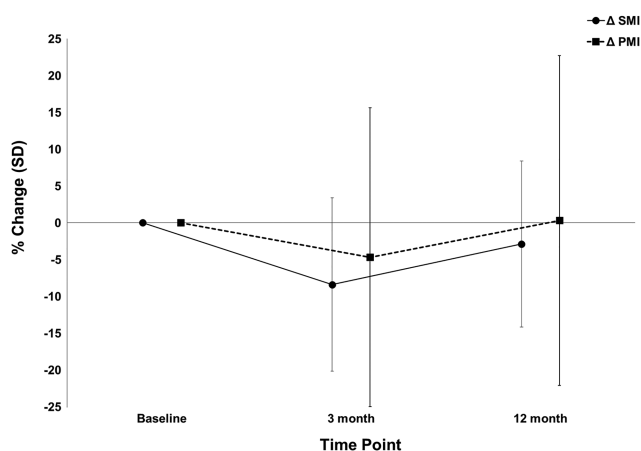


**Figure 3** One year longitudinal muscle mass loss assessment of sepsis patients. Baseline muscle mass metrics of skeletal muscle index (SMI) and psoas muscle index (PMI) were measured by computed tomography (CT) morphometric analysis. Change from baseline muscle mass (ΔSMI/ΔPMI) was determined by comparing baseline measurements to follow-up assessments at 3 and 12 months.

muscle mass at three months and those that did not (*Figure S3*). However, there were notable differences when comparing sarcopenic and non-sarcopenic patients (*Figure 4*). Sarcopenic patients had persistently higher levels of inflammatory biomarkers (IL-6, IL-8, and TNF-α) beyond Day 14 (*Figure 4*). However, there were no statistically significant differences ($P < 0.05$) in catabolism, as measured by urine 3-MH/creatinine ratio, between groups at any time point (*Figure 4*).

### Predictive models of poor inpatient and long-term outcomes

Overall, low baseline muscle mass was an independent predictor of both poor inpatient and long-term outcomes after intra-abdominal sepsis (*Table 4*). When analysed independently, both sarcopenia (dichotomous) and baseline low SMI (continuous) metrics were independent predictors of a complicated inpatient clinical trajectory (early death/CCI) after controlling for APACHE II, age, and Charlson Comorbidity Index (*Table 4*). Regarding long-term outcomes, low SMI and Charlson Comorbidity Index were independent predictors of death or dismal functional status (Zubrod score 4 or 5) at 12 months (*Table 4*). Acute muscle wasting (negative ΔSMI or ΔPMI from baseline) that persisted at least 3 months was not associated with poor long-term outcomes.

