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Acute skeletal muscle wasting in patients with acute kidney injury requiring continuous kidney replacement therapy: a prospective multicenter study

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Author Statement

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Abstract

Purpose: Acute kidney injury (AKI) requiring continuous kidney replacement therapy (CKRT) has been hypothesized to increase the risk of developing intensive care unit-associated weakness (ICU-AW), but prospective data are lacking.

Materials and Methods: This prospective observational study evaluated critically ill adults with AKI requiring CKRT at two U.S. academic hospitals. Using ultrasonography (US), we quantified changes in rectus femoris (RF) muscle mass and quality in the first week after CKRT initiation. At hospital discharge, we assessed for ICU-AW, physical function, and frailty.

Results: Twenty-three patients with median age 56 [IQR 47–60] years, BMI 29 [26–36] kg/m^2, and Charlson Comorbidity Index 3 [1.5–5] were enrolled. The baseline Sequential Organ Failure Assessment (SOFA) score was 9 [7.5–11.5] and CKRT duration was 4 [1–7] days. Six (26%) patients died in the ICU and one (4%) transitioned to comfort measures before study completion. Substantial muscle wasting occurred between Day 1 and Day 7: RF muscle thickness (mT) decreased by 10% [3%–20%]; RF cross-sectional area (CSA) decreased by 19% [12%–22%]; and echo intensity (EI) increased (implying worse muscle quality) by 14% [5%–25%]. A significant effect of time within subjects was observed for all three ultrasound measures (CSA: $F=66.2$, $p<0.001$; mT: $F=27.1$, $p<0.001$; EI: $F=22.5$, $p<0.001$). At hospital discharge, 67% of survivors (n=10/15) met criteria for ICU-AW.

Conclusions: Patients with AKI requiring CKRT experienced significant muscle wasting in the first week following CKRT initiation and had high rate of ICU-AW at hospital discharge.

Trial Registration: NCT05287204, Registered 20 October 2021

Keywords

Acute kidney injury; continuous kidney replacement therapy; dialysis; physical function; physical frailty; Muscle weakness; ICU-acquired weakness

INTRODUCTION

Intensive care unit-acquired weakness (ICU-AW) is reported in up to 80% of critically ill patients and is associated with long-term mortality, impaired functional status, and decreased quality of life (1–4). Acute skeletal muscle atrophy in the ICU is a common consequence of critical illness which precedes the development of ICU-AW (5). Skeletal muscle atrophy develops rapidly, with data demonstrating that 2–3% of baseline rectus femoris muscle size is lost in the first day of ICU admission and up to 30% lost in the first 10 days (5–7). A recent meta-analysis of over 50 studies and over 3,000 critically ill patients found a pooled prevalence of ICU-AW of 48% with an average rate of loss of muscle of nearly 2% per day during the first week of ICU admission (8). Previously recognized risk factors for ICU-AW include high illness severity, acute respiratory failure and the need for mechanical ventilation (MV), sepsis, prolonged immobilization, hyperglycemia, advanced age, and prolonged exposure to corticosteroids, sedatives, or paralytic agents (9, 10).

Acute kidney injury (AKI) complicates up to 50% of all ICU admissions and 5–15% of critically ill patients develop AKI requiring kidney replacement therapy (AKI-KRT), which is associated with a short-term mortality of ≥50% across a variety of ICU populations (11–13). Preclinical studies suggest that the extremely high mortality of AKI may relate to a series of non-traditional effects, including inflammatory injury or dysfunction of a variety of distant organs, including potentially skeletal muscle (14–17). The direct effects of AKI may be exacerbated in patients requiring KRT by the non-selective clearance of amino acids and other micronutrients (17–19). However, while muscle wasting is well-described in patients with chronic kidney disease (CKD) (20), AKI and specifically AKI requiring continuous KRT (AKI-CKRT) have only recently been proposed to contribute to an increased risk of ICU-AW (17). Studies evaluating the risk of muscle wasting in critically ill patients with AKI or those undergoing KRT are limited (21–25).

This study aimed to prospectively quantify the changes in RF muscle mass and quality in the first 7 days following CKRT initiation and measure the incidence of ICU-AW at hospital discharge in adults with severe AKI requiring CKRT.

METHODS

Ethics:

This study was approved by the Institutional Review Board of the University of Kentucky as the central IRB of record (MedExp # 71153). Written informed consent was obtained for all subjects, and the study was conducted in accordance with the Helsinki Declaration.

Study Design:

This was a prospective multicenter observational study performed at the hospitals of the University of Kentucky (UKY) and University of New Mexico (UNM). The study protocol was previously published (21). However, one of the three planned sites (University of Iowa) was ultimately unable to enroll any subjects due to unanticipated disruptions in research coordinator support related to the COVID-19 pandemic. In brief, patients with AKI-CKRT or their legal authorized representatives consented to participate in longitudinal

ultrasonographic assessment of rectus femoris (RF) muscle size and quality with carefully aligned assessments of mobility status in the ICU (acute phase) and muscle strength, physical function, frailty, and quality of life at hospital discharge and short-term outpatient follow-up (recovery phase). Muscle ultrasound images were obtained within 48 hours of CKRT initiation (Day 1) and repeated on study Days 3 and 7, at ICU and hospital discharge, and at outpatient follow-up at 1–3 months after discharge (Figure 1a). Biospecimens were collected as reported in the protocol; the results of these analyses will be separately disseminated. The protocol was developed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (21, 26).

Patient Population:

Eligible subjects were adults (≥18 years) with AKI-CKRT. All patients met KDIGO criteria for AKI (27) prior to CKRT initiation. Subjects with baseline estimated glomerular filtration rate <20 mL/min/1.73 m^2, as calculated by the 2021 CKD-EPI equation (28), or those previously treated with KRT at any point were excluded. Additional prespecified exclusion criteria were admission to ICU for >7 days before CKRT initiation, treatment with extracorporeal membrane oxygenation, and underlying neuromuscular or systemic disorders that may lead to baseline muscle wasting. Patients with weight-bearing restrictions that would preclude functional testing (e.g., orthopedic surgery or trauma) were also excluded. To potentially inform future study design, detailed screening data were obtained at one site (UNM; Supplemental Table 1). Enrollment and the initial assessments were completed within 48 hours of CKRT initiation.

Primary Outcomes:

The primary outcomes were the change in RF muscle size (cross-sectional area [CSA] and muscle thickness [mT]) and the change in echo intensity (EI, a measure of muscle quality) as measured by ultrasound. The methodology and standardization of muscle ultrasonography in critically ill subjects have been previously reported, with the results shown to have high clinical utility, reliability, and validity (5, 29, 30). Muscle ultrasonography parameters are valid estimates of muscle size and quality, but, given the inherent limitations of the technique, are not considered absolute measurements. We examined RF muscle at two-thirds of the distance from the anterior superior iliac spine to the superior border of the patella in neutral alignment with the knee in neutral flexion. The right lower extremity was imaged unless an interfering femoral vascular catheter was present; in all cases the limb assessed at baseline was utilized for all subsequent time points. A minimal-to-no probe compression technique was used with a linear probe (5–15 Hz) using excess ultrasound gel, auto-gain setting, and depth of 5.9–6 cm. At each time point, a minimum of 3 images were obtained by resetting the probe each time to reduce potential variations in EI. At UKY, one sonographer with >8 years of muscle ultrasound expertise (KPM) obtained all images using the Sonosite IViz (FUJIFILM Sonosite, Inc., Bothell, WA, USA) (29–31). At UNM, two independent sonographers (two of JPT, VQT, CAP, ZTS, or HPI) at each time point obtained ultrasound images within 4 hours of each other using the Butterfly iQ (Butterfly Network Inc., Burlington, MA, USA). Sonographers at UNM received dedicated teleconference training led by KPM. Training is detailed in the protocol, with the inter-rater reliability previously reported as excellent for CSA and mT and poor for EI, with intraclass

correlation coefficients of 0.92 (95% CI: 0.83–0.96), 0.96 (95% CI: 0.91–0.98), and 0.41 (95% CI: 0.04–0.68), respectively (21, 32). For both sites, muscle ultrasound images were coded according to subject, sonographer, location, and time point, blinding the image analysis. Images were analyzed using MyoVision-US, an artificial intelligence-powered software program (33), and the average of the 3 images collected at each time point was used in statistical analyses. Our primary focus was on describing the rate and severity of muscle wasting as measured by the change in RF CSA, RF mT, and RF EI. In addition, we compared to a historical control group of critically ill patients that were not treated with KRT. Specifically, the controls consisted of 21 subjects with complete data who were selected from a cohort of critically ill adults admitted for sepsis or acute respiratory failure to the medical ICU at one of the study sites (UKY) from a prior study of similar design published in 2020 (5). In contrast to the current cohort, these control patients underwent initial ultrasound assessment on ICU Day 1.

