OBSERVATIONAL STUDY

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Muscle Ultrasound Changes and Physical Function of Critically Ill Children: A Comparison of Rectus Femoris Cross-Sectional Area and Quadriceps Thickness Measurements

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IMPORTANCE: Quadriceps thickness (QT) and rectus femoris cross-sectional area (RF_{CSA}) are both used to evaluate muscle changes in critically ill children. However, their correlation and association with physical function has not been compared.

OBJECTIVES: To compare QT with RF_{CSA} changes, and their association with physical function in critically ill children.

DESIGN, SETTING, AND PARTICIPANTS: Secondary analysis of a prospective cohort study of children 0–18 years old admitted to a tertiary mixed PICU between January 2015 and October 2018 with PICU stay greater than 48 hours and greater than or equal to one organ dysfunction.

MAIN OUTCOMES AND MEASURES: Ultrasound QT and RF_{CSA} were measured at PICU admission, PICU discharge, hospital discharge, and 6 months post-discharge. QT and RF_{CSA} changes from baseline were compared with each other and with change in motor function, physical ability, and physical health-related quality of life (HRQOL).

RESULTS: Two hundred thirty-seven images from 66 subjects were analyzed. RF_{CSA} change was not significantly different from QT change at PICU (−8.07% [interquartile range (IQR), −17.11% to 4.80%] vs −4.55% [IQR, −14.32% to 4.35%]; $p = 0.927$) or hospital discharge (−5.62% [IQR, −15.00% to 9.42%] vs −8.81% [IQR, −18.67% to 2.39%]; $p = 0.238$) but was significantly greater than QT change at 6 months (32.7% [IQR, 5.74–109.76%] vs 9.66% [IQR, −8.17% to 25.70%]; $p < 0.001$). Motor function change at PICU discharge was significantly associated with RF_{CSA} change (adjusted β coefficient, 0.02 [95% CI, 0.01–0.03]; $p = 0.013$) but not QT change (adjusted β coefficient, −0.01 [95% CI, −0.02 to 0.01]; $p = 0.415$). Similar results were observed for physical HRQOL changes at hospital discharge (adjusted β coefficient for RF_{CSA} change, 0.51 [95% CI, 0.10–0.92]; $p = 0.017$ and adjusted β coefficient for QT change, −0.21 [−0.76 to 0.35]; $p = 0.458$). Physical ability was not significantly associated with RFCSA or QT changes at 6 months post-discharge.

CONCLUSIONS AND RELEVANCE: Ultrasound derived RF_{CSA} is associated with PICU motor function and hospital discharge physical HRQOL changes, unlike QT, and may be more useful for in-hospital muscle monitoring in critically ill children.

KEY WORDS: critically ill children; quadriceps; rectus femoris; skeletal muscle; ultrasonography

With decreasing mortality rates in critically ill children, greater emphasis has been placed on the functional outcomes and health-related quality of life (HRQOL) of pediatric critical care survivors

DOI: 10.1097/CCE.0000000000000937

KEY POINTS

Question: How do quadriceps thickness or rectus femoris cross-sectional area compare when assessing muscle and physical function changes in critically ill children?

Findings: In this longitudinal observational study, change in rectus femoris cross-sectional area was significantly associated with change in physical function at PICU and hospital discharge, while change in quadriceps thickness was not.

Meaning: Rectus femoris changes appears to be a better indicator of physical function than quadriceps thickness in critically ill children.

(1, 2). Muscle wasting has been demonstrated to affect functional status of critically ill children (3). In recent years, muscle ultrasound has been increasingly recognized as a noninvasive tool to detect muscle changes in critically ill patients (4, 5). Muscle size is one of the most commonly studied properties, as ultrasound-derived decreases in muscle size have been shown to reflect muscle catabolism in the ICU (6). Decreasing muscle size visualized on ultrasonography have also been associated with muscle strength and function in critically ill adults, enabling the early detection of ICU-acquired weakness (7).

Several muscle features have been used to monitor muscle size changes (4). The most common is the thickness of the quadriceps (QT) muscles, which is defined as the thickness of the rectus femoris and vastus intermedius combined (5). Another commonly studied muscle feature is the rectus femoris cross-sectional area (RF_{CSA}), which is obtained by automated areal computation based on the circumscribed tracing of the inner echoic border of the rectus femoris muscle (6). Changes in RF_{CSA} appeared to underestimate muscle wasting as measured by change in myofiber cross-sectional area (CSA) and protein: DNA ratio (8). In critically ill adults, changes in RF_{CSA} and QT correlate, but unlike QT, RF_{CSA} is related to muscle weakness (8).