## Discussion

Sepsis is an acute disease of immune dysregulation and hyperinflammation, with significant morbidity and mortality. Over the last 20 years, advances in evidence-based critical care and sepsis resuscitation strategies have led to significant decreases in sepsis hospital mortality. However, the burden of poor outcomes after sepsis has shifted from inpatient death to a growing population of 'sepsis survivors' with a clinical trajectory of CCI. Sepsis survivors that develop CCI are characterized by an inability to rehabilitate and ultimately suffer dismal long-term outcomes. Persistent weakness in critically ill patients, often termed ICU-acquired weakness (ICUAW) is prevalent and associated with poor clinical outcomes.[33,34] While weakness and acute myopathy in critical illness are well-established,[35] the long-term effects of sepsis on muscle mass remain unknown. Additionally, the impact of pre-existing sarcopenia and/or weakness to ICUAW is poorly understood. In this prospective longitudinal cohort study of 47 septic patients, we demonstrated that acute muscle wasting occurs following intra-abdominal sepsis and persists at least 3 months after sepsis onset. However, we also found that baseline sarcopenia, rather than acute muscle wasting in itself, was the primary factor that predicted poor long-term outcomes and mortality in these critically ill patients. These findings support the hypothesis that ICUAW is actually an acute on chronic exacerbation of muscle loss associated with chronic comorbid disease and more prevalent in frail patients with low baseline muscle mass.
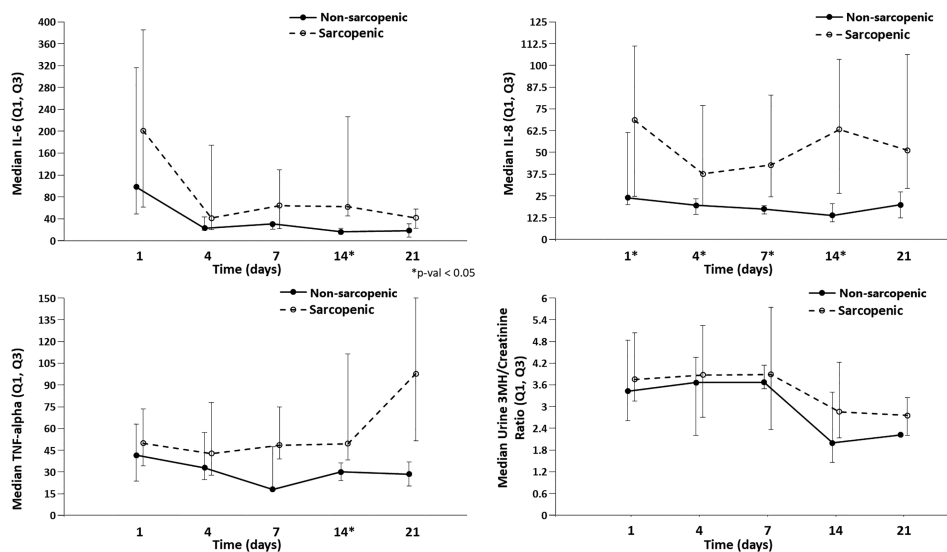
**Figure 4** Inflammatory and catabolic biomarker measurements of sepsis patients with and without baseline sarcopenia. Circulating plasma and urine samples were collected on days 1, 4, 7, 14, and 21 days after sepsis onset while hospitalized. Measured biomarkers included interleukin 6 (IL-6), interleukin 8 (IL-8), tumour necrosis factor alpha (TNF-α), and urine 3-methylhistidine to creatinine ratio (3-MH/Cr). *$P < 0.05$.

**Table 4** Multivariate prediction models for poor inpatient and long-term outcomes

| Multivariate risk outcome models | OR | 95% CI | P | AUC (95% CI) |
|---|---|---|---|---|
| Early death/CCI[a] | | | | |
|   Baseline sarcopenia | 11.87 | (1.88, 74.9) | 0.009 | 0.880 (0.781, 0.979) |
|   Charlson Comorbidity Index | 1.49 | (1.08, 2.06) | 0.01 | 0.880 (0.781, 0.979) |
| Early death/CCI[b] | | | | |
|   Baseline SMI | 0.9 | (0.82, 0.99) | 0.033 | 0.846 (0.732, 0.961) |
|   Charlson Comorbidity Index | 1.55 | (1.14, 2.11) | 0.005 | 0.846 (0.732, 0.961) |
| Death or dismal functional status at 1 year[c,d] | | | | |
|   Baseline SMI | 0.89 | (0.80, 0.99) | 0.039 | 0.867 (0.759, 0.974) |
|   Charlson Comorbidity Index | 8.29 | (1.14, 2.28) | 0.006 | 0.867 (0.759, 0.974) |

AUC, area under the curve; CI, confidence interval; OR, odds ratio; SMI, skeletal muscle index; early death, death less than 14 days from sepsis onset; CCI, chronic critical illness (≥14 days in intensive care unit with persistent organ dysfunction).
[a]Covariates including age, APACHE II score, and either Sarcopenia.
[b]Covariates including age, APACHE II score, and SMI.
[c]Defined as Zubrod score of 4 or 5.
[d]Sarcopenia not significant on univariate analysis, not included in multivariate model.