Secondary Outcomes:

We examined mobility levels using the ICU Mobility Scale (IMS) (34) at the same time points as ultrasound image acquisition. Muscle strength was examined by physical therapists at hospital discharge and short-term outpatient follow-up with two techniques: (1) Medical Research Council sum score (MRC-SS) with <48/60 indicating a diagnosis of ICU-AW (35); and (2) knee extensor force production using a hand-held dynamometer (Lafayette Instrument Company, Lafayette, IN, USA). At hospital discharge, physical function was assessed with Short Physical Performance Battery (SPPB), including the 4-meter gait speed test and Chair-Rise Test (36). At outpatient follow up, SPPB was completed plus the 6-minute walk test (6MWT), 30-second sit-to-stand test, and Timed Up and Go (TUG) test (37, 38). Frailty was assessed using the Clinical Frailty Scale (CFS) (39).

Statistical Analysis Plan:

Descriptive statistics are presented as medians and interquartile ranges [IQR], means ± standard deviations, or ranges and percentages, as appropriate. To examine the primary outcome of within-subject changes in muscle size and quality over the course of 7 days following CKRT enrollment, we conducted a repeated measures ANOVA (rmANOVA) to examine the effects of change over time in muscle ultrasound parameters (Day 1 and Day 7) within each subject and the effect of the group (prospective CKRT group vs. historical control group) as well as sex, age, and Charlson Comorbidity Index (CCI) as *a priori* selected covariates. The approach to analysis accounted for repeated measurements within individuals, allowing us to assess not only the within-subject changes but also the interactions between groups and time points. We calculated Pearson's correlation between Day 1 and Day 7 measurements for both prospectively enrolled CKRT subjects and historical controls, and correlation coefficients were compared between the CKRT subjects and controls using Fisher's Z transformation. Wilcoxon signed-rank tests were used to compare the distributions of RF mT, RF CSA, and RF EI measurements for each group between Day 1 and Day 7. P-values were adjusted for multiple testing using the Benjamini-Hochberg method.

The characteristics of survivors to hospital discharge with and without ICU-AW were compared using the Mann Whitney U test and Fisher's Exact test. Finally, *post-hoc* exploratory regression was performed by combining the CKRT and historical groups to examine if CKRT exposure is independently associated with muscle strength at hospital discharge using two approaches: (1) multivariable linear regression using MRC-SS as a continuous dependent variable and (2) multivariable logistic regression with the binary outcome of ICU-AW diagnosis (i.e., MRC-SS <48/60 or ≥48). To avoid overfitting, we selected *a priori* the following covariates: age, sex, CKRT exposure, and exposure to MV. For sensitivity and transparency, we defined exposure to CKRT and MV with two approaches equating to four total models: yes/no need for CKRT and MV and duration of CKRT and MV in days.

RESULTS

Twenty-three patients (9 female, 14 male) with median [IQR] age 56 [47–60] years, BMI 29 [26–36] kg/m^2, and CCI 3 [IQR 1.5–5] were enrolled (Table 1). At enrollment, the median Sequential Organ Failure Assessment (SOFA) score was of 9 [7.5–11.5]. The median duration of CKRT was 4 [1–7] days and the most common modality was continuous venovenous hemodiafiltration (CVVHDF, n = 18, 78%) followed by continuous venovenous hemodialysis (CVVHD, n = 3, 13%) and continuous venovenous hemofiltration (CVVH, n = 2, 9%). Fifteen (65%) required concurrent MV with median duration of 5 [4–13] days. Eleven (48%) were clinically diagnosed with sepsis. The median ICU and hospital LOS were 7 [5–15] days and 13 [9–33] days, respectively. Six (26%) patients died in the ICU and one (4%) transitioned to comfort measures before study completion. Six (26%) patients were discharged to a secondary facility, five (22%) went home with home health (HH) services, and six (26%) were discharged home without HH services. Patients treated with CKRT had low levels of mobility as measured by IMS with median of 0 [0–0] on Day 1, 0.5 [0–1] on Day 3, and 3 [0.5–3.5] on Day 7.

Rectus femoris Ultrasound:

Ultimately, a total of 234 axial images of the RF were obtained, with a representative example shown in Figure 1b. Baseline images were not obtained in 3 subjects due to death or transition to comfort measures shortly after enrollment, and 1 set of images was unable to be analyzed due to poor quality from excess adipose tissue and edema, yielding 19 subjects with baseline images. Three additional patients died before discharge, whereas two sets of images at the Day 7 time point and two different sets of images at hospital discharge were unable to be analyzed due to edema and/or adiposity reducing quality. Ultimately, change over time analyses were performed in 14 patients with matched pairs (Figure 2).

Rectus Femoris Muscle Thickness: The median baseline RF mT was 1.35 [1.1–1.7] cm which decreased by median 10% [3%–20%] from Day 1 to 7 and 17% [8%–22%] from Day 1 to hospital discharge (Figure 3A).

Rectus Femoris Cross-sectional Area: The median baseline RF CSA was 3.89 [3.3–4.4] cm^2 which decreased by median 19% [12%–22%] from Day 1 to 7 and 15% [12%–25%] from Day 1 to hospital discharge (Figure 3B).

Rectus Femoris Echo Intensity: The median baseline RF EI was 92 [70–101] grayscale units, which increased (implying worse muscle quality) by median 14% [5%–25%] from Day 1 to Day 7 and 13% [0.5%–28%] from Day 1 to hospital discharge (Figure 3C).

Comparison of CKRT-treated subjects to historical controls:

There were no statistically significant differences in demographic or baseline clinical characteristics between the CKRT-treated and non-KRT control groups (Supplemental Table 2), apart from time from ICU admission to first ultrasound exam (mean 2.8 vs. 1.1 days, respectively). Correlation coefficients between Day 1 to 7 for muscle parameters were similar between the CKRT and control groups (Supplemental Table 3), indicating a similar degree of change between muscle parameters in both groups. Both the CKRT and control groups showed statistically significant within-group change in RF CSA (decrease) and RF EI (increase) measurements between Day 1 and Day 7 ($p < 0.05$, Figure 3). RF MT (decrease) measurements differed significantly between Day 1 to Day 7 in only the control group ($p<0.001$, Supplemental Table 4).

The rmANOVA for RF CSA and RF mT revealed a significant main effect of groups ($F = 13.9$, $p = 0.003$, and $F = 27.1$, $p <0.001$, respectively), indicating differences in trajectory of RF muscle size between CKRT and control groups. However, there were no significant main effects for RF EI. The main effects of age, sex, and CCI were not statistically significant for any of the three measures of muscle wasting. There was a significant within-subject effect of time (baseline to Day 7) for all three measures of muscle wasting (RF mT: $F = 27.1$, $p < 0.001$; RF CSA: $F= 66.2$, $p < 0.001$; RF EI: $F = 22.5$, $p < 0.001$, Figure 3), meaning the change in all 3 muscle measurements across time was significant in both groups. However, the interaction effect between group and time was not statistically significant for any of the measures, indicating that the amount of change in muscle mass and quality over time did not differ significantly between CKRT and control subjects (Supplemental Table 5).