Muscle ultrasonography has also been used to identify changes in muscle size in critically ill children (3, 9, 10). However, it is unknown how muscle thickness changes compare with CSA measurements in critically ill children. Our aim was to compare the magnitude of QT and RF_{CSA} changes in critically ill children, and their similarities or differences in correlation with physical function throughout critical illness to recovery.

MATERIALS AND METHODS

This study is a secondary analysis of a prospective observational study of children admitted to a tertiary mixed PICU between January 2015 and October 2018, which has been published elsewhere (3). Inclusion criteria were children 1 month to 18 years old admitted to the PICU, expected PICU stay greater than or equal to 48 hours, and at least one organ dysfunction according to the 2005 International Pediatric Sepsis Consensus Conference criteria (11). Exclusion criteria were patients with oncological or progressive neuromuscular disease, or an expected survival of less than 1-year post-discharge. Ethics approval for the original study was obtained from the SingHealth Centralized Institutional Review Board (Protocol Title: Functional Outcomes in Children Post Critical Illness, CIRB Ref: 2014/2073, approved January 5, 2015) and all procedures were carried out in accordance with the Helsinki Declaration. The Strengthening the Reporting of Observational Studies in Epidemiology checklist was used in the report of this study (12).

Data and Measurements

Baseline demographic data were obtained, including the Pediatric Index of Mortality (PIM) 3 score (13), the presence of complex chronic conditions as defined as Feudtner et al (14), PICU length of stay (LOS), and need for mechanical ventilation.

Ultrasound quadriceps measurements were performed on patients at four major timepoints: within 48 hours of PICU admission, at PICU discharge, at hospital discharge, and at 6 months post-discharge using previously described methods (3). Measurements were conducted in a supine position, on the right limb where possible, at a landmark at ½ and ⅔ the distance between the anterior superior iliac spine to the superior border of the patella in children less than 6 years and greater than or equal to 6 years, respectively. Measurements were conducted on the same limb for each subject throughout the study, and all measurements were performed in triplicate using the LOGIQ e (GE Healthcare, Chicago, IL) ultrasound machine with

a linear probe of frequency 5–13 MHz. Measurements were performed by a single operator (C.O.) trained in basic muscle ultrasound measurements.

Images were exported in digital imaging and communications in medicine format, and analyzed using ImageJ software (National Institutes for Health, Bethesda, MD). RF_{CSA} was measured by automated computation of circumscribed area based on manual tracing the inner echoic border of the rectus femoris muscle. QT was measured by measuring the distance from the top of the rectus femoris muscle to the bottom of the vastus intermedius muscle. Patients with images where compression of the muscle during ultrasound (defined as the loss of the convex curve of skin and rectus femoris muscle) may have compromised the accuracy of the QT measurement were excluded from analysis.

Physical function was assessed using three tools that individually measured motor function, physical ability, and physical HRQOL. Motor function was assessed by a single study author (C.O.) using the motor score component on the Functional Status Scale (FSS) at PICU admission (i.e., premorbid baseline function), PICU discharge, hospital discharge, and follow-up (2). The FSS is an objective tool with clear descriptions for scoring in six domains (mental status, sensory functioning, communication, motor functioning, feeding, and respiratory status), which reduces subjectivity in assessment. Motor impairment was defined as an increase in motor scores of two or more from baseline (2). Physical ability was measured using the Pediatric Evaluation of Disability Inventory-Computer Adaptive Test Daily Activities and Mobility subscales at PICU admission and at follow-up, completed by a caregiver (15). Caregiver-reported physical HRQOL was measured using the Pediatric Quality of Life Inventory physical domain at admission, hospital discharge, and follow-up (16).

Statistical Analysis

Percent change in RF_{CSA} and QT from baseline were calculated at each timepoint. Change in RF_{CSA} and QT were compared against each other at each timepoint using Wilcoxon signed-rank tests. PICU muscle changes were also compared in patients with and without PICU-acquired functional impairment using Mann-Whitney *U* tests. Finally, regression analysis was used to compare muscle changes with changes in FSS motor function, physical ability, and physical HRQOL scores, while adjusting for baseline function, age, body mass index (BMI) *z* score, and PIM 3 score. Baseline function, age, and PIM3 score were chosen as covariates due to their reported association with functional outcomes in existing literature (1, 17), while BMI *z* score was included as a covariate to account for differences in body habitus potentially affecting muscle growth. A two-tailed *p* value of less than 0.05 was considered statistically significant.