This study adds to the growing evidence that low muscle mass is a strong risk factor for poor outcomes among hospitalized patients with acute disease processes. Pre-operative low muscle mass has been suggested to be a risk factor for post-operative complications and/or death across numerous surgical specialties, including transplant, colorectal, and emergency general surgery.[9–11] Low muscle mass has also been retrospectively shown to be a risk factor for inpatient mortality in specific patient populations with sepsis, such as the elderly or those with cirrhosis.[11,12] Our study builds on these in a number of ways. It is prospective in nature, but more importantly has detailed longitudinal assessment with high subject retention. Along with sarcopenia having worse commonly reported in-patient outcomes (ICU LOS, poor discharge disposition, and inpatient mortality), it was also associated with developing a clinical trajectory of CCI. This is

important as we have previously shown that developing CCI after sepsis is associated with sepsis recidivism, hospital readmissions, and poor long-term survival.[36] Importantly, on multivariate modelling with other known risk factors of CCI, sarcopenia (along with comorbidities) remained an independent risk factor for the poor inpatient outcome of CCI.

We also have shown in this study that low baseline muscle mass is predictive of poor long-term outcomes after sepsis. Interestingly, while the dichotomous criterion of sarcopenia was not independently predictive of a dismal long-term outcome at 1 year, lower baseline SMI was. This likely signifies that while lower baseline muscle mass is an important risk factor for poor long-term outcomes in sepsis, the cut-offs for sarcopenia used for this study were not ideal for this cohort, especially with the study's relatively small sample size. This is not surprising given this widely published

SMI-based criterion is essentially arbitrary. While we a priori selected commonly published cut-offs for sarcopenia in surgical literature, numerous other cut-offs exist in the literature.[6]

While the presence and significance of muscle wasting is well established across many chronic disease processes, it is less well described among acute conditions. In a landmark 2013 study on acute skeletal muscle wasting in critical illness, Puthucheary performed serial rectus femoris ultrasound measurements on critically ill patients and found that cross-sectional area decreased by over 10% in just 7 days.[14] Another subsequent study showed that muscle wasting in prolonged critical illness (also by serial ultrasound) was associated with decreased measures of strength and function.[13] However, it is still unclear how long this acute muscle wasting persists after ICU discharge. Our finding of greater than 8% muscle mass loss at 3 months provides convincing evidence that the acute muscle loss in critical illness persists well beyond ICU discharge. The average return to near baseline muscle mass measures at 12 months was likely a combination of some muscle recovery, but was also likely driven by survival bias (especially among sarcopenic patients) due to mortality between 3 and 12 months. There is evidence that muscle recovery occurs over time after acute illness. Dos Santos *et al.* performed longitudinal morphometric analyses (of CT quadriceps cross-sectional area) on patients with prolonged mechanical ventilation at 7 days and 6 months after ICU discharge (but without baseline evaluations). They found that the majority of these patients had relative muscle atrophy at 6 months as compared with age/sex matched healthy controls, but also showed an increase in muscle mass in that post-discharge timeframe suggesting some recovery.[15] Interestingly, we found that patients with higher baseline muscle mass still had significant loss at 12 months (despite having better overall clinical outcomes). This suggests that the magnitude of acute muscle loss may be proportionate to baseline muscle mass. Interestingly, we found that greater muscle loss at 3 or 12 months was not associated with poor long-term outcome. While a surprising finding, this could be due to selection bias among patients with the worst outcomes being unable to return for follow-up CT scans due to death or severe functional disability.

Finally, to gain insight into mechanisms behind this sepsis-induced acute muscle wasting, we obtained serial biomarkers associated with sarcopenia, cachexia, and catabolism.[27–29] We hypothesized that patients with increased muscle loss at follow-up would have elevations in these biomarkers, due to acute exacerbation and persistence of an underlying inflammation and a catabolic state. As we have shown before, there were overall elevated markers of inflammation and catabolism in the sepsis study population. However, there was surprisingly no difference in systemic inflammatory or catabolic biomarker levels between those who did and did not experience acute muscle wasting. Rather, patients with baseline sarcopenia showed persistently higher levels of IL-6, IL-8, and TNF-α beyond 2 weeks as compared with non-sarcopenic patients. It is possible these elevations in the sarcopenic patients were caused by an acute exacerbation of a chronic pro-inflammatory and catabolic state (e.g. due to underlying comorbidities or 'inflammaging'). However, this also could be explained by their worsened physiologic derangement during the sepsis episode. Future studies should evaluate these inflammatory cytokines and other serum myokines, such as irisin and myostatin[37,38] in longitudinal fashion to determine if persistent elevation effects sustained muscle loss after critical illness.