Muscle Strength and Physical Function:

Ultimately, 6 total patients died in hospital and 1 additional subject (due to agitation) was unable to safely participate in testing at hospital discharge, yielding 15 subjects who completed testing (Figure 2). At discharge, 67% of patients (n = 10/15) met criteria for ICU-AW based on MRC-SS (Table 2). Patients meeting criteria for ICU-AW were younger and more likely to be female, but no differences were observed in the Day 1–7 muscle ultrasound parameters compared to those without ICU-AW. The median SPPB at discharge was 3 [1–6], indicating significant levels of physical disability and impaired mobility. Only 2 of 15 subjects were able to complete the Chair-Rise test of the SPPB. The median CFS score was 6 [5–7], representing moderate frailty, with overall 93% of subjects (n = 14/15) exhibiting frailty.

Four subjects returned to clinic for testing at short-term follow-up. Three patients performed 6MWT with median distance of 308 (range 274–455) meters, with 1 subject unable to complete the 6MWT due to weakness requiring a wheelchair. Among the 4 subjects, the median SPPB was 6 (range 4–12), with 3 subjects exhibiting significant functional impairment (SPPB <10).

Exploratory Regression Analyses:

In a combined cohort of 31 patients who participated in muscle strength testing at hospital discharge (n = 15 CKRT-treated subjects and n = 16 historical controls), when controlling for age, sex, and receipt of MV, the receipt of CKRT was independently associated with lower MRC-SS examined as continuous variable ($\beta = -6.4$, $p = 0.033$) and associated with the binary diagnosis of ICU-AW (adjusted OR = 6.97, p=0.0326, Table 3). When reanalyzing exposure to CKRT or MV as continuous variables in days, the associations between CKRT exposure and MRC-SS or diagnosis of ICU-AW are attenuated (Table 3).

DISCUSSION

In this prospective multicenter study, we found that critically ill adult patients requiring CKRT for AKI experience a significant reduction in muscle size and worsening of muscle quality during the first week following CKRT initiation. Specifically, the degree of RF wasting observed in the first 7 days after CKRT initiation was similar, in the case of mT (10% vs. 12%, respectively), or substantially greater, in the case of CSA (19% vs. 15%, respectively), when compared to the pooled rates of muscle loss reported during the first week of ICU admission in a 2023 meta-analysis of 3,251 patients, most of whom underwent MV (8). Moreover, we found that patients treated with CKRT for AKI exhibit high rates of muscle weakness and physical function impairment, with two-thirds of subjects who survived to hospital discharge meeting diagnostic criteria for ICU-AW and with all subjects exhibiting impaired physical function and/or frailty. To our knowledge, this is the first prospective study demonstrating that patients with AKI-CKRT are at high risk of experiencing skeletal muscle atrophy and developing ICU-AW. These findings suggest that patients with AKI-CKRT may benefit from frequent skeletal muscle assessment in the ICU to improve functional prognostication and to prompt clinicians to consider implementing strategies to mitigate physical impairment. Our findings also suggest that the short- and immediate-term sequalae of CKRT on skeletal muscle should be the subject of additional prospective research.

We utilized a pragmatic approach to assess muscle wasting and weakness in patients with CKRT. We employed ultrasonography to longitudinally track muscle size and quality based on time points frequently used in the broader ICU-AW literature. Although muscle ultrasound may not be considered the gold standard for assessing muscle size and quality, it is the most utilized method for assessing muscle wasting in critical care research (8, 40). Specifically, muscle ultrasonography has excellent inter-rater reliability, good construct validity, and high clinical utility (6, 29, 32, 41–43). However, our ultrasound data must be interpreted with caution given our sample size and the exclusion of a few subjects due to poor image quality related to adiposity and edema. Muscle ultrasound is less sensitive

to detecting changes with edema compared to other imaging modalities (44), which may have led to artifactual changes (45) and poor reliability in EI in this study (32). Another possible reason that the change in EI seen in our cohort was somewhat less than that in the non-CKRT controls is that the use of CKRT effectively treated or mitigated volume overload which commonly develops in critically ill patients. More research is necessary to understand the sensitivity and specificity of ultrasound for patients with severe AKI who are at risk of muscle atrophy.

A variety of prior human observational studies have suggested that CKRT may increase the risk of ICU-AW (22–25). For example, a prospective multicenter cohort study of 642 mechanically ventilated patients identified days on KRT as an independent risk factor for ICU-AW (24). Likewise, a retrospective cohort study of >100 ICU survivors found that patients with stage 2 or 3 AKI had increased severity of muscle weakness, lower health-related quality of life, and impaired ability to return to work or driving, with survivors of AKI-KRT being the most severely affected (25). In our study, we detected an association between AKI-KRT and muscle strength as measured by MRC-SS and the diagnosis of ICU-AW at hospital discharge. The presence of weakness at discharge, however, was not associated with changes in muscle size and quality as assessed by ultrasonography. Though multiple reasons for this discrepancy are possible, including the potential limitations of the ultrasonographic assessment of muscle, these findings are nonetheless consistent with data from other studies of critical illness and other settings which demonstrate that muscle size does not always equate to strength (46).

Though additional data are needed, AKI and CKRT are proposed to influence ICU-AW through a variety of mechanisms (17). Animal studies suggest that the high mortality of AKI in the ICU may be a result of organ cross-talk, in which renal ischemia-reperfusion injury, though a variety of cytokines and other inflammatory mediators, induces injury and dysfunction of multiple distant organs including the lung, brain, and myocardium (14–16). Similarly, AKI has been associated in human observational studies with a variety of non-renal effects, such as infection, bone fracture, and stroke (47–49). In skeletal muscle, AKI appears to trigger, through multiple mediators and metabolic pathways, altered amino acid utilization and enhanced muscle tissue catabolism, which may be exacerbated in patients requiring KRT by the non-selective clearance of phosphate, amino acids, and small peptides (17–19, 50–53). CKRT—which provides the highest total cumulative dose of small solute clearance of all available KRT modalities—may especially contribute to the development of muscle wasting, with studies demonstrating that CKRT can remove up to 10–20 g of amino acids per day (18, 19, 51–54). Additional mechanistic studies are required to better clarify the effects of AKI and/or KRT on skeletal muscle and specifically on the development of ICU-AW.

Likewise, additional studies are needed to better define strategies to mitigate the possible contribution of AKI-CKRT to the development of ICU-AW. Most basically, this may include the provision of early physical rehabilitation. Notably, observational studies suggest that physical therapy is feasible and safe during CKRT (55), though prospective data demonstrating beneficial outcomes from physical rehabilitation in patients receiving CKRT are lacking. Likewise, parenteral amino acid supplementation to counteract losses through

CKRT holds some promise and, in a small study, has been shown to effectively maintain serum amino acid levels (56), but the impact on development of ICU-AW or other relevant clinical outcomes is unknown. Finally, observational data suggest that prevention of CKRT-induced hypophosphatemia may decrease the duration of MV, an association felt likely to be mediated by respiratory muscle function, but the impact of the development or the prevention of CKRT-induced hypophosphatemia on non-respiratory muscle function has not been prospectively investigated (57–59).

Notably, we did not detect significant differences in the rates of change in muscle size and quality between the CKRT patients and the historical controls. However, both cohorts exhibited high rates of acute muscle wasting when controlling for age, sex, and pre-existing comorbidity, suggesting that both groups—patients with sepsis and/or respiratory failure and those with AKI-CKRT—are at high risk for ICU-AW. In addition, in two exploratory regression analyses, CKRT exposure appeared to be independently associated with reduced muscle strength at hospital discharge when controlling for age, sex, and exposure to MV, though these analyses are limited by their *post-hoc* nature and potential selection bias. Potential reasons for the lack of statistically significant difference in muscle ultrasound parameters between the CKRT-treated group and the control group include the limited sample size, limitations inherent to the use of historical controls, limitations in the methodology of muscle ultrasound, and differential timing of ultrasound assessment relative to ICU admission. Larger studies including both CKRT-treated subjects and contemporaneously enrolled controls are necessary.

Of note, patients with AKI-CKRT who developed ICU-AW at hospital discharge had a somewhat higher incidence of sepsis and higher WBC at time of CKRT initiation with longer MV times. Though these differences did not reach statistical significance and the overall difference in SOFA scores between subjects that did and did not develop ICU-AW was relatively small, these trends suggest a potentially higher severity of illness in these specific parameters that have been previously linked to the development of ICU-AW (9, 10). Furthermore, we did not capture every mediator or confounder of our outcomes in this prospective study. Notably, we did not analyze creatinine, urea, or urea-creatinine ratio (UCR). These biomarkers of kidney function may provide additional value when evaluating skeletal muscle wasting. UCR holds particular interest as previous studies have demonstrated a strong correlation between higher UCR and lower muscle mass in the ICU (60). However, more research is needed to understand and validate biomarkers of muscle wasting, as these measures frequently lack specificity (61).