RESULTS

A total of 77 patients were recruited, of which 73 survived to hospital discharge. After excluding images where the muscle was compressed during ultrasound measurement, a total of 237 images were analyzed across 66 patients for QT and RF_{CSA}, of which 39 images were available at follow-up 6 months post-discharge (**Table 1**). Total FSS scores at each time point are reported in **Supplementary Table S1** (http://links.lww.com/CCX/B214). Motor impairments occurred in 25 of 66 (37.9%) and 10 of 66 (15.2%) patients at PICU and hospital discharge, respectively, and persisted in five of 39 (12.8%) at 6 months.

Quadriceps Thickness Versus Rectus Femoris Cross-Sectional Area Changes

Children with PICU motor impairment demonstrated significant decreases in RF_{CSA} (median change, –1.76%

TABLE 1.
Demographics of Patients

Variables	Participants (*n* = 66)
Age, yr	3.91 (0.76–9.55)
Male gender, *n* (%)	32 (48.5)
Weight, kg	14.55 (7.48–30.15)
Body mass index *z* score	–0.78 (–1.80 to 0.26)
Complex chronic conditions, *n* (%)	27 (40.9)
Pediatric Index of Mortality 3 % probability of death	0.80 (0.40–1.88)
PICU stay, d	4.56 (1.96–13.87)
Mechanical ventilation required, *n* (%)	48 (72.7)

Above shown variables are median (interquartile range) unless otherwise specified. Complex chronic conditions as defined by Feudtner et al (14).

per day; interquartile range [IQR], –8.25 to 0.03 per day; $p = 0.014$) but not QT (–0.47% per day; IQR, –1.79 to 2.11 per day; $p = 0.455$) during PICU stay (**Fig. 1**). Longitudinal muscle changes are summarized in **Table 2**. During PICU stay, median change in QT from baseline was –4.55% (IQR, –14.32% to 4.35%; $p = 0.009$), which translated to approximately –0.88% per day (IQR, –3.02% to 0.70% per day). Change in RF_{CSA} during PICU stay was –8.07% (IQR, –17.11% to 4.80%; $p = 0.003$), which translated to –1.65% per day (IQR, –6.30% to 1.42% per day). Overall, PICU changes in RF_{CSA} did not differ from that of QT ($p = 0.927$). However, in a comparison of patients with PICU LOS less than 4 days ($n = 30$, 45.5%) compared with PICU LOS greater than or equal to 4 days, RF_{CSA} change was significantly different (–6.16% per day [IQR, –11.25% to 0.62% per day] vs –0.76% per day [IQR, –2.16% to 1.63% per day]; $p = 0.004$), whereas QT change was not (–2.60% per day [IQR, –6.50% to 1.00% per day] vs –0.71% per day [–2.16% to 0.47% per day]; $p = 0.180$).

Change in QT at hospital discharge and 6 months were –8.81% (IQR, –18.67% to 2.39%; $p = 0.002$) and 9.66% (IQR, –8.17% to 25.70%; $p = 0.007$), respectively, while change in RF_{CSA} at hospital discharge and 6 months were –5.62% (IQR, –15.00% to 9.42%; $p = 0.255$) and 32.7% (IQR, 5.74–109.76%; $p < 0.001$), respectively. There was no significant difference between QT and RF_{CSA} changes at hospital discharge ($p = 0.238$) but change in RF_{CSA} was significantly higher at 6 months compared with QT changes ($p < 0.001$). These findings were similar regardless of baseline BMI *z* score and age (**Supplementary Table S2**, http://links.lww.com/CCX/B214).