This study has several limitations that need to be addressed. First, there are limitations inherent to recall assessment of baseline 'pre-sepsis' functional status. It is possible that recall bias has over or estimated baseline functional status assessments. As stated and cited in the Methods section, patient/proxy recall of functional and performance status has been used and reported in the context of critical illness, although it clearly carries risk of recall bias. Unfortunately, in this population of patients, patient/proxy recall is the set of assessment tools currently available, as there is no feasible or practical way to prospectively evaluate and follow a population of subjects, and then enrol patient who happen to later develop sepsis and are hospitalized emergently. Of note, only nine patients (19%) did not have, or were unable to recover, the capacity to perform the assessments during their hospitalization and thus have to rely on proxy reporting. Second, while we used the phrase 'sarcopenia' to describe low muscle mass in accord with previous recommendations (specifically in surgical literature), morphometric analysis gives no information on muscle strength or function that is required by most recent European Working Group on Sarcopenia in Older People (EWGSOP) guidelines for definition of sarcopenia.[39] Third, this study is of a relatively small size, with nearly half of study patients subsequently missing CT scans due to either patient death or lack of in-person follow-up. This may have left certain comparisons between cohorts underpowered which need to be further investigated with larger future studies. Finally, it is unclear the effect any tissue oedema (as the Hounsfield unit for water is 0, which is within the range used for muscle delineation) would have on SMI calculation, or changes in SMI over time. Similarly, any intra-abdominal process near L3 axial muscles could have affected SMI calculations. However, it is important to note that two blinded reviewers had a strong inter-rater reliability by concordance correlation coefficient. Despite these potential issues, CT imaging is more accurate for tissue distinction in the setting of major acute volume shifts and tissue oedema as seen in critically ill patients, in comparison with other commonly utilized modalities such as x-ray absorptiometry (e.g. dual-energy x-ray absorptiometry) or electrical impedance measurements.

In conclusion, we have demonstrated that there is a significant loss of muscle mass in critically ill patients with intra-abdominal sepsis that persists through at least

3 months. However, it appears that lower baseline muscle mass rather than sepsis-associated acute muscle loss is the predominant risk factor for poor inpatient and long-term outcomes.

## Author contributions

The authors of this manuscript certify that they comply with the ethical guidelines for authorship and publishing in the *Journal of Cachexia, Sarcopenia and Muscle*. All authors made substantial contributions to the conception and design and/or acquisition of data, and/or analysis and interpretation of data. All authors participated in the drafting or critical revision of the manuscript and gave final approval of the submitted version. M. C., M. B., A. G., S. A., C. L., and S. B. contributed to study conception and design. M. C., M. B., A. G., and S. B. contributed to acquisition of data. M. C., M. B., G. G., Z. W., A. G., R. H., D. D., C. L., L. M., F. M., P. E., S. A., and S. B. contributed to analysis and interpretation of data. M. C., G. G., and S. B. drafted the manuscript with M. B., G. G., Z. W., A. G., R. H., D. D., C. L., L. M., F. M., P. E., and S. A. contributing to critical revision.

## Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Figure S1.** CONSORT Diagram
**Figure S2.** Representative image of persistence of acute muscle wasting at 3 months after sepsis.
**Figure S3.** Inflammatory and catabolic biomarker measurements of sepsis patients with and without persistent muscle mass loss at 3 months after sepsis onset.

## Conflict of interest

Michael Cox, Matthew Booth, Gabriela Ghita, Zhongkai Wang, Anna Gardner, Russell Hawkins, Dijoia Darden, Christiaan Leeuwenburgh, Lyle L. Moldawer, Frederick Moore, Philip Efron, Steven Anton, and Scott Brakenridge all declare that they have no conflict of interest.

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