Our study has limitations, including the relatively small sample size, reducing the certainty in our findings. Likewise, the exploratory multivariable regression analyses which are inherently hypothesis-generating in nature and should be interpreted with caution. Moreover, the high rate of attrition inherent to studying a condition with a ≥50% in-hospital mortality rate and the challenges of attempting to perform outpatient follow-up in an ICU cohort ultimately limited our evaluation of outcomes. Studies of this patient population are subject to selection and survivorship biases, as death or transition to hospice precludes evaluation of the sickest subjects. Therefore, we did not have enough subjects returning for outpatient assessment to analyze longer-term functional outcomes. The lack of granular

data on nutrition, provision of physical therapy, and fluid balance are additional relevant limitations with potential impact on the measured changes of muscle size and quality and on functional outcomes. Indeed, though proving consistent benefit in randomized trials has been challenging, recent observational studies suggest that the provision of physical therapy and, to a less consistent degree, nutrition could influence the development of muscle wasting and the functional status of ICU survivors (62–67). Future larger studies would ideally capture detailed information on protein, micronutrient, and phosphate supplementation, the delivery of early physical rehabilitation, and fluid intake and output to include as covariates in the analyses. Furthermore, though AKI itself and the need for CKRT have been proposed to independently contribute to ICU-AW (17), an inherent limitation of our study population is the inability to tease apart the effects of AKI and CKRT exposure on our study outcomes. Finally, severity of illness and duration of MV are known important contributors to weakness which could confound the relationship between AKI-CRRT and ICU-AW; we attempted to evaluate or adjust for these factors in our analyses, though ultimately neither severity of illness nor exposure to MV were statistically significant in our modeling, possibly due to our limited sample size. Further studies with larger sample sizes should focus on the interactions between CKRT, MV, and overall severity of illness, muscle strength, and physical function.

In conclusion, in this prospective multicenter study we found that patients with critical illness and AKI requiring CKRT experienced a substantial reduction in muscle size and worsening of muscle quality during the first week following CKRT initiation. The degree of ultrasonographic muscle wasting detected was comparable to that observed in a historical control group of patients with respiratory failure and/or sepsis and the pooled rate of wasting reported from a recent large meta-analysis (8), suggesting that patients with AKI-CKRT comprise a relevant subgroup of patients with critical illness at high risk of ICU-AW. In addition, CKRT-treated subjects who survived to discharge exhibited substantial deficits in physical function, with two-thirds meeting criteria for ICU-AW, and significant degrees of frailty. Additional prospective studies analyzing larger cohorts of patients with critical illness and AKI-CKRT will be required to more definitively elucidate the relationship between AKI, KRT, and the risk of development of ICU-AW and, ultimately, to determine whether patients with AKI-CKRT benefit from targeted rehabilitation and other strategies to mitigate ICU-AW and improve patient-centered functional outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Competing interests:

JPT reports receiving consulting fees from Outset Medical and owning stock or options in Eli Lilly and Company, Novo Nordisk A/S, and Pfizer Inc. JAN reports receiving consulting fees from Baxter Healthcare. The remaining

authors report no financial disclosures. YW is the owner of MyoVision-US, an open-source AI-powered software to analyze muscle ultrasound images. The remaining authors report no financial disclosures.

Declaration of interests

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Availability of data and materials:

The datasets generated and/or analyzed during the current study are not publicly available due ongoing analyses and secondary studies by the authors, but are available from the corresponding author on reasonable request.

References

1. Appleton RT, Kinsella J, Quasim T. The incidence of intensive care unit-acquired weakness syndromes: A systematic review. Journal of the Intensive Care Society. 2015;16(2):126–36. [PubMed: 28979394]
2. Latronico N, Herridge M, Hopkins RO, Angus D, Hart N, Hermans G, et al. The ICM research agenda on intensive care unit-acquired weakness. Intensive Care Med. 2017.
3. Kress JP, Hall JB. ICU-acquired weakness and recovery from critical illness. N Engl J Med. 2014;370(17):1626–35. [PubMed: 24758618]
4. Hermans G, Van Mechelen H, Clerckx B, Vanhullebusch T, Mesotten D, Wilmer A, et al. Acute outcomes and 1-year mortality of intensive care unit-acquired weakness. A cohort study and propensity-matched analysis. Am J Respir Crit Care Med. 2014;190(4):410–20. [PubMed: 24825371]
5. Mayer KP, Thompson Bastin ML, Montgomery-Yates AA, Pastva AM, Dupont-Versteegden EE, Parry SM, Morris PE. Acute skeletal muscle wasting and dysfunction predict physical disability at hospital discharge in patients with critical illness. Critical Care. 2020;24(1):637. [PubMed: 33148301]
6. Parry SM, El-Ansary D, Cartwright MS, Sarwal A, Berney S, Koopman R, et al. Ultrasonography in the intensive care setting can be used to detect changes in the quality and quantity of muscle and is related to muscle strength and function. J Crit Care. 2015;30(5):1151.e9–14.
7. Puthucheary ZA, Phadke R, Rawal J, McPhail MJ, Sidhu PS, Rowlerson A, et al. Qualitative Ultrasound in Acute Critical Illness Muscle Wasting. Crit Care Med. 2015;43(8):1603–11. [PubMed: 25882765]
8. Fazzini B, Markl T, Costas C, Blobner M, Schaller SJ, Prowle J, et al. The rate and assessment of muscle wasting during critical illness: a systematic review and meta-analysis. Crit Care. 2023;27(1):2. [PubMed: 36597123]
9. Herridge MS, Tansey CM, Matte A, Tomlinson G, Diaz-Granados N, Cooper A, et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med. 2011;364(14):1293–304. [PubMed: 21470008]
10. Jolley SE, Bunnell AE, Hough CL. ICU-Acquired Weakness. Chest. 2016;150(5):1129–40. [PubMed: 27063347]
11. Bouchard J, Acharya A, Cerda J, Maccariello ER, Madarasu RC, Tolwani AJ, et al. A Prospective International Multicenter Study of AKI in the Intensive Care Unit. Clin J Am Soc Nephrol. 2015;10(8):1324–31. [PubMed: 26195505]

12. Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med. 2015;41(8):1411–23. [PubMed: 26162677]
13. Griffin BR, Liu KD, Teixeira JP. Critical Care Nephrology: Core Curriculum 2020. Am J Kidney Dis. 2020;75(3):435–52. [PubMed: 31982214]
14. Liu M, Liang Y, Chigurupati S, Lathia JD, Pletnikov M, Sun Z, et al. Acute kidney injury leads to inflammation and functional changes in the brain. Journal of the American Society of Nephrology : JASN. 2008;19(7):1360–70. [PubMed: 18385426]
15. Fox BM, Gil HW, Kirkbride-Romeo L, Bagchi RA, Wennersten SA, Haefner KR, et al. Metabolomics assessment reveals oxidative stress and altered energy production in the heart after ischemic acute kidney injury in mice. Kidney Int. 2019;95(3):590–610. [PubMed: 30709662]
16. Teixeira JP, Ambruso S, Griffin BR, Faubel S. Pulmonary Consequences of Acute Kidney Injury. Semin Nephrol. 2019;39(1):3–16. [PubMed: 30606405]
17. Teixeira JP, Mayer KP, Griffin BR, George N, Jenkins N, Pal CA, et al. Intensive Care Unit-Acquired Weakness in Patients With Acute Kidney Injury: A Contemporary Review. Am J Kidney Dis. 2023;81(3):336–51. [PubMed: 36332719]
18. Oh WC, Mafrici B, Rigby M, Harvey D, Sharman A, Allen JC, et al. Micronutrient and Amino Acid Losses During Renal Replacement Therapy for Acute Kidney Injury. Kidney Int Rep. 2019;4(8):1094–108. [PubMed: 31440700]
19. Stapel SN, de Boer RJ, Thoral PJ, Vervloet MG, Girbes ARJ, Oudemans-van Straaten HM. Amino Acid Loss during Continuous Venovenous Hemofiltration in Critically Ill Patients. Blood Purif. 2019;48(4):321–9. [PubMed: 31291614]
20. Wang XH, Mitch WE, Price SR. Pathophysiological mechanisms leading to muscle loss in chronic kidney disease. Nat Rev Nephrol. 2022;18(3):138–52. [PubMed: 34750550]
21. Teixeira JP, Griffin BR, Pal CA, Gonzalez-Seguel F, Jenkins N, Jones BM, et al. Critical illness myopathy and trajectory of recovery in acute kidney injury requiring continuous renal replacement therapy: a prospective observational trial protocol. BMJ Open. 2023;13(5):e072448.
22. De Jonghe B, Sharshar T, Lefaucheur JP, Authier FJ, Durand-Zaleski I, Boussarsar M, et al. Paresis acquired in the intensive care unit: a prospective multicenter study. Jama. 2002;288(22):2859–67. [PubMed: 12472328]
23. Frithiof R, Rostami E, Kumlien E, Virhammar J, Fallmar D, Hultstrom M, et al. Critical illness polyneuropathy, myopathy and neuronal biomarkers in COVID-19 patients: A prospective study. Clin Neurophysiol. 2021;132(7):1733–40. [PubMed: 33875374]
24. Raurell-Torreda M, Arias-Rivera S, Marti JD, Frade-Mera MJ, Zaragoza-Garcia I, Gallart E, et al. Care and treatments related to intensive care unit-acquired muscle weakness: A cohort study. Aust Crit Care. 2021.
25. Mayer KP, Ortiz-Soriano VM, Kalantar A, Lambert J, Morris PE, Neyra JA. Acute kidney injury contributes to worse physical and quality of life outcomes in survivors of critical illness. BMC Nephrol. 2022;23(1):137. [PubMed: 35392844]
26. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, Initiative S. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med. 2007;147(8):573–7. [PubMed: 17938396]
27. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl. 2012;2(1):2–138.
28. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, et al. New Creatinine- and Cystatin C-Based Equations to Estimate GFR without Race. N Engl J Med. 2021;385(19):1737–49. [PubMed: 34554658]
29. Mayer KP, Dhar S, Cassity E, Denham A, England J, Morris PE, Dupont-Versteegden EE. Interrater Reliability of Muscle Ultrasonography Image Acquisition by Physical Therapists in Patients Who Have or Who Survived Critical Illness. Phys Ther. 2020;100(9):1701–11. [PubMed: 32302406]

30. Mayer KP, Kosmac K, Wen Y, Parry SM, Dhar S, Foster S, et al. Construct and criterion validity of muscle ultrasonography for assessment of skeletal muscle in patients recovering from COVID-19. Frontiers in Physiology. 2023;14.
31. Gonzalez-Seguel F, Pinto-Concha JJ, Rios-Castro F, Silva-Gutierrez A, Camus-Molina A, Mayer KP, Parry SM. Evaluating a Muscle Ultrasound Education Program: Theoretical Knowledge, Hands-on Skills, Reliability, and Satisfaction of Critical Care Physiotherapists. Arch Rehabil Res Clin Transl. 2021;3(3):100142. [PubMed: 34589692]
32. Gonzalez-Seguel F, Tran VQ, Pal CA, Shareef ZT, Israel HP, Horikawa-Strakovsky A, et al. Inter-rater reliability of muscle ultrasonography performed by multidisciplinary novice sonographers in the evaluation of critically ill patients with acute kidney injury requiring continuous kidney replacement therapy. Ren Fail. 2025;47(1):2472990. [PubMed: 40069097]
33. Calulo Rivera Z, González-Seguel F, Horikawa-Strakovsky A, Granger C, Sarwal A, Dhar S, et al. MyoVision-US: an Artificial Intelligence-Powered Software for Automated Analysis of Skeletal Muscle Ultrasonography. medRxiv. 2024.
34. Tipping CJ, Bailey MJ, Bellomo R, Berney S, Buhr H, Denehy L, et al. The ICU Mobility Scale Has Construct and Predictive Validity and Is Responsive. A Multicenter Observational Study. Ann Am Thorac Soc. 2016;13(6):887–93. [PubMed: 27015233]
35. Hermans G, Clerckx B, Vanhullebusch T, Segers J, Vanpee G, Robbeets C, et al. Interobserver agreement of Medical Research Council sum-score and handgrip strength in the intensive care unit. Muscle Nerve. 2012;45(1):18–25. [PubMed: 22190301]
36. Parry SM, Denehy L, Beach LJ, Berney S, Williamson HC, Granger CL. Functional outcomes in ICU - what should we be using? - an observational study. Crit Care. 2015;19(1):127. [PubMed: 25888469]
37. Parry SM, Nalamalapu SR, Nunna K, Rabiee A, Friedman LA, Colantuoni E, et al. Six-Minute Walk Distance After Critical Illness: A Systematic Review and Meta-Analysis. J Intensive Care Med. 2021;36(3):343–51. [PubMed: 31690160]
38. Denehy L, Nordon-Craft A, Edbrooke L, Malone D, Berney S, Schenkman M, Moss M. Outcome measures report different aspects of patient function three months following critical care. Intensive Care Med. 2014;40(12):1862–9. [PubMed: 25319384]
39. Brummel NE, Bell SP, Girard TD, Pandharipande PP, Jackson JC, Morandi A, et al. Frailty and Subsequent Disability and Mortality among Patients with Critical Illness. Am J Respir Crit Care Med. 2017;196(1):64–72. [PubMed: 27922747]
40. Hermans G, De Jonghe B, Bruyninckx F, Van den Berghe G. Clinical review: Critical illness polyneuropathy and myopathy. Crit Care. 2008;12(6):238. [PubMed: 19040777]
41. Strasser EM, Draskovits T, Praschak M, Quittan M, Graf A. Association between ultrasound measurements of muscle thickness, pennation angle, echogenicity and skeletal muscle strength in the elderly. Age (Dordrecht, Netherlands). 2013;35(6):2377–88. [PubMed: 23456136]
42. Zaidman CM, Wu JS, Wilder S, Darras BT, Rutkove SB. Minimal training is required to reliably perform quantitative ultrasound of muscle. Muscle & nerve. 2014;50(1):124–8. [PubMed: 24218288]
43. Sarwal A, Parry SM, Berry MJ, Hsu FC, Lewis MT, Justus NW, et al. Interobserver Reliability of Quantitative Muscle Sonographic Analysis in the Critically Ill Population. J Ultrasound Med. 2015;34(7):1191–200. [PubMed: 26112621]
44. Mul K, Horlings CGC, Vincenten SCC, Voermans NC, van Engelen BGM, van Alfen N. Quantitative muscle MRI and ultrasound for facioscapulohumeral muscular dystrophy: complementary imaging biomarkers. J Neurol. 2018;265(11):2646–55. [PubMed: 30191320]
45. Campbell IT, Watt T, Withers D, England R, Sukumar S, Keegan MA, et al. Muscle thickness, measured with ultrasound, may be an indicator of lean tissue wasting in multiple organ failure in the presence of edema. Am J Clin Nutr. 1995;62(3):533–9. [PubMed: 7661114]
46. Goodpaster BH, Park SW, Harris TB, Kritchevsky SB, Nevitt M, Schwartz AV, et al. The Loss of Skeletal Muscle Strength, Mass, and Quality in Older Adults: The Health, Aging and Body Composition Study. The Journals of Gerontology: Series A. 2006;61(10):1059–64.

47. Wang WJ, Chao CT, Huang YC, Wang CY, Chang CH, Huang TM, et al. The impact of acute kidney injury with temporary dialysis on the risk of fracture. J Bone Miner Res. 2014;29(3):676–84. [PubMed: 23929760]
48. Wu VC, Wu PC, Wu CH, Huang TM, Chang CH, Tsai PR, et al. The impact of acute kidney injury on the long-term risk of stroke. J Am Heart Assoc. 2014;3(4).
49. Griffin BR, Teixeira JP, Ambruso S, Bronsert M, Pal JD, Cleveland JC, et al. Stage 1 acute kidney injury is independently associated with infection following cardiac surgery. J Thorac Cardiovasc Surg. 2021;161(4):1346–55 e3. [PubMed: 32007252]
50. Druml W, Fischer M, Liebisch B, Lenz K, Roth E. Elimination of amino acids in renal failure. Am J Clin Nutr. 1994;60(3):418–23. [PubMed: 8074076]
51. Berg A, Norberg A, Martling CR, Gamrin L, Rooyackers O, Wernerman J. Glutamine kinetics during intravenous glutamine supplementation in ICU patients on continuous renal replacement therapy. Intensive Care Med. 2007;33(4):660–6. [PubMed: 17318498]
52. Fiaccadori E, Regolisti G, Cabassi A. Specific nutritional problems in acute kidney injury, treated with non-dialysis and dialytic modalities. NDT Plus. 2010;3(1):1–7. [PubMed: 25949400]
53. Ostermann M, Summers J, Lei K, Card D, Harrington DJ, Sherwood R, et al. Micronutrients in critically ill patients with severe acute kidney injury - a prospective study. Sci Rep. 2020;10(1):1505. [PubMed: 32001725]
54. Teixeira JP, Neyra JA, Tolwani A. Continuous KRT: A Contemporary Review. Clin J Am Soc Nephrol. 2023;18(2):256–69. [PubMed: 35981873]
55. Mayer KP, Joseph-Isang E, Robinson LE, Parry SM, Morris PE, Neyra JA. Safety and Feasibility of Physical Rehabilitation and Active Mobilization in Patients Requiring Continuous Renal Replacement Therapy: A Systematic Review. Crit Care Med. 2020;48(11):e1112–e20. [PubMed: 33001619]
56. Scheinkestel CD, Adams F, Mahony L, Bailey M, Davies AR, Nyulasi I, Tuxen DV. Impact of increasing parenteral protein loads on amino acid levels and balance in critically ill anuric patients on continuous renal replacement therapy. Nutrition. 2003;19(9):733–40. [PubMed: 12921882]
57. Aubier M, Murciano D, Lecocguic Y, Viires N, Jacquens Y, Squara P, Pariente R. Effect of hypophosphatemia on diaphragmatic contractility in patients with acute respiratory failure. N Engl J Med. 1985;313(7):420–4. [PubMed: 3860734]
58. Gravelyn TR, Brophy N, Siegert C, Peters-Golden M. Hypophosphatemia-associated respiratory muscle weakness in a general inpatient population. Am J Med. 1988;84(5):870–6. [PubMed: 3364446]
59. Thompson Bastin ML, Stromberg AJ, Nerusu SN, Liu LJ, Mayer KP, Liu KD, et al. Association of Phosphate-Containing versus Phosphate-Free Solutions on Ventilator Days in Patients Requiring Continuous Kidney Replacement Therapy. Clin J Am Soc Nephrol. 2022.
60. Haines RW, Zolfaghari P, Wan Y, Pearse RM, Puthucheary Z, Prowle JR. Elevated urea-to-creatinine ratio provides a biochemical signature of muscle catabolism and persistent critical illness after major trauma. Intensive Care Med. 2019;45(12):1718–31. [PubMed: 31531715]
61. Paulus MC, Melchers M, van Es A, Kouw IWK, van Zanten ARH. The urea-to-creatinine ratio as an emerging biomarker in critical care: a scoping review and meta-analysis. Crit Care. 2025;29(1):175. [PubMed: 40317012]
62. Lambell KJ, King SJ, Forsyth AK, Tierney AC. Association of Energy and Protein Delivery on Skeletal Muscle Mass Changes in Critically Ill Adults: A Systematic Review. JPEN J Parenter Enteral Nutr. 2018;42(7):1112–22. [PubMed: 29603281]
63. Team Study Investigators, Anzics Clinical Trials Group, Hodgson CL, Bailey M, Bellomo R, Brickell K, et al. Early Active Mobilization during Mechanical Ventilation in the ICU. N Engl J Med. 2022;387(19):1747–58. [PubMed: 36286256]
64. Zaragoza-Garcia I, Arias-Rivera S, Frade-Mera MJ, Marti JD, Gallart E, San Jose-Arribas A, et al. Enteral nutrition management in critically ill adult patients and its relationship with intensive care unit-acquired muscle weakness: A national cohort study. PloS one. 2023;18(6):e0286598. [PubMed: 37285356]
65. Watanabe S, Hirasawa J, Naito Y, Mizutani M, Uemura A, Nishimura S, et al. Association Between Intensive Care Unit-Acquired Weakness and Early Nutrition and Rehabilitation Intensity

in Mechanically Ventilated Patients: A Multicenter Retrospective Observational Study. Cureus. 2023;15(4):e37417. [PubMed: 37182030]

66. de Man AME, Gunst J, Reintam Blaser A. Nutrition in the intensive care unit: from the acute phase to beyond. Intensive Care Med. 2024;50(7):1035–48. [PubMed: 38771368]
67. Mayer KP, Haezebrouck E, Ginoza LM, Martinez C, Jan M, Michener LA, et al. Early physical rehabilitation dosage in the intensive care unit associates with hospital outcomes after critical COVID-19. Crit Care. 2024;28(1):248. [PubMed: 39026370]

Highlights

- Patients in the ICU with acute kidney injury (AKI) who required continuous kidney replacement therapy (CKRT) suffered 2–3% per day of rectus femoris muscle wasting in the first week.
- 67% of AKI-CRKT survivors had clinically detectable ICU-acquired weakness at hospital discharge.
- Patients with AKI who required CRKT were at risk of significant short- and long-term impairments in muscle and physical function.

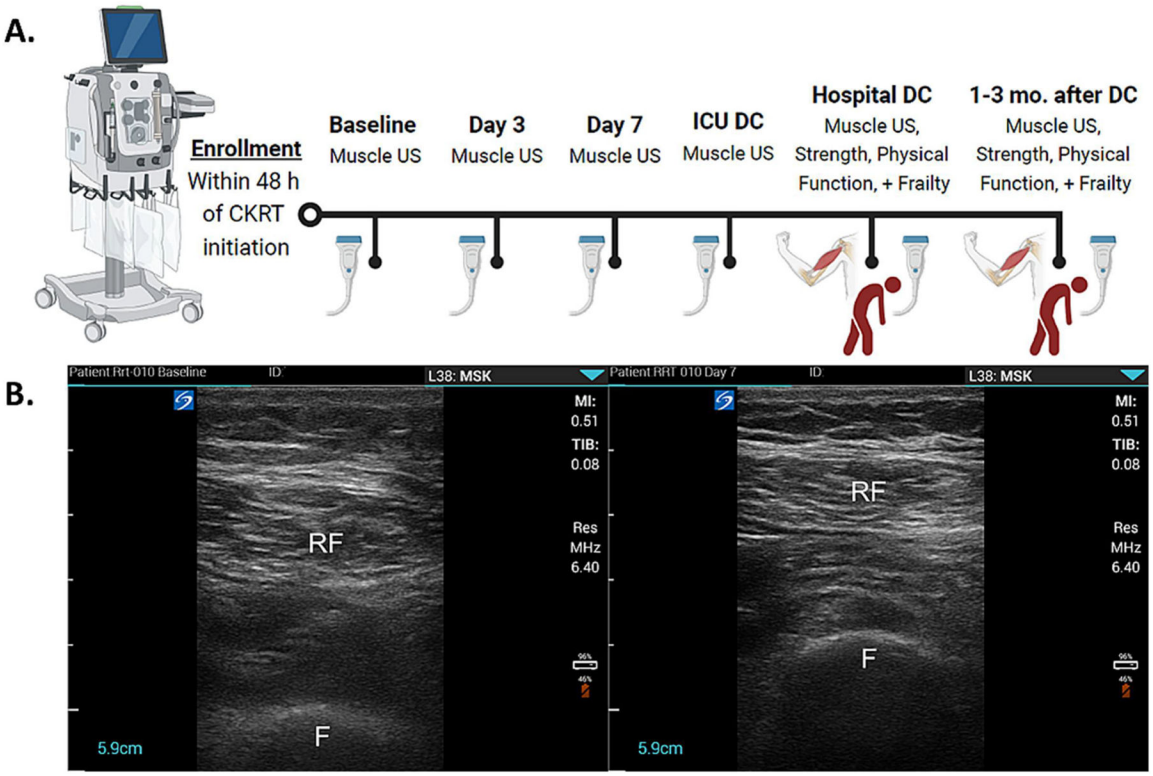

Figure 1:

Study overview and representative muscle ultrasound images. **Panel A**) Schematic showing schedule of longitudinal assessment and study activities at each time point. **Panel B**) Representative pair of images obtained at Day 1 and Day 7 in the same subject demonstrating significant decrease in rectus femoris (RF) thickness and cross-sectional area. *Panel A created with* BioRender.com. *Images in Panel B obtained with Sonosite IViz (FUJIFILM Sonosite, Inc., Bothell, WA, USA) and linear probe*.

CKRT = continuous kidney replacement therapy; DC = discharge; F = femur; ICU = intensive care unit; US = ultrasound.

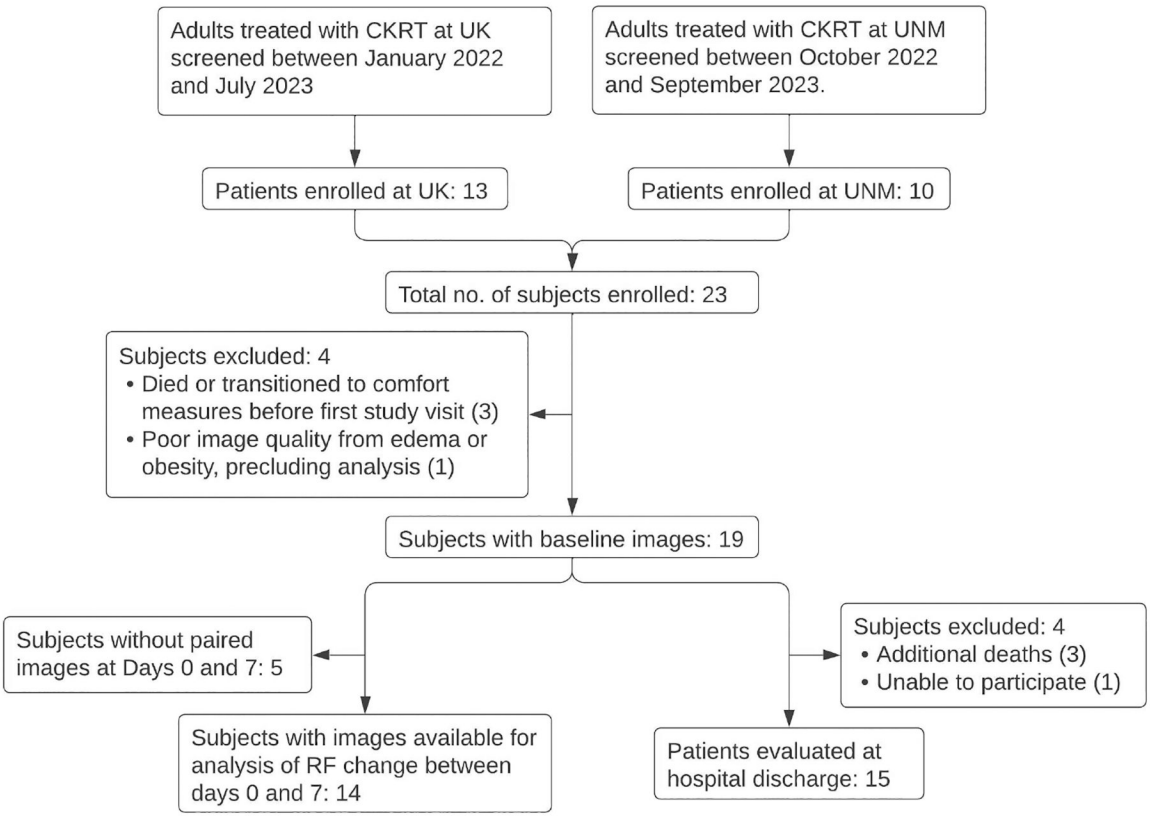

Figure 2:

Flow diagram of recruitment, enrollment, and follow-up

CKRT = continuous kidney replacement therapy; UK = University of Kentucky; UNM = University of New Mexico.

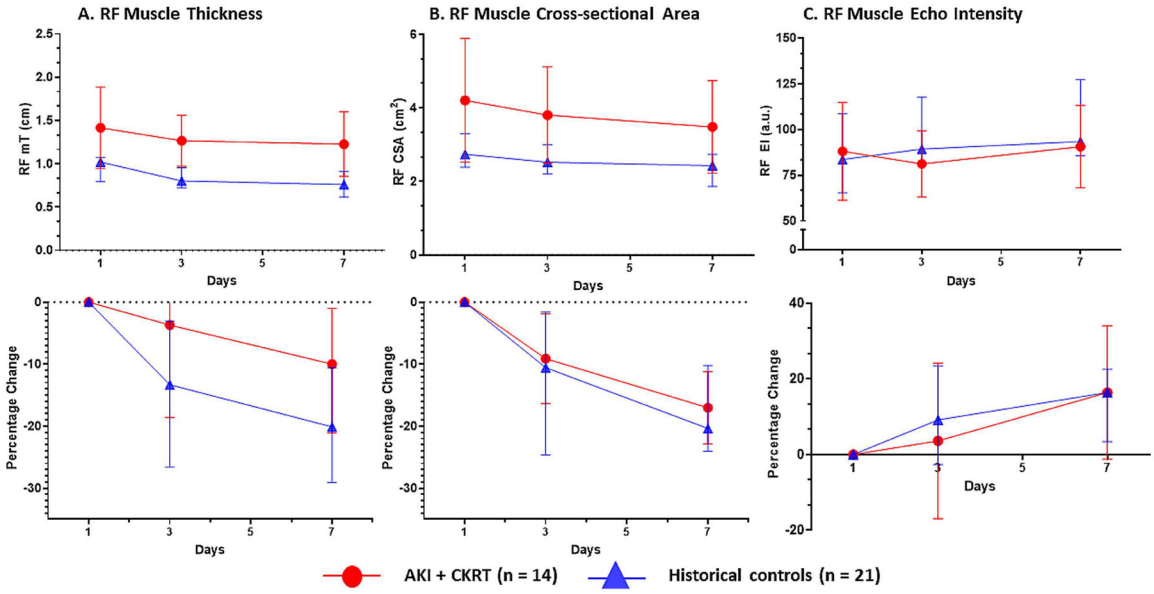

Figure 3:

Change in rectus femoris (RF) muscle size and quality in patients with AKI treated with CKRT compared to historical control group of critically ill adult patients not treated with KRT. **Panel A**) *Rectus Femoris Muscle Thickness* (mT) displays the decrease in raw mT (in cm) and the percent change from Day 1 to 7. **Panel B**) *Rectus Femoris Cross-sectional Area* (CSA) displays the decrease in raw CSA (in cm^2) and the percent change from Day 1 to 7. **Panel C**) *Rectus Femoris Echo Intensity* (EI) displays the increase in the raw EI (in arbitrary units, a.u.) and the percent change from Day 1 to 7. An increase in EI increased implies worsening muscle quality. There was a significant effect of time (i.e., day) within subjects for all three measures of muscle wasting (RF mT: $F = 27.1$, $p < 0.001$; RF CSA: $F = 66.2$, $p < 0.001$; RF EI: $F = 22.5$, $p < 0.001$), meaning the change across time in all three muscle mass measurements in CKRT-treated patients was significant. However, the interaction effect between group and day was not statistically significant for any of the measures, indicating that the amount of change in muscle mass and quality over time did not differ significantly between the CKRT and historical control groups. Displayed are medians with whiskers indicating interquartile range.

AKI = acute kidney injury; CKRT = continuous kidney replacement therapy; cm = centimeters.

Table 1.

Demographic and clinical data of CKRT cohort

Parameter	CKRT cohort (n = 23)
Age, median [IQR]	56 [37–60]
Sex, Female (%)	9 (39)
Body mass index, kg/m^2, median [IQR]	29 [26–36]
Charlson Comorbidity Index, median [IQR]	3 [1.5–5]
SOFA score at study enrollment, median [IQR]	9 [7.5–11.5]
Time from ICU admission to CKRT initiation, days, median [IQR]	1 [1–2]
CKRT days, median [IQR]	4 [1–7]
Sepsis^, n (%)	11 (48)
White blood cell count (× 10^9/L)	
• ICU admit, median [IQR]	16 [12 – 18]
• CKRT initiation, median [IQR]	18 [14 – 21]
Nutritional delivered during first week of study	
• Oral Diet, n (%)	8 (35)
• Enteral, n (%)	13 (56)
• Parenteral, n (%)	2 (9)
MV, yes (%)	15 (65)
MV duration, days, median [IQR]	5 [4–13]
ICU LOS, median [IQR]	9 [8–11]
Hospital LOS, median [IQR]	13 [8.5–33]
Days from ICU admit to 1st US exam, mean ± SD	2 [1.8 – 3.2]

CKRT = continuous kidney replacement therapy; ICU = intensive care unit; IQR = interquartile range; LOS = length of stay; MV = mechanical ventilation; SD = standard deviation; SOFA = Sequential Organ Failure Assessment; US = ultrasound.

Table 2.

Demographic and clinical data of AKI-CKRT patients evaluated at discharge for ICU-AW and the results of physical function testing.

Parameter	Subjects evaluated at discharge (n = 15)	Diagnosis of ICU-AW*		
		Yes (n = 10)	No (n = 5)	p-value†
Age, median [IQR]	57 [36 – 63]	49 [32–57]	67 [60–69]	0.014
Sex, Female (%)	7 (47)	7 (70)	1 (20)	0.021
Body mass index, kg/m^2, median [IQR]	29 [24 – 40]	28 [23–40]	35 [27–38]	0.918
Charlson Comorbidity Index, median [IQR]	3 [1.5 – 5.5]	2 [1–5]	5 [3–6]	0.289
SOFA score at study enrollment, median [IQR]	9 [8–10]	9.5 [5.5–10.75]	8 [8–9]	0.867
Time from ICU admission to CKRT initiation, days, median [IQR]	1 [0.9 – 1.4]	1 [0.6 – 1.8]	1 [1–1]	0.820
CKRT days, median [IQR]	4 [3–7]	4 [3–7]	5 [4–6]	0.626
Sepsis^, n (%)	7 (47)	6 (60)	1 (20)	0.343
White blood cell count (× 10^9/L)				
• ICU admit, median [IQR]	16 [12 – 18]	17 [16–19]	12 [11–13]	0.258
• CKRT initiation, median [IQR]	17 [14 – 22]	18 [17–24]	10 [8–12]	0.075
Nutritional delivered during first week of study				0.550
• Oral Diet, n (%)	8 (53)	4 (40)	4 (80)	
• Enteral, n (%)	6 (40)	5 (50)	1 (20)	
• Parenteral, n (%)	1 (7)	1 (10)	0 (0)	
MV, yes (%)	8 (53)	5 (50)	3 (60)	0.657
MV duration, days, median [IQR]	12 [4 – 17]	17 [13–17]	9 [6–11]	0.108
ICU LOS, median [IQR]	9 [5–21]	9 [5–28]	9 [8–11]	0.489
Hospital LOS, median [IQR]	18 [12–41]	32 [16–50]	11 [10–15]	0.092
Days from ICU admit to 1st US exam, mean ± SD	2 [1–3]	2.5 [1.3 – 3]	2 [1–4]	0.835
Muscle & Physical Function Testing at Hospital Discharge				
MRC-SS (0–60), median [IQR]	44 [42–50]	42 [40–44]	50 [50–50]	0.014
Knee extensor strength, kg, median [IQR]	13 [11–16]	11 [7–12]	16 [15–20]	0.012
Handgrip strength, kg, median [IQR]	16 [12–23]	14 [12–18]	22 [19–25]	0.008
Short Physical Performance Battery, median [IQR]	3 [0.5 – 6]	1.5 [0–3]	6 [6–8]	0.025
Clinical Frailty Scale, median [IQR]	6 [5–7]	7 [6–7]	4 [4–5]	0.007
Discharge destination				
Home, n (%)	11 (73)	6 (60)	5 (100)	0.154#
Secondary care facility (Long-term acute care, skilled nursing or acute rehabilitation), n (%)	4 (27)	4 (40)	0 (0)	

*Diagnosis of ICU-AW is based on MRC-SS <48/60 at hospital discharge.

† p-value represents Fisher's exact test or Mann Whitney U test.

^ Sepsis assessed in binary fashion as present or absent upon study enrollment or during the subsequent ICU course, based upon clinical documentation.

Fisher's exact test comparing ICUAW (yes, no) with discharge home or secondary care facility.

AKI-CKRT; acute kidney injury requiring CKRT; CKRT = continuous kidney replacement therapy; ICU = intensive care unit; ICU-AW = ICU-associated weakness; IQR = interquartile range; LOS = length of stay; MRC-SS = Medical Research Council sum score; MV = mechanical ventilation; SD = standard deviation; SOFA = Sequential Organ Failure Assessment; US = ultrasound.

Table 3.

Exploratory multivariable regression models predicting muscle strength and ICU-AW in the combined cohort (n = 31) of CKRT-treated subjects and historical controls

Outcome variable: MRC-SS (continuous)				
Independent variables	**Unstandardized β (95% CI)**	**Std Error**	**T**	**p-value**
Constant	52.5 (38 – 67)	6.7	7.62	<0.001
Age	−0.05 (−0.2 – 0.2)	0.95	−0.47	0.641
Sex (Male compared to female)	0.72 (−5.2 – 6.6)	0.05	0.25	0.805
Mechanical ventilation (yes)	−1.67 (−8.0 – 4.6)	3.01	−0.55	0.587
CKRT (yes)	−6.39 (−12 - −0.6)	2.83	−2.26	0.033
Outcome variable: MRC-SS (continuous)				
Independent variables	**Unstandardized β (95% CI)**	**Std Error**	**T**	**p-value**
Constant	62 (38 – 86)	11.2	5.532	<0.001
Age	−0.11 (−0.4 – 0.2)	0.14	−0.80	0.444
Sex (Male compared to female)	−2.6 (−10 – 5.2)	3.66	−0.71	0.486
Mechanical ventilation duration (days)	−0.43 (−1.2 – 0.3)	0.36	−1.19	0.251
CKRT duration (days)	−0.55 (−1.7 – 0.6)	0.53	−1.05	0.311
Outcome variable: Diagnosis of ICU-AW				
Independent variables	**aOR (95% CI)**	**Std Error**	**p-value**	
Constant	2.32	1.99	0.673	
Age	0.98 (0.9 – 1.0)	0.03	0.531	
Sex (Male compared to female)	0.34 (0.1 – 1.8)	0.87	0.212	
Mechanical ventilation (yes)	2.23 (0.4 – 13.1)	0.90	0.375	
CKRT (yes)	6.97 (1.2 – 41.1)	0.91	0.032	
Outcome variable: Diagnosis of ICU-AW				
Independent variables	**aOR (95% CI)**	**Std Error**	**p-value**	
Constant	0.02	4.98	0.210	
Age	1.1 (0.9 – 1.2)	0.07	0.887	
Sex (Male compared to female)	0.6 (0.1 – 7.3)	1.26	0.324	
Mechanical ventilation duration (days)	1.8 (0.9 – 3.5)	0.34	0.245	
CKRT duration (days)	0.7 (0.4 – 1.3)	0.30	0.611	

Medical Research Council Sum Score (MRC-SS) is the dependent outcome of interest at hospital discharge; a diagnosis of ICU-AW based on of <48/60

aOR = adjusted odds ratio; CI = confidence interval; CKRT = continuous kidney replacement therapy; ICU-AW = intensive care unit acquired weakness.