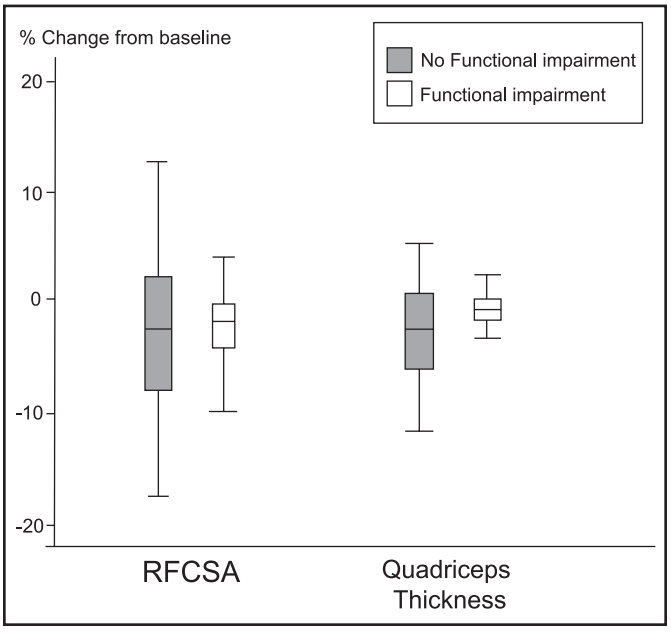

Figure 1. Muscle changes during PICU stay in children with and without acquired motor impairment. RF_{CSA} = rectus femoris cross-sectional area.

Muscle Changes and Physical Function

Children with PICU-acquired motor impairment demonstrated significant decreases in RF_{CSA} (median change, –1.62% per day; IQR, –4.47% to 0.08% per day; $p = 0.011$) but not QT (–0.71% per day; IQR, –1.59% to 0.48% per day; $p = 0.331$) during PICU stay. Change in FSS motor scores were significantly associated with RF_{CSA} change (adjusted β coefficient, 0.02 [95% CI, 0.01–0.03]; $p = 0.013$) but not QT change (adjusted β coefficient, –0.01 [–0.02 to 0.01]; $p = 0.415$). Similar results were observed for physical HRQOL changes at hospital discharge (adjusted β coefficient for RF_{CSA} change, 0.51 [95% CI, 0.10–0.92]; $p = 0.017$ and adjusted β coefficient for QT change, –0.21 [–0.76 to 0.35]; $p = 0.458$). However, there was no significant association between QT or RF_{CSA} changes and motor function, physical ability, or physical HRQOL score changes at 6 months (**Table 3**).

DISCUSSION

This study sought to compare ultrasound-derived thickness versus CSA changes of the quadriceps muscle in critically ill children, and their association with physical function change. There was no significant difference in the magnitude of change between QT and RF_{CSA} during PICU and hospital stay; although percent muscle growth was significantly higher for RF_{CSA} than QT at 6 months post-PICU discharge. However, RF_{CSA} changes were associated with motor function change at PICU discharge and physical HRQOL change at hospital discharge but QT changes were not.

Muscle thickness and CSA are two of the most commonly measured properties in muscle ultrasound (18). In muscle wasting studies conducted in critically ill children, both QT and RF_{CSA} has been shown to have good inter-rater reliability and has been associated with nutritional adequacy in critically ill children (3, 19). However, quadriceps muscle thickness has been more commonly measured than CSA (3, 9, 10, 19). A possible explanation for this may be the ease of visualization of the muscle thickness compared with CSA,

TABLE 2.
Quadriceps Thickness and Rectus Femoris Cross-Sectional Area Changes at Various Time Points

Timepoint	*n*	Median Percent Change in Quadriceps Thickness From Baseline (IQR)	Median Percent Change in Rectus Femoris Cross-Sectional Area From Baseline (IQR)	*p*[a]
PICU discharge	66	−4.55 (−14.32 to 4.35)	−8.07 (−17.11 to 4.80)	0.927
Hospital discharge	66	−8.81 (−18.67 to 2.39)	−5.62 (−15.00 to 9.42)	0.238
6 mo	39	9.66 (−8.17 to 25.70)	32.7 (5.74–109.76)	< 0.001

IQR = interquartile range.
[a]*p* between change in thickness and cross-sectional area.

TABLE 3.
Regression Analysis Between Muscle Changes and Physical Function Changes at Follow-Up

Functional Measure	Unadjusted β Coefficient	*p*	Adjusted β Coefficient	*p*
Rectus femoris cross-sectional area				
FSS motor function	0 (−0.01 to 0.01)	0.792	0.01 (0–0.01)	0.80
PedsQL physical function	0.08 (−0.01 to 0.15)	0.053	0.42 (−0.83 to 1.67)	0.501
PEDI-CAT daily activity	0.07 (0.01–0.13)	0.045	1.26 (−0.49 to 3.01)	0.152
PEDI-CAT mobility	0.13 (0.05–0.21)	0.003	1.07 (−0.14 to 2.28)	0.080
Quadriceps thickness				
FSS motor function	0.01 (−0.01 to 0.01)	0.653	0.01 (−0.01 to 0.01)	0.601
PedsQL physical function	−0.04 (−0.19 to 0.12)	0.615	−0.02 (−0.53 to 0.50)	0.948
PEDI-CAT daily activity	0.04 (−0.15 to 0.23)	0.681	0.18 (−0.59 to 0.96)	0.633
PEDI-CAT mobility	0.11 (−0.15 to 0.63)	0.383	0.13 (−0.41 to 0.67)	0.620

FSS = Functional Status Scale, PEDI-CAT = Pediatric Evaluation of Disability Inventory-Computer Adaptive Test, PedsQL = Pediatric Quality of Life Inventory.
Model adjusted for age, Pediatric Index of Mortality 3 probability of death, body mass index *z* score, and baseline FSS.

as the latter requires an ultrasound probe with an adequately large footprint for complete visualization of the muscle, which may be difficult in larger or more muscular patients (20).

The field of muscle mass measurements in the critically ill patient was born partially from an inability to measure muscle function objectively in unstable, unconscious patients. Muscle function is central to physical function and HRQOL. Measures of muscle mass are only of use if they accurately provide a read out that offers insight into alterations in muscle function. In our cohort, significant decreases in RF_{CSA} were observed in those with PICU acquired functional impairment, while QT change was not. Significant associations were observed between change in physical function and RF_{CSA} but this was not observed with QT changes. These results suggest that RF_{CSA} changes may be able to better identify physical function change compared with QT during PICU stay. This is similar to findings in critically ill adults, where RF_{CSA} changes were shown to be more reflective of muscle strength and function compared with QT changes (8). This was likely due to the unidimensional property of QT compared with the 2D property of RF_{CSA}, mathematically resulting in the latter being more sensitive and reflective of changes in size (21). Similarly, in a population of children 2–6 years old with spastic cerebral palsy, ultrasound thickness and CSA of the gastrocnemius muscle were compared in their ability to predict muscle volume (22). The authors found that CSA was

more useful in predicting the gastrocnemius medial head volume, with the regression model containing CSA having an r^2 of 0.903 compared with an r^2 of 0.831 for muscle thickness. Considering that muscle volume is closely associated with strength and function (23), our findings suggest that RF_{CSA} is a more appropriate measure of muscle mass for future research into altered physical function in pediatric critical care.

Longitudinal muscle changes were measured, which allowed visualization of both RF_{CSA} and QT changes with time. While small changes in muscle were not significantly different between QT and RF_{CSA}, RF_{CSA} at follow-up were significantly greater than QT changes, demonstrating greater responsiveness in RF_{CSA} compared with QT. While we did not measure muscle volume, this could be attributable to the closer relationship of CSA and volume compared with thickness and volume (22). A similar finding was shown in healthy adult males undergoing resistance training (24). Measurements of changes in the vastus lateralis CSA, but not thickness, were correlated with changes in muscle volume after resistance training. The authors hypothesized that this was to heterogeneity in hypertrophy of the muscle, resulting in a nonuniform increase in thickness and CSA. This further reinforces the need to consider differences in thickness and CSA of muscle when measuring change over time.

This study had several limitations. Muscle measurements and motor function was assessed by a single study author, potentially introducing bias, although efforts were undertaken to reduce bias by using an objective scoring tool with clear descriptions of each level of function (2). There was no association between either RF_{CSA} or QT changes with motor function, physical ability, or physical HRQOL at follow-up. This is likely due to small numbers in our cohort, limiting the power to detect statistically significant associations, as we had previously found that RF_{CSA} was associated with physical mobility function in a larger cohort (6). While motor function was measured at every time point, physical ability and physical HRQOL were not, thus limiting our ability to assess shorter-term muscle changes with physical function changes. Nevertheless, this study cohort remains one of the larger cohorts analyzing longitudinal muscle changes in critically ill children, contributing to the methodological development of techniques to measure muscle mass in this group of patients.

CONCLUSIONS

Change in RF_{CSA} is associated with PICU motor function and hospital discharge physical HRQOL, unlike change in QT. We recommend the use of RF_{CSA} over QT measurements in future studies examining muscle mass in hospitalized critically ill children.

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This study was supported by a grant from the KK Women's and Children's Hospital Health Endowment Fund (KKHHEF/2014/05).

Dr. Ong was supported by a graduate research scholarship from the Yong Loo Lin School of Medicine, Singapore. